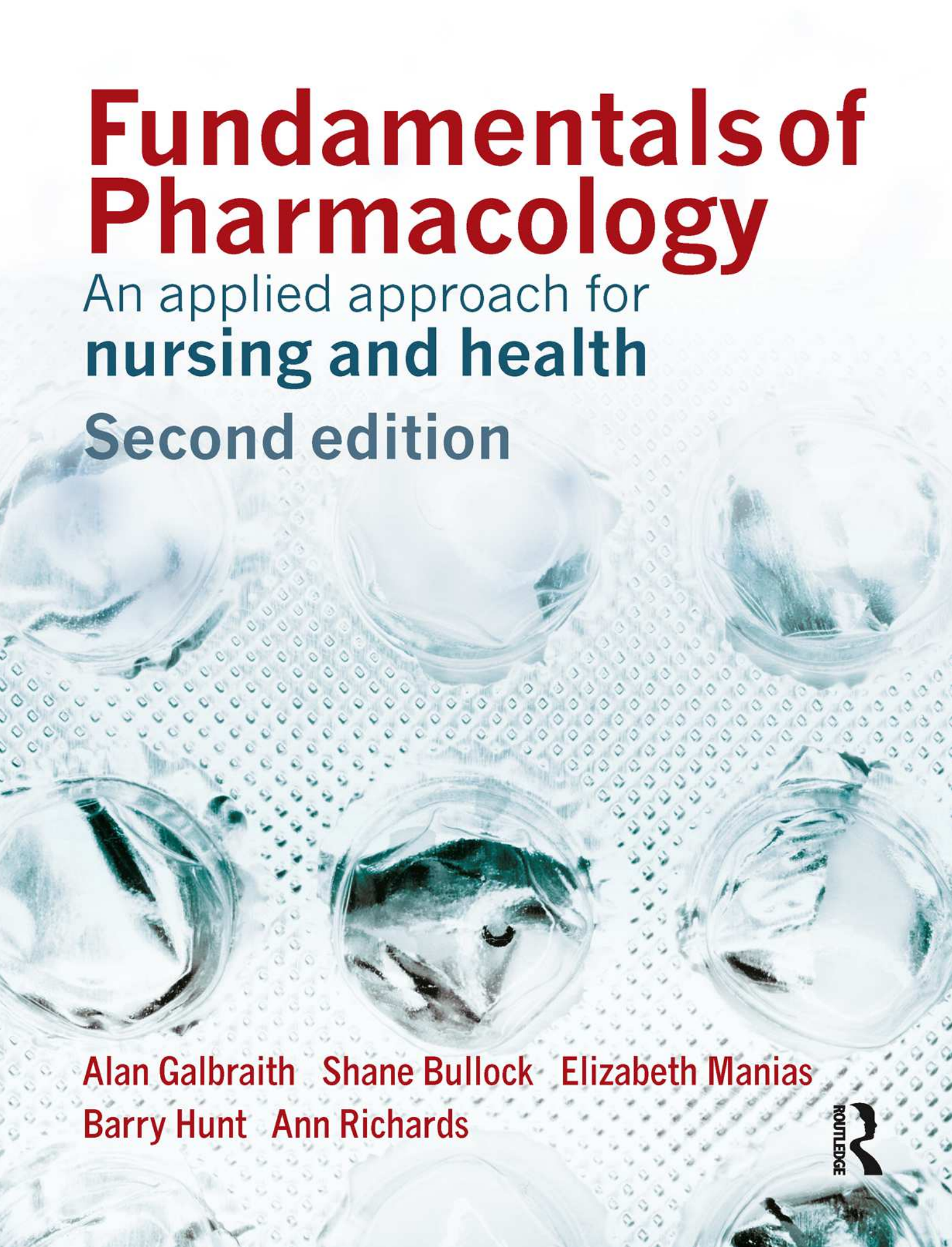
Fundamentals of Pharmacology

An applied approach for nursing and health

Second edition



Alan Galbraith Shane Bullock Elizabeth Manias
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AN APPLIED APPROACH FOR NURSING AND HEALTH

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FUNDAMENTALS OF PHARMACOLOGY:

AN APPLIED APPROACH FOR NURSING AND HEALTH

ALAN GALBRAITH SHANE BULLOCK ELIZABETH MANIAS
BARRY HUNT ANN RICHARDS

SECOND 2 EDITION

Routledge
Taylor & Francis Group
LONDON AND NEW YORK

First published 2007 by Pearson Education Limited

Published 2013 by Routledge
2 Park Square, Milton Park, Abingdon, Oxon OX14 4RN
711 Third Avenue, New York, NY 10017, USA

Routledge is an imprint of the Taylor & Francis Group, an informa business

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ISBN 13: 978-0-13-186901-1 (pbk)

British Library Cataloging-in-Publication Data
A catalogue record for this book is available from the British Library

Library of Congress Cataloging-in-Publication Data
Fundamentals of pharmacology : an applied approach for nursing and health / Alan Galbraith . . . [et al.]. — 2nd ed.
p. ; cm.
Includes bibliographical references and index.
ISBN 978-0-13-186901-1
1. Pharmacology. 2. Nursing. I. Galbraith, Alan.
[DNLM]: 1. Pharmacology—Nurses' Instruction. 2. Pharmaceutical Preparations—Nurses' Instruction. QV 4 F981 2007]
RM300.F87 2007
615′.1—dc22
2007012828

Typeset in 10.5/12.5pt Bembo by 35

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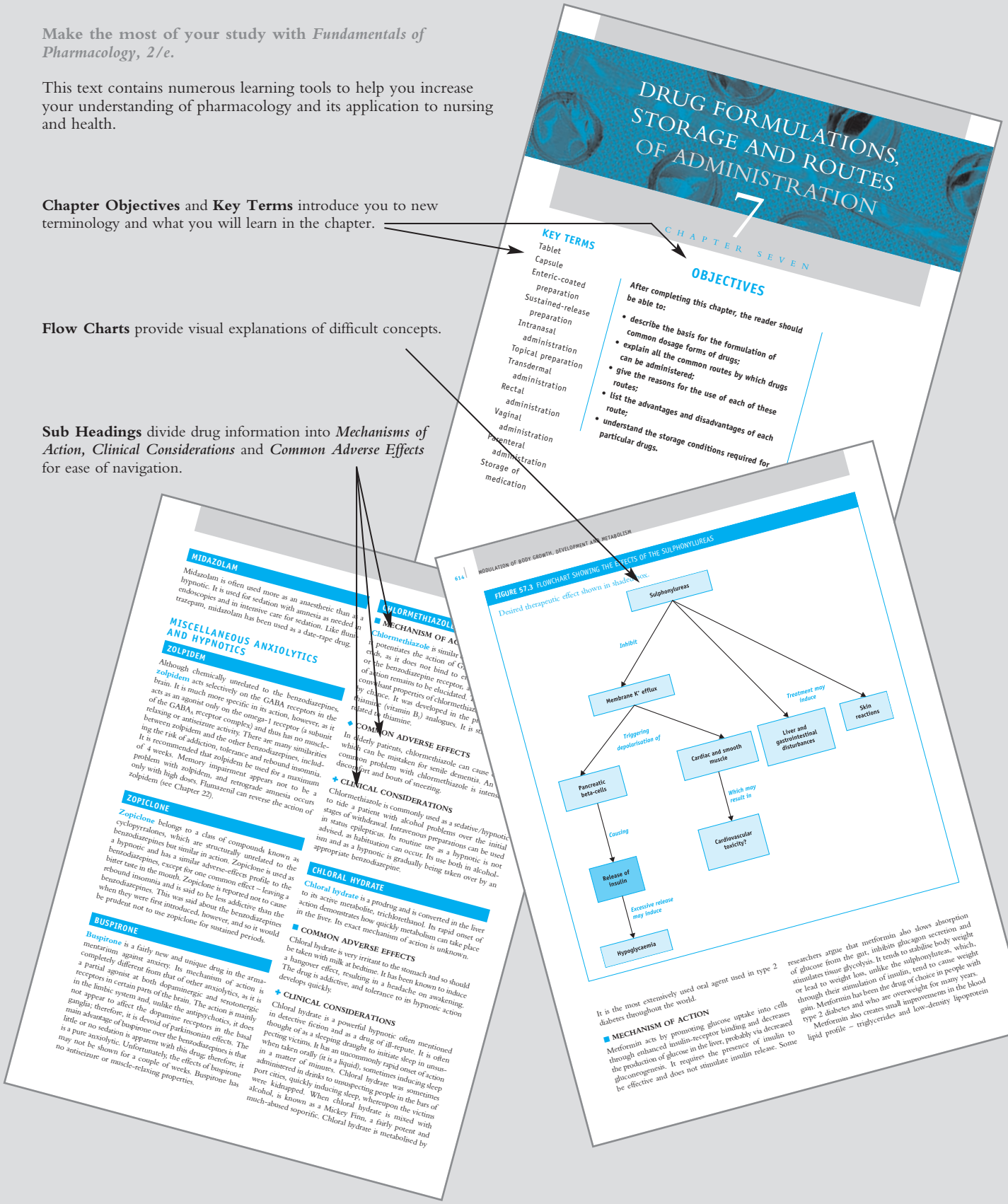
Flow Charts provide visual explanations of difficult concepts.

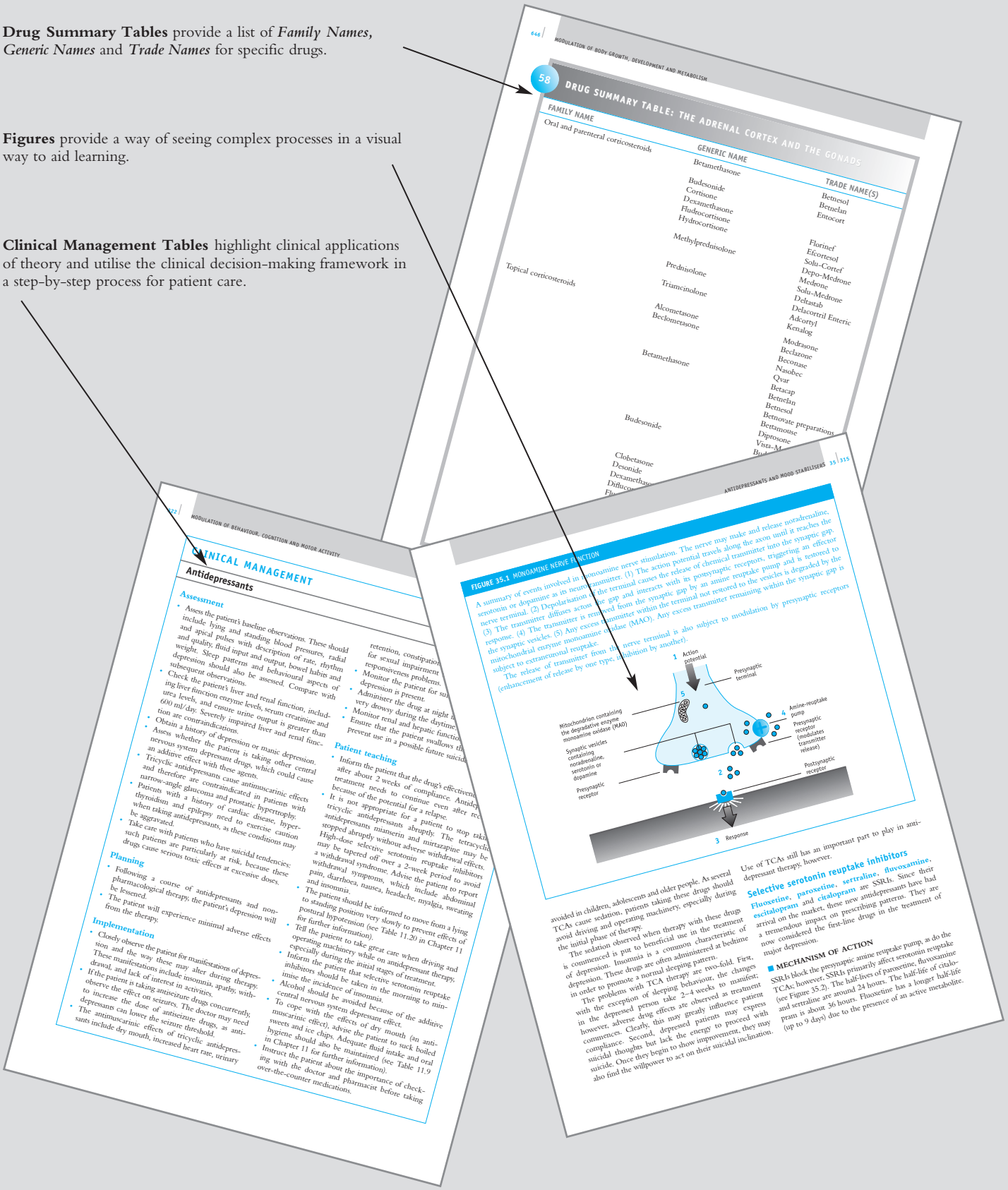
Sub Headings divide drug information into *Mechanisms of Action, Clinical Considerations* and *Common Adverse Effects* for ease of navigation.



Drug Summary Tables provide a list of *Family Names*, *Generic Names* and *Trade Names* for specific drugs.

Figures provide a way of seeing complex processes in a visual way to aid learning.

Clinical Management Tables highlight clinical applications of theory and utilise the clinical decision-making framework in a step-by-step process for patient care.



646 | MODULATION OF BODY GROWTH, DEVELOPMENT AND METABOLISM

58 DRUG SUMMARY TABLE: THE ADRENAL CORTEX AND THE GONADS

FAMILY NAME	GENERIC NAME	TRADE NAME(S)
Oral and parenteral corticosteroids	Betamethasone	Betnesol Betnelan Entocort
	Budesonide Cortisone Dexamethasone Fludrocortisone Hydrocortisone	
	Methylprednisolone	Florinef Efcortesol Solu-Cortef Depo-Medrone Medrone Solu-Medrone Delastrab Delacortil Enteric Adcortyl Kenalog
Topical corticosteroids	Prednisolone Triamcinolone	
	Alcometasone Beclometasone	
	Betamethasone	Modrasone Beclazone Becotase Nasobec Qvar Betacap Betnelan Betnesol Betnovate preparations Bettamouse Diprosone Vista-M
	Budesonide	
	Clobetasone Desonide Dexametha… Diflucor… Flu…	

ANTIDEPRESSANTS AND MOOD STABILISERS 35 | 318

FIGURE 35.1 MONOAMINE NERVE FUNCTION

A summary of events involved in monoamine nerve stimulation. The nerve may make and release noradrenaline, serotonin or dopamine as its neurotransmitter. (1) The action potential travels along the axon until it reaches the nerve terminal. (2) Depolarisation of the terminal causes the release of chemical transmitter into the synaptic gap. (3) The transmitter diffuses across the gap and interacts with its postsynaptic receptors, triggering an effector response. (4) The transmitter is removed from the synaptic gap by an amine reuptake pump and is restored to the synaptic vesicles. (5) Any excess transmitter within the terminal not restored to the vesicles is degraded by the mitochondrial enzyme monoamine oxidase (MAO). Any excess transmitter remaining within the synaptic gap is subject to extraneuronal reuptake.

The release of transmitter from the nerve terminal is also subject to modulation by presynaptic receptors (enhancement of release by one type, inhibition by another).

avoided in children, adolescents and older people. As several TCAs cause sedation, patients taking these drugs should avoid driving and operating machinery, especially during the initial phase of therapy.

The sedation observed when therapy with these drugs is commenced is put to beneficial use in the treatment of depression. Insomnia is a common characteristic of depression. These drugs are often administered at bedtime in order to promote a normal sleeping pattern.

The problems with TCA therapy are two-fold. First, with the exception of sleeping behaviour, the changes in the depressed person take 2–4 weeks to manifest; however, adverse drug effects are observed as treatment commences. Clearly, this may greatly influence patient compliance. Second, depressed patients may express suicidal thoughts but lack the energy to proceed with suicide. Once they begin to show improvement, they may also find the willpower to act on their suicidal inclination.

Use of TCAs still has an important part to play in anti-depressant therapy, however.

Selective serotonin reuptake inhibitors

Fluoxetine, **paroxetine**, **sertraline**, **fluvoxamine**, **escitalopram** and **citalopram** are SSRIs. Since their arrival on the market, these new antidepressants have had a tremendous impact on prescribing patterns. They are now considered the first-line drugs in the treatment of major depression.

MECHANISM OF ACTION

SSRIs block the presynaptic amine reuptake pump, as do the TCAs; however, SSRIs primarily affect serotonin reuptake (see Figure 35.2). The half-lives of paroxetine, fluvoxamine and sertraline are around 24 hours. The half-life of citalopram is about 36 hours. Fluoxetine has a longer half-life (up to 9 days) due to the presence of an active metabolite.

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CLINICAL MANAGEMENT

Antidepressants

Assessment

- Assess the patient's baseline observations. These should include lying and standing blood pressures, radial and apical pulses with description of rate, rhythm and quality; fluid input and output, bowel habits and weight. Sleep patterns and behavioural aspects of depression should also be assessed. Compare with subsequent observations.
- Check the patient's liver and renal function, including liver function enzyme levels, serum creatinine and urea levels, and ensure urine output is greater than 600 ml/day. Severely impaired liver and renal function are contraindications.
- Obtain a history of depression or manic depression.
- Assess whether the patient is taking other central nervous system depressant drugs, which could cause an additive effect with these agents.
- Tricyclic antidepressants cause antimuscarinic effects and therefore are contraindicated in patients with narrow-angle glaucoma and prostatic hypertrophy.
- Patients with a history of cardiac disease, hyperthyroidism and epilepsy need to exercise caution when taking antidepressants, as these conditions may be aggravated.
- Take care with patients who have suicidal tendencies: such patients are particularly at risk, because these drugs cause serious toxic effects at excessive doses.

Planning

- Following a course of antidepressants and non-pharmacological therapy, the patient's depression will be lessened.
- The patient will experience minimal adverse effects from the therapy.

Implementation

- Closely observe the patient for manifestations of depression and the way these may alter during therapy. These manifestations include insomnia, apathy, withdrawal, and lack of interest in activities.
- If the patient is taking antiseizure drugs concurrently, observe the effect on seizures. The doctor may need to increase the dose of antiseizure drugs, as antidepressants can lower the seizure threshold.
- The antimuscarinic effects of tricyclic antidepressants include dry mouth, increased heart rate, urinary retention, constipation, …for sexual impairment, …responsiveness problems.
- Monitor the patient for su… depression is present.
- Administer the drug at night t… very drowsy during the daytime.
- Monitor renal and hepatic function…
- Ensure that the patient swallows th… prevent use in a possible future suicid…

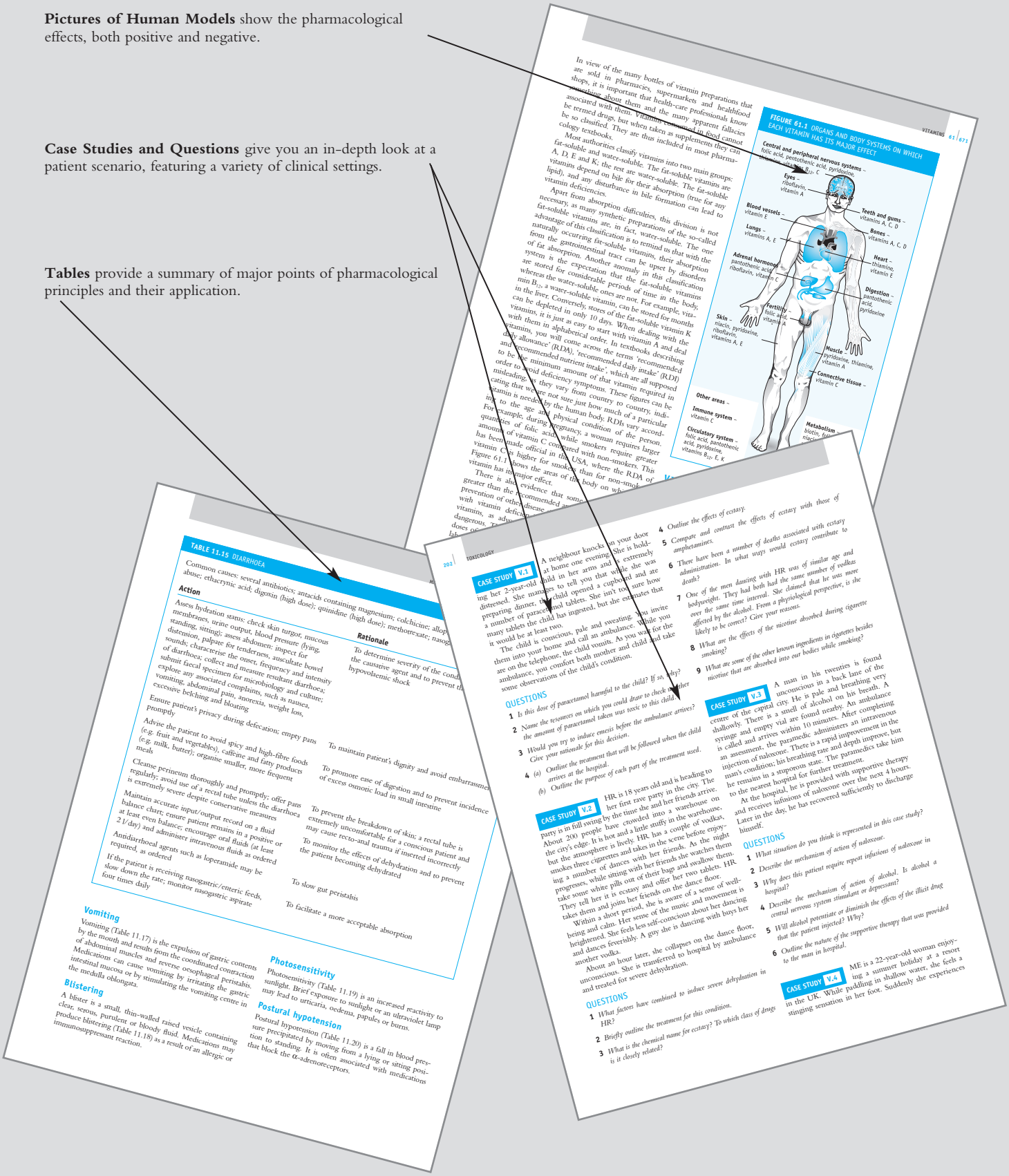
Patient teaching

- Inform the patient that the drug's effectiveness… after about 2 weeks of treatment. Antidep… treatment needs to continue even after rec… because of the potential for a relapse.
- It is not appropriate for a patient to stop taki… tricyclic antidepressants abruptly. The tetracyclic… antidepressants, mianserin and mirtazapine may be… stopped abruptly without adverse withdrawal effects. High-dose selective serotonin reuptake inhibitors may be tapered off over a 2-week period to avoid a withdrawal syndrome. Advise the patient to report withdrawal symptoms, which include abdominal pain, diarrhoea, nausea, headache, myalgia, sweating and insomnia.
- The patient should be informed to move from a lying to standing position very slowly to prevent effects of postural hypotension (see Table 11.20 in Chapter 11 for further information).
- Tell the patient to take great care when driving and operating machinery while on antidepressant therapy, especially during the initial stages of treatment.
- Inform the patient that selective serotonin reuptake inhibitors should be taken in the morning to minimise the incidence of insomnia.
- Alcohol should be avoided because of the additive central nervous system depressant effect.
- To cope with the effects of dry mouth (an antimuscarinic effect), advise the patient to suck boiled sweets and ice chips. Adequate fluid intake and oral hygiene should also be maintained (see Table 11.9 in Chapter 11 for further information).
- Instruct the patient about the importance of checking with the doctor and pharmacist before taking over-the-counter medications.

Pictures of Human Models show the pharmacological effects, both positive and negative.

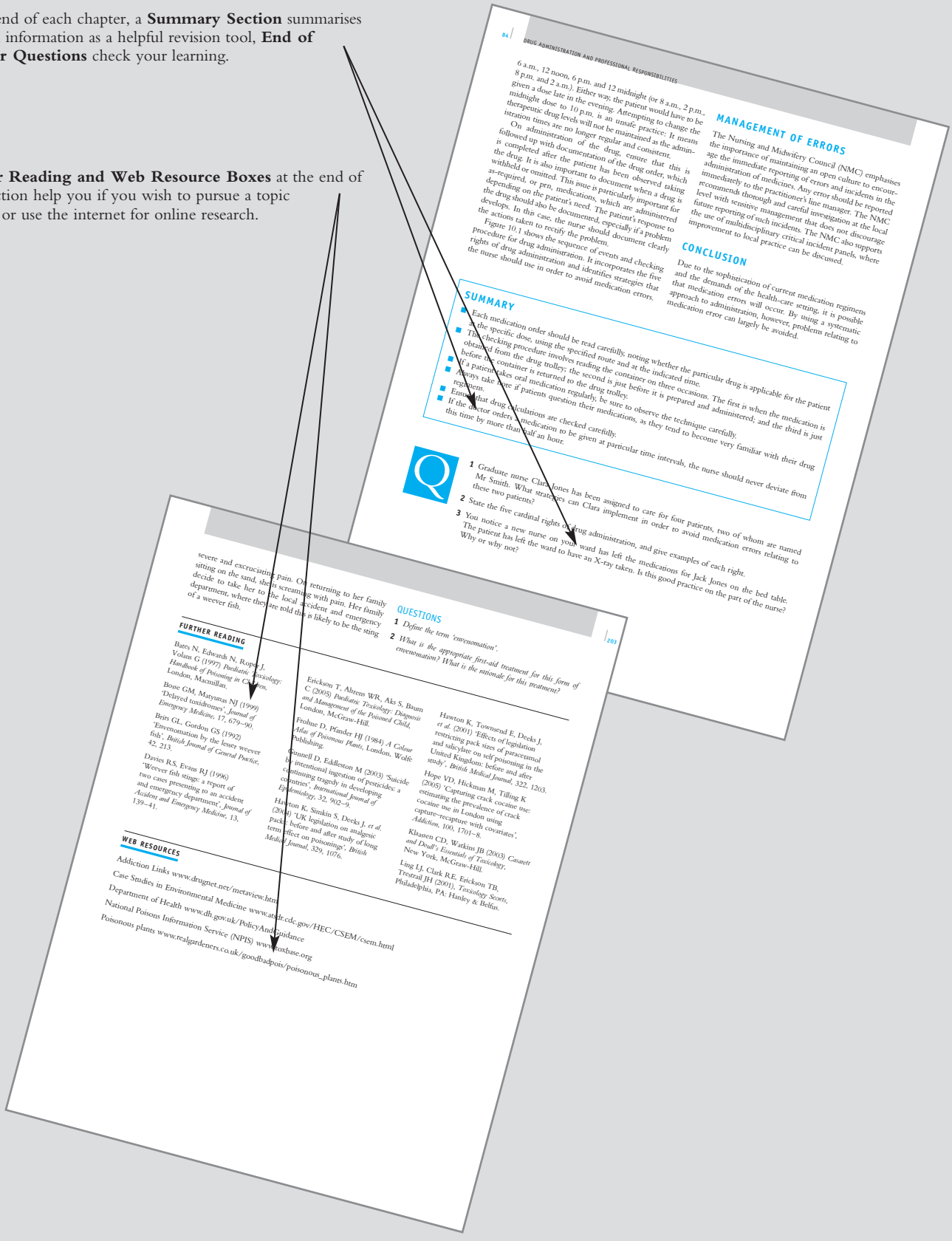
Case Studies and Questions give you an in-depth look at a patient scenario, featuring a variety of clinical settings.

Tables provide a summary of major points of pharmacological principles and their application.



At the end of each chapter, a **Summary Section** summarises essential information as a helpful revision tool, **End of Chapter Questions** check your learning.

Further Reading and Web Resource Boxes at the end of each section help you if you wish to pursue a topic further, or use the internet for online research.



84 DRUG ADMINISTRATION AND PROFESSIONAL RESPONSIBILITIES

6 a.m., 12 noon, 6 p.m. and 12 midnight (or 8 a.m., 2 p.m., 8 p.m. and 2 a.m.). Either way, the patient would have to be given a dose late in the evening. Attempting to change the midnight dose to 10 p.m. is an unsafe practice: It means therapeutic drug levels will not be maintained as the administration times are no longer regular and consistent.

On administration of the drug, ensure that this is followed up with documentation of the drug order, which is completed after the patient has been observed taking the drug. It is also important to document when a drug is withheld or omitted. This issue is particularly important for as-required, or prn, medications, which are administered depending on the patient's need. The patient's response to the drug should also be documented, especially if a problem develops. In this case, the nurse should document clearly the actions taken to rectify the problem.

Figure 10.1 shows the sequence of events and checking procedure for drug administration. It incorporates the five rights of drug administration and identifies strategies that the nurse should use in order to avoid medication errors.

MANAGEMENT OF ERRORS

The Nursing and Midwifery Council (NMC) emphasises the importance of maintaining an open culture to encourage the immediate reporting of errors and incidents in the administration of medicines. Any error should be reported immediately to the practitioner's line manager. The NMC recommends thorough and careful investigation at the local level with sensitive management that does not discourage future reporting of such incidents. The NMC also supports the use of multidisciplinary critical incident panels, where improvement to local practice can be discussed.

CONCLUSION

Due to the sophistication of current medication regimens and the demands of the health-care setting, it is possible that medication errors will occur. By using a systematic approach to administration, however, problems relating to medication error can largely be avoided.

SUMMARY

- Each medication order should be read carefully, noting whether the particular drug is applicable for the patient at the specific dose, using the specified route and at the indicated time.
- The checking procedure involves reading the container on three occasions. The first is when the medication is obtained from the drug trolley; the second is just before it is prepared and administered; and the third is just before the container is returned to the drug trolley.
- If a patient takes oral medication regularly, be sure to observe the technique carefully.
- Always take note if patients question their medications, as they tend to become very familiar with their drug regimens.
- Ensure that drug calculations are checked carefully.
- If the doctor orders a medication to be given at particular time intervals, the nurse should never deviate from this time by more than half an hour.

1 Graduate nurse Clara Jones has been assigned to care for four patients, two of whom are named Mr Smith. What strategies can Clara implement in order to avoid medication errors relating to these two patients?

2 State the five cardinal rights of drug administration, and give examples of each right.

3 You notice a new nurse on your ward has left the medications for Jack Jones on the bed table. The patient has left the ward to have an X-ray taken. Is this good practice on the part of the nurse? Why or why not?

severe and excruciating pain. On returning to her family sitting on the sand, she is screaming with pain. Her family decide to take her to the local accident and emergency department, where they are told this is likely to be the sting of a weever fish.

QUESTIONS 203

1 *Define the term 'envenomation'.*

2 *What is the appropriate first-aid treatment for this form of envenomation? What is the rationale for this treatment?*

FURTHER READING

Bates N, Edwards N, Ropper J, Volans G (1997) *Paediatric Toxicology: Handbook of Poisoning in Children*, London, Macmillan.

Boase GM, Matymas NJ (1999) 'Delayed toxidromes', *Journal of Emergency Medicine*, 17, 679–90.

Brits GL, Gordon GS (1992) 'Envenomation by the lesser weever fish', *British Journal of General Practice*, 42, 213.

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Hope VD, Hickman M, Tilling K (2005) 'Capturing crack cocaine use: estimating the prevalence of crack cocaine use in London using capture–recapture with covariates', *Addiction*, 100, 1701–8.

Klaassen CD, Watkins JB (2003) *Casarett and Doull's Essentials of Toxicology*, New York, McGraw-Hill.

Ling LJ, Clark RE, Erickson TB, Trestrail JH (2001), *Toxicology Secrets*, Philadelphia, PA: Hanley & Belfus.

WEB RESOURCES

Addiction Links www.drugnet.net/metaview.htm

Case Studies in Environmental Medicine www.atsdr.cdc.gov/HEC/CSEM/csem.html

Department of Health www.dh.gov.uk/PolicyAndGuidance

National Poisons Information Service (NPIS) www.toxbase.org

Poisonous plants www.realgardeners.co.uk/goodbadpois/poisonous_plants.htm

FIGURES

TABLES

PREFACE

Fundamentals of Pharmacology is primarily a text for undergraduate and postgraduate students of nursing and allied health professions. We have written a pharmacology textbook that does not compromise the scientific basis of the discipline. Many pharmacology texts previously published have been strong on clinical considerations and yet relatively weak in the science of pharmacology.

OUR APPROACH

Philosophically, our goal is to empower health-care professionals through an understanding of the fundamental scientific principles of pharmacology. We believe that in order to promote understanding, the effects of drugs on physiological and pathophysiological processes have to be explained clearly. We have included a small amount of chemistry and biochemistry where appropriate in order to facilitate this understanding. With a greater appreciation of the action of drugs and their target tissues, the reader should be able to deduce the adverse effects to expect and the precautions and contraindications to consider.

Furthermore, where possible we have tended to describe the important characteristics of drug groupings rather than to focus on individual agents, and we have used prototypes and common generics as examples. The rationale for this approach is that new drug agents regularly enter the market while older agents are deleted. The average practitioner cannot possibly keep up with all these changes. If one knows the grouping to which a new agent belongs, however, the principal characteristics of the drug can be deduced easily.

This book is designed primarily to establish the foundations in pharmacology. We encourage students to refer to the references commonly found in the clinical setting and in hospital wards, such as the *British National Formulary* (BNF), for more detailed information regarding individual therapeutic agents, for example dosage, special precautions and toxicological information.

We hope that readers will find this textbook a valuable companion in their pursuit of a fundamental understanding in a most fascinating area of clinical knowledge – pharmacology.

CHANGES TO THE SECOND EDITION

In this second edition of *Fundamentals of Pharmacology*, we have endeavoured to improve on the foundation provided in the previous edition. All chapters have been updated and reviewed for clarity and currency in preparation for the publication of this edition. As a result, a number of chapters have been subjected to substantial restructuring in accordance with current clinical practices. The chapters have a new look and include a number of new features, which will further enhance the educational value and effectiveness of the book.

New chapters and section

A number of new chapters have been included in this edition. Chapter 24 (Drug abuse in sport) and Chapter 60 (Obesity) address important topics where the misuse of drugs can occur as a result of societal pressures and expectations. The other new chapters – Chapter 28 (Introduction to chemical mediators), Chapter 31 (Nitric oxide and the endothelins) and Chapter 77 (Gene therapies) – describe the classification of chemical mediators and discuss their roles in normal and pathophysiological processes, while also flagging some future directions in therapeutics.

The new Section III (Drug administration and professional responsibilities) brings together the theoretical and practical aspects of the drug administration process. Presentation of the material in this way will enable students to better link the properties of drug formulations, the administration of drugs, the avoidance of medication errors, the monitoring of patients after administration and the management of common drug adverse reactions.

More figures and tables

In this edition, there are more diagrams, tables and photographs to illustrate and summarise important concepts. The common effects of major drug groups and families are presented using flowcharts and, new to this edition, diagrammatic representations of human forms.

End-of-section features

The case studies at the end of the sections have been reviewed and a number of new ones added. Lists of useful Web resources relevant to the chapters in each section are also provided.

Herbal medicines

As interest in and use of herbal medicines is increasing within our community, it is important for health-care professionals to be more aware of the issues associated with herbal treatments. Chapter 65 (Herbal medicines) has been

expanded to include a discussion on the uses and actions of aloe vera, cranberry juice and evening primrose oil. In addition, a new appendix (Appendix G: Drug–herb interactions) has been included for quick reference to important common interactions between herbal medicines and conventional drugs.

New index

The index has been expanded to aid navigation and the finding of specific information more readily. The index includes drug proprietary names to facilitate the matching of brand names to generic and family names.

Changes to the website

The website provides separate online environments for lecturers and students to support their courses in pharmacology. Lecturers have access to course materials and a digital media archive of text figures, tables and drug summary tables. Students are provided with feedback on their progress and understanding of the content through access to drug updates.

Ann Richards, Barry Hunt, Alan Galbraith,
Shane Bullock, Elizabeth Manias 2007

ACKNOWLEDGMENTS

We would like to thank a number of people who have contributed to the development of this book. First, we acknowledge the support of our families during the writing and production of this edition. In particular, we appreciate the expert input of Ann's daughter, Julia, in anaesthesia and Barry's daughter, Abigail, in biochemistry.

The UK authors would like to thank Alan Galbraith, Shane Bullock and Elizabeth Manias for allowing us the opportunity to use their book as the basis of what we hope will be a useful text for nurses, paramedics and all health-care professionals in the UK.

We would like to thank the entire team at Pearson Education for their support during the preparation of this edition. Special thanks to our Publisher, Kate Brewin, for her support and encouragement. We are grateful to our copy-editor, Colette Holden, for her thorough and detailed work and the proofreader, Colin Owens, who did an excellent job of proofreading these pages.

We are grateful to the following people who acted as members of a reviewer editorial board; their comments and insights greatly assisted in the development of this edition:

Richard Osborne
Faculty of Applied Sciences
University of the West of England

Sheila Cunningham
School of Health and Social Sciences
Middlesex University

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Staffordshire University

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Judith Gonda, Lecturer
School of Nursing & Midwifery
Flinders University

Alan Tulloch, Lecturer
School of Nursing
Curtin University of Technology

Annabel Kanakis, Lecturer in Pharmacology
Edith Cowan University
Curriculum Consultant
Catholic Education Office

M. J. (Nick) Nicol, PhD, Senior Lecturer
School of Health Sciences
Massey University

We also express our thanks to colleagues and students who have provided us with feedback on the book. We have incorporated a number of their suggestions and corrections in this new edition.

A considerable number of people, have either directly or indirectly, been involved in the development, design, writing and publication of this book. If we have inadvertently omitted anyone, our apologies.

Ann Richards and Barry Hunt

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PHARMACOLOGY WITHIN THE SOCIAL CONTEXT

O, (abundant) is the powerful grace that lies
In herbs, plants, stones . . .

WILLIAM SHAKESPEARE – *ROMEO AND JULIET*

The quote from Shakespeare's *Romeo and Juliet* alludes to two important points explored in this section. The first is that drugs can be obtained from a variety of sources within our environment. The other is that these substances produce a powerful influence on the body. The nature of the influence of drugs, both good and adverse, is the main theme of this book.

Historical records show that drug use has long been a part of human culture. A brief outline of the history of drug use and the sources from which drugs are obtained is provided in Chapter 1.

In Chapter 2, we move to the present with a discussion of the sociocultural aspects of pharmacology. Our society is coming to grips with a number of issues related to drug use, and health professionals must be aware of these. Some of the issues raised in Chapter 2 include the following:

- the use of generic substances versus proprietary agents;
- drug advertising;
- perspectives of drug use in elderly people;
- cultural differences;
- the use of over-the-counter (OTC) preparations.

The effect of these issues on health professionals, such as nurses and doctors, is also considered.

I

AN HISTORICAL PERSPECTIVE

1

CHAPTER ONE

OBJECTIVES

KEY TERMS

Pharmacology
Biotechnology
Genetic engineering
Natural products
Recombinant DNA technology

After completing this chapter, the reader should be able to:

- **define the term 'pharmacology';**
- **identify the roles of drugs in human society;**
- **identify the three ages of pharmacology;**
- **briefly describe the major characteristics of each of the three ages and their implications for society.**

PHARMACOLOGY IS THE SCIENCE THAT DEALS WITH THE properties and characteristics of drugs. The actions and effects of these chemicals on physiological systems are of particular interest. Drug effects on physiological systems may be explored in organs and tissues isolated from the body and artificially maintained – in-vitro situations – and within living whole organisms – in-vivo situations.

DRUGS AND SOCIETY

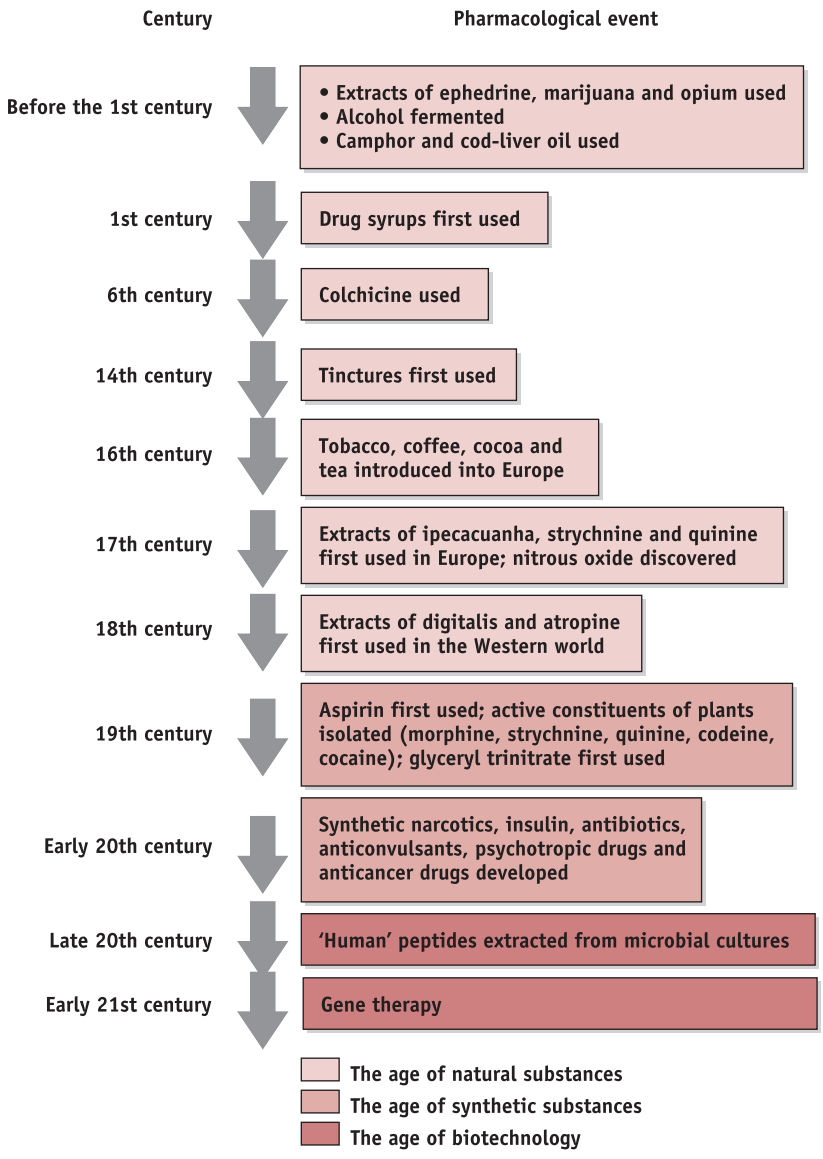
The use of drugs for medicinal and social purposes extends through the course of human history itself. In fact, it probably even predates human history, as evidence of drug use seems apparent among other animals (particularly chimpanzees). The methods used to identify useful pharmacological agents involve trial and error as well as careful observation. Indeed, many valuable therapeutic agents have been discovered serendipitously during scientific investigations carried out for other purposes. A famous example of this is the discovery of penicillin by Sir Alexander Fleming.

From the most primitive human communities to the most developed, there exists a drug culture. Drugs are used for recreational, religious and medicinal purposes. The first recorded systematic register of medicines dates back to the ancient Greek and Egyptian civilisations. In all societies, it is apparent that the individuals who make and administer these agents possess power and influence over their fellows.

THE AGES OF PHARMACOLOGY

The history of pharmacology is represented by the timeline in Figure 1.1. It can be subdivided into three eras according to the characteristics of drug development: the first, in which the use of natural substances dominated; the next, in which products of laboratory chemistry emerged and became pre-eminent; and now, in the early twenty-first century, when biotechnological products are the focus of attention.

FIGURE 1.1 TIMELINE HIGHLIGHTING SOME MAJOR PHARMACEUTICAL EVENTS



The age of natural substances

Probably the earliest-known natural substance used because of its profound effects on the human body is **alcohol** (ethanol). In fact, the process of fermentation is illustrated on pottery from Mesopotamia made around 4200 BC. While the Mesopotamians would have been aware of the physiological effects of fermented beverages, it is a matter for conjecture whether or not alcohol was ascribed any medicinal properties. We had to wait a couple of millennia before medicinal uses were documented. Alcohol has been used as a skin antiseptic, a rubefacient, an appetite stimulant, a gastric-acid stimulant, an analgesic, an anaesthetic and a tocolytic agent. One famous literary example of alcohol's medicinal use is in the Bible in a letter from St Paul to Timothy: 'use a little wine for thy stomach's sake and thine often infirmities'. Today, while the social use of alcohol dominates any therapeutic applications that might remain, there is some evidence that St Paul's words contain an element of truth (see Chapter 23).

The period in which therapeutic agents were derived from plants is by far the longest: The first recorded use dates back to around 2700 BC. Every culture throughout history has used plant derivatives – the leaves, fruit, bark, roots, flowers and sap – as a means to heal or reduce suffering. Drugs such as **atropine**, **ergotamine**, **curare**, **morphine**, **reserpine**, **cocaine** and **marijuana** were extracted from these sources. Indeed, consideration of the origins and uses of just a few of these substances serves to broaden our view of pharmacology.

ATROPINE: LEGENDS AND LADIES

Atropine is derived from the fruits of various plants of the potato family, particularly deadly nightshade, *Atropa belladonna*. As is obvious from the common name, the fruits of this plant have long been known to be deadly poisonous. Throughout history, nightshade has been used for nefarious purposes as an effective method of poisoning. Indeed, the scientific name for deadly nightshade does reflect atropine's action: Atropos was one of the three Fates from Greek mythology. She, along with the other two Fates, decided individual destiny. It was her role to dispatch mortals by cutting the threads of life with a pair of shears. Belladonna means beautiful lady, and in the early part of the second millennium it was known that extracts from this plant would cause dilation of the pupils, an attribute that was considered desirable in women. This action is still one of the uses of atropine and its derivatives today.

ERGOTS: HEADACHES, HALLUCINATIONS AND HYSTERIA

Ergotamine and its cousin **ergometrine** are derived from the fungus *Claviceps purpurea*, an important pathogen of the cereal rye. These two drugs are used respectively to treat migraine and to induce uterine contractions in obstetrics, but in overdose they can cause hallucinations (not surprisingly, as lysergic acid diethylamide – LSD – is a derivative of ergotamine) and seizures. It has been suggested that many witches in the Middle Ages, and even up to the Salem witchcraft trials in America in the seventeenth century, could have been tried and burnt at the stake for having been intoxicated after ingesting infected cereals. How many migraine sufferers realise that an overdose of Migril™ or Cafergot™ could have had them burnt at the stake in previous eras?

TUBOCURARINE: MACUSIS AND MUSCLES

Tubocurarine has been used in surgery to paralyse skeletal muscle, a procedure that makes the surgeon's task easier. (Nowdays, newer drugs have replaced it.) This drug is derived from plants belonging to the genus *Strychnos* (some of which also provide strychnine). An impure preparation of the drug is called curare, which has been used as an arrow poison by the Macusi people of Guyana. The interesting fact about this drug is that the Macusi people, unwittingly, were making use of an important pharmacological property – the nature of drug absorption. The majority of drugs are given by mouth but some, if given by this route, are not absorbed; tubocurarine is one of these. The Macusi people observed that death would soon come to the shot animal as curare was absorbed into the blood from the arrow wound. No harm came to the tribe, however, when they consumed the meat of that animal contaminated with curare.

OPIUM AND COCA: ASSYRIA, ANALGESIA, THE ANDES AND ANAESTHESIA

Morphine comes from opium, which is the dried exudate of the opium poppy, *Papaver somniferum* (meaning the sleep-bearing poppy). The word 'morphine' is derived from the Greek god of dreams, Morpheus. Opium was mentioned in one of the earliest and most influential pharmacology texts, that of Dioscorides, which was published in the first century AD. It is probable that opium was grown in Assyria, Greece and Mesopotamia long before this time. Many people think that opium came originally from China, but it probably did not reach there until at least the sixth century AD.

Cocaine is obtained from the leaves of *Erythroxylum coca*, a shrub that grows wild in the Andes of Peru and Bolivia. It has been used for centuries as a stimulant by the native Peruvians of these areas. Its principal action is on the central nervous system, but it has some peripheral effects, namely that it reduces the desire for food and drink because of its local anaesthetic action. This action, much more than its stimulant properties, is the reason for its legitimate therapeutic value today. Cocaine is used as a local anaesthetic only occasionally today, principally in

nasal surgery. Like the Macusi people who used curare, the native Peruvians who utilised cocaine crudely applied some pharmacology. The leaves of this plant were mixed with lime before chewing; this prolonged the effect of the drug by altering its rate of excretion from the body, and showed that drug preparation has an important influence on drug behaviour in the body. (Drug preparations are discussed in detail in Chapter 7.)

RESERPINE: BRAIN IMBALANCE AND BLOOD PRESSURE

Reserpine has an unusual place in the annals of historical pharmacology because its original use in treating mental illness is quite different from its more recent use, which is to treat hypertension (although it has now been superseded by other, safer antihypertensive agents). Reserpine comes from the powdered root of *Rauwolfia serpentina* and was used in India to treat mentally disturbed people. One of the undesirable effects of reserpine is that it can cause depressive illness. This adverse drug reaction helped to establish the theory that depression is not always due to reactions to life events but may well be related to changes in brain biochemistry (viz. that an imbalance in the level of brain neurotransmitters may underlie the behaviour).

MARIJUANA: MALINGERER OR MEDICINE?

Marijuana is, in most countries, predominantly a substance of abuse, as its effects are only recently being considered for their potential clinical value. This drug comes from the plant *Cannabis sativa* and has been used intermittently since about 2700 BC as a sedative and analgesic. After the Second World War particularly, marijuana became a common recreational drug and was outlawed by the World Health Organization as a drug of abuse with no therapeutic use. This seems now to be inaccurate, and one of the main active substances of marijuana, δ-9-tetrahydrocannabinol (THC), appears to have more potent antiemetic applications than most other antiemetics. Two related compounds, dronabinol and nabilone, have been approved in some countries for the treatment of the nausea and vomiting associated with the use of anticancer drugs. Substances containing, or derived from, THC are called cannabinoids. Clinical applications for the cannabinoids are still being explored. An example is as an appetite stimulant for people with human immunodeficiency virus (HIV)/acquired immunodeficiency syndrome (AIDS) and in the treatment of pain associated with multiple sclerosis.

ANTIBIOTICS: MEDICINAL MOULDS

In the early part of the twentieth century, we realised that there were other natural sources of therapeutic substances. Certain fungi and bacteria produce secretions that protect them from, or kill, other microbes. These secretions are known as antibiotics and are among the most effective means available to combat the many infectious diseases that have plagued humankind (see Section XIV). Interestingly, it was known in ancient times that the application of mouldy bread (presumably contaminated by fungus of the genus *Penicillium*) could help cure wound infections.

SOURCES OF NATURAL SUBSTANCES

Natural substances with the potential to heal or reduce suffering are all around us. You may have some common clinical agents growing in your garden at home (see Figure 1.2) – for example, a heart drug from the purple foxglove (see Chapter 48), atropine from deadly nightshade (see Chapter 27) and anticancer drugs from the common periwinkle plant (see Chapter 76). Indeed, that we are surrounded by natural substances with medicinal properties is the *raison d'être* for the use of herbal medicines. For many of these natural medicines, however, evidence of a therapeutic benefit, by the same methods used to authenticate conventional medicines, is less than convincing.

There are many habitats and human cultures that remain relatively unexplored sources of natural drugs. The number of potential drugs that remain undiscovered amid the diversity of plants growing in the world's rainforests has been put forward as an economic argument by conservationists for not destroying the remaining rainforests. Around the world, pharmacologists are busy examining traditional indigenous medicines, searching for substances that may prove to be potential clinical agents in mainstream medical practice.

Even today, the advantage of using products derived from living things is that the biologically active constituent has already been made by nature and the drug, therefore, may be more readily accessible in both developed and undeveloped areas of the world.

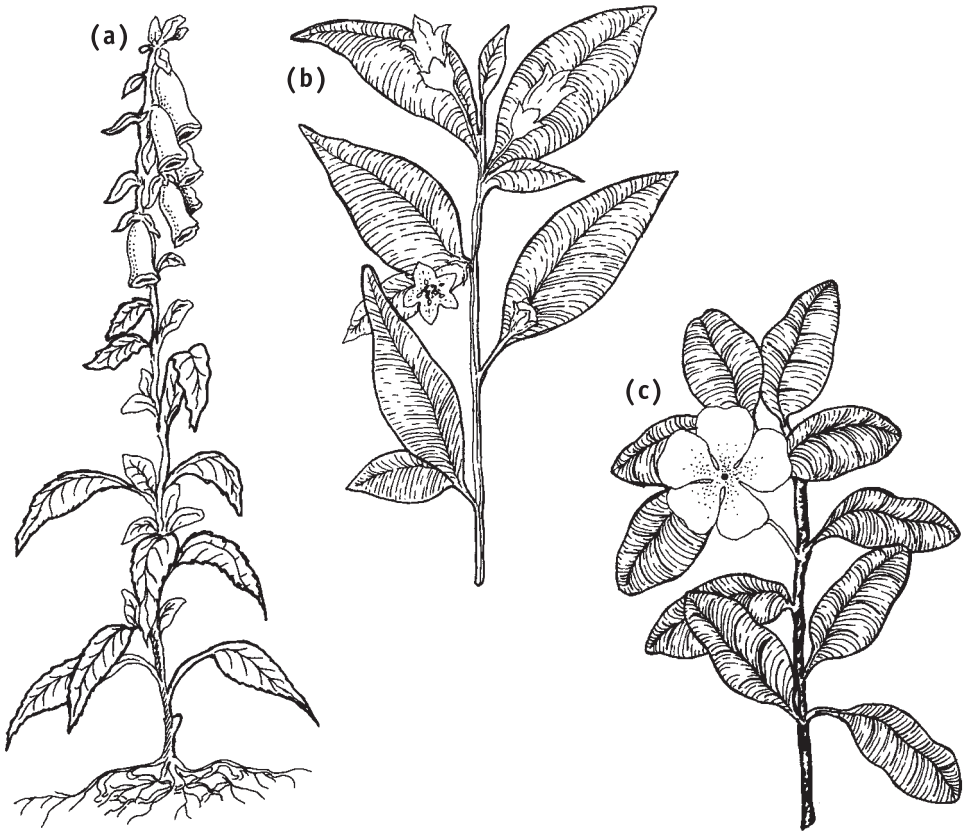
The age of synthetic agents

The twentieth century is characterised by the development of synthetic drugs, mass-produced relatively cheaply in pharmaceutical laboratories. The companies that run these laboratories are some of the most profitable industries in the world today. Once the molecular structure of a natural drug is identified, it may be more convenient to synthesise it wholly in the laboratory instead of extracting it, or else to modify it chemically for better absorption, greater effectiveness or fewer side effects.

Enormous resources (money, equipment, staff) are committed to the manufacture of novel synthetic compounds, which are then screened extensively for any potential pharmacological activity. The process of drug screening is also used on natural substances from microbial sources (e.g. fungal and bacterial secretions), plants (e.g. leaves, stems, roots) and animals (e.g. corals, venoms, frog skin secretions). Successful drug development by this method could produce a profit for the company, measured in millions of dollars, not to mention a useful clinical agent.

FIGURE 1.2 MEDICINAL PLANTS COMMONLY FOUND IN SUBURBAN GARDENS

(a) Purple foxglove (*Digitalis purpurea*) – tubular flowers are characteristically purple.
(b) Deadly nightshade (*Atropa belladonna*) – a shrub with red or bluish-purple flowers and black berries.
(c) Periwinkle (*Vinca rosea*) – white or rose-tinted flowers.



The dominance of technology and the realisation of the carcinogenic potential of synthetic chemicals has led some people in Western societies to reject mainstream drug therapies. Their search for alternative therapies often leads them back to methods of healing involving the use of more traditional natural substances.

The age of biotechnology

The recent emergence of biotechnology as a means to produce drugs heralds a new age of drug development. It involves the production of endogenous proteins and peptides for therapeutic purposes by decidedly unnatural means. These proteins are highly complex compounds where the functional characteristics are determined by subtle chemical bonds and structural arrangements. At this time, it is beyond our capacity to duplicate such structures in laboratories for use as therapeutic agents.

Biotechnological techniques involve the manipulation of microbial and human genetic material. A human gene can be inserted into one bacterium or fungal cell, which in turn divides to produce a colony in which each microbe contains the gene. The colony subsequently produces large quantities of the natural human peptide, which can be extracted in an extremely pure, low-allergenic form for clinical purposes. This process is referred to as recombinant DNA technology or genetic engineering. The best clinical examples of this are substances used in hormone-replacement therapy (e.g. insulin, growth hormone, erythropoietin) and the supplementation of plasma constituents such as clotting factors.

Now, in the early stages of the twenty-first century, the focus of biotechnological development appears to be on gene therapy. The applications, procedures and implications of this technology are discussed in Chapter 77.

SUMMARY

- Pharmacology is the study of the actions and effects of drugs on physiological systems.
- Drugs have been used for medicinal and social purposes throughout human history.
- The history of drug development and use can be broadly divided into three ages.
- The age of natural substances is characterised by the use of plant derivatives.
- The age of synthetic substances is characterised by the mass production of synthetic medicines and drug-screening techniques.
- The age of biotechnology is characterised by the isolation, characterisation and manufacture in a laboratory of endogenous signalling chemicals for use as therapeutic agents. Genetic engineering techniques are being used to make and deliver drug treatments.

SOCIOCULTURAL ASPECTS

2

CHAPTER TWO

OBJECTIVES

After completing this chapter, the reader should be able to:

- **discuss factors affecting drug advertising;**
- **discuss the types of over-the-counter preparation available and the reasons for their use;**
- **describe the difference between generic and brand-name preparations with advantages and disadvantages associated with the prescription of each type;**
- **discuss relevant sociocultural factors influencing drug therapy in older individuals, immigrants and indigenous people.**

KEY TERMS

Drug advertising
Over-the-counter preparation
Generic preparation
Brand-name preparation
Older individual
Immigrant
Indigenous person

IF A MAJOR FOCUS OF DRUG THERAPY IS TO PROMOTE *adherence* by the patient to their prescribed regimen and *self-care*, then a wider view of health care that encompasses the sociocultural context must be considered.

Health-care professionals socialised through their educational and professional experiences, and influenced by their own demographic characteristics, tend to hold a particular view of health care. This set of beliefs is institutionalised in the large organisational structures evident in our health-care settings and legal systems and is influenced by the advertising and marketing of drugs by the large multinational drug companies.

Patients have their own sociocultural context, which influences their view of health care; these factors include demographic characteristics such as age and ethnicity. Their view of health is also influenced by drug advertising and packaging and is reinforced by the current emphasis on self-care conveyed through the media, ranging from lifestyle television programmes to magazines and newspapers.

This chapter highlights the interplay of these belief systems – in other words, the relationship between the health-care professional and the patient. These issues impact on the drugs that health-care professionals wish to administer, the drugs that patients wish to use and patients' adherence to a drug therapy regimen. Specifically, this chapter discusses drug advertising, over-the-counter (OTC) preparations, generic versus brand-name preparations, drug therapy in older people and drug therapy in ethnic groups.

DRUG ADVERTISING

Two important institutions influence our decisions in Western society: these are the media and multinational corporations. These two institutions rely on advertising to maintain their viability and to promote particular preparations. Advertising targets health-care professionals and the consumers of medicinal preparations in different ways. This section focuses on the effects of advertising of prescription preparations on health-care professionals. The following section on OTC preparations covers the effects of advertising on the general public.

Advertising of medicinal preparations has been a common feature of medical journals and some nursing journals since they were first produced. Other, more subtle forms of advertising have also come into existence. These include the sponsorship of continuing education seminars and conferences by multinational drug companies, the support of which is often needed for the very existence of these programmes. Conference organisers and journal editors rely upon promotional advertising in an effort to keep subscription and registration costs at an affordable level and to cover production costs. Other marketing methods include direct mail and visits from drug representatives.

Health-care professionals would like to think that they are not swayed by drug promotion. If drug companies believed this, however, they would not continue to spend large amounts of money on advertising. Research indicates that drug promotion influences doctors and nurses. Media focus on certain drugs in mainstream circles has also been instrumental in promoting the use of certain medications. One study, which examined the types of information source used by doctors, found that doctors' preferences were not influenced by how they valued these sources. For instance, doctors did not value highly the opinions of medical sales representatives, and yet these individuals were the most frequently used source of drug information. Advertising obtained from journals and direct mail sources produced similar results. On the other hand, doctors valued the opinions of their medical colleagues very highly, but they were not often used as sources of information about drugs. Another study showed that the majority of a random sample of doctors denied being influenced by industry-sponsored information. Their knowledge of pharmacology, however, was more congruent with advertising material than with data in the scientific literature.

The antidepressant drug **fluoxetine**, with the better-known trade name of Prozac™, is an impressive illustration of this point. People have been exposed to heavy media coverage about the drug in mainstream areas, such as television, newspapers and radio. A popular book has been written about the drug. From this information, patients may construe that Prozac successfully produces an improvement in personality, elation of mood and a happy spirit. The promotional effect of advertising has created a situation where people believe it is quite fashionable to be prescribed Prozac. Doctors appear also to have been influenced by the promotional campaign and the drug's clinical effectiveness, as shown by the increased number of prescriptions for Prozac. Reports suggest that some of the people who request and obtain a prescription for Prozac may not even be suffering from depression. Clearly, doctors are not only impressed by the clinical success of Prozac in documented cases but also subjected to the whims of their patients. Although Prozac has been available for some years, it is only since the recent intensive promotional campaigns that sales have exploded.

The antibacterial product co-amoxiclav (Augmentin™) is a combination of a **penicillin** (**amoxicillin**) and clavulanic acid and is another example where sales have improved through promotional claims. These are instances where doctors have been persuaded to prescribe Augmentin for the treatment of otitis media and sinusitis in young children. According to research studies, however, Augmentin in most cases has no significant benefit over amoxicillin alone in treating children over 2 years of age with acute otitis media. The additional problem with Augmentin is that it can cause hepatotoxicity.

Nurses are not exempt from exposure to promotional activities. Drug companies have been known to offer generous grants to nurses who wish to research aspects of particular drugs produced by these drug companies. Nurses are also subjected to advertising in international nursing journals for specialty areas such as critical care nursing. Drug company representatives visit health-care agencies and provide educational sessions for nurses in a way that may also promote their products.

One of the major problems with drug promotion for the health-care professional is that advertisers often disguise promotional material as important information rather than advertising. Doctors and nurses continue to be influenced by the subtleties of drug promotion. There are, however, various ways in which the issue can be addressed. For instance, journal editors have a responsibility to protect their readers. Editors should ban the placement of a drug advertisement next to an article about that drug. Another way is to place all advertisements in a section separate from the articles. The *Journal of the American Medical Association* (JAMA) and *Heart & Lung* incorporate this layout style. Perhaps even more pertinent is the need for medical and nursing students to learn skills in the critical analysis of published advertising data. Continuing education sessions within the workplace for health-care professionals will also assist in addressing this issue.

OVER-THE-COUNTER PREPARATIONS

Health-care professionals must be aware that their patients are also making personal choices regarding drugs introduced into their therapy. OTC preparations are available to the general public at pharmacies and, depending on the restrictions imposed, in other places such as supermarkets. These products are available without a prescription and often without restriction or supervision by a pharmacist. Complementary forms of therapy, such as chamomile, garlic, ginger and ginseng, can also be purchased from pharmacies, health-food stores and supermarkets without a prescription. (Chapter 3 covers the legal controls placed on medications, while Chapter 65 presents an overview of herbal and related medicines.) Patients frequently use these preparations to relieve a wide range of illnesses and minor complaints, including the common cold, mild pain, upset stomach and constipation.

The focus for health is geared increasingly towards patient self-care. This phenomenon is indicated by the decreased length of hospital stays following both acute illness and elective surgery and the increased emphasis on patient health education (see also Chapter 5). Patient self-care constitutes a significant factor that affects the cost of health care. Patients are also encouraged to practise self-care through advertising, product literature found in their local pharmacy, discussions with friends and relatives about preparations they use, and articles in popular general magazines. The effects of packaging, pricing and other marketing ploys used by supermarkets also influence patients' decisions. Consequently, the self-medicating patient is a day-to-day reality for most health-care professionals.

The health-promotion movement has also identified the possibility of changing lifestyles as an important factor in the battle to prevent disease. Through health promotion, health-care professionals redirect their efforts towards disease prevention rather than cure. Individuals and communities achieve this goal by setting up their own health agendas. The growth in popularity of dietary supplements such as vitamins, minerals and fish oils reflects the current public interest in health maintenance. In the UK, the market value of these products is now approaching £350 million per year. Current estimates are that in excess of 40 per cent of the population uses these products at some time. There has been extensive debate as to whether individuals on well-balanced diets need to take vitamins in excess of the recommended daily amount (RDA). For some, because of their circumstances or lifestyle, they do not achieve the RDA in their diet. Additionally, RDAs are set at the level that prevents deficiency disorders, and this may not be enough to reduce the risk of heart disease and cancer if this is possible by dietary supplementation; more clinical data are required. Most important is that the consumption of these products by the public is at a safe and non-toxic level. Clearly, people are not aware of the ramifications of excessive vitamin intake: if they consume a healthy, well-balanced diet, then these preparations are not required (see Chapter 61). Furthermore, vitamin C, the most commonly used vitamin, is taken in the belief that it will prevent infections and colds: People obtain this information from promotional advertising for vitamin C. Controlled trials, however, have demonstrated that vitamin C has no significant preventive effect.

People are now also more likely to buy OTC or complementary therapy preparations before visiting their doctor for advice. Even if they then decide to consult their doctor, they may not tell the doctor about their use of these treatments. This is because patients often do not consider OTC preparations or complementary therapies as proper drugs: these preparations do not require a prescription, and so the lay public often believe that they can be taken without concern or risk. If the patient takes prescription medications and OTC preparations or complementary therapies concurrently, however, drug interactions are more likely to occur (see also Chapter 15). In their role as patient advocates, nurses should encourage patient self-care and health promotion and offer advice on the appropriate use and possible problems of these non-prescription products. The patient should also be encouraged to obtain advice from pharmacists and doctors.

Despite scepticism from health professionals about the possible benefits of complementary therapies, individuals are increasingly using these therapies to either supplement or replace traditional medical treatment. Doctors, pharmacists, nurses and other health-care professionals have struggled to access or accept current knowledge about these therapies, which they need to help their patients make informed choices about their use and to separate legitimate claims from unproven claims and hype. Although health-care professionals may not be in a position to answer patients' questions about complementary therapies, patients have

often sought out this information for themselves. People have been able to obtain a wealth of information from the Internet. The Internet also now provides sophisticated processes whereby individuals can purchase complementary therapies without the need to speak to any health-care professional at all. A situation in which health-care professionals do not have complete knowledge of all the medication therapies used by patients may present a challenge for the traditional health-care establishment. Undoubtedly, individuals will continue to independently seek out complementary therapies to promote their state of health and wellbeing. It is up to health-care professionals to become cognisant of the types of therapy that may be sought in order to enable them to inform patients about the benefits and potential risks and complications of complementary therapies.

OTC preparations and complementary therapies used in the appropriate manner and according to the supplied directions can have a positive effect on health. Conversely, inappropriate use of these treatments can cause adverse effects. Self-diagnosis and prolonged treatment without advice from a health-care professional may delay the appropriate intervention and mask the symptoms of a serious condition. For example, a patient with chronic obstructive airways disease (COAD) should see a doctor and receive prescription medication. The patient with obstructed airways should not treat the condition with the inappropriate use of cough-and-cold preparations. Instead, the doctor will plan a specific regimen for the patient to follow. Furthermore, a preparation that is perceived harmless by the patient may produce serious effects. For example, **tretinoin** is marketed as a topical treatment of acne vulgaris and is available as a cream, liquid and gel. Drug companies have also, however, promoted tretinoin in the general media as an effective agent for the prevention and treatment of wrinkles. Sales of the preparation grew and birth defects were noted in babies born to women who used topical tretinoin during pregnancy. These defects included stillbirths, cleft lip, cataract, and hand and abdominal malformations. The popularity of the preparation and its potent teratogenic effects have prompted the rescheduling of tretinoin from OTC to prescription status. Complementary therapies may also cause serious adverse effects in individuals. For instance, the use of chamomile oil in aromatherapy for an individual who has allergic tendencies may lead to anaphylactic shock.

Switching of prescription drugs to OTC availability is increasingly common, but a controversial area in the UK has been the introduction of statins (see Chapter 43) as OTC medication. These drugs inhibit an enzyme in the liver that is needed for the production of cholesterol and so are extremely effective drugs for reducing cholesterol levels. These drugs do have side effects that increase with higher doses, however, and so the OTC dose available is small and, some would argue, not likely to be effective. Pharmacists undergo training to assess a patient's risk factors for the development of coronary heart disease, but a cholesterol test is not necessary – although is offered by some pharmacists. The government claims to be increasing patient choice but has been accused in some of the press of using OTC sales to reduce the National Health Service (NHS) medicine bill.

Common characteristics of over-the-counter preparations

A major concern of manufacturers of OTC preparations is safety. A drug's toxicity and adverse effects are related to the unit dosage in a preparation. This risk is, therefore, theoretically minimised when the unit dosage is low. For example, many pharmacies supply codeine-containing products without a doctor's prescription. For solid-dose preparations, each dosage unit must contain no more than 20 mg of codeine. A dosage unit is likely to be two tablets. OTC codeine is always sold in combination with a mild analgesic such as paracetamol. These products are heavily advertised and typically promoted as providing 'stronger' pain relief. Clinical trials on codeine suggest, however, that codeine does not contribute effectively as an analgesic, cough suppressant or antidiarrhoeal agent in the doses recommended in OTC products. There is evidence that some people do become addicted to codeine (an opioid) and exceed the stated dose on the packet.

Many OTC preparations contain a combination of several drugs. These are called *fixed-combination preparations* because the dosage unit of each drug is fixed within the preparation. For example, if a patient is taking a preparation containing 6 mg of one drug and 60 mg of another drug and wants to increase the dosage, each drug will be increased proportionally when administered. Each drug has its own pharmacological activity, which increases the potential for adverse effects and drug interactions with other prescription preparations (see also Chapter 15).

On the other hand, several OTC products contain only one drug as the active ingredient. These are often more advantageous for patients, as complete control over drug dosage is possible. It is also more appropriate for the patient to receive specific single drugs for defined symptoms in order to decrease the incidence of adverse effects. For example, a dry cough warrants a cough suppressant, while nasal congestion would require a decongestant. Furthermore, single-drug preparations tend to be less expensive than combination products. (For further discussion on OTC respiratory preparations, see Chapter 52.)

There are several groups of OTC preparations. Table 2.1 lists some of the more common OTC groups. By understanding the modes of action, specific uses and potential adverse effects of these preparations, the health-care professional can evaluate their effectiveness and recommend the most appropriate preparation for a patient.

TABLE 2.1 COMMON TYPES OF OVER-THE-COUNTER PREPARATION

Analgesic preparations
- Aspirin
- Paracetamol
- Ibuprofen
- Codeine

Cold preparations
- Sympathomimetics
- Antihistamines
- Analgesics

Vitamin preparations

Cough preparations
- Expectorants
- Cough suppressants

Decongestant nasal drops and sprays
- Sympathomimetics

Weight-control preparations
- Bulk producers
- Sympathomimetics
- Sleeping aids
- Antihistamines

Ophthalmic preparations
- Eye rinses
- Artificial tears
- Decongestants
- Contact-lens preparations

Acne preparations
- Sulphur
- Resorcinol
- Salicylic acid
- Benzoyl peroxide

Haemorrhoidal preparations
- Local anaesthetics
- Vasoconstrictors
- Antiseptics
- Astringents
- Emollients and lubricants
- Keratolytics

Gastrointestinal preparations
- Antacids
- H_2 receptor antagonists
- Antidiarrhoeals
- Laxatives

GENERIC VERSUS BRAND-NAME PREPARATIONS

Each drug has an approved name called the generic name but also has one or more brand names chosen by the manufacturing company. Some controversy still exists over whether drugs should be prescribed and supplied by a generic name or a brand name. The generic name of a drug is the shortened, simplified version of the chemical name. Medications that are chemically identical but sold by different manufacturers will have the same generic name but different brand names. The drug's brand name (also called the trade or proprietary name) is the registered trademark used by the drug company to identify the preparation of a specific drug (see also Chapter 12). An example of a generic name is **paracetamol**, which is sold under the brand name of, for example, Panadol™. Doctors are encouraged to prescribe by using generic names to lessen confusion and possible mistakes and because generic medicines often cost less. In the UK, for example, it is much cheaper to buy paracetamol (generic name) than Panadol (trade name) from a pharmacy, although they are the same drug.

More than one drug company can assign its own specific brand name to a drug, as long as one company does not hold the patent rights for the sale of that drug. Early in the development of a new drug, the developing company will take out a patent that restricts other companies from producing or selling that drug without permission from the original patent holder. Much of the patent period protects the drug company while it conducts clinical tests on the drug. Once the drug company puts the drug on the market, the latter part of the patent period protects it from competition by other drug companies. When the patent period expires, other companies are free to manufacture and sell the drug. During the stage of expired patency, drug companies rely heavily on promotional advertising in an effort to encourage doctors to prescribe one specific brand name over another.

Price differences for alternative brands of drugs exist. Under current government policy, drug companies can set their prices depending on market competition. Often the brand name originally protected by a patent agreement is more expensive than competitive brands because it had to bear the cost of the groundwork in research and development for the drug. Furthermore, within different countries of the European Union (EU), the cost of the same product, while still under patent, may vary significantly. This is a reflection of differing government policies on profit regulation within the pharmaceutical industry. These price differentials, coupled with free trade agreements

within the EU, can make it financially advantageous to import certain products, thereby undercutting the manufacturer's normal UK price. This has become known as *parallel importing*.

One of the major fears relating to the use of generic preparations of a specific drug is that they may not be interchangeable or bioequivalent. In other words, it is feared that they may not be absorbed or may not act in the same way following drug administration. Most brand-name preparations of the same generic drug, however, do not create different clinical responses when administered. All drugs are now evaluated carefully for comparable effects on absorption and clinical response with the original patented drug, so that practically all brand names of a particular generic drug are equivalent to each other. Drug companies submit supporting data regarding the absorption and clinical response of their drugs to the Medicines and Healthcare Products Regulatory Agency (MHRA), which determines whether different brands are bioequivalent. This information is readily available to the prescribing doctor and the pharmacist. There may be circumstances when generic prescribing can cause problems, however. Research appears to show that any change in medication from branded to generic, or vice versa, can cause a problem for people with epilepsy. As a result, it is now generally recommended that when treating people with epilepsy, every effort should be made to ensure continuity of supply by the same manufacturer.

Patient confusion can occur if the doctor prescribes, or the pharmacist dispenses, different brand names of the same generic drug for the patient at different times. If the patient is used to taking a 'little blue pill' and suddenly receives a 'little white pill', a great deal of time is often spent correcting the patient's misunderstanding. In recent times, drug companies have attempted to solve this problem by trying to make their product look the same as another already on the market. Overall, it would seem appropriate that doctors prescribe generically. Certainly in the hospital situation, regardless of whether the drug is written up by trade or generic name, the pharmacist will dispense the formulation that is stocked. In the community, generic prescribing has also been encouraged. The main advantage of this approach is that it contributes to reducing the overall costs of medicines to the health service. Eighty per cent of prescriptions were written generically in 1994 in England. Students of pharmacy, medicine and nursing are taught pharmacology by reference to the generic names of drugs. Identifying drugs by their brand names in the institutional setting means there is a greater potential for making mistakes. It is important, therefore, for health-care professionals to refer to drugs by their generic names.

Advocates for the prescription of specific brand names believe that it is the only way of ensuring high standards and well-tested products. The research and development required of a newly developed drug is very expensive, and the ultimate success of a particular product often depends on the continued sales of that product. It is further believed that a patient may favour one product over another because of flavour, appearance, packaging or past experience.

If brand-name prescribing is to be undertaken, then the final choice of brand should arise from consultations between the patient and the prescribing doctor. If more than one brand exists, the prescribing doctor can choose which is most appropriate for the patient. Within the prescription, the doctor needs to indicate whether brand substitution is permitted. Sometimes, however, company advertising will sway the doctor towards one brand name over another. The doctor may, therefore, present a biased view of which brand name is more suitable for the patient's needs. Nurses and pharmacists should inform patients when alternative brand preparations are available, so if patients experience problems with a particular brand they can consult their doctor about the possibility of changing to another.

It should be apparent at this point in our discussion that an individual's choice of drug is not a clear-cut decision. Choices, made by both health-care professionals and patients, are influenced by a number of external factors. The advertising in professional journals, the information placed on the packaging of drugs in supermarkets and the confusion that may arise when presented with any number of drugs have been discussed. This information is processed by every individual differently, and the choices made are complicated further if we also consider issues such as the age and ethnic background of a patient.

DRUG THERAPY IN THE OLDER PERSON

With increasing life expectancy, the proportion of the UK population over 65 years has increased significantly since the beginning of the twentieth century. Sixteen per cent of the population are now over 65 years and the proportion of people over 85 years increased from 7 per cent of the population in 1971 to 12 per cent in 2005. Elderly people accounted for 64 per cent of prescription items dispensed in 2004. Thirty-seven items per head were dispensed to people over 60 years. These statistics are important because they have significant implications for drug administration in older people. These individuals are also more prone to illnesses than other groups, which leads to the use of more medications. (Chapter 20 discusses the practical aspects of drug administration in the older person.) One of the problems encountered with older patients is the excessive or unnecessary use of medications. This practice is known as *polypharmacy*.

Polypharmacy

Polypharmacy may arise from actions taken by patients, their families, their doctors, their nurses, their pharmacists

TABLE 2.2 COMMON FEATURES OF POLYPHARMACY

- Use of medication with no apparent indication
- Use of duplicate medications
- Concurrent use of interacting medications
- Use of contraindicated medications
- Use of inappropriate dosage
- Use of drug therapy to treat adverse drug reactions
- Improvement following discontinuation of medications

and other health-care professionals. As in aspects relating to the administration of OTC preparations, polypharmacy is also affected by advertising; thus, the reasons for this condition are complex. Table 2.2 lists some of the features that might be associated with polypharmacy. These are discussed below.

USE OF MEDICATION WITH NO APPARENT INDICATION

This occurs when the patient is taking drug therapy for a condition not currently diagnosed in that patient. This practice may occur in residents newly admitted to nursing homes who continue with previous medications without a re-evaluation of their appropriateness.

USE OF DUPLICATE MEDICATIONS

Sometimes drug therapy is duplicated where the older patient receives similar medications with identical effects. This practice may increase the types of adverse effect and drug interaction that are likely to occur.

CONCURRENT USE OF INTERACTING MEDICATIONS

The older patient may take medications that have the potential to alter the effects of other drugs. Medications may also produce interactions with food. (See Chapter 15 for a detailed discussion of drug interactions.)

USE OF CONTRAINDICATED MEDICATION

The older patient may take medications that are not appropriate for a particular condition. For example, corticosteroid therapy may not be appropriate for the elderly patient with asthma who also has diabetes, as such therapy enhances blood glucose levels and may worsen the diabetic condition. Contraindicated medications may also include drugs known to cause allergic or toxic reactions in the elderly patient.

USE OF INAPPROPRIATE DOSAGE

The patient may receive a dose that is too high or too low. Possible reasons for this include inappropriate adjustments for a patient's physical size, incorrect frequency of administration, and kidney or liver malfunction.

TABLE 2.3 CONSEQUENCES OF POLYPHARMACY

- Adverse drug reactions
- Drug interactions
- Financial expense
- Decreased levels of orientation and alertness
- Diagnostic problems, with a drug mimicking a disease state

USE OF DRUG THERAPY TO TREAT ADVERSE DRUG REACTIONS

Common in polypharmacy is the management of adverse drug reactions with the administration of yet more medications. The drug used to treat the adverse effects usually has its own adverse effects, which may lead to the administration of even more medications. If this is allowed to continue, the elderly patient may get on a merry-go-round of multiple drug administration.

IMPROVEMENT FOLLOWING DISCONTINUATION OF MEDICATIONS

Sometimes it appears difficult for the team of health-care professionals to determine whether medications are helping or hindering the patient's condition. In this situation, the doctor may decide to discontinue all medications. Specific medications can then be introduced gradually and their clinical effects assessed. Table 2.3 lists the possible consequences arising from polypharmacy. (These factors are discussed further in Chapter 20.)

Nurses and polypharmacy

As important members of the team of health-care professionals, nurses can decrease the incidence of polypharmacy by developing an awareness of the characteristics associated with the unnecessary use of medications in older patients. As nurses maintain contact with patients for extended periods, they can provide valuable information about the patient's clinical response to medications (refer also to Chapter 8).

DRUG THERAPY IN ETHNIC GROUPS

Differences among various ethnic groups in their susceptibility to drug toxicity are becoming well established, and evidence shows that identifiable genetic factors may explain these differences.

In addition, the traditional beliefs and values of a particular culture influence perception and expectation of drug therapy. Conflicts may arise if these perceptions differ from those of the health-care professional, thus affecting the quality and effectiveness of care. Deeply rooted beliefs and values may affect the patient's ability to comply with

prescribed medication regimens. For example, some people of Asian origin use traditional medicines either simultaneously with, or before seeking, more conventional means of health care. They may be influenced by the Chinese concept of yin (cold air) and yang (hot air) energy forces. The feminine energy force, yin, represents darkness, softness and cold, while the masculine energy force, yang, represents light, strength and heat. Excess of either energy force will lead to a lack of equilibrium and subsequent disease. Certain diseases are thought to occur through cold or hot aspects of substances present in medicines, food, air and the body itself. Treatment is by the application of a substance or food that is opposite to the cause. Disorders such as paralysis, pneumonia and earache are thought to arise from cold conditions. Consumption of hot foods such as chocolate, cheese, alcohol, eggs and cereal grains is used to treat a cold condition. Hot medicines and herbs include penicillin, tobacco, ginger root, garlic and castor oil. On the other hand, hot conditions such as rashes, ulcers, fever, infections and liver problems are treated with cold foods such as dairy products, honey, tropical fruits and raisins. Cold medicines, bicarbonate of soda and herbs such as sage are also used. Traditional medicines can take the form of herbs and other plant extracts. As these preparations have their own pharmacological actions, and they may interfere with the actions of more conventional therapy used in health-care agencies. Patients may not perceive these naturally derived agents as drugs. Thus, in determining the patient's medication history, the health-care professional should ask specifically whether herbs, plants or any other types of preparation are being or have been used to treat a condition (see also Chapter 8).

In many Asian cultures, a number of techniques for the cure of illnesses have evolved. 'Coin rubbing' is a technique commonly used to treat minor ailments of the forehead, nose, neck, chest and back. The coin, having been dipped in Tiger Balm™, is rubbed forcefully over the body. If done properly, this procedure leaves long lines of dark bruises on the skin. Unfortunately, health-care professionals not familiar with the procedure sometimes misdiagnose this home treatment as child abuse. In addition to traditional medicines, it is therefore important to determine what other kinds of home remedy are practised by ethnic groups.

Asian people often use conventional medicines concurrently with traditional medicines. Self-medication is a popular behaviour in many Asian countries, where many medications do not require a prescription. Readily available antibiotics may explain in part the increasing resistance of bacteria. It may also explain patients' preference for complex or drastic drug therapy; for example, they may consider that two tablets must be better than one tablet. Contrary to their feelings about medication, patients may be extremely uncomfortable about invasive procedures, such as surgery. Furthermore, certain ethnic groups equate operations and visits from the hospital clergy with a grave prognosis. These views may have evolved from patients' hospital experiences in their country of origin.

Different ethnic groups show varying degrees of distress when communicating their illness to doctors and nurses. Some may exhibit an extravagant display of emotion in the presence of pain, while others show restraint to pain. A study examining reactions to pain experienced by Italian and Irish immigrants found the Italian response was emotional and dramatic, while the Irish response tended to underplay and ignore the pain. The Italian patients' way of coping with the pain was by repeatedly expressing the anxiety of the ordeal, while the Irish patients felt guilty about complaining of the pain. The different types of communication exhibited by different ethnic groups may have negative effects on the types of treatment these patients receive. In the above example, the health-care professional may perceive the Italian patient as overemotional and melodramatic, and so the Italian patient's concerns may be trivialised or invalidated. On the other hand, the same health-care professional may ignore the needs of the Irish patient. In either case, the pain may be indicative of a serious illness that is not detected by health-care professionals, as they have not considered the underlying messages.

In several cultures, the symptom of pain is seen as only one type of suffering and may be linked with other types of suffering. If the pain is viewed as a punishment for the patient's misbehaviour, then coping with the pain without complaint may, in itself, be considered as a form of treatment. If the pain is viewed as a form of punishment from God or some other religious being, then the response may involve fasting or prayer rather than communication with a health-care professional. This wider view of pain is common in some cultures, and individuals from these societies may find the conventional treatment of pain (the administration of an analgesic drug) unsatisfying and insufficient.

In many cultural groups, kinship networks form strong social support systems that influence the patient's decision-making processes. For instance, for an elderly Greek female patient to complete a course of cytotoxic therapy, approval may need to be obtained from an authoritative member of the family (e.g. her son or husband). To ensure rapport and to promote cooperation, family members will need the opportunity to understand and appreciate the recommendations before the cytotoxic therapy programme begins.

Consequently, where ethnicity is likely to affect medication therapy, the health-care professional must assess the beliefs, values and other activities that could have an impact on each situation. In accepting, valuing and understanding patients' health practices, it is possible to determine appropriate methods of administering drug therapy without compromising their beliefs and values.

SUMMARY

- Advertising of medications can affect the medication management activities of health-care professionals.
- Advertising can influence the medicinal activities of consumers.
- Over-the-counter preparations are available to consumers without a prescription, and often without supervision by a health-care professional.
- The generic name of a drug is the shortened, simplified version of the chemical name.
- The brand name of a drug is the registered trademark used by a pharmaceutical company to identify the preparation of a particular drug.
- Polypharmacy, which is a major issue for older patients, involves the excessive or inappropriate use of medications.
- The traditional beliefs and values of a particular culture influence an individual's perceptions and expectations about medication therapy.

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WEB RESOURCES

Brief History of pharmacology http://pubs.acs.org/subscribe/journals/mdd/v04/i05/html/05timeline.html

History of Biomedicine www.mic.ki.se/History.html

What is Pharmacology? www.pharmacology.med.umn.edu/whatispharm.html

PHARMACOLOGY WITHIN THE PROFESSIONAL CONTEXT

Conciseness and decision are, above all things, necessary with the sick. Let your thought expressed to them be concisely and decidedly expressed. What doubt and hesitation there may be in your own mind must never be communicated to theirs, not even (I would rather say especially not) in little things. Let your doubt be to yourself, your decision to them.

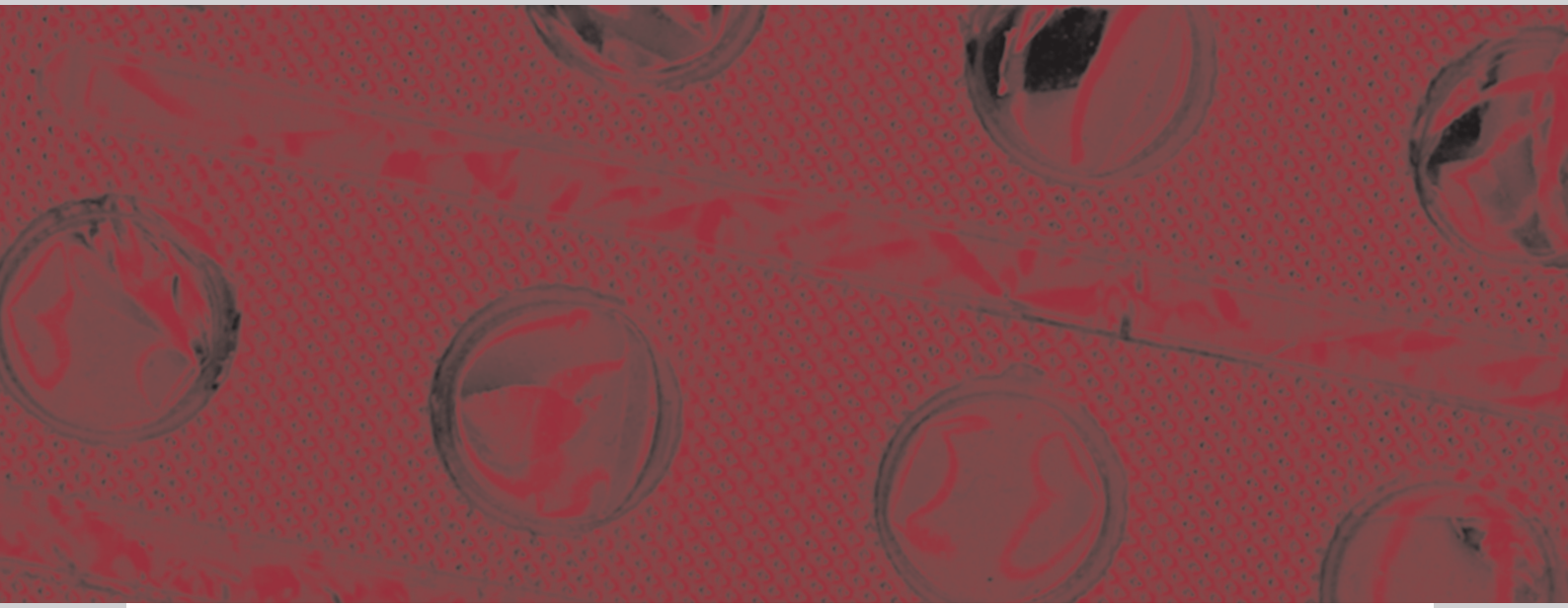
FLORENCE NIGHTINGALE – *NOTES ON NURSING*

During Florence Nightingale's era, the caretaker of the sick was always held as being in the right. Paternalistic attitudes were prevalent, the patient had little say in the choice of treatment, and the views of health workers, especially doctors, were held in high esteem.

This perspective differs somewhat from that of today, in which a major aim of health professionals in providing care is for patients to make decisions for themselves. This means that patients must have access to adequate and easily understandable knowledge of medicines before they can agree to a proposed therapeutic regimen. This goal of independence and self-care provides the major underpinning of the following chapters.

Florence Nightingale also saw the need for precision and decisiveness in communicating and caring for patients. In contemporary society, this situation is reflected in the way nurses and other health-care professionals provide care for their patients in relation to therapeutic drug regimens. This care involves drug legislation, the ethical perspective, patient education and advocacy, and the dispensing, prescribing, administration and evaluation of drug therapy.

II



The complex array of medications available has created the need for legislative controls in the manufacture, sale, distribution, storage, labelling and administration of medications. A discussion of controls over drug use in the UK is covered in Chapter 3. Specific areas of nursing responsibility, including emergency situations, nurse practitioners, midwifery practice, nurse prescribing and supplementary prescribing, are discussed briefly. The legal right to prescribe in the UK was limited to doctors, dentists and veterinary surgeons by the Medicines Act of 1968. Forty years on, there are now major changes within the NHS as non-medical prescribing increases in importance. Prescribing responsibilities are now extended to nurses, pharmacists and some other health-care professionals. These developments are described briefly. In Chapter 4, ethical issues of pharmacology are discussed using the six principles of ethics. These principles are veracity, autonomy, non-maleficence, beneficence, justice and confidentiality. Ethical situations, however, often involve more than one principle, which may lead to conflicts regarding which principle should take precedence. The potential for conflict between ethical principles and the legal perspective underlying these principles is highlighted.

The health-care worker's role in pharmacology with reference to patient adherence, patient education, patient advocacy and research is discussed in Chapter 5. Principles that can be used to promote patient advocacy, compliance and learning are also considered.

Chapter 6 covers the roles of the prescriber, pharmacist, physiotherapist, paramedic, podiatrist, dietitian and naturopath in relation to drug therapy. The roles of these health-care professionals are changing constantly in light of the increasing complexity of drug therapy, the value placed on non-drug therapy and the need for economic rationalism. These factors are also considered briefly.

DRUG ADMINISTRATION AND THE LAW

3

CHAPTER THREE

OBJECTIVES

After completing this chapter, and with further reference to the legislation pertaining to a jurisdiction, the reader should be able to:

- **describe the Acts and regulations pertaining to the distribution, storage, labelling, recording and administration of drugs;**
- **describe the schedules and the types of drug allocated to each schedule;**
- **describe the requirements for prescription, storage and administration of prescription medicines and controlled drugs;**
- **develop an awareness of health-care professionals' responsibilities in drug administration in emergency situations;**
- **develop an awareness of the drug-administration responsibilities of nurse practitioners and midwives.**

KEY TERMS

Legislation
Schedule
Prescription medicine
Controlled drugs
Standing order

MEDICATIONS HAVE THE POTENTIAL TO PRODUCE ADVERSE reactions, with possible fatal consequences. Furthermore, problems can arise associated with inappropriate use by the health-care professional or the patient. Consequently, legislative controls have been developed for the manufacture, sale, distribution, storage, labelling and administration of drugs. The legislation

is in place to protect patients from harm arising from the inappropriate use of drugs, and to provide nurses and other health-care professionals with a comprehensive framework for their clinical practice.

In this chapter, the term 'nurse' has been used to cover all levels of nursing staff. It should be noted that some drugs may be administered only by certain qualified nurses within the general ranks of 'nurse'.

Before the middle of the nineteenth century, in Britain there were no legal restrictions on the sale of poisons or drugs, and anyone could describe themselves as a pharmaceutical chemist. Statutory control over sales was first applied to arsenic in the Arsenic Act of 1851. The Pharmacy Act of 1868 introduced a poisons list, with 15 entries; preparations containing poisons could be sold only by 'pharmaceutical chemists'. The list of poisons was extended in 1908 with the Poisons and Pharmacy Act to include poisons used for agricultural and horticultural purposes. In 1933, the Pharmacy and Poisons Act established a poisons board to advise the secretary of state on what should be included in the poisons list. Poisons were divided further into different schedules, and all registered pharmacists were now required to be members of the Pharmaceutical Society. Pharmacy and poisons were firmly linked together by statute, but the sale and manufacture of medicines was not regulated in any way, except for medicines containing poisons.

Some control over quality was provided by a series of Food and Drugs Acts, but a manufacturer of a proprietary medicine did not have to disclose its composition until the Pharmacy and Medicines Act of 1941, which required a disclosure of the composition of each container. Legislation surrounding medicines developed in a piecemeal fashion, each problem being dealt with as it arose. An example was the advent of **antibiotics**. It became necessary to control their sale and supply, and the Penicillin Act of 1947 did this. An increasing number of potent substances were becoming available, and a working party was set up by the government in 1959 to examine the need for new controls. The Medicines Act of 1968 was based on this and was designed to replace all earlier legislation relating to medicines.

International agreement about the control of the sale of narcotics began with the International Opium Convention signed at The Hague in 1912 but not implemented until after the First World War. A series of Dangerous Drugs Acts, beginning with the Dangerous Drugs Act of 1920, brought the various international agreements into force in Great Britain. The Single Convention on Narcotic Drugs 1961 replaced all the earlier international agreements and was reflected in the Dangerous Drugs Act of 1965. The misuse of amphetamines and other psychotropic drugs widened the problems of abuse; as problems of drug abuse continued to increase, the law was extended and recast in the Misuse of Drugs Act 1971, which repealed the various Dangerous Drugs Acts and the Drugs (Prevention of Misuse) Act 1964.

In Britain today, the Medicines Act 1968 and the Poisons Act 1972, together with the Misuse of Drugs Act 1971, regulate the use of all medicines and poisons:

- The Medicines Act 1968 controls the manufacture and distribution of medicines.
- The Poisons Act 1972 regulates the sale of non-medicinal poisons.
- The Misuse of Drugs Act 1971 deals with the abuse of drugs.

In NHS hospitals, the statutory provisions are supplemented by the recommendations of a number of official reports such as the Aitken Report of 1958 and the Gillie Report of 1970. Advice is also given in the form of notes and circulars issued by the Department of Health.

The reports give additional advice on the ordering and storing of controlled drugs in hospitals and the keeping of records. The Aitken Report recommended that the person in charge of a ward should keep a register; this is accepted practice, although it is not a requirement of the Misuse of Drugs Regulations. The Aitken and Gillie Reports both recommended the use of lockable storage cupboards, the keys of which should be kept by the practitioner in charge of the ward.

THE MEDICINES ACT 1968

This was the first comprehensive legislation on medicines in the UK. The Act and various secondary legislation produced since 1968 regulate the manufacture, distribution and importation of all medicines for human and animal use. The health and agriculture ministers of the UK are responsible for the administration of the Act and have always had the benefit of advice from the Medicines Commission, established in 1968. The Medicines Commission was amalgamated with the Committee on Safety of Medicines (CSM) in 2005 to become the Commission on Human Medicines. The Commission meets monthly and advises ministers on medicinal products, advises the licensing authority where it has consulted the commission, and promotes the collection and investigation of information relating to adverse drug reactions in order to enable the advice to be given. Data from the Yellow Card Scheme is used to detect new safety issues.

There are three classes of product under the Medicines Act 1968. These are:

- *General sales list medicines (GSL):* products that can be sold to the public without the supervision of a pharmacist. Certain conditions apply to the sale of these products, including that the product must be made up for sale in a container or package elsewhere and not previously opened and that premises selling these medicines can be locked to exclude the public.
- *Pharmacy medicines (P):* products that may be sold only under the supervision of a pharmacist.
- *Prescription-only medicines (POM):* medicinal products that may be sold or supplied by retail in accordance with a prescription given by an appropriate practitioner. UK registered doctors and dentists are appropriate practitioners for all POMs. There are some exemptions from POM status, including all preparations of insulin and some controlled drugs, when these are in preparations containing only one controlled drug below a stated strength. A person may not administer a POM, except to themselves, unless he or she is a practitioner or acting in accordance with the directions of a practitioner. Some medicines for use by parenteral administration are exempt from this restriction when administered to save life in an emergency; this list includes **adrenaline**, **atropine**, **glucagon** and **promethazine**.

The restrictions on sale and control of some POMs do not apply to a registered midwife in the course of his or her professional practice. This exemption applies to POMs containing ergometrine maleate or **pentazocine hydrochloride**, for example. Some midwives may also administer parenterally in the course of their professional practice certain POMs such as **oxytocin** and **pethidine**. Paramedics who hold a certificate of proficiency in paramedic skills issued with the approval of the secretary of state may administer certain parenteral POMs, including **Diazemuls™**, **naloxone** and intravenous succinylated gelatine (**Gelofusine™**).

To be valid, a prescription has to fulfil certain requirements, including that it should:

- be written in ink or be otherwise indelible;
- be signed and dated by the person issuing it;
- specify the name and address of the person for whose treatment it is issued, except for patients in hospital and nursing-home situations;
- specify the dose to be taken and the form of preparation.

There are other recommendations to be found in the *British National Formulary*, including the following:

- Avoid the unnecessary use of decimal points, e.g. use 3 mg rather than 3.0 mg. Quantities of less than 1 g should be written in milligrams, e.g. 500 mg rather than 0.5 g.
- Quantities of less than 1 mg should be written in micrograms, e.g. 100 micrograms rather than 0.1 mg.
- The terms 'micrograms', 'nanograms' and 'units' should not be abbreviated.
- The dose and dose frequency should be stated; where a drug is to be taken 'as required', the minimum dose interval should be specified.
- Directions should be provided in English, without abbreviations (but it is recognised that some Latin abbreviations are used; see Appendix A).

The Medicines Act 1968 also has a section on homeopathic medicines and includes lists of substances that may be sold when diluted to at least one part in a million and others that may be sold when diluted to at least one part in ten. Most herbal remedies are exempted from licensing requirements, but there are lists of substances of plant origin that can be sold only by registered pharmacies. More detail on this can be found in Chapter 65.

There are regulations that promote the safety of medicinal products by ensuring that they are described correctly and readily identifiable. Appropriate warnings, information and instructions must be given. These regulations may apply to the labelling of containers and leaflets supplied with medicines, for instance. In 1994, a European Community directive came into force that outlined requirements for the labelling of medicines and for the format and content of user leaflets to be supplied with each medicine. Packs that conform to the directives are known as 'patient packs' in the UK. These are ready-to-dispense packs containing a patient information leaflet (PIL) that has been approved by the Medicines Control Agency (MCA). All new medicines are required to comply with this directive. The packs usually contain enough medicine for 1 month, but packs of other sizes are available.

There are also regulations applying to general-sale medicines. One example is that if a product contains **aspirin** or paracetamol, it must be labelled with the words 'if symptoms persist, consult your doctor'; if a product contains paracetamol, it must be labelled 'do not exceed the stated dose'.

THE MISUSE OF DRUGS ACT 1971

This Act came into operation on 1 July 1973. It controls the export, import, production, supply and possession of dangerous or otherwise harmful drugs and consolidates and extends earlier legislation. It is also designed to promote education and research relating to drug dependence and to deal with the control and treatment of addicts. It is mainly restrictive, and the general effect is to render unlawful possession of the drugs controlled under the Act, except as provided in the regulations made under the Act.

The Advisory Council on the Misuse of Drugs (ACMD) is an independent expert panel that advises government

on drug-related issues in the UK. It consists of no fewer than 20 members appointed by the secretary of state after consultation with the appropriate organisations. The Council is required to keep under review the situation with respect to drugs that are likely to be misused. It can advise on such aspects as restricting availability of medications, education of the public and the promotion of research into relevant areas. Ministers may refer to the Council matters relating to drug dependence on which they require advice.

The drugs subject to control are termed 'controlled drugs'. These are divided into three parts, or classes, largely on the basis of decreasing harmfulness. This division is for the purposes of determining penalties for offences under the Act and is not directly relevant to patient care:

- Part I (Class A), e.g. **diamorphine**, **cocaine**, **lysergide (LSD)**, **methadone**.
- Part II (Class B), e.g. oral amphetamines, **barbiturates**, **codeine**.
- Part III (Class C), e.g. **buprenorphine**, **diazepam**, **anabolic steroids**, **cannabis**.

In the UK, cannabis was reclassified from Class B to Class C in 2004. This lessens the penalties for the possession of the drug and has been the subject of intense debate as some politicians have argued that cannabis can trigger serious mental illness and should revert to its original classification. At present, there are proposals by the UK government to review the whole classification system, and a consultation paper on the subject is in preparation.

The use of controlled drugs in medicine is permitted by the Misuse of Drugs Regulations 1985. The drugs controlled are classified into five schedules in descending order of control (Table 3.1). The most stringent controls apply to those drugs in Schedule 1.

A registered midwife may possess and administer a controlled drug that the Medicines Act 1968 permits him or her to administer. This applies to pethidine and supplies may be made to the midwife on the authority of a midwife's supply order, which is signed by the appropriate medical officer (doctor). Very strict records have to be kept surrounding the administration of such drugs.

Requisitions

A requisition in writing must be obtained by a supplier before he or she delivers any controlled drug, except those in Schedules 4 and 5, to any of the following recipients:

- a practitioner;
- the person in charge of a hospital or nursing home;
- a person in charge of a laboratory.

TABLE 3.1 THE FIVE SCHEDULE REGULATIONS – 1985

Schedule 1	Drugs in Schedule 1 may not be used for medicinal purposes. Their possession is limited to involvement in research and other special cases. The requirements of the Misuse of Drugs Regulations relating to documentation, keeping of records, procedure for destruction, etc. apply in full to these drugs. Examples are coca leaf, lysergide and raw opium.
Schedule 2	This schedule includes the opiates (such as diamorphine, morphine and methadone) and the major stimulants (such as the amphetamines). A licence is needed to import and export drugs in this category, but they may be supplied by a pharmacist to a patient on the authority of a prescription in the required form, issued by an appropriate practitioner (such as a doctor or dentist). Requirements for safe custody and control over destruction apply to these drugs, and the keeping of records must be observed.
Schedule 3	This includes a number of minor stimulant drugs and barbiturates. Buprenorphine, pentazocine and temazepam are in this class. When misused, these drugs are not thought to be as harmful as those in Schedule 2. They are subject to special prescription requirements but not to safe custody requirements. Entries in the Register of Controlled Drugs need not be made, but invoices and similar records must be kept for a period of 2 years.
Schedule 4	This schedule contains benzodiazepines, such as diazepam. Anabolic steroids and androgenic steroids are also in this class. Records do not have to be kept by retailers, and there are no safe custody requirements.
Schedule 5	These are preparations of controlled drugs that have only minimal risk of abuse. Included are preparations that, because of their strength, are exempt from virtually all controlled drug requirements other than retention of invoices for 2 years. Examples are medicinal opium containing not more than 0.2% morphine and preparations containing not more than 0.1% cocaine.

The requisition must be signed by the practitioner, state his or her name, address and profession, and specify the total quantity of the drug and the purpose for which it is required. In hospital, a sister or nurse in charge of any ward must supply a requisition for controlled drugs in writing, signed by him or her and specifying the total quantity of the drug required. The person responsible for dispensing and supply must mark the requisition to show it has been supplied and must retain a copy of the requisition in the dispensary.

Safe custody of drugs

There are regulations for the safe custody of controlled drugs, except those in Schedules 4 and 5. The drugs must be kept in a locked cabinet or cupboard, and the keys should be in the possession of the person authorised, which would be the ward charge nurse or sister or their deputy.

Records must be kept in the form of controlled drugs registers. Each controlled drug must have its own page within the register. The drug must be specified at the head of each page; the date and time of each administration is recorded, together with the name of the patient to whom the drug was given and the signatures of the person administering the drug and a witness. The number of ampoules or tablets present before the current usage is counted and the number remaining after the drug has been administered is recorded. Entries must be in ink, and no cancellation, obliteration or deletion must be made.

Drug addiction

There are separate rules relating to the notification of addicts and the supply of certain controlled drugs to them. A person is regarded as being addicted to a certain drug if he or she has, as a result of repeated administration, become so dependent on a drug that he or she has an overpowering desire for the administration of the drug to continue. Any doctor attending a person whom he or she considers to be addicted to any of the drugs listed below must, within 7 days of the attendance, supply the Chief Medical Officer at the Home Office with certain details about the person.

The drugs to which this ruling applies include cocaine, methadone, morphine, opium and pethidine.

NURSES, MIDWIVES AND HEALTH VISITORS: *STANDARDS FOR THE ADMINISTRATION OF MEDICINES*

In April 2002, the Nursing and Midwifery Council (NMC) replaced the UK Central Council for Nursing, Midwifery and Health Visiting (UKCC) and the national boards as the body responsible for establishing and improving standards of nursing, midwifery and health visiting in the UK, in order to serve and protect the public. The UKCC had produced *Standards for the Administration of Medicines* in 1992 in the form of a small booklet. This has since been replaced by a similar booklet produced by the NMC in 2002 and available from their website. A registered nurse, midwife or health visitor is personally accountable for their practice, and the booklet emphasises the importance of drug administration in professional practice. It advises that the administration of drugs requires the exercise of professional judgement and should not be a mechanistic task to be performed in strict compliance with the written prescription of a medical practitioner.

The *Standards for the Administration of Medicines* state that the nurse is expected to confirm the correctness of a prescription and to judge the suitability of administration at the scheduled time. The nurse should reinforce the positive effects of the treatment and enhance the understanding of patients with regard to their medication. The nurse should also assist in evaluating the efficacy of medicines and the identification of side effects and interactions.

The *Standards* list the expectations of a prescription written by a medical practitioner, which should satisfy certain criteria:

- The patient should be aware of the purpose of the treatment and have consented to receiving it.
- The prescription should be written in ink or be otherwise indelible and should be clearly written, typed or computer-generated, and dated.
- When a new prescription replaces an older prescription, the latter should have been clearly cancelled and signed and dated by the medical practitioner.
- The substance to be administered should be specified clearly and, where necessary, its form stated, together with the strength, dosage, timing, frequency of administration and route of administration.
- In outpatient and community settings, the duration of the course of medicine before review should be stated.

It is stated in the *Standards for the Administration of Medicines* that instruction by telephone to a practitioner to administer a previously unprescribed substance is not acceptable. If the medicine has previously been prescribed but the prescriber is unable to issue a new prescription, and a change of dose is necessary, then fax or email is the preferred method of communication; instruction by telephone is not acceptable.

Nurses administering, assisting in the administration of, or overseeing the self-administration of medicines need to be satisfied that they have an understanding of the drugs given and are able to be accountable for any actions taken. It is, therefore, necessary that the practitioner is certain of the identity of the patient, is aware of the patient's current programme of care, and questions the medical practitioner or pharmacist if there is any information that is unclear, ambiguous or incomplete. The practitioner should refuse

to administer the prescribed substance if there are any doubts in the above or in the dose or route prescribed for administration.

The *Standards for the Administration of Medicines* also detail other essentials, such as checking the expiry date of the medication and considering any drug interactions. The *Standards* emphasise the importance of completing clear and accurate records at the time of administration and the need to chart down refusal of medication and to contact the prescriber in these situations should it be deemed necessary.

In a hospital setting, only a registered practitioner who is competent for the purpose and aware of his or her personal accountability should administer prescribed medications. The *Standards* state that 'in the majority of circumstances, a first level registered nurse, a midwife, or a second level nurse, each of whom has demonstrated the necessary knowledge and competence, should be able to administer medicines without involving a second person'. There are exceptions to this, such as when instructing a student nurse or when local circumstances make the involvement of two nurses desirable in the interests of patients, such as in a paediatric unit. Some drugs may need complex calculations to be made; in these instances, the calculation should be checked by a second practitioner. When substances are being prepared for injection, this should not be done in advance and should be done only by the practitioner who will administer the drug. If preparing a drug for a doctor, the doctor should be present and must make the appropriate checks.

The NMC welcomes the self-administration of medicines in hospitals and nursing homes and the administration by parents to children. It also supports the administration by carers, where appropriate. The *Standards* emphasise the need for appropriate, safe and secure storage of the medicines and for agreed procedures to be in place.

Management of errors and incidents in the administration of medicines

The NMC *Standards* emphasise the importance of an open culture so that early reporting of any error is encouraged. The error should be reported to the line manager or employer. Local disciplinary action may lead to the discouragement of reporting and thus be detrimental to patients. The NMC states that it believes that all errors require a thorough and careful investigation at a local level, taking full account of the context and circumstances as well as the position of the practitioner involved. The use of local multidisciplinary critical incident panels is supported, where improvements to local practice in the administration of medicines can be discussed.

Where there are allegations of misconduct arising from errors in the administration of medicines, the NMC states that cases where the error was a result of rash or incompetent practice or was concealed are differentiated from those resulting from situations such as serious pressure at work and where there was an immediate and honest disclosure of mistakes made.

NON-MEDICAL PRESCRIBING

The Medicines Act 1968 allowed only doctors, dentists and veterinary surgeons to prescribe, but this has been changing rapidly within the NHS in recent years. In England, from May 2006, certain nurse and pharmacist prescribers can prescribe any licensed medicine (apart from most controlled drugs) within their sphere of competence.

Nurse prescribing has been on the professional agenda since 1986, when the Cumberledge Report recommended that community nurses should be able to prescribe from a limited list of items. The Advisory Group on Nurse Prescribing, chaired by Dr June Crown, was established in 1987 and has led to two Reviews of Prescribing, known as the Crown Reports. These have led to developments in non-medical prescribing in the UK.

The first report was published in 1989 and recommended that district nurses and health visitors who completed the necessary training should be allowed to prescribe from a limited list. Nurses were also to be allowed to supply medicines within 'group protocols'. The second report was commissioned in 1997 and was part of the Review of Prescribing, Supply and Administration of Medicines. Current group protocols were thought to perhaps be breaching the Medicines Act and, following this, review patient group directions (PGDs) were introduced in 2000 to replace the group protocols. A PGD is a written instruction for the supply or administration of medicines to groups of patients who may not be individually identified before presentation for treatment. The review also defined two types of non-medical prescribing. These are independent prescribing and supplementary prescribing (dependent prescribing). Independent prescribing means that the prescriber takes full responsibility for prescribing a medicine to a patient and for the appropriateness of the prescription. The independent prescriber is responsible and accountable for the assessment of patients with both diagnosed and undiagnosed conditions and for decisions regarding their clinical management, including prescribing. Supplementary prescribing is a voluntary partnership between an independent prescriber, who must be a doctor or dentist, and a supplementary prescriber to implement an agreed patient-specific clinical management plan (CMP) with the patient's agreement.

Independent nurse and pharmacist prescribing

In 1992, the Act of Parliament entitled Medicinal Products: Prescription by Nurses Act 1992 became law.

Secondary legislation amending the Medicines Act came into force in 1994, as did an amendment to pharmaceutical regulations to allow pharmacists to dispense nurse-prescribed medicines. This legislation allowed health visitors and district nurses who had recorded their additional qualification on the NMC register to prescribe from the *Nurse Prescribers' Formulary*. The formulary was piloted from 1994 and extended to all NHS regions in 1998. It included such items as laxatives, local anaesthetics, drugs for threadworms, skin preparations, urinary catheters, mild analgesics, drugs for scabies and headlice, stoma-care products and fertility and gynaecology products. Specific drugs included aspirin tablets, lactulose solution, magnesium hydroxide mixture, nystatin, paracetamol and senna tablets. The majority of these were not POMs, but financially they accounted for about 10 per cent of the total drugs bill in the UK. By 2006, over 29 000 such nurse prescribers were registered with the NMC. The formulary is now named the *Nurse Prescribers' Formulary for Community Practitioners* (NPFCP).

In 2002, a second form of independent prescribing for nurses was introduced in England. This allowed registered nurses and midwives with additional training to prescribe from the *Nurse Prescribers' Extended Formulary* (NPEF). These practitioners were known as extended formulary nurse prescribers. The formulary included over 120 POMs for specific conditions. By 2006, it had been extended and included medicines for emergency and first-contact care and certain controlled drugs for specified conditions.

From May 2006, independent prescribing for nurses and pharmacists from a full formulary (excluding most controlled drugs) is permitted by legislation. The NPEF ceases to exist, and extended formulary nurse prescribers have become nurse independent prescribers. Prescribing is allowed only within the nurse's area of competence and if agreed by his or her employer.

Independent nurse prescribers can prescribe any medicine for any condition within their competence. Thirteen controlled drugs from the extended formulary are also included for specified conditions. These drugs are shown in Table 3.2. Pharmacist independent prescribers are not currently able to prescribe any controlled drugs. Independent nurse and pharmacist prescribers can also prescribe medicines outside their licensed indications, where this is accepted clinical practice. They cannot prescribe unlicensed medicines.

Under current legislation, nurse prescribers must have sufficient knowledge and competence to:

- assess a patient's clinical condition;
- undertake a thorough history, including medical history and medication history (including over-the-counter medicines and complementary therapies) and diagnose where necessary;

TABLE 3.2 CONTROLLED DRUGS THAT INDEPENDENT NURSE PRESCRIBERS ARE ABLE TO PRESCRIBE

Drug	Route	Medical condition
Buprenorphine	Transdermal	Palliative care
Chlordiazepoxide	Oral	Alcohol withdrawal symptoms
Diamorphine	Oral, parenteral	Palliative care
		Pain relief in suspected MI or severe pain following trauma or postoperatively
Fentanyl	Transdermal	Palliative care
Morphine sulphate	Oral, parenteral, rectal	Palliative care
		Pain relief in suspected MI or severe pain following trauma or postoperatively
Morphine hydrochloride	Rectal	
Oxycodone hydrochloride	Oral, parenteral	Palliative care
Diazepam	Oral, parenteral, rectal	Palliative care
		Alcohol withdrawal
Lorazepam	Oral, parenteral	Palliative care
Midazolam	Parenteral	Palliative care
Codeine phosphate	Oral	
Dihydrocodeine tartrate	Oral	
Co-phenotrope	Oral	

MI, myocardial infarction.

- decide on the management of the presenting condition and whether or not to prescribe;
- identify appropriate products if medication is required;
- advise the patient on effects and risks;
- prescribe if the patient agrees;
- monitor the patient's response to medication and offer lifestyle advice.

Clearly, it is important for nurses to possess a sound knowledge of the relevant legislation relating to drugs. It is equally important that nurses are aware of potential problem areas and of their need to maintain a duty of reasonable care to their patients. Programmes of education and training for prescribing must equip nurses with the necessary principles to enable them to be safe and effective prescribers. The NMC produced standards of proficiency for nurse and midwife prescribers in 2006. These include standards for:

- admission to programmes to be awarded a qualification to prescribe;
- the structure and nature of the preparation of nurse prescribers' education programmes;
- the content of education programmes;
- the assessment of programmes.

There are also standards for prescribing practice that registrants are required to maintain.

The Department of Health produced the *Guide to Implementing Nurse and Pharmacist Independent Prescribing within the NHS in England* in 2006, available on the Department's website. This guide specifies which nurses, midwives and pharmacists are eligible to undertake the programmes leading to independent prescribing and provides some history and discusses the necessary education.

Supplementary prescribing

Supplementary prescribing was introduced into the UK in 2003 for nurses and pharmacists and was extended in England in 2005 to chiropodists/podiatrists, physiotherapists, radiographers and optometrists. A clinical management plan (CMP) must be in place before supplementary prescribing can begin. The CMP is drawn up by the independent prescriber following diagnosis, in partnership with the supplementary prescriber, who can then prescribe any medicines specified within the plan. The CMP is held within the patient's records. Controlled drugs can be prescribed if specified in the CMP.

Patient group directions

These are not a type of prescribing but enable specified health-care professionals to supply and administer a range of medicinal products. A patient group direction is a written instruction for the sale, supply and/or administration of a named medicine for a defined clinical condition.

PGDs allow a range of specified health-care professionals to supply and/or administer a medicine directly to a patient with an identified clinical condition without the patient necessarily seeing a prescriber. The health-care professional working within the PGD is responsible for assessing that the patient fits the criteria set out in the PGD. Implementing PGDs may be appropriate both in circumstances where groups of patients may not have been identified previously (e.g. minor injuries, first-contact services) and in services where assessment and treatment follow a clearly predictable pattern (e.g. immunisation, family planning).

In general, a PGD is not meant to be a long-term means of managing a patient's clinical condition. This is best achieved by a health-care professional prescribing for an individual patient on a one-to-one basis. Legal requirements and guidance on PGDs are set out in the circular HSC 2000/026 (www.portal.nelm.nhs.uk/PGD).

The following health professionals can legally carry out a PGD's instructions: nurses, midwives, health visitors, optometrists, pharmacists, chiropodists/podiatrists, radiographers, orthoptists, physiotherapists, ambulance paramedics, dieticians, occupational therapists, prosthesists and orthotists, and speech and language therapists.

SUMMARY

- There are laws in the UK today that regulate the use of drugs.
- Drugs are divided into categories called schedules. The schedules indicate specific drugs by generic name according to particular characteristics.
- There has been an increase in prescribing by health-care workers other than doctors and dentists. This includes both nurse prescribing and supplementary prescribing.
- The law requires that all health-care professionals should show a reasonable standard and duty of care in medication management.

1 Indicate the schedule to which the following drugs belong:

(a) morphine;
(b) amoxicillin;
(c) paracetamol;
(d) nystatin.

2 Differentiate the requirements for storage and administration of restricted substances and drugs of dependence.

3 Explain the meaning of the following terms:

(a) telephone orders;
(b) standing orders;
(c) supplementary prescribing.

4 Explain the nurse's responsibility for drug administration in an emergency situation.

ETHICAL ISSUES

4

CHAPTER FOUR

KEY TERMS

Principles of ethics
Autonomy
Veracity
Non-maleficence
Beneficence
Justice
Confidentiality
Informed and valid consent
Euthanasia

OBJECTIVES

After completing this chapter, and with further clinical practice, the reader should be able to:

- **describe the six principles of ethics and provide examples of each principle;**
- **describe the connection between the six principles of ethics, with reference to the legal position;**
- **explain the ways in which principles may conflict with one another.**

CONDITIONS ALLOWING FOR IMPROVED HEALTH AND prolongation of life, together with recent advances in pharmacology, have led to more emphasis on the ethical issues of clinical practice. There are six fundamental principles that are relevant and applicable to almost any ethical situation (see Table 4.1). These principles enable the health-care professional to follow a more structured approach to ethical issues arising out of pharmacological situations. This chapter discusses these principles and relates them to common ethical situations pertaining to drug therapy. Discussion points are provided to illustrate some of the principles and form the basis for further discussion.

TABLE 4.1 ETHICAL PRINCIPLES AND THEIR MEANINGS

Principle	Meaning
Autonomy	Self-determination
Veracity	Trust through truth-telling
Non-maleficence	Do no harm
Beneficence	Prevent harm, do good
Justice	Give to each person his or her right or due
Confidentiality	Not to divulge information without consent

AUTONOMY

This principle asserts the patient's right to make decisions without interference from other people. It is important, however, that these decisions do not impinge on the moral interests of other people. The principle of autonomy comprises the two elements of informed and valid consent, and rights of refusal.

Informed and valid consent

Health-care professionals and patients must share knowledge before patients can agree to their proposed course of treatment. A patient agrees on a particular treatment by means of an informed and valid consent. Table 4.2 indicates the requirements for an informed and valid consent, which will be discussed in turn.

APPROPRIATE DISCLOSURE OF INFORMATION

Health-care professionals have a duty to inform their patients adequately of the effects, risks and complications arising from a proposed drug regimen. Doctors and nurses encounter a common problem related to the amount and type of information to be disclosed to patients. The decision to prescribe a certain medication should be taken on the basis of informed discussion with the patient, who has a right to information about their condition and the treatment options available to them. The amount of information given is likely to vary according to the complexity of the treatment and the patient's wishes, but all should be informed as fully as possible before the decision to prescribe a certain drug is made.

A less common standard of disclosure is the 'reasonable person' standard, which is based on the needs of a hypothetical patient. This hypothetical patient is an ideal representative of all reasonable patients in society. In this instance, the health-care professional discloses the information that a reasonable patient would expect to receive. Unfortunately, as society is made up of people of different sociocultural backgrounds, it is difficult to determine what comprises a reasonable patient (see also Chapter 2).

Regardless of whether a standard is used, the doctor and nurse should offer simple but thorough information about the common effects and problems of a drug regimen. If the patient asks a specific question, then the law requires that health-care professionals give an accurate answer. In the case of clinical trials for new drugs, patients should attempt to obtain more thorough information due to the uncertain and experimental nature of these drugs. In addition, patients who take complementary therapies should endeavour to obtain information about these preparations so that they are well informed about their therapeutic and unwanted effects. Certain complementary therapies, however, have untested properties that may not be known to the health-care professional or the patient. In such circumstances, a health-care professional would not be held responsible if the patient experienced an unexpected adverse drug reaction. Nevertheless, information about complementary therapies is growing all the time, and it is important that health-care professionals and patients improve their knowledge about them.

TABLE 4.2 REQUIREMENTS FOR INFORMED AND VALID CONSENT

Elements that enable informed consent
- Appropriate disclosure of information
- Understanding of information

Elements that enable valid consent
- Free and voluntary consent
- Competence

UNDERSTANDING OF INFORMATION

Patients must understand their drug therapy adequately, otherwise their consent to the treatment will be uninformed. Patients may not understand information about their drug therapy for various reasons: they may be very young, elderly or suffering from a physical or psychiatric impairment, or there may be other reasons, such as a patient being of a cultural background that does not align

with Western views (see also Chapter 2). Problems may also occur when the doctor or nurse provides the patient with too much information to process adequately. If the doctor or nurse provides insufficient information, the patient will not understand their drug regimen adequately. (Chapter 5 contains further information on effective teaching and learning strategies to facilitate better understanding by patients of their drug regimens.) In addition, health-care professionals such as doctors, nurses and pharmacists may have an inadequate knowledge base in complementary therapies, usually because the education of health-care professionals tends to focus on more traditional and conventional therapies. As a result, patients may not have an adequate understanding of complementary therapies and of the ways these may interact with more conventional therapies. Alternatively, patients may obtain information about complementary therapies from sources such as popular magazines, radio, television and the Internet. Subsequently, it is the health-care professional's responsibility to ensure that the patient's information is reliable and accurate, therefore enabling informed consent.

DISCUSSION POINT: WHAT WOULD YOU DO?

The following example reflects the dilemma concerning the amount of information the health-care professional should tell the patient about a drug treatment.

A woman has a fatal reaction to the radio-opaque dye used during a myelogram. The radiologist and nurse indicate that they did not warn the patient about a possible allergic reaction because she had never experienced an allergic drug reaction and the chances of an allergic reaction were extremely remote.

FREE AND VOLUNTARY CONSENT

Free and voluntary consent means the ability to choose and act freely without the influence of others. If a patient faces the decision of whether or not to have drug therapy for a particular condition, then the doctor and nurse should provide adequate and unbiased information about each option. The patient can then make a free and voluntary decision. Sometimes patients' mental or physical functions are impaired to the point where they are unable to make voluntary decisions. If possible, health-care professionals should wait until the patient can consent voluntarily before proceeding with treatment. The NHS Plan 2001 identified the need for changes in the way in which patients are asked to give their consent to treatment and emphasised the importance of patient-focused consent.

DISCUSSION POINT: WHAT WOULD YOU DO?

The following example shows how a patient's cultural beliefs and values may affect acceptance of information about a proposed drug regimen.

An elderly Chinese woman is admitted to hospital following a fractured neck of femur. Her hospital tests reveal the presence of breast cancer that is amenable to chemotherapy and surgery. The patient refuses to follow these options, preferring to use Chinese herbal remedies to treat the cancer. The patient continues to hold this view despite arguments to the contrary.

DISCUSSION POINT: WHAT WOULD YOU DO?

The following example demonstrates the problem confronting a health-care professional when a patient is not informed fully about the beneficial as well as the harmful effects of a herbal medication. Refer to Chapter 65 for further information about herbal therapies. Although herbal medications are often freely available from pharmacies and health-food stores, patients do not always receive adequate information about their use.

A 35-year-old woman who is 20 weeks pregnant comes in to the health clinic for her prenatal check-up. She comments to the midwife that she has been able to sleep better over recent months because she has started taking chamomile supplements. The woman adds that she had read in a women's magazines about the benefits of taking chamomile supplements to assist with insomnia, and purchased the supplements from her local pharmacy. The midwife comments that although chamomile supplements may be normally beneficial, they should not be taken during pregnancy. Immediately the woman begins waving her arms around anxiously and states: 'But they are supposed to be natural, so surely they should be OK?'

COMPETENCE

The patient must be competent in order for the consent to be valid. According to the law, everybody except minors and mentally ill patients are competent to make their own decisions. Competence is the ability to perform a task. It can occur only if the patient makes decisions based on rational reasons. In the case of a minor (under the age of 18 years in the UK), the doctor may obtain consent from a parent or a legally appointed guardian. A minor aged between 16 and 18 years may give consent for treatment, but if treatment is refused parental consent may be used.

There are occasions when people under 16 years can give their own consent for treatment provided they are able to understand what is involved. They cannot, however, take the decision to refuse treatment. In Scotland, the Age of Legal Capacity Act 1991 gives authority to adolescents over the age of 16 years to refuse treatment, but this does not apply in England and Wales. UK law does not fix any specific age below which a child is automatically presumed incapable of consenting to treatment. The child's ability to consent depends mainly on whether the child is mature enough to understand and appreciate the implications of the treatment undertaken. Legislation also permits certain emergency treatments without parental consent. Furthermore, it allows health-care professionals to override the parental decision if it is in conflict with the child's survival. An emergency situation here is one where the child will die or suffer serious damage if the treatment is not given.

In providing emergency procedures to adults, health-care professionals are forced to make difficult decisions, as patients may not be able to decide for themselves. Examples include patients who have a head injury following a motor car accident, patients who are under the influence of drugs or alcohol, and patients who have a massive myocardial infarction. In these situations, health-care professionals can perform procedures without seeking the patient's consent.

The UK has legislation in place that deals with the care of intellectually impaired people. Intellectually impaired individuals who are able to function in the greater community and live independently are often considered competent in making their own decisions about health care. The legislation addresses the needs of severely impaired adults who possess the mental age of young children and therefore may not be able to protect themselves. The legislation is designed to prevent abuse, neglect and exploitation of these adults. Parents or appointed guardians have the authority to consent to treatments that are necessary for the wellbeing of intellectually impaired adults.

Other people suffering from mental illness, such as depression, are often legally capable of making their own decisions about treatment. During an acute stage of their illness, they may lack the legal capacity to consent to treatment. Sometimes it is up to health-care professionals to decide whether these people are competent enough to make decisions about treatment.

Rights of refusal

Competent patients can refuse drug treatment at any time. Continuing to give treatment when patients have clearly refused consent constitutes trespass. Even if the treatment is life-saving, it should not be given to competent patients without their consent. As nurses are the most likely health-care professionals to administer medications, patients who refuse their medications usually direct their comments to the nurse. For many nurses, the patient's refusal of medication means the unnecessary interruption of an already hectic administration schedule. It is important, however, that the nurse examines the reasons for the patient's refusal.

DISCUSSION POINT: WHAT WOULD YOU DO?

The following two situations illustrate differing capacities for competence and how consent may be waived depending on the urgency of treatment.

A 20-year-old footballer is brought into the emergency department with a gash on the side of his face that has stopped bleeding. He refuses to have the area sutured as he does not like injections or pain. He also does not mind if a scar develops on the area.

A 20-year-old man smelling of alcohol is brought into the emergency department after a fight outside a local pub. He sustains a deep stab wound to the abdomen and a cut on his hand. The patient refuses treatment, even though his vital signs indicate that internal haemorrhage has occurred.

It may be that the patient has not been informed adequately about a newly prescribed medication. The patient may be experiencing adverse effects of the medication, warranting a change in medication or reassurance that the medication is having the desired effect. Sometimes the patient is adamant that an error has been made in the drug order, leading to their refusal of the medication. Patients often become very familiar with their drug regimens, so the nurse should determine the various potential sources of error (refer also to Chapter 10). If a confused patient refuses medication, a hurried and abrupt approach is hardly likely to produce a positive effect. Instead, the nurse should be reassuring and give the confused patient some sense of control by offering a choice, such as whether the patient would like water or lemonade with a tablet. Ultimately, the nurse should communicate in a pleasant and positive manner and never be forceful or intimidating. If the patient still refuses the medication, this should be documented on the patient's drug chart. The nurse should also document in the patient's health history the reasons given for refusal, the attempts made to explain the situation to the patient, and the nursing actions taken.

VERACITY

Veracity relates to an obligation to tell the truth and not to lie or deceive others. It is associated closely with the principle of autonomy. A patient cannot express autonomy

unless the consent is informed and valid. The consent depends, therefore, on truthful communication in helping the patient to make decisions about treatment.

Due to the specialised knowledge of doctors and nurses, health care sometimes takes a paternalistic approach, where patients and relatives are given just enough information to keep them content. This approach assumes that patients do not expect to be told everything as they lack specialised medical knowledge. But patients often need more thorough explanations in order for information to make sense. The principle of veracity stresses the need for health-care professionals to honour the trust and confidence bestowed on them by patients. Health-care professionals can do this by maximising the amount and types of information they share with patients. Furthermore, as society is becoming better educated about health care, fewer patients are prepared to entrust themselves to the care of secretive and non-disclosing health-care professionals.

The law and therapeutic privilege

A legal exception to the rule of veracity relates to therapeutic privilege, where a doctor may intentionally and validly withhold information based on 'sound medical judgement'. In this instance, the patient may be depressed, emotionally drained or physically unstable; the disclosure of information is then potentially harmful. Health-care professionals may use therapeutic privilege in emergency and critical-care situations. The provision of important information may be breached in favour of the more urgent need for life-saving treatment.

Sometimes, doctors take this role of therapeutic privilege further by deliberately withholding information that they consider to be dangerous to the physical and mental wellbeing of patients. It is the nurse's responsibility as the patient's advocate to ensure that all members of the team of health-care professionals openly discuss treatment options with patients. If a case involving therapeutic privilege were ever to go to court, the onus would be on the doctors and nurses caring for the uninformed patient to prove that the disclosure of information would indeed have been dangerous to the patient's health.

Exceptions to veracity

Occasionally, there are situations where it is not appropriate to divulge information to a patient. Some of these have been alluded to in the above section. In addition, failing to tell a patient immediately following surgery that an inoperable cancer was found in theatre, or failing to tell a patient that their family has been killed in the same accident that landed the patient in hospital, are clearly exceptions to the principle. The intention is not to deceive but simply to convey the information at a more appropriate time.

DISCUSSION POINT: WHAT WOULD YOU DO?

The following situation illustrates the conflict between meeting the obligation of veracity and trying to protect the patient from needless suffering (beneficence).

A 50-year-old man presents with a recent growth of a thyroid mass and a hoarse voice. Only partial removal of the tumour is possible during surgery. During discussions with the patient's spouse and children, the doctor and charge nurse inform them of the patient's poor prognosis. The family and health-care professionals decide to conceal the diagnosis and prognosis from the patient and simply to tell him that he needs 'preventive' treatment. The patient receives irradiation and chemotherapy but soon becomes quite concerned and upset that his condition is not improving. He is never offered the chance to talk about his impending death as everyone around him pretends that he will recover. He dies 5 months after the initial diagnosis.

NON-MALEFICENCE

The principle of non-maleficence involves the duty of not harming or injuring others. Examples of harm include the possibility of residual disability from an operation, and adverse effects from conventional and complementary therapies. According to law, the health-care professional should provide the patient with information about the nature of the intended treatment and problems that may occur.

Negligence, which is a failure to provide adequate care and to guard the patient against harm or injury, involves conduct that falls below the professional standard set by law. The level of expertise and standard of care is that expected of an ordinary and competent practitioner. Thus, a graduate first-year registered nurse is not expected to perform to the same standard as a clinical nurse specialist. It is important that nurses be constantly aware of their level of expertise and consistently aim to achieve a high standard of practice in all aspects of patient care (see also Chapter 8).

Euthanasia

Doctors and nurses continually face emotional issues of life and death in their working environments. Euthanasia is an example of such an issue. The literature commonly distinguishes between voluntary, involuntary and non-voluntary euthanasia, and between active and passive euthanasia. With voluntary euthanasia, the patient voluntarily and freely chooses death. With involuntary euthanasia, the health-care professionals carry out actions without the patient's consent. In non-voluntary euthanasia, the patient is incapable of either giving or denying consent (e.g.

permanently comatose or brain-injured patients). Active euthanasia is the intentional act that leads to the patient's death (e.g. the administration of a lethal injection). Passive euthanasia involves allowing the patient to die by deliberately withholding or withdrawing life-supporting measures. Examples of passive euthanasia include the withholding or withdrawal of antibiotics, nutrition, respiratory mechanical support and cardiac drugs in a terminally or chronically ill patient.

LEGAL PERSPECTIVE

In the UK, there is no law dealing directly with euthanasia, but it is against the law to actively end another person's life. This does make euthanasia illegal.

In the the UK, when a health-care professional assists a patient to die, the law considers it an act of homicide. Currently, patients have the right to refuse treatment and treatment can be withheld, but a patient cannot legally receive assistance from health-care professionals to end their life. This would be assisted suicide and against the law.

Proponents of euthanasia typically argue that it is morally wrong to allow people to suffer unnecessarily. Using the principle of autonomy that is associated with the right to make decisions, individuals should also have the right to choose death. Given this right, other individuals should not interfere with the patient's right to die. Another supporting argument relates to the moral non-acceptance of intolerable and intractable suffering.

Several arguments are raised against euthanasia. One popular stance relates to the 'sanctity of life' doctrine. This contends that as all life is sacred, even if it involves suffering, and nothing can justify taking it. Another argument deals with the risk of misdiagnosis and the possibility of recovery. Medicine is not an infallible profession, and doctors themselves recognise that they can make mistakes. In addition, patients may make an unexpected recovery, or medical scientists may find a cure for a particular condition. Another popular argument is the 'slippery slope' (give an inch, take a mile) problem. Briefly, this suggests that if society allows euthanasia to occur with certain consenting individuals, then eventually it will permit any individual to have euthanasia.

Withholding and withdrawing treatment

Health-care professionals do make and carry out euthanasia-type decisions in the health setting. These decisions relate to whether treatment should be withheld or withdrawn. Although it may not be the health-care professional's intention to cause death in these situations, death may ultimately occur. Confusion often exists about the distinction between withholding (not starting) and withdrawing (stopping) treatments. Many health-care professionals and family members appear more comfortable withholding treatments than withdrawing treatments that have already started. In withdrawing treatment, health-care professionals may feel more responsible for a patient's death than in not starting a treatment to sustain life. There is also the belief among health-care professionals that starting a treatment often creates an expectation that the treatment will continue. To avoid this situation, it is important for doctors and nurses to communicate with the family that they will act according to the patient's wishes and best interests.

As far as the law is concerned, health-care professionals have no duty to continue treatment if it is proven ineffective. Instead, there should be a balancing of burdens and benefits to determine the overall effectiveness of treatment, and the patient, in consultation with family members, ought to be the primary decision-maker.

This distinction between not starting and stopping treatment may account for the relative ease with which health-care workers accept a 'not for resuscitation' (NFR) order. This order means that if a patient suffers a cardiac or respiratory arrest, then the health-care professionals will not resuscitate. It is often unclear whether NFR orders imply anything about other aspects of nursing and medical care. For instance, some patients with NFR orders receive chemotherapy, surgery, admission to intensive care, respiratory support and full nursing care, while others do not. Decisions relating to NFR orders are also problematic as they are often made without consultation with patients or their families.

Decisions relating to life and death situations can be extremely difficult and sensitive. As a result, occasionally the patient and family are not involved, and naturally this affects the patient's right to autonomy. Health-care professionals must, therefore, confront these life and death situations openly and always involve the patient and family in the decision-making process.

BENEFICENCE

Beneficence is conduct aimed at the good and wellbeing of others. The main difference between non-maleficence and beneficence is that the former involves restraint, prevention and prohibition, whereas the latter involves positive action, intervention and provision. In cases of conflict between the two principles, the duty of non-maleficence usually has priority over beneficence.

Duty of beneficence

The duty of beneficence involves the delivery of appropriate treatment and the assurance that the treatment will produce more good than harm. There are complex situations where it may be difficult to determine whether the treatment will be of ultimate benefit to the patient. Some examples include when considering the administration of an antianxiety drug to a suicidal patient instead of improving support networks and counselling facilities, and the

provision of expensive drug therapy to an extremely old and senile patient. In assessing these decisions, the health-care professional needs a genuine responsibility for the patient's wellbeing. It involves consideration of the patient's desire not to have treatment, the long-term versus short-term benefits, the psychological and physical prognosis, and the presence of suffering accompanying the prolongation of life. From the legal perspective, health-care professionals should offer treatment and services deemed to be of benefit to the patient.

Problems with paternalism

Beneficence can lead to paternalism. This occurs when health-care professionals carry out a particular treatment deemed to be of benefit and then neglect to inform the patient about this treatment. In some cases, the health-care professional may provide beneficent action when the patient is not able to give informed consent, such as when a road-accident victim sustains head trauma. In other cases, a health-care professional may provide beneficent action even if it opposes a competent patient's wishes, which is against the principle of autonomy.

Conflicts with other principles

Sometimes the principle of beneficence conflicts with other principles. A nurse may be torn between beneficence and non-maleficence when considering the use of highly sophisticated or experimental treatment. The impulse towards beneficence can, therefore, lead to excessive and unnecessary treatment and increase patient suffering.

Beneficence can conflict with the principle of justice. A too-eager approach to beneficence may threaten the equitable allocation of resources, such that those who are most in need of health care may not receive it.

Beneficence may also affect veracity and confidentiality. With veracity, a doctor or nurse may believe it is best to withhold the news of a patient's poor prognosis as it may affect the psychological wellbeing of the patient. A doctor or nurse may feel beneficence is served best by telling the patient's family about the patient's poor prognosis. Health-care professionals must obtain approval from the patient before they can tell the family about the patient's condition, otherwise this action is contrary to the duty of confidentiality.

DISCUSSION POINT: WHAT WOULD YOU DO?

The following situation illustrates how a health-care professional's duty of beneficence may lead to an infringement of patient autonomy.

After receiving his preoperative medication, a 20-year-old man scheduled for a knee reconstruction states to the nurse that he does not want his bed's side rails up. He does not believe the hospital's rules should apply to him as he is not drowsy from the medication and he will not fall out of bed. After some discussion with the patient, the nurse responsible for his care decides to put the side rails up. The nurse argues that she has restricted this patient's autonomy in order to protect him from harm.

JUSTICE

Justice means that patients will be assured equal access to the benefits available. It aims to provide all people with reasonable, dignified health care based on the need for this care. Equal access to health care ensures that no one is the subject of unreasonable discrimination. Unfortunately, not all sectors of the community have adequate access to this care, and subsequently their health suffers. Cases have been brought to our attention in the media where such phrases as 'prescription by postcode' are used when expensive drugs may be prescribed more readily in some areas than others.

Allocation of scarce resources

The growing cost of treatment and the presence of only limited health resources means that health services must be rationalised. The process of rationalisation is divided into two areas: macroallocation and microallocation.

MACROALLOCATION

Macroallocation decisions determine the amount to be expended and the kinds of health services to be made available to the community. Government and health organisations carry out these decisions. Macroallocation decisions have become increasingly difficult to make for various reasons. There is concern that expensive technology is often employed unnecessarily and that the money is taken away from other, less costly areas, such as health promotion and education. Furthermore, antagonism sometimes exists between hospitals and branches of the health sector (e.g. community health versus acute care) for a larger share of the limited resources.

MICROALLOCATION

Microallocation decisions determine who will obtain and use the available resources. Health-care professionals make these decisions for patients based on need. The idea of microallocation can be applied to the triage situation in hospitals. The model of triage used in emergency and critical-care departments involves sorting patients to ensure that available resources are used as effectively and efficiently as possible. Triage decisions, which are generally made by nurses, involve the determination of the greatest good for the greatest need. The nurse sorts patients into those who would die without immediate help, those whose treatments

can be delayed without immediate danger, and those with minor injuries. These decisions do not involve judgements about a patient's worth to society. Judgements about social worth, however, may need to be made in some situations. For example, in an outbreak of a contagious disease or following a serious earthquake, health-care professionals who are affected by the outbreak should, in some instances, be given priority of treatment. Once treated, these health-care professionals can care for other victims.

Clearly, there are several approaches used in determining the allocation of health resources, and not everyone will have adequate access to health care. In developing an understanding of the complex factors impinging on the allocation of health resources, and of the sociocultural factors affecting people's access to care, health-care professionals will be in a better position to help those most in need.

CONFIDENTIALITY

Confidentiality occurs when one individual discloses information to another in the belief that the information will not be divulged without permission being given.

Difficulties in maintaining confidentiality

The principle of confidentiality is often clouded by the need to protect the patient and other individuals from harm. The following situations illustrate the difficulties that may occur. For example, if a patient tests positive for exposure to the human immunodeficiency virus (HIV), then health-care professionals must counsel the patient to tell his or her spouse and sexual partners. The situation regarding an HIV-positive patient is very difficult, as the disclosure of information regarding a patient's HIV status may have repercussions in several areas of the patient's life. Ultimately, therefore, the rights of the patient may conflict with the rights of others.

Conversely, health-care professionals may know of a patient with severe coronary problems who wants to continue with dangerous and strenuous sporting activities. The family may know nothing about the situation. In this instance, issues of autonomy and confidentiality combine to make it difficult for health-care professionals to do anything else but give advice to the patient.

Furthermore, if a girl, regardless of age, wants to receive a prescription for the contraceptive pill, her doctor or community nurse should not inform her parents. If the girl has a family history of blood-clotting disease and she insists on continuing to take the contraceptive pill, the doctor or nurse should encourage her to tell her family. Without her consent, however, her family should not be told.

In contemporary society, it can be difficult to maintain confidentiality in care relating to elderly, chronically ill and acutely ill patients. The delivery of care for these patients often involves a number of specialists, all of whom are handling the patient's personal details. The increasing use of computers in the health-care setting to store patients' data and progress notes adds to the possibility of accidental disclosure.

The issue of confidentiality exposes a conflict between the obligation to preserve confidentiality and the duties relating to doing no harm and doing good. As shown, sometimes the respect for confidentiality must yield to the welfare of the patient and of other people.

CONCLUSION

The principles approach towards ethical issues in pharmacology enables a more systematic and structured study than an independent explication of ethical issues relating to a particular situation. Health-care professionals will confront several situations in practice where there are conflicts between two or more principles. Equipped with a knowledge of these principles, the health-care professional can identify the conflicts that may arise, and either develop a set order of priority or choose a course of action that preserves the principles at stake. Ethical issues commonly abound in the area of pharmacology, and for health-care professionals to function effectively as moral practitioners, mediators and negotiators, they need to develop and maintain a responsible and accountable ethic of care.

SUMMARY

- There are six fundamental principles that are applicable to almost any ethical situation.
- The principle of autonomy asserts the patient's right to make decisions without interference from other people.
- Veracity relates to an obligation to tell the truth and not to lie or deceive others.
- The principle of non-maleficence involves the duty of not harming or injuring others.
- Beneficence is conduct aimed at the good and wellbeing of others.
- Justice means providing all individuals with equal access and reasonable, dignified health care based on the need for this care.
- Confidentiality is when one individual discloses information to another in the belief that this information will not be divulged without permission being given.

THE ROLES AND RESPONSIBILITIES OF NURSES

5

CHAPTER FIVE

OBJECTIVES

After completing this chapter, the reader should be able to:

- **describe the nurse's role in pharmacology with reference to patient adherence, patient education, patient advocacy and nursing research;**
- **describe factors affecting patient adherence with medication regimens;**
- **discuss learning and teaching principles that the nurse can use in developing and implementing a teaching plan;**
- **describe principles that the nurse can use to promote patient advocacy;**
- **describe the nurse practitioner role;**
- **describe how scientific research in pharmacology differs from nursing research in this area.**

KEY TERMS

Medication adherence
Patient education
Patient advocacy
Nursing research
Nurse practitioner

WITH THE GROWING COMPLEXITY OF HEALTH CARE, NURSES have a dynamic, responsible and active role in drug administration. Nurses contribute to the planning and modification of drug therapy from their assessment of patient factors and evaluation of progress and problems occurring during drug therapy. As vital members of the health-care team, nurses share information with other health-care professionals to provide the most effective medication regimen for the patient. Furthermore, nurses have many opportunities in preparing patients to participate as responsible contributors to their own care and to evaluate critically the existing therapeutic plans. Nurses achieve these multifaceted roles with pharmacology by means of patient adherence, patient education, patient advocacy and nursing research.

PATIENT ADHERENCE

Patient adherence relates to concordance to a prescribed drug regimen, including dosage, method of administration, frequency, specific recommendations and precautions for the drug. Non-adherence refers to the deviation from a prescribed drug regimen. Research indicates that many patients fail to follow their prescriptions correctly in the home setting. Although attempts have been made to elucidate demographic characteristics affecting adherence, research indicates that factors such as gender, age, social class, education and mental status play only a small part in non-adherence. In fact, factors affecting non-adherence are more complex, relating to a lack of patient–nurse interactions, disease consideration, medication characteristics and patient characteristics. Table 5.1 summarises these factors. Nurses can play a vital role in minimising the level of non-adherence through individualised instruction according to the patient's particular circumstances.

Patient information leaflets (PILs) have been provided with all medicines since 1999. These leaflets provide essential information on medicines for the patient; their content is closely regulated and reviewed by the Medicines and Healthcare Products Regulatory Body (MHRA) before being supplied with the medicine. There is a growing need for patients to be able to access high-quality information about their medicines, but the Committee on Safety of Medicines (CSM) has found the quality of the statutory information variable. The Consumer's Association reviewed PILs and stressed the importance of basing the information provided around the patient. A working group was set up and provided several recommendations emphasising the need to involve the patient in the design of PILs and noting that information about risk is often not communicated well. Following this report, PILs should improve in clarity and the risks and benefits of medicines made more freely available in alternative formats.

Each PIL provides information about a particular medicine and should be used by health-care professionals as a complementary aid to existing educational resources rather than as a replacement for an individualised approach. Many patients appreciate the chance to ask questions about

TABLE 5.1 FACTORS AFFECTING PATIENT ADHERENCE TO MEDICATION REGIMENS

Patient characteristics
- Age extremes
- Absence of family support (social isolation)
- Cost of medications
- Personal/cultural beliefs
- Physical impairment (e.g. hearing, vision)
- Intellectual/mental impairment (e.g. congenital)
- Lack of cognitive skills

Patient–nurse interactions
- Communication barriers (e.g. language, culture, anxiety)
- Misunderstanding of directions
- Absence of patient confidence in drug regimen
- Patient dissatisfaction with or lack of confidence in nurse
- Lack of effective use of time

Disease considerations
- Chronic long-term condition with no cure
- Benefits of treatment not easily seen (e.g. hypertension)
- Disease requiring a long treatment period before benefits apparent (e.g. depression)

Medication considerations
- Multiple medications (polypharmacy)
- Frequent doses
- Doses at inconvenient times
- Complex dosage regimen
- Adverse drug effects perceived as worse than condition treated
- Route of administration not tolerated (e.g. unpleasant taste, vomiting, diarrhoea)
- Inappropriate dosage form (e.g. tablets too big)
- Extended duration of therapy

their medication and should be given this opportunity. Increased understanding may aid adherence to the drug schedule. As shown in Table 5.1, several factors influence a patient's adherence to medication regimens. With the aid of PILs, nurses are in a position to explain to patients the particular ways in which medications may affect their lifestyle. Through the increasing use and availability of PILs as a medication resource for patients, together with counselling provided by nurses and other health professionals, medication adherence among patients should be greatly enhanced.

PATIENT EDUCATION

The nurse plays an important role in the assessment, planning, implementation and evaluation of patient education for medication therapy. Developing an awareness of learning and teaching principles will assist in the transmission of information and further facilitate patient adherence to medications.

Learning principles

With the help of a nurse, the patient can apply certain learning principles to reinforce the knowledge gained about drugs. The following points cover important aspects that promote learning.

ACTIVE PARTICIPATION

An effective way for the patient to develop new skills or change a behavioural pattern is to play an active role in the education process. For example, a patient who is to administer subcutaneous **insulin** for diabetes will learn this skill more effectively by practising the procedure with the nurse. This method is useful in promoting cognitive and psychomotor skills. In this example, cognitive skills relate to how much insulin to draw up depending on the blood glucose level. The psychomotor skills focus on how to draw up the insulin and how and where to administer the injection.

MOTIVATION TO LEARN

The nurse must be aware of the patient's motivation to learn. Without adequate motivation, the patient will not retain or use the information. The nurse can attempt to boost a patient's motivational level by assessing the patient's perception of disease and the patient's social, cultural and environmental background, and incorporating this information in the learning process.

PRIOR EXPERIENCE AND KNOWLEDGE

Knowledge is achieved more effectively if it builds on ideas and experiences already familiar to the patient. Aspects of relevance to this area include the patient's educational level, occupation, cultural and ethnic beliefs and familial predisposition to a particular disease. For instance, if the assessment indicates that the patient's father has had an acute myocardial infarction, then the nurse should ask the patient what was learnt from the experience and build on it.

IMMEDIATE APPLICATION OF KNOWLEDGE

Learning is enhanced if a particular skill is practised immediately. For example, when locating injection sites for the administration of insulin in a newly diagnosed diabetic patient, the nurse will demonstrate the procedure and then allow the patient to indicate these sites. This process enables the nurse to provide immediate feedback.

PHYSICAL AND EMOTIONAL READINESS

This principle focuses on the nurse's awareness of the patient's physical, intellectual, emotional and spiritual traits so that adjustments can be made. For example, for a patient recovering from a motor-car accident with head injuries and bone fractures, the nurse will assess characteristics that may interfere with learning, such as pain, confusion, drowsiness, anxiety and adverse reactions to drugs.

CONGRUENCE WITH PATIENT'S EXPECTATIONS AND GOALS

Before beginning a teaching session, the nurse should assess the patient's expectations and goals for the prescribed medications and adjust the plan accordingly. For instance, if the nurse is teaching the patient about **warfarin** therapy and the patient wants to focus on how his or her daily activities will be affected, the nurse will incorporate these ideas in the session. This strategy promotes the feeling of security in the patient.

REINFORCEMENT OF LEARNING WITH REPETITION

Repetition provides the patient with opportunities to practice psychomotor skills and observe improvement in the dexterity of these skills and allows for feedback between the patient and the nurse.

Teaching principles

Besides factors impinging on a patient's ability to learn, the nurse should be aware of principles influencing teaching strategies. The following points cover important strategies that facilitate effective teaching. Table 5.2 indicates the relevant aspects of patient teaching with use of the clinical decision-making process (see also Chapter 8).

NURSE–PATIENT RAPPORT AND COMMUNICATION

If the nurse and patient have established effective rapport, then the nurse is able to assess the patient's learning needs. Effective reciprocal rapport is achieved through communication, which has elements of friendliness, empathetic concern and a willingness to take the time to offer

TABLE 5.2 PATIENT TEACHING THROUGH THE CLINICAL DECISION-MAKING PROCESS

Patient assessment
- Knowledge base
- Physical abilities/disabilities (ability to perform motor functions)
- Cognitive abilities/disabilities (thinking and intellectual processes)
- Affective state (feelings, beliefs, values)
- Barriers to communication (language, deafness, blindness)
- Perceived needs
- Attitudes towards health/disease state
- Support networks (family, friends)
- Self-esteem
- Cultural, ethnic and religious beliefs

Clinical diagnoses
- Relation of knowledge deficit to information identified in assessment

Planning
- Development of teaching plan
- Identification of patient's goals

Implementation
- Use of effective learning and teaching principles depending on patient's needs

Evaluation
- Made at conclusion of teaching/learning process or occurring continuously throughout teaching/learning process
- Modification of steps to facilitate successful completion of goals

explanations. In examining responses and attitudes towards the patient from the patient's perspective, the nurse assesses the patient's values, beliefs, vocabulary and ability to assimilate information. The nurse is responsible for respecting patient autonomy in decision-making about treatment (see Chapter 4) and is aware that there will always be patients who fail to comply with the most logical and rational therapeutic recommendations. A mutually negotiated contract will assist in preserving the autonomy of and respect for the patient.

ENVIRONMENTAL CONTROL

Environmental factors such as noise, temperature, lighting and patient privacy can enhance or interfere with the effectiveness of a teaching session. Although the environment is not always amenable to change, the nurse should attempt to minimise detracting factors that may interfere with the patient's ability and willingness to participate in a teaching session.

MUTUALLY NEGOTIATED CONTRACT

A mutually negotiated contract, outlining expected outcomes to be achieved, serves as a structured guideline for the patient and the nurse. Following the teaching session, the outcomes provide the means for evaluating the effectiveness of teaching and learning and help the nurse and patient identify areas that require further emphasis.

VARIETY OF TEACHING STRATEGIES

The nurse should use a variety of teaching strategies to enhance learning. Examples include small-group or one-to-one discussions, demonstrations, simulations, anatomical models and simple illustrations. The approach taken depends on information derived from the nurse's assessment of the patient.

PATIENT ADVOCACY

Patient advocacy is another important role performed by nurses in relation to drug therapy. In their role as advocates, nurses inform patients about their rights in a particular situation, making sure they have all the information necessary to make informed decisions. The nurse supports patients in their decisions and protects and safeguards their interests. In this role, nurses are often confronted by adversaries that render the patient powerless to make an informed decision. In this context, an adversary is something or someone that prevents the patient from making an informed decision. Most commonly, these adversaries are members of the team of health-care professionals, such

as other nurses, doctors, social workers and family members. The adversaries may even include the rules, policies and protocols of the health-care agency or sustained chronic illness, paraplegia, ageing, trauma or poverty in vulnerable patients.

Advocacy also relates to ideas of power and empowerment. The nurse advocate may experience this powerlessness and vulnerability when confronted by adversaries to the patient's autonomy. It may be difficult for nurses to act as patient advocates as they lack the self-esteem and professional identity required to stand up and represent the patient. If the adversary is a confident person with a high professional status, such as a doctor, then it can be particularly difficult for the nurse to represent the patient's wishes.

Nurses need to develop and implement strategies aimed at recognising, promoting and enhancing patients' abilities to determine their needs and to solve their situations. Nurses must present the information in a manner that promotes patient understanding. If nurses impose their own feelings, this may lead to distortion of information. Another strategy is for nurses to reassure patients in the decisions they make and to convey to patients that patients have the right to make these decisions. Nurses should also resist pressure from other individuals who attempt to undermine a patient's confidence in their decision-making.

There are several indicators of the necessity for nurses to address themselves as patient advocates. Some of these indicators include the increase in the number of elderly, well-educated or demanding patients, combined with the escalating costs of technology. Furthermore, patient advocacy forms an important basis of nursing practice that is concomitant with the essence of caring. Advocacy is supported by ethical issues and ideas of informed consent, which are discussed in Chapter 4.

THE NURSE PRACTITIONER ROLE

The evolution of the nurse practitioner role has been instrumental in allowing nurses to take a more proactive approach in addressing the needs of patients in a safe and effective manner (see Chapter 3). With the increasing complexity of health care, the demand for nurses to take on advanced clinical roles continues to gather momentum. The nurse practitioner is a registered nurse with appropriate accreditation to practise in the role. This nurse has developed expert clinical skills, knowledge and experience in a specific area of clinical practice, such as general practice, palliative care, wound care or diabetes mellitus. The role allows for autonomy in the workplace and the freedom to make consistent decisions within the designated scope of practice. Expected standards of quality have also been demonstrated, which include exemplary professional behaviour, managerial capability and positive patient reports. From studies already completed, the evidence suggests that nurse practitioners provide quality health care. In contrast to other types of nurse, nurse practitioners have some prescribing rights, are able to order context-specific pathology and radiology tests, and are able to make limited referrals. The accountability associated with this position adds another complex dimension to nurses' interdependent and independent roles in patient advocacy. It is important to note that nurse practitioners are expert nurses who are not meant to act as a substitute for medical practitioners.

Various models of practice have been researched and subsequently advocated as suitable areas of work for nurse practitioners. These include women's health, primary health, emergency psychiatric liaison, wound care, neonatal nursing, perioperative nursing, intensive-care nursing, emergency nursing, family planning and sexual health. It is readily apparent that the nurse practitioner role varies in different contexts and that nurses in these roles require appropriate education in broad and context-specific aspects of their responsibilities. In 1996, the Royal College of Nursing first agreed on appropriate educational preparation for the role, and this has recently been reviewed. The nurse should undertake a specific course of study to at least honours degree level, and components of study should include core areas such as applied pharmacology and evidence-based prescribing as well as specific elements that capture the context in which the nurse practitioner operates.

NURSING RESEARCH

Research plays an important role in assisting nurses to establish a professional practice base in the area of pharmacology. An ultimate goal of nursing is to improve a nurse's practice so that all aspects relating to medication management are conducted using a high standard of care. A nurse's obligation towards research pertains to the areas of professionalism, accountability and social relevance of nursing practice. These areas are discussed in relation to clinical research on drug administration.

Nursing is currently seeking to maintain a professional base that is differentiated from other professions. As health-care professionals who have ongoing and often uninterrupted contact with patients, nurses are ultimately responsible for the delivery of drugs and the assessment of their effects. Medical research focuses on the scientific experimentation of drug protocols and regimens to determine those most effective for patient use. Medical scientists often call on nurses to assist in organising data entry on to computers, obtaining blood samples for drug analysis, and recruiting suitable participants for drug trials. Nurses should not accept this involvement with medical research as indicating a fulfilment of their own responsibilities for research in drug therapy. Relevant issues for nursing research on medications may include nurses' and patients'

knowledge about medications; the use of teaching and learning strategies in an effort to improve this knowledge; the effects of nurses' and patients' cultural, religious and value systems on patient adherence; and the legal and ethical issues confronting drug therapy. Another important aspect of nursing research involves nurses' ability to assess the need for medication and to evaluate clinical outcomes. Thus, nurses must recognise the need to extend their knowledge base and endorse investigations from a nursing perspective as a means of developing and further broadening their unique knowledge base.

Nursing research also facilitates professional accountability with drug therapy. This issue is of relevance when considering the nurse teacher's role in dealing with students and the clinical nurse's role in interacting with doctors in health-care agencies. Professional accountability further warrants nurses to use their research findings on drug therapy and to evaluate the confidence placed in these findings.

Nurses need to document their role carefully in the provision of medication therapy to determine the social relevance of nursing in health-care delivery. As consumers recognise that health care is a right rather than a privilege, nurses must evaluate carefully their quality of care in drug administration and abandon practices found to be ineffective and unsafe. Nursing research facilitates this process.

SUMMARY

- Nurses have a dynamic, responsible and active role in medication management.
- Patient concordance relates to adherence to a prescribed medication regimen, including dosage, method of administration, frequency, specific recommendations and precautions for the drug.
- The nurse plays an important educational role in the assessment, planning, implementation and evaluation of medication use.
- In their role as advocates, nurses inform patients about their rights in a particular situation, making sure they have all the necessary information to make informed decisions.
- A nurse practitioner is a registered nurse in an advanced clinical role who has developed expert clinical skills, knowledge and experience in a specific area of clinical practice.
- An ultimate goal of nursing research is to improve nurses' practice so that medication management is conducted using a high standard of patient care.

THE ROLES AND RESPONSIBILITIES OF OTHER HEALTH-CARE PROFESSIONALS

6

CHAPTER SIX

OBJECTIVES

After completing this chapter, the reader should be able to:

- **describe the roles of the prescriber, pharmacist, physiotherapist, radiographer, podiatrist, dietician, paramedic and naturopath in relation to drug therapy;**
- **determine which health-care professionals are able to perform the following duties: dispense medications, prescribe medications and administer medications;**
- **describe ways in which the roles of these health-care professionals are changing in relation to drug therapy.**

KEY TERMS

Prescriber
Pharmacist
Physiotherapist
Podiatrist
Dietician
Paramedic
Radiographer
Naturopath

ALTHOUGH THE NURSE USUALLY ASSUMES RESPONSIBILITY for administering medications, there are several other health-care professionals who have important direct and indirect roles to play in the supply, distribution, prescription and administration of medications to patients. This chapter examines the roles of the prescriber, pharmacist, physiotherapist, radiographer, podiatrist, dietician and paramedic in drug therapy and how these roles intertwine with those performed by the nurse.

THE PRESCRIBER

According to drug legislation, the prescriber may be a medical practitioner, dentist or veterinary surgeon, depending on the working environment. As nurses tend to associate with medical practitioners (doctors) in the health-care setting, the term 'prescriber' will relate to this particular group. The medical practitioner is responsible for the diagnosis of illness and disease, and the initiation of therapy. According to legislation, doctors are authorised to have in their possession, use, sell and supply any drug, as long as this occurs within the lawful practice of their profession. With some exceptions, a prescription or drug order can be written only by a medical practitioner (see Chapter 3). The prescription must include the route, dose and frequency of administration. If the order or prescription is unclear or ambiguous, then the doctor must be contacted to obtain clear instructions. In an emergency situation, however, the doctor may verbally direct a registered nurse to administer a drug to a patient. The doctor should then document this order on the patient's drug chart within 24 hours. Doctors also play an important role in educating patients about their drug therapy in the community and hospital contexts. As prescribers of drug therapy, doctors can provide patients with the reasons for choosing one particular medication over another. Doctors also determine the therapeutic and adverse effects of drug therapy on the patient's medical condition and are responsible for any changes to the drug regimen. As nurses are present at the patient's bedside more often than any other health-care professional, doctors rely quite heavily on the assessment skills of nurses as a means of evaluating the effectiveness of the drug regimen.

Some medical courses are incorporating non-drug therapies in their syllabus along with clinical pharmacology. With the importance of non-drug therapies advocated by other health-care professionals (e.g. massage, therapeutic touch, relaxation), the goal is for less emphasis to be placed on the medicalisation of a patient's health problems.

Nurse prescribing in the UK began with an Act of Parliament in 1992 entitled Medicinal Products: Prescription by Nurses. The legislation permitted district nurses and health visitors to undertake a prescribing course in a higher education institute and to prescribe products from the *Nurse Prescribers' Formulary* (NPF). This contained 13 POMs, some pharmacy and general sales list medicines, and a list of dressings and appliances relevant to community nursing. Nurses needed to register their qualification with the Nursing and Midwifery Council before they could start prescribing.

As nurse prescribing progressed, the *Nurse Prescribers' Extended Formulary* (NPEF) for independent prescribing by nurses was published. This listed the specific medical conditions for which nurses could prescribe and the medicines they could prescribe. It covered more than 80 medical conditions and about 180 POMs. All first-level nurses and registered midwives could legally train to prescribe from the NPEF but needed 3 years post-registration experience. From 1 May 2006, the NPEF was discontinued and qualified nurse independent prescribers (formerly known as extended formulary nurse prescribers) can now prescribe any licensed medication for any medical condition within their competence, including some controlled drugs. Additional training needs are addressed through continued professional development.

From 1 May 2006, a new category of prescriber – the pharamacist independent prescriber – was created. They too, once qualified, can prescribe any medicine for any medical condition within their competence, with the exception of controlled drugs.

Supplementary prescribing was introduced in April 2003. The supplementary prescriber works in partnership with the independent prescriber (doctor) to implement an agreed patient specific clinical management plan (CMP) with the patient's agreement. Nurses and pharmacists may train to be supplementary prescribers. There is no formulary and no restrictions on medical conditions that can be managed. Supplementary prescribing is being extended to other allied health professions (AHPs), including physiotherapists, radiographers, podiatrists and optometrists.

THE PHARMACIST

The pharmacist is responsible for a number of duties, including the supply and distribution of drugs, counselling patients, educating health-care professionals in all facets of drug use, and the preparation of medications.

One of the most important roles of the pharmacist is the supply and distribution of medicines. Supply and distribution involve the all-encompassing term of dispensing. Dispensing a drug means making it available from the central supply area of the pharmacy to patients and health-care professionals.

The role of pharmacists in dispensing differs depending on their area of employment. If employed within a community pharmacy, pharmacists supply medications to the general public. The community pharmacist keeps a record of the prescription drugs supplied to the public and retains these records for a period of time, according to legislation. Legislation also requires that community pharmacists keep drugs secure. Prescription drugs are stored in the dispensary area, where the pharmacist carries out the task of supplying medications. The pharmacist personally supervises the dispensary area, ensuring that it is restricted to pharmacy employees only. The dispensary is separated from the rest of the premises, and access is not allowed to the general public.

A hospital pharmacist is responsible for the issuing of drugs to health-care professionals who are authorised to

possess medications, and to patients. In this instance, the whole pharmacy department is out of bounds to all individuals except pharmacists.

Under normal circumstances, community pharmacists are unable to supply drugs requiring a prescription if one has not been presented, although pharmacists can now train to be supplementary prescribers (see above).

Hospital pharmacists are also responsible for checking and supplying imprest stocks of drugs. Imprest stocks of drugs are stored in wards as a matter of convenience. If these are prescription medications, they are not administered until the doctor writes a drug order. Imprest drugs, which are kept in a locked cupboard, include drugs given by different routes of administration and those that are commonly administered in the ward. Oral medications for patients are also checked and restocked. These are usually placed in a locked mobile drug trolley for easy access. Alternatively, oral drugs may be placed in a locked drawer at the patient's bedside. Parenteral therapy, which is usually placed in a locked cupboard near the central ward station, is also checked and restocked. The hospital pharmacist also supplies drugs on receipt of a written requisition form from the nurse in charge of the shift. The nurse in charge over a weekend often completes these requisitions on weekend shifts to tide patients over to the following week.

Hospital pharmacists have the further responsibility of supplying controlled drugs to the wards. Most controlled drugs are ordered from the hospital pharmacy by a written requisition from the nurse in charge. On supply to the ward, the pharmacist and a senior nurse will sign the requisition form and the balance in the administration book, indicating the stock on hand initially and the quantity of drug supplied. To move controlled drugs from the pharmacy department to the ward, the pharmacist places them in a locked container and transports them to their destination. The container remains locked until the counting procedure is ready to begin between the pharmacist and the nurse.

Pharmacists also prepare a variety of medicinal products. These items include ointments; creams; powders; ear, nose and eye drops; lotions; mixtures; pessaries; suppositories; gels; antiseptic solutions; and syrups. Standard formulae (or recipes) used to prepare these items are located in literature such as the *British Pharmacopoeia* (BP) and the *British Pharmaceutical Codex* (BPC). As these formularies are legal standards, it is obligatory for the pharmacist to make a preparation conforming with these standards. Hospital pharmacists also prepare intravenous infusions with additives. Total parenteral nutrition (see Chapter 64), which involves the incorporation of a number of amino acids, vitamins, electrolytes and trace elements in a highly concentrated glucose solution, is made up in hospital pharmacy departments under laminar flow cabinets. The incorporation of cytotoxics, antibiotics and narcotics in intravenous fluids is also commonly done in hospital pharmacy departments.

One of the most important tasks of the pharmacist is to ensure that medicines are taken or administered in a manner promoting the therapeutic efficacy (see Chapter 16) of the drug. In a community pharmacy and the outpatient area of a hospital pharmacy, the pharmacist performs an important counselling role with patients. Studies have indicated that patients often do not retain much of the information provided by a general practitioner during the medical consultation. Furthermore, this retention rate drops in proportion to the time spent with the doctor. Although the community pharmacist may counsel verbally, information is reinforced by attaching written instructions to the primary container of the medicine. These written instructions serve two major functions. First, they warn against undesirable effects, including interactions with other drugs and foods. An example of this function includes the reduced activity of tetracyclines if given with milk, antacids or preparations containing iron. Second, these written instructions are advisory, in that they help improve the drug's efficacy. Examples of this function include the administration of a whole course of antibiotics to ensure that an infection is treated adequately, and the administration of gastric irritants such as **theophylline** and **ferrous sulphate** immediately after food.

In the ward setting, the pharmacist acts as a specialist consultant, attending to the needs of doctors, clinical nurses and allied health-care professionals on a variety of aspects relating to drug use. For this reason, pharmacists attend ward rounds and team meetings to familiarise themselves with patients' medical conditions and how these impinge on drug therapy.

With drug technology becoming more complex, it may be anticipated that drug information centres located within hospital pharmacy departments will play a more important and focal role in the dissemination of information to health-care professionals. In the community sector, with the movement of items formerly available only on prescription to non-prescribed schedules, there exists the opportunity for pharmacists to be more active in the management of common health problems and the promotion of personal communication with patients. Some pharmacists now have consultation rooms in their pharmacies and are helping to lessen the burden on general practitioners by offering advice to patients with minor ailments.

Pharmacists are also involved in producing comprehensive medication regimen reviews for individuals in residential aged-care facilities and in the home. The target group for a medication review are those individuals who are at risk of medication misuse due to age, social circumstances, complexity of their medication regimen, health-care status and knowledge about their medications. In conducting these reviews, pharmacists work in collaboration with an individual's local medical officer to collate and evaluate medication information. Reviews draw on information

relating to all aspects of care for a particular individual. Some sources of information include the progress or case notes, treatment plans, laboratory tests, and nurses and other health-care professionals who provide services within the aged-care facility. Pharmacists and doctors work together to make recommendations concerning medication-related problems. They also document outcomes arising from these recommendations.

Professional and educational bodies of pharmacy have been instrumental in developing a framework that pharmacists can use in their interactions with patients. This framework is termed the pharmaceutical care process. The basic components of the framework are similar to the clinical decision-making process discussed in Chapter 8, which contains the following components: interviewing the patient, assessing drug therapy, formulating a plan, implementing the plan, and evaluating patient outcomes. One of the major reasons for the creation of this framework is that major professional and education bodies were concerned that the pharmacist's role in the future should place greater emphasis on the particular needs of patients. As a growing number of retail outlets and groups of health professionals obtained approval for the supply or dispensing of medications, it was considered important that pharmacists re-establish their position in tending to patients' needs in medication therapy. According to the UK Clinical Pharmacy Association (UKCPA), pharmacists are evolving into patient-focused health-care providers. As mentioned above, pharmacists can now train to be independent prescribers.

THE PHYSIOTHERAPIST

Physiotherapists assess and treat patients with a temporary or permanent physical disability, with the aim of achieving the highest degree of recovery. Treatment modalities include exercise, mobilisation and manipulation, massage, splinting, the application of hot and cold compresses, and electrical stimulation. Conditions treated include birth deformities, fractures, back strain, arthritis, spinal injuries, strokes and multiple sclerosis. Rehabilitation for preoperative and postoperative surgery, such as open-heart, orthopaedic and abdominal surgery, is also an area of responsibility. Physiotherapists work in hospitals, private practice, rehabilitation centres, community health centres, sports medicine clinics, psychiatric hospitals, maternity hospitals and industrial clinics.

Physiotherapists play an important role in drug therapy. In many cases, for treatment modalities to be thoroughly effective, medications need to be administered for prophylactic and therapeutic reasons. For example, an asthmatic patient who is undertaking coughing and deep-breathing exercises under the supervision of a physiotherapist will benefit more from therapy if bronchodilators and corticosteroids are administered beforehand. Bronchodilators promote widening of constricted airways, while corticosteroids reduce the inflammation, thus improving lung expansion, the ability to cough up mucus and ultimately gas exchange. Similarly, open-heart, orthopaedic and abdominal surgery involve aggressive manipulation of bone and tissues, leading to intense pain in the immediate postoperative period. In this instance, the physiotherapist often requires pain relief to be administered before physical modalities can be implemented successfully. Patients with open-heart sternotomy wounds are unlikely to comply with coughing and deep-breathing exercises if they have not received narcotic analgesia beforehand. Female patients who have had a caesarian section for the birthing process may need analgesic therapy before undertaking ambulatory activities. Cooperation with other health-care professionals is obviously essential to the success of therapeutic regimens of patients.

Physiotherapists play a vital role in the implementation of physical treatment modalities that the community views as important strategies for recovery. Meanwhile, with greater emphasis on non-drug therapies in the acute hospital setting, it is hoped that these will become established as integral modes rather than adjuncts to recovery.

THE PODIATRIST

The podiatrist is involved with the prevention, diagnosis and treatment of foot disorders. These disorders may arise as a result of endocrine disease (e.g. diabetic neuropathy), biomechanical abnormalities (e.g. flat feet), arthritis, neuromotor disease (e.g. multiple sclerosis), vascular disease or skin conditions. Podiatrists work in hospitals, community health centres, private practice and as part of general medical practices.

Podiatrists use a range of skills, including surgical procedures, physical therapy and the manufacture of orthoses (foot supports). In implementing these skills, podiatrists are permitted to have in their possession and administer local anaesthetics and topical preparations. For instance, podiatrists commonly administer **lidocaine** intradermally or as a nerve block for a surgical procedure. Antiseptic lotions and antifungal creams are often used for skin disorders.

Podiatrists play an important role in educating patients about the correct use of drug therapy in relation to how medications affect foot conditions. For example, a podiatrist would inform patients with insulin-dependent diabetes that they must comply with their **insulin** therapy, otherwise they are more predisposed to leg ulcers and decreased circulation of the lower extremities. Podiatrists are in an ideal position to explain how non-concordance will create a deterioration in the status of foot disorders. In collaboration with doctors, podiatrists may also assist in deciding the proper course of drug therapy for foot disorders. For example, if a patient has a foot infection, the podiatrist can evaluate the effect of a particular antibiotic or

antiseptic on the infection and advise the doctor whether a change in therapy is warranted. In the UK, it has been recommended that supplementary prescribing be extended to registered podiatrists.

THE DIETICIAN

The dietician (or nutritionist) possesses detailed knowledge of the principles of nutrition as they apply to health and disease states; the biochemical properties of food; the theory underlying food absorption, metabolism, digestion and elimination; and the indications for nutritional support. Dieticians work mainly in general hospitals, psychiatric hospitals and community health centres.

Although dieticians are not directly or legally involved with drug administration, they play an important role in the decision to introduce parenteral or enteral feeding and other forms of nutrient supplementation for a patient. Patients are susceptible to malnutrition in hospital while undergoing medical and surgical treatment, and disease states may alter the digestive process of nutrients. In collaboration with doctors, dieticians determine the requirements for energy, protein, vitamins, minerals, essential fatty acids, electrolytes and water. Enteral feeds are made in a diet kitchen within a hospital, the process of which is supervised by the dietician. Hospital pharmacists prepare parenteral nutrition using a sterile laminar flow environment.

It is important that dieticians continue to monitor the effects of hospitalisation and illness on the nutritional needs of patients. With greater participation of dieticians in teams of health-care professionals, this process should be readily facilitated.

THE PARAMEDIC

Paramedics attend to the general public in medical emergency situations and promptly transport these individuals to the nearest hospital. There are usually two levels of ambulance officers: the ambulance technician and the paramedic. Both are permitted to administer medications for chronic and potentially life-threatening conditions such as asthma and angina, but the paramedic is trained to administer a wider range of emergency drugs than the technician. Paramedics follow strict patient protocols to ensure accurate and prompt assessment and treatment. In some ambulance trusts, paramedics can thrombolyse patients following diagnosis of acute myocardial infarction on a 12-lead electrocardiograph (ECG). They also carry defibrillator monitors for use in life-threatening cardiac dysrhythmias, which may lead to cardiac arrest, respiratory arrest or unconsciousness. Some of the tasks performed by paramedics include the insertion of intravenous lines, the insertion of chest drains for tension pneumothorax, and intubation (the insertion of a breathing tube through the nose or mouth into the trachea).

On arriving at the emergency scene, paramedics stabilise the patient's condition and prevent any further deterioration in health status. Consideration is given primarily to maintaining the patient's airway, breathing and circulation, as these factors are imperative to the patient's survival. For example, if the patient sustains a life-threatening cardiac dysrhythmia, such as ventricular fibrillation or ventricular tachycardia, then the paramedic will administer treatment that will prevent a compromised circulatory or respiratory status. If the patient experiences a non-life-threatening dysrhythmia, the paramedic is less likely to treat the condition unless clinical manifestations occur that compromise the patient's health status.

Paramedics play an important role in collaborating with doctors and nurses in the hospital setting. They provide detailed assessment of the patient's condition before admission to hospital, the therapeutic effects observed from the drug regimen and medical procedures administered to the patient. Furthermore, the patient's therapeutic regimen before hospital admission often has a bearing on the therapeutic regimen used in hospital.

THE NATUROPATH

Naturopaths treat medical conditions and implement preventive health measures by using nutrition, homeopathy, herbalism, iridology and other natural therapies. Naturopathy is a way of maintaining health and of helping in the removal of disease by stimulating the body to repair itself without the use of conventional medications and surgery. Naturopaths tend to work in private practice, either alone or in association with other health-care professionals, such as medical practitioners, osteopaths, chiropractors and physiotherapists. Some naturopaths work in large pharmacies, where they provide advice about therapies other than the traditional pharmaceutical formulations usually available in pharmacies.

Naturopaths perform many roles that support the individual's wellbeing. They examine the overall health of individuals and assess the foods they eat. Based on this information, they suggest specific diets, foods, minerals and vitamins to help improve general health. They may recommend and dispense concentrated strengthened doses of substances made from herbal, mineral or animal sources (see Chapter 65). Naturopaths also examine the individual's iris (the coloured part of the eye) to diagnose and treat illnesses in various locations of the body.

Homeopathic and naturopathic preparations can produce profound interactions with more conventional therapies. These preparations can produce desired and unwanted effects, as do conventional therapies. Naturopaths thus have an important role to play in interdisciplinary collaboration, with the aim of providing optimal medication management for patients.

SUMMARY

- According to drug legislation, the prescriber is usually a medical practitioner, dentist or veterinary surgeon.
- Nurses and pharmacists can now train to become independent prescribers.
- The pharmacist is responsible for the supply and distribution of medications, counselling patients, educating health-care professionals, and the preparation of medications.
- Physiotherapists play an important role in medication therapy because, in order for their treatment modalities to be effective, medications need to be administered.
- Podiatrists undertake a range of skills, including surgical procedures, physical therapy and the manufacture of orthoses. They administer local anaesthetics and topical preparations in performing these skills.
- Paramedics administer medications for chronic and potentially life-threatening conditions and also carry defibrillator monitors.
- Naturopaths recommend and dispense concentrated strengthened doses of substances made from herbal, mineral or animal sources.

CASE STUDY II.1

Ms RK was a 68-year-old woman who was admitted to the intensive care unit following a diagnosis of pancreatic cancer. She had a very supportive family network, and before her hospitalisation she was actively involved with several community organisations. After admission to the intensive care unit, she received intravenous medications for cardiac support and was connected to a ventilator. Over a 10-day period, her condition deteriorated progressively to the point where she lost consciousness and required excessively high doses of cardiac medications to sustain normal circulation. The doctor and primary nurse for the patient organised a family meeting to discuss Ms RK's grim prognosis and deteriorating condition. After a prolonged discussion, the family members decided that they did not want Ms RK to continue to suffer unnecessarily and requested that all cardiac medications and ventilatory support be withdrawn.

Over the next 24 hours, the primary nurse began to wind down Ms RK's cardiac medications and ventilatory support. She also provided Ms RK with adequate levels of pain relief and sedation to increase her level of comfort. The next day, the doctor arrived in the unit and informed the nurse that he wanted Ms RK to have a computed tomography (CT) scan to determine the possible reason for her sudden deterioration. He also requested all cardiac medications and ventilatory support to be increased to previous levels. When the nurse protested that this decision went against what was decided at the family meeting, the doctor replied: 'We need to find out what caused her sudden deterioration. Her family has the right to know that. We should also try and give her one last chance. I will explain it to them when they come in.' The primary nurse sighed with frustration and called on the nurse manager to discuss the situation.

QUESTIONS

1 *Did the doctor provide the family with an informed and valid consent for his actions? Explain.*

2 *The doctor indicated that he wanted to provide detailed information to the family about Ms RK's deteriorating condition. What ethical principle does this action uphold?*

3 *Explain how ethical principles may have conflicted with each other in Ms RK's situation.*

CASE STUDY II.2

Mr JB is a 28-year-old Italian man who recently migrated from Italy. He is married, with a 2-year-old child, and has only a minimal command of English. Over a 3-week period, Mr JB experienced symptoms of lethargy, polyuria, polydipsia and polyphagia, with increasing loss of weight. His wife recommended that he should see the doctor to determine the problem. Mr JB was diagnosed with insulin-dependent diabetes, which was confirmed by blood glucose levels and urinalysis. His doctor explained the condition and organised for Mr JB's admission to the nearest public hospital for stabilisation of the diabetes. The team of health-care professionals at the hospital arranged group sessions for Mr JB, where instruction was given on insulin administration, diet control and glucose assessment. Unfortunately, no one at these group sessions was Italian, but the health-care professionals believed Mr JB understood what was expected. After 2 weeks, he was discharged with the services of a district nurse.

On her fourth visit, the district nurse found Mr JB lying down on the couch, breathing quite rapidly. On further examination, he was nauseated and very weak, with acetone-smelling breath. A blood glucose test found him to be extremely hyperglycaemic, warranting hospital admission.

In hospital, an Italian nurse who was looking after Mr JB informed the health-care team that he had developed a cold soon after his initial discharge. His wife, Ms CB, put him to bed and gave him plenty of sweetened lemon drinks to promote recovery. Mr JB and Ms CB did not believe the insulin injections were required during this time. Mr JB also explained to the Italian nurse that he did not really understand his condition, but he did not want to upset people or take up their time by asking a lot of questions.

QUESTIONS

1 *Did Mr JB have informed and valid consent for the insulin therapy required for his condition? Provide reasons to support your answer.*

2 *What are the barriers impeding Mr JB's understanding of his diabetes?*

3 *What hospital and community resources could the nurse use to assist in promoting Mr JB's understanding of his diabetes?*

4 *What specific teaching and learning strategies could the nurse effectively employ in this situation?*

CASE STUDY II.3

Nurse GK is the primary nurse allocated to care for Mr MJ, a 51-year-old man who had abdominal surgery 3 days ago. Mr MJ had been on intravenous morphine for pain, but this order was ceased by the doctor. During the ward round, Nurse GK asks the doctor whether Mr MJ could have a morphine order written up as he is beginning to experience quite severe incisional pain. 'Yes, that's fine', replies the doctor. 'Just give him 5 mg morphine through his IV drip and I'll write it up later', he adds. Wanting to give the morphine straight away, Nurse GK seeks out Nurse AB, to assist in the checking procedure of the morphine from the locked cupboard. 'I'm just a bit busy at the moment. Just check it out from the cupboard yourself and I'll verify the amount after you've finished. I'll only be a few minutes', comments Nurse AB.

Nurse GK obtains the keys for the locked cupboard from a hook on a nearby ledge. She checks out one ampoule containing 10 mg morphine and documents the procedure in the drugs register. She signs her name in the register to verify that the procedure has taken place. She carefully locks the cupboard and places the key back on the hook. Within a few minutes, Nurse AB arrives to check that the number of morphine ampoules on the register corresponds with the number in the cupboard and countersigns her name on the register. She then walks to the medication equipment trolley, where she finds Nurse GK assembling the syringe and needle and drawing up the required amount of morphine. 'I've countersigned the drug register', she states, before walking away. 'Thanks, that's great', replies Nurse GK, as she continues with the task. As the ampoule contains 10 mg/ml morphine, she draws up 0.5 ml and proceeds to Mr MJ's bedside. Nurse GK checks Mr MJ's identification label with the label on the treatment chart, before administering the morphine through the intravenous line. She discards the used needle and syringe in the sharps container but decides to keep the 5 mg morphine remaining in the ampoule by the bedside. She reasons that if Mr MJ is in pain again within a few hours, she will be able to administer the remaining contents of the ampoule. There is just no point in wasting it.

QUESTIONS

1. *From a legal perspective, of prescribing, checking and administering morphine, detail the tasks that were performed incorrectly.*
2. *Explain how you would perform these tasks if you were put in Nurse GK's situation. Provide the rationale for your answer.*
3. *To which drug group does morphine belong? Why should it be stored in a locked cupboard?*
4. *To which schedule does morphine belong? What regulations and characteristics are associated with this schedule? State the names of three other drugs that belong to this schedule.*
5. *From an ethical perspective, state which principles have not been followed in this situation. Explain your answer.*

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WEB RESOURCES

Chartered Society of Physiotherapy www.csp.org.uk

Department of Health – full guidance for Independent Nurse and Pharmacist Prescribing www.dh.gov.uk

Medicines and Healthcare Products Regulatory Agency www.mhra.gov.uk

National Prescribing Centre www.npc.co.uk

NHS Modernisation Agency www.modern.nhs.uk

Nurse Prescribing www.nurse-prescriber.co.uk

Nursing and Midwifery Council www.nmc-uk.org

Patient Group Directions (PGDs) www.pgd.nhs.uk

Patient UK www.patient.co.uk

PRODIGY Patient Information Leaflets www.prodigy.nhs.uk

UK Clinical Pharmacy Association www.ukcpa.org

DRUG ADMINISTRATION AND PROFESSIONAL RESPONSIBILITIES

All drugs are poisons – what matters is the dose.

PARCELSUS (1493–1541)

Health-care professionals play an enormous role in medication management to ensure patients' safety. All substances, including synthetic drugs, vitamins, minerals, natural herbs and food, have beneficial or adverse effects on the body and can interact with other substances. While Parcelsus advocated the importance of the correct dose, other aspects of medication administration are important, such as the time, the individual, the route of administration and the medication itself.

This section, which covers medication management responsibilities applicable to any medication and clinical situation, is divided into five chapters. Chapter 7 addresses drug formulations, routes of administration and storage conditions. Chapter 8 focuses on the clinical decision-making process, which incorporates assessment, diagnosis, planning, implementation and evaluation. Chapter 9 looks at common examples of drug administration strategies and documentation processes, while Chapter 10 examines how to avoid making medication errors. Finally, Chapter 11 gives an overview of common adverse drug reactions, the types of medication that cause these reactions and strategies to deal with such reactions.

III

DRUG FORMULATIONS, STORAGE AND ROUTES OF ADMINISTRATION

7

CHAPTER SEVEN

KEY TERMS

Tablet
Capsule
Enteric-coated preparation
Sustained-release preparation
Intranasal administration
Topical preparation
Transdermal administration
Rectal administration
Vaginal administration
Parenteral administration
Storage of medication

OBJECTIVES

After completing this chapter, the reader should be able to:

- **describe the basis for the formulation of common dosage forms of drugs;**
- **explain all the common routes by which drugs can be administered;**
- **give the reasons for the use of each of these routes;**
- **list the advantages and disadvantages of each route;**
- **understand the storage conditions required for particular drugs.**

PHARMACEUTICS IS THE BRANCH OF PHARMACY THAT DEALS with the formulation of drugs. The people who prescribe and administer drugs may not need the following information on a day-to-day basis; however, it is useful to know something about some of the terms that pharmaceutical manufacturers use to describe their products.

TABLETS

Solids are usually administered in tablet form, sometimes described erroneously as pills. Note that the word 'pill' means a round or ovoid body, usually coated with sugar or even silver or gold paint. (There was a drug once used in the UK for male potency problems that looked like the gold balls used for decorating cakes.) Pills are, in fact, rarely manufactured today. A tablet is a disc containing one or more medications, prepared by compressing a granulated powder in the die of a suitable machine. As most drugs are administered in very small quantities, sometimes less than a milligram, other materials must be added to make them easy to handle and, in extreme cases, allow them to be seen. This problem is overcome by incorporating the appropriate amount of an inert filler. Tablets have to disintegrate in the gastrointestinal tract; to make this easier, a substance such as starch, which swells when in contact with fluids, is incorporated. These substances are termed excipients. The other two substances incorporated in tablets are a binding agent to help keep the tablet whole in the container and a lubricating material to help prevent the ingredients from sticking to the manufacturing machinery.

Tablets may be sugar-coated or film-coated to disguise bad-tasting drugs. Some drugs that are unstable in solution can be administered as chewable tablets to patients who have difficulty in swallowing, and various flavourings can be added to disguise the taste of the drug. When chewable tablets are sugar-coated, they are called dragees – a name used for the coloured balls used as cake decorations. **Nicotine** is even available in a chewing-gum formulation.

ENTERIC-COATED PREPARATIONS

Sometimes tablets are formulated so that disintegration takes place in the intestines rather than in the stomach. These tablets are coated with a material that disintegrates not in the acidic conditions of the stomach but in the alkaline conditions of the intestine. These tablets are known as enteric-coated preparations. This may be abbreviated as EC on the drug container. With patients who have difficulty in swallowing tablets, it is imperative that such tablets are not crushed to enable easier swallowing. Many enteric-coated preparations now come in a form in which small portions of drug are enteric-coated into tiny balls and enclosed in a capsule (see below). These capsules may be opened and the contents sprinkled on some suitable medium for swallowing.

CAPSULES

Capsules come in two main forms, hard and soft gelatine types. Hard gelatine capsules contain the drug as a solid. In soft gelatine capsules, the drug is in a non-aqueous solution. If the drug is a liquid, such as the oily form of vitamin E, it may be dissolved in another oil, usually soybean oil.

Hard capsules have an advantage over tablets in that they can be opened up and the powdered contents sprinkled on jam or honey; tablets need to be crushed, sometimes with difficulty. Capsules can come in many colours, which may make identification easier. This method of identification should not always be relied on, as mistakes are easily made, but in cases of overdose emergencies it may be useful in determining how to treat the patient. The barbiturate drugs **pentobarbitone** and **amylobarbitone** were once compounded in a preparation called Tuinal. The capsule had three colours and a memorable psychedelic appearance.

Soft gelatine capsules are completely sealed and contain a drug in liquid or semiliquid form. They are useful not only for liquid drugs but also for drugs that are not dissolved easily in water. In the latter case, the drug can be dissolved in a relatively non-toxic solvent such as propylene glycol, thus enabling the drug to be absorbed more rapidly from the gastrointestinal tract. Drug addicts have abused some preparations prepared in this way; for example, the liquid-filled capsule of the hypnotic **temazepam** has had its liquid aspirated with a needle and then injected. This practice is exceedingly dangerous. Occasionally these liquid-filled capsules are useful if fast action is required. It is not unusual for **nifedipine** capsules (which are used in angina and hypertension) to be pricked and the contents dropped on to the tongue in the case of an acute attack of angina.

Many people prefer capsules over tablets as the former are good for camouflaging bad-tasting drugs; otherwise, capsules offer no other real advantages over tablets. The name 'caplet' has been coined to describe a capsule-shaped tablet coated with a gelatine-like material. Recently, vegetable-based capsule shells have been produced without the use of the animal-derived gelatine as an ingredient.

SUSTAINED-RELEASE PREPARATIONS

With drugs that have a short half-life in the body, it is sometimes convenient to formulate the drug in such a way that it is released slowly into the gastrointestinal tract. These preparations are termed sustained-release, slow-release or retard forms. Many drugs are formulated in this way as it increases patient compliance – it is easier to remember to take a drug once or twice a day rather than three or four times a day. There are various ways in which slow release can be brought about. The active drug can be embedded in a matrix of relatively inert material, which disintegrates gradually in the gut, thus releasing the drug slowly. The drug can be prepared in a layered tablet, with layers of drug enclosed in successive layers of inert coating. As one layer of coating disintegrates, some drug is

released and no further amount is released until the next inert layer is dissolved. Sometimes the drug is coated with an inert substance to produce many pellets, each pellet having a different thickness of coating. The thinner coating dissolves quickly to enable a rapid release of the drug, while the thicker coatings allow the release of the drug at a later stage. These pellets can be presented as capsules, sometimes termed spansules, or compressed into tablets, sometimes called durules. At least one drug is presented bound to a resin and is then released slowly from the resin in the basic surroundings of the small intestine but not in the acidity of the stomach.

A more recent development in sustained-release preparations has been the controlled-release tablet. With sustained-release preparations, there can be considerable variation in the disintegration, solubilisation or emulsification and absorption of the tablet or capsulated pellets. This could be due to various factors, such as rate of transit through the gastrointestinal tract. In addition, individual variations in the composition of the gastrointestinal fluids (e.g. pH differences, types of food consumed) can affect the rate of dissolution of the coatings protecting the drug. The use of a controlled-release tablet attempts to overcome this problem by a novel and ingenious method. The active drug is coated by a semipermeable membrane through which a 'hole' is made using a laser. When the tablet is ingested, water flows through the semipermeable membrane by an osmotic process, thus increasing the pressure inside the tablet and forcing the contents out through the 'hole'. As the 'hole' is minute, this process takes a considerable time, and the drug is released slowly into the lumen of the gut. This release is more or less constant between individuals because it is not pH-dependent and the presence of solutes in the gut fluids has minimal effects on this process. At the time of writing, only one drug is available using this delivery technique; this is nifedipine under the trade name of Adalat Oros™, an antihypertensive drug (see Chapter 44). As this type of preparation is patented by one company, it may be some time before other drugs are formulated in this way. The semipermeable membrane remains unscathed in its passage through the gut and it therefore appears in the faeces as tablet ghosts; patients should be told of this. There are other pharmaceutical formulations that have been developed to enable slow absorption of a drug, but their description is beyond the scope of this text. Sustained-release formulations may be identifiable by the abbreviations CR or SR on the drug container. (See Chapter 20 for more information about formulation abbreviations.)

ORAL LIQUID PREPARATIONS

Many patients, especially children, find the swallowing of tablets difficult; for these people, pharmacists have formulated many drugs in liquid form. These preparations are usually made according to the characteristics of the drug concerned. Flavourings, varying from raspberry to the more exotic tastes of coconut and passionfruit, are usually added to such preparations to make them more palatable. It is better not to make the taste too attractive in order not to encourage children to treat medicines as overtly pleasant. Sugar can be added to liquid preparations to form syrups, which enhance palatability, but it is common today to use sugar alcohols, such as sorbitol, as sweetening agents. Sorbitol has a lower calorific value than sucrose and is therefore more suitable for diabetics, while also helping to prevent dental caries. Another advantage of sorbitol use in syrups is that, taken in excess, it can act as an osmotic laxative and will discourage drug abuse of potentially addictive preparations, such as codeine syrups. Saccharin or cyclamates can be used to make liquids completely free of calories.

A *linctus* is a syrup formulated specifically for coughs.

In cases where the drug is insufficiently soluble in water, alcoholic solutions may be prepared. Such preparations are termed *elixirs*. Tinctures, like elixirs, contain alcohol but are more concentrated. Most tinctures, such as tincture of **iodine**, are used mainly for topical treatment.

In cases where relatively insoluble drugs are used without alcohol and the drug is a solid, the resulting preparation is termed a *suspension*; if the drug is a liquid, the term *emulsion* is used. Even with the addition of stabilisers, these preparations have the tendency to separate into two or more layers. Therefore, thorough mixing before administration of such preparations is essential, as with all liquid medicines, because even in homogeneous mixtures there may be a gradation in concentration due to the liquid being stored undisturbed for prolonged periods.

Some drugs, such as **penicillin**, are relatively unstable in solution and are prepared as desiccated powders, water being added to the powder before use. Even after reconstitution, the resulting suspensions usually need refrigeration until the course is finished, the shelf life being only a fortnight.

Tables 7.1 and 7.2 provide information about medications administered by the oral and nasogastric routes, respectively.

TOPICAL PREPARATIONS

The application of a drug to an area of the body for direct treatment is termed topical application. This type of application is not restricted to the skin and hair: the mouth and the entire gastrointestinal tract can have medications applied for topical treatment. Even body cavities can have topical applications applied, such as antibiotics during surgery and the lumen of varicose veins during sclerosing therapy.

TABLE 7.1 ADMINISTERING DRUGS BY THE ORAL ROUTE

Action	Rationale
The patient should be sitting upright (if not contraindicated)	To prevent aspiration of medication into lungs. Aspiration causes dyspnoea and may lead to pneumonia
Ensure the patient has enough water to assist in swallowing medications	Drugs that lodge in the oesophagus can cause irritation and burning, leading to poor absorption. Water promotes dissolution and absorption of drugs
Wash hands before preparing medications; without touching the medications, place tablets or capsules in a medicine cup	To prevent infection and cross-contamination
Give medications before, during or after meals, according to directions	Food in the stomach generally slows down drug absorption and decreases gastric irritation. The significance of each factor is considered when determining whether a drug is to be given with meals
Shake the stock bottle of a suspension thoroughly before dispensing	To ensure even distribution of ingredients
Hold the medicine measure at eye level when pouring liquid; the base of the meniscus (lowest level) should be level with the required volume	The meniscus is caused by surface tension against the walls of the measure
Do not give drugs orally if the patient is nil by mouth, vomiting, excessively sedated or unconscious	Oral drugs can interfere with the visualisation of organs for diagnostic tests. During surgery, intubation requires the patient to have an empty stomach to prevent aspiration pneumonia
	Oral drugs increase vomiting, with further irritation to the gastrointestinal tract. Very little drug will be absorbed through the tract
	To avoid aspiration into the lungs due to an impaired gag reflex

Drops

Eye and nose drops must be made isotonic in order to avoid pain or discomfort on application. Eye drops are aqueous or oily solutions or suspensions for instillation into the eye. Nose drops are liquid preparations used in the nasal passages. Oily solutions should not be used for nose drops as the oil hinders the ciliary action of the nasal mucosa. Oily solutions may cause additional problems by entering the trachea and causing aspiration pneumonitis. Ear drops are formulated as oily solutions to efficiently coat and adhere to the aural cavity.

Creams and ointments

By far the most common topical preparations are those used for the treatment of skin conditions, ointments and creams being the most frequently used. Many drugs are available in both forms, especially corticosteroid preparations.

Creams have an aqueous base, the water evaporating fairly quickly and leaving the drug on only the superficial layers of the skin. Very little of the drug is absorbed through the skin, where it could have a systemic action.

Ointments are lipid-based and accordingly have a greasy appearance and feel. The presence of water-repellent (hydrophobic) substances on the skin, such as petroleum jelly, acts like an occlusive dressing. An occlusive dressing completely shuts out the skin from the air but sweating still occurs. The sweat is trapped under the dressing and the horny layer of the skin is softened, thus enabling the drug to penetrate the tissues deeply. (Think how skin looks after being immersed in water for a considerable time, for example after a long bath.) Absorption into the

TABLE 7.2 ADMINISTERING DRUGS BY THE NASOGASTRIC ROUTE

Action	Rationale
Use dissolvable medications or mixtures if available. Otherwise, finely crush drugs separately and administer with water	To ensure complete passage of drug to stomach and prevent interaction between drugs in the tubing
Check the position of the internal end of the tube using syringe with air, listen with stethoscope for gurgles; aspiration of fluid from the tube, should have acidic pH	Nasogastric tube should be in the stomach before drugs are administered
Nasogastric tube should be flushed with water before administering medication, between medications and after all medication is administered	To ensure subsequent drugs do not precipitate with remains of earlier drug and to maintain patency of tubing
Slow-release and enteric-coated preparations should not be given through a nasogastric tube	These preparations cannot be crushed
Medications should either be syringed gently down the nasogastric tube or be allowed to run down the syringe barrel	Forcing the medication may cause damage to gastric mucosal membranes
If the tube is on free drainage, the drainage bag must be elevated after administration of medication	To prevent the medication from draining out
Nasoenteric tubes are not suitable for drug administration	These contain a radio-opaque mercury tip, which can break if medications are forced through

body can be significant. Ointments are better reserved for the treatment of dry or scaly skin conditions and should not normally be used on areas where skin is thinner, such as the face and genitals. Eye ointments are formulated to melt quickly on application so that vision is not seriously impaired.

Tables 7.3 and 7.4 provide information about medications administered by the optic route and aural route respectively. Figures 7.1 and 7.2 show the appropriate techniques for administering eye and ear drops. Ophthalmic pharmacology is covered in more detail in Chapter 79.

Pastes

Pastes have a high powder content and are useful in protecting areas of skin from moisture, as they are water-repellent. Clothes must be protected from pastes (although some dry quickly) and ointments, as they can be messy. Nappy rash and other conditions of the perineal area in babies respond well to pastes.

FIGURE 7.1 APPROPRIATE TECHNIQUE FOR ADMINISTERING EYE DROPS

FIGURE 7.2 APPROPRIATE TECHNIQUE FOR ADMINISTERING EAR DROPS

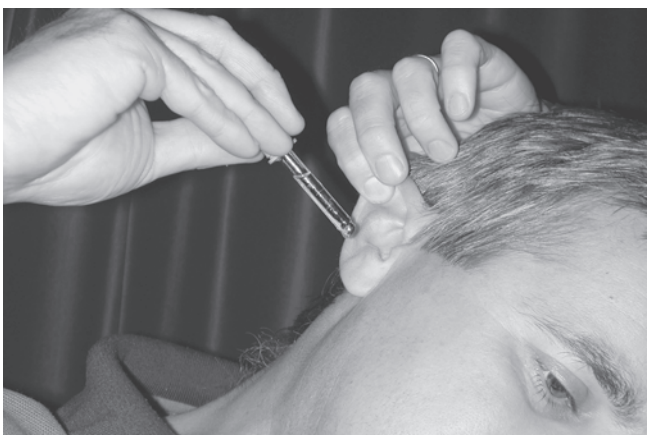


TABLE 7.3 ADMINISTERING DRUGS BY THE OPTIC ROUTE

Action	Rationale
Use only preparations marked for ophthalmic use	Ophthalmic preparations are made under sterile conditions and are usually isotonic to the eye's contents
Avoid touching the eyelid and other eye structures with dropper tip or ointment tube; use medication only for the affected eye if the problem relates to infection; never allow a patient to use another patient's preparation	Risk of contamination of infection from one eye to the other is high
All eye preparations should be discarded within 1–4 weeks after opening; some deteriorate more rapidly and should not be used after 1 week from the date of opening (e.g. corticosteroids, particularly **betamethasone** and **dexamethasone**)	There is greater chance of contamination if the preparation is administered beyond this period
If any crusts or discharge are present along eyelid margins, remove by applying a wool swab dampened with normal saline over the eye for a few minutes; wipe the eye clean from the inner to the outer canthus (inner to outer corner)	The presence of crusts and discharge promotes microorganism growth; cleaning from inner to outer canthus avoids entrance of microorganisms to the lacrimal duct
To instil, gently pull down lower lid as patient looks up; place the eye drop or ointment in the lower conjunctival sac	The cornea is rich with pain fibres and thus very sensitive
Advise the patient to close and not rub the eyes; the patient should not blink for a short period of time	Lack of movement of the eye following instillation allows for maximum absorption
After administering eye drops, apply gentle pressure for a few minutes to the bridge of the nose	Prevents the medication from being drained away from the eye
After insertion of ointment, instruct the patient to wait until vision clears before attempting to drive vehicles or undertake hazardous activities	Ointments usually cause blurring for about 15 minutes following insertion
Do not use an eye-drop preparation if it is discoloured or in some way changed since purchase	This prevents possible damage to the eye

TABLE 7.4 ADMINISTERING DRUGS BY THE AURAL ROUTE

Action	Rationale
If cerumen or drainage occludes the outer part of the ear canal, wipe it out gently with cotton-tipped buds. Never force wax inwards through the ear canal	Occlusion of the ear impedes normal sound conduction, harbours microorganisms and blocks distribution of medication
Instil ear drops at room temperature	Failure to instil drops at room temperature may cause vertigo and nausea
In children under the age of 3 years, the auricle of the ear is pulled down and back; in children over the age of 3 years and in adults, the auricle is pulled up and back	In older children and adults, the ear canal is longer and composed of underlying bone; straightening the ear canal provides access to the internal ear structures
The patient should lie down with the affected ear facing up for about 10 minutes	To allow the medication to disperse and absorb

TABLE 7.5 ADMINISTERING DRUGS TOPICALLY (ON THE SKIN)

Action	Rationale
Disposable gloves should be worn for this procedure; if the patient has an open wound, sterile gloves should be worn; if hands need to be placed in a large jar (e.g. silver sulfadiazine cream), use sterile gloves; ensure gloves provide a snug fit	Locally applied medications can create local and systemic effects; sterile gloves prevent cross-contamination with an open wound and ensure contents of jar remain sterile; snug-fitting gloves promote ease of application
Clean skin thoroughly with soap and water before applying medication	Skin encrustations, dried exudate and remnants of medication from previous applications can harbour microorganisms and block the passage of medication to the tissue
When applying preparation on the face, take care to avoid the eyes and lips	Irritation may lead to tissue damage
Spread the medication evenly over the skin, covering the area well, without using a thick layer; never rub the preparation in; use soft, gentle but firm strokes	To ensure proper penetration and absorption and to minimise irritation
A gauze or non-adhesive dressing may be applied over the area	To prevent soiling of clothes and wiping away of the medication

Gels and lotions

For hairy areas of the body, alcoholic gels or lotions are less messy than conventional ointments or creams; however, as evaporation of the carrier is rapid, there is little penetration of the drug. Gels are semisolid in consistency, whereas lotions are more liquid in character.

Table 7.5 provides information about medications administered topically through the skin.

SUBLINGUAL AND BUCCAL ADMINISTRATION

The mucosa of the mouth is not meant to be an absorptive surface, but a drug that is active in very low concentrations in the blood can be administered by allowing absorption to take place here. Administration of drugs by this route avoids the mixing of the drug with food and/or gastric juices, which may impede absorption or destroy the drug. For some drugs, notably **glyceryl trinitrate** (see Chapter 45), sublingual administration gives rapid absorption and avoids the hepatic first-pass effect (see Chapter 13). Some people believe that **aspirin** applied directly to the gum relieves the pain of toothache. This may be the case, but the analgesic effect is due mainly to the absorption of the drug into the bloodstream and the subsequent production of its normal systemic effect to relieve the pain. A high local concentration of aspirin may contribute to its effect. This method of administration is to be deplored, as aspirin is an acid and can irritate the gum to such an extent that it causes fairly severe ulceration.

Oxytocin, a polypeptide hormone, is destroyed by gastrointestinal proteinases but is absorbed fairly efficiently from the oral mucosa. In many developing countries, where administration of oxytocin by continuous infusion is not practical, the drug is sometimes administered using a buccal (pertaining to the cheek) tablet. The tablets are too large to administer sublingually. The antiemetic **prochlorperazine** (see Chapter 55) is available as a buccal tablet and is allowed to dissolve after being placed high up between the upper lip and gums. For obvious reasons, the swallowing of drugs to stop vomiting may not always be successful. A drug used in migraine, **rizatriptan**, is presented as a wafer for solubilisation and absorption through the tongue and oral mucosa (this is an oral lyophisilate also referred to in trade names as a 'melt').

A more detailed discussion on the reasons for sublingual administration is given in Chapter 13. Table 7.6 provides information about medications administered by the sublingual and buccal routes and Figure 7.3 shows the location for administering drugs by the sublingual and buccal routes.

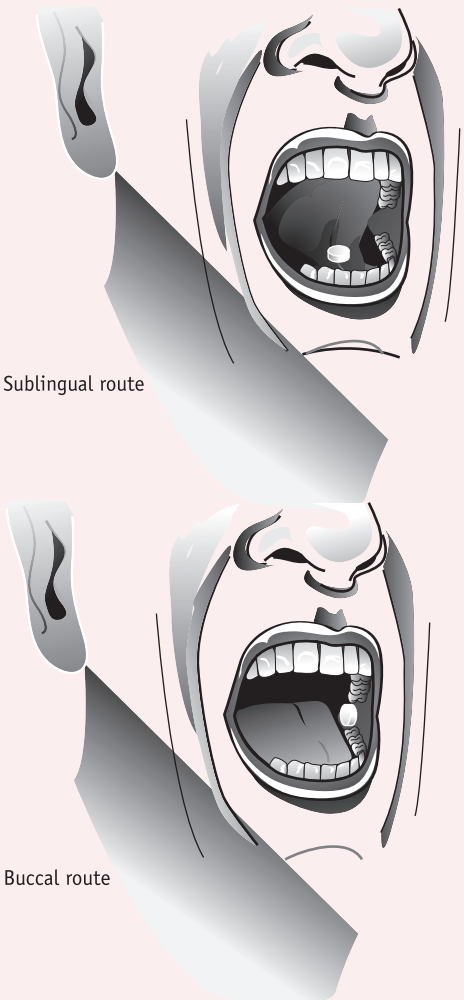
INTRANASAL ADMINISTRATION

Most drugs that are administered intranasally are solely for topical use. These topical applications are commonly used for the symptomatic relief of nasal congestion, such

TABLE 7.6 ADMINISTERING DRUGS BY THE SUBLINGUAL AND BUCCAL ROUTES

Action	Rationale
Sublingual Instruct the patient to allow the tablet to dissolve under the tongue; the patient should not drink any fluid while the drug is dissolving	The tablet is absorbed into the blood vessels surrounding the sublingual gland, bypassing the gastrointestinal tract, where the drug may be destroyed by gastric secretions or metabolism in the liver
Buccal The tablet is held between the cheek and gum and allowed to dissolve; the patient should alternate cheeks with each subsequent dose	The tablet is absorbed into the blood vessels surrounding the buccal glands, bypassing the gastrointestinal tract, where the drug may be destroyed by gastric secretions; alternating cheeks minimises mucosal irritation

FIGURE 7.3 LOCATION OF SUBLINGUAL AND BUCCAL SITES



as that which can occur with hayfever and colds. These formulations are found as drops, sprays and metered sprays with a propellant to eject the drug from its canister. The drugs used in nasal preparations can be absorbed systemically, especially with frequent use. Systemic absorption of many decongestants can lead to adverse cardiac effects (see Chapter 52).

Only a few drugs are administered intranasally for systemic action, the common examples being the posterior pituitary hormones, oxytocin and **antidiuretic hormone** (ADH). The latter is administered as **vasopressin** or one of its analogues. Polypeptides of low molecular weight are absorbed quickly through the nasal epithelium. If taken by mouth, enzymic destruction would take place rapidly in the stomach, long before absorption could occur. An unusual method of intranasal administration is using the ADH analogue **desmopressin**, in which the drug in solution is poured into a flexible plastic tube termed a rhinyle. One end of the tube is placed in the nasal cavity through a nostril and the other into the mouth. The solution is then blown into the nasal area – a novel but rather complicated method of administration, and one wonders whether this is really necessary. **Insulin**, being a much larger polypeptide, is not absorbed efficiently by this route, but tests incorporating insulin with a surfactant (which would render the mucosal cells more absorbent) have met with some success and could in the future obviate the use of hypodermic needles by diabetic patients. Tables 7.7 and 7.8 provide information about medications administered by nasal drops and nasal sprays, respectively.

TRANSDERMAL ADMINISTRATION

As the epithelial surfaces of the body are used to administer drugs, the skin can also be used for direct administration of drugs. The big difference between skin and the other epithelial areas of the body is the presence of keratin in the cells, which affords skin its toughness. Skin is therefore

TABLE 7.7 ADMINISTERING DRUGS BY THE NASAL ROUTE: DROPS

Action	Rationale
Instruct patient to blow nose before procedure (unless contraindicated)	Removes secretions, which can impede distribution of medication
Position the patient lying down on their back with head over the edge of the bed; support the patient's head with your non-dominant hand while the head and neck are extended; then turn patient's head to each side while head and neck are extended	Position provides access to nasal passages; ensures even distribution to all sinuses
Hold dropper above nares (nostrils) during administration	Avoids contamination of the dropper
After administration of drops, ask the patient to remain in this position for about 5 minutes	Prevents premature loss of medication through nares
The dropper should be used by only one person and rinsed after each use	Prevents infection
The preparation should not be used more often than directed	Overuse results in rebound congestion, which is often worse than the original manifestation

TABLE 7.8 ADMINISTERING DRUGS BY THE NASAL ROUTE: SPRAYS

Action	Rationale
The patient should be sitting upright with their head tilted slightly back; the spray is inhaled into one nostril while occluding the other	Allows thorough inhalation to affected sinus area
Apply strictly as directed	Overuse results in rebound congestion, which is often worse than the original manifestation

relatively more impermeable to drugs than other stratified epithelia, and only drugs that are very lipophilic and active in very small amounts can be administered successfully in this way. The skin is useful for administering drugs that conform to these properties and when low blood levels are required for long periods of time. Most of these drugs are administered as sticky discs called transdermal patches; a few drugs are applied using a quick-drying gel or spray (e.g. glyceryl trinitrate and **oestradiol**, respectively). The drugs commonly administered by this route are shown in Table 7.9. Figure 7.4 shows the design of patches used for transdermal administration of drugs. Table 7.10 provides information on medications administered by the transdermal route.

TABLE 7.9 TRANSDERMAL PRODUCTS

Drug	Use	Chapter(s)
Glyceryl trinitrate	Prophylaxis of angina	45
Fentanyl citrate	Prevention of severe pain	39
Hyoscine	Prophylaxis of motion sickness	55
Nicotine	To aid smoking cessation	23, 27
Oestradiol	Prevention of menopausal symptoms	58
Oestradiol + norethisterone	Prevention of menopausal symptoms	58

FIGURE 7.4 DESIGN OF PATCHES USED FOR TRANSDERMAL ADMINISTRATION OF DRUGS

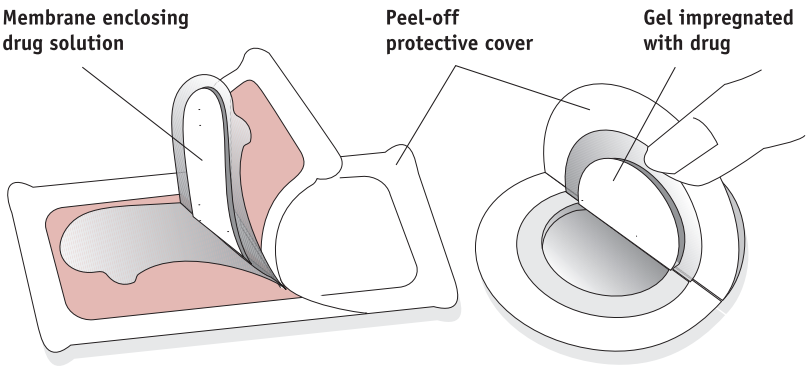


TABLE 7.10 ADMINISTERING DRUGS BY THE TRANSDERMAL ROUTE

Action	Rationale
Apply disposable gloves or ensure hands are washed thoroughly immediately after the procedure	To avoid coming into contact with the medication and absorbing it systematically
Apply required amount of ointment/cream on the piece of ruled paper; place paper against skin and secure with adhesive tape	To ensure correct amount is administered
If using discs, ensure area is free of hair	The disc will not stick on a hairy surface, thus affecting absorption

RECTAL ADMINISTRATION

Suppositories

In most English-speaking countries, the use of the word 'suppository' is usually reserved for solid drug formulations for rectal use. In the USA, however, the word is also used to describe similar-shaped (usually like a torpedo) medications for vaginal administration. It seems obvious that suppositories should be inserted pointed end first, and this is indeed the usual recommended method; recently, however, there have been reports that patient discomfort is less if suppositories are inserted blunt end first. The stated reason for this is that the external anal sphincter opens better when a larger surface area is pushed against it (cf. faeces). The converse is also true: if the blunt end is facing down towards the internal sphincter, then rejection can take place; this is less likely to happen with the pointed end facing downwards. Many suppositories are now manufactured with both ends relatively blunt. Suppositories should not be halved, as the distribution of drug in the matrix may be uneven.

The administration of drugs for systemic absorption through the rectal mucosa is becoming more and more popular owing to certain advantages of this method. Unfortunately, many patients are averse to this method of administration for aesthetic reasons and because of embarrassment if administered by another person.

ADVANTAGES

The advantages of suppository administration are as follows:

- If the patient is unconscious, oral administration is relatively difficult unless an enteral tube has been passed. The same goes for children and difficult or uncooperative patients.
- Nauseous or vomiting patients may find oral administration less than effective. Thus, many antinauseants and antiemetics are available as suppositories.
- Patients who have difficulty in swallowing due to oesophageal strictures or other oral and oesophageal pathologies can be given suppositories. Drugs that are destroyed by gastric acid can be given this way.
- The hepatic first-pass effect can be avoided as long as the suppository is not inserted into the upper third of the rectum, which is drained by the hepatic portal system. Thus, most suppositories that are not for topical use should be inserted only past the internal anal sphincter.

TABLE 7.11 ADMINISTERING DRUGS BY THE RECTAL ROUTE: SUPPOSITORIES

Action	Rationale
Assist the patient in getting into the side-lying Sim's position with the knee and hip of the upper leg flexed	This position exposes the anus and helps to relax the anal sphincter
Ask the patient to relax the area	Forcing a suppository through a constricted sphincter causes discomfort
Wear disposable gloves; lubricate the rounded end of the suppository with water-soluble lubricant; with the index finger of the dominant hand, insert the suppository the entire length of the finger; the suppository must be pushed through the anus, past the internal sphincter and through to the mucosal rectal wall for absorption; impress on the patient the need to retain the suppository for at least 20 minutes	To allow absorption of suppository and prevent expulsion

- In cases where a vein is difficult to find for intravenous injection, rectal administration of lipid-soluble drugs can result in rapid action.
- The opposite can also be true, however, particularly with acidic drugs, when absorption at a slower rate can be beneficial. This is the case with anti-inflammatory preparations, when long action is desired. Very often patients with rheumatoid arthritis who take an oral preparation at night find they have difficulty getting out of bed in the morning, as the effect of the drug has worn off; a suppository used before going to bed often avoids this consequence.

DISADVANTAGES

- Insertion of suppositories can cause anal or rectal irritation. This can be a problem with haemorrhoidal preparations containing local anaesthetics, which mask the irritation.
- Aesthetic considerations from both administrator and patient should always be observed when rectal administration is performed.
- Patient education is required for suppository use.
- If not self-administered, suppositories should be inserted with the patient in the left lateral position, which lessens the risk of perforation of the rectum. (Think about the anatomy of the lower gastrointestinal tract.)
- Suppositories are made to melt at body heat and are best kept refrigerated to maintain their shape. A drop of a lubricant jelly may help in their insertion. Patients must be told to remove the plastic or foil wrapping before use and exactly where to insert it. Many people are not aware of their own anatomy and have inserted suppositories with and without wrapping into all sorts of body orifices. (These stories are not merely apocryphal.)

Table 7.11 contains information about the administration of suppositories.

Enemas

Enemas are liquid preparations for rectal administration. Enemas can be used for topical or systemic treatment or to cause a bowel motion. When used for topical or systemic treatment, they are termed retention enemas and are hypotonic solutions so that the fluid will be taken up by the body and the active ingredient left in contact with both the rectal and colonic mucosa. Some drugs will also, in all probability, be absorbed and if appropriate can be administered by this method. Enemas are better than suppositories if the lower reaches of the colon are to be treated. When used as laxatives, enemas are hypertonic to cause an outward flow of water from the body into the distal portion of the digestive system and thus promote defecation (see Chapter 54).

In very rare instances, enemas have been reported to cause vagal inhibition, leading to cardiac arrest. Most abdominal and thoracic structures are innervated by the vagus nerve, including the rectum. The vagal supply to the heart consists of parasympathetic fibres, which cause bradycardia. Any receptor of the vagus nerve, when stimulated, can cause a reflex increase in parasympathetic activity, which can lead to frank bradycardia or even cardiac arrest.

Table 7.12 provides information about the administration of enemas.

VAGINAL ADMINISTRATION

Suppository-shaped medications for vaginal administration are usually termed 'pessaries'. As vaginal administration of drugs is always for topical treatment, it is important that the drug coats all the vaginal mucosa. To enable this to happen, the medication should be inserted as high in the vagina as possible. Thus, vaginal medications, whether in pessary or

TABLE 7.12 ADMINISTERING DRUGS BY THE RECTAL ROUTE: ENEMAS

Action	Rationale
Place the patient in the side-lying Sim's position, with the upper leg flexed	Promotes access to the anal area and relaxes the anal sphincter
Wear disposable gloves; lubricate the tip of the catheter with water-soluble lubricant; administer medication slowly	Prevents contamination and friction to anal walls; a slow rate of administration prevents expulsion
Use appropriate-sized tubing depending on the patient (adults: 14–30 French gauge) and insert the tube to a specific length (adults: 7.5–10 cm)	To prevent damage to the rectal wall
Following insertion of the enema, ask the patient to gently hold the buttocks together	Allows the immediate urge to defecate to subside
The patient should be instructed to hold the medication for as long as stated by the medication's directions	Allows adequate time for the enema to perform its action before defecation

cream form, come with applicators designed to reach the upper parts of the vaginal canal. Some manufacturers have modified the shapes of vaginal drugs, and you may see terms such as 'ovules' (egg-shaped) and 'vaginal tablets' being used. You may also see strange treatment requests: for example, one of the authors of this book had to treat a male patient with **nystatin** pessaries (see Chapter 74), which had been prescribed p.o. (by mouth). Thinking the doctor had made a mistake on the prescription, the author administered p.r. (by rectum). The doctor had not, in fact, made a mistake: the patient had ulcerative colitis, which prohibited the use of rectal medications. (The patient was meant to chew the pessary.) The moral of this story is always to query suspected prescribing errors. The instructions may not be wrong (see also Chapter 10).

Creams for vaginal administration come with precalibrated applicators to facilitate insertion. Vaginal douches containing antimicrobial substances are available for thorough vaginal washouts.

Vaginal preparations to be left in situ are best used at night. The vagina, unlike the anus, has no sphincters and therefore the medication can leak out, lessening its effectiveness and causing possible embarrassment. The latter could be considerable with iodine preparations. If patients have to insert vaginal medications during the day, they should be advised to wear protection, such as panty liners or sanitary towels. Tampons should not be used with vaginal medications.

Table 7.13 contains information about the administration of medications by the vaginal route.

TABLE 7.13 ADMINISTERING DRUGS BY THE VAGINAL ROUTE

Action	Rationale
The patient should be lying down with the legs flexed and extended apart	This position promotes ease of application and facilitates relaxation
If the patient prefers and is able, provide supplies for self-administration	Some women may be embarrassed and prefer to self-administer
The tip of the applicator should be moistened with water-soluble lubricant	Prevents friction against the vaginal wall during insertion
If the patient is using one dose a day, it should be inserted just before sleep and after urination If the dose is ordered on a more frequent basis, the patient should lie down for about 20–30 minutes after administration	To ensure medication does not drain out or become expelled

PARENTERAL ADMINISTRATION

Any method of drug administration that avoids the gastrointestinal tract is termed **parenteral** administration. Transdermal, lung and intranasal administration, discussed earlier, are thus parenteral methods. The use of this term, however, is normally reserved for cases where invasive procedures are used, namely injections. Drugs can be administered to almost any part of the body by injection; some of these techniques are highly specialised whereas others are routine. The routine methods are those discussed here. Injections, being invasive, require the use of aseptic procedures.

Intradermal administration

In intradermal administration, a drug or substance is injected into the dermis using a fine needle or needles (as is the case with an intradermal punch used in some vaccination procedures).

Drugs are rarely administered by this route, as absorption is slow and only very small quantities can be given. Local anaesthetics are occasionally given by this method to stop pain during superficial suturing procedures. Immunity procedures are commonly carried out using this method when only a localised response is wanted or a systemic response could prove dangerous. Likewise, antigen tests for allergies are performed using this procedure.

Subcutaneous injections

The blood supply to the subcutaneous tissue is poor, and so absorption of an injected drug will be relatively slow. This is often an advantage with drugs that cannot be given by mouth. An example is the protein insulin, which is digested if given orally; when injected intravenously, the resultant fast action is not always desirable.

Absorption rate of drugs given by subcutaneous injection can be slowed down further by incorporating **adrenaline** in the injection. Adrenaline promotes vasoconstriction, which decreases the distribution of the injected material. This vasoconstriction will also decrease bleeding when adrenaline is injected with a local anaesthetic for minor surgical procedures. Conversely, if the enzyme **hyaluronidase** is added to a subcutaneous injection, the tissue cement hyaluronic acid (which helps cells to adhere to each other) is destroyed, enabling the other drug to diffuse into the tissues. Sustained effects can be achieved using subcutaneous injections by dissolving the drug in a slowly dispersible oil or by implanting a pellet containing the drug in the tissues. Steroid hormones used for contraception or for treating menopausal symptoms are sometimes given in this way. Subcutaneous injections are useful when other routes may be hazardous, as is the case with **heparin**. When injected into a muscle, heparin, being an anticoagulant, could lead to intramuscular haemorrhage, producing a painful haematoma.

Tablets, especially some sex hormones, can be implanted into subcutaneous tissues for prolonged action. Table 7.14 contains information about the administration of medications by the subcutaneous route.

Intramuscular injections

Skeletal muscle is highly vascular, and its capillaries contain small pores that enable substances of small molecular weight to pass through into the bloodstream. Lipid-soluble drugs are taken up rapidly by direct diffusion through the capillary walls. Substances of high molecular size, which are lipophobic, can be absorbed slowly into the lymphatic system. Several muscles of the body have considerable mass and are able to be injected with quantities of up to several millilitres of fluid, generally without undue discomfort to the patient. The gluteus medius of the buttocks is the best muscle to use in this respect. The deltoid muscle of the upper arm has a richer blood supply than the gluteus muscle and so is good for rapid absorption of many drugs, but its size limits the injectable amount to about 1 ml.

Intramuscular injections are not always given for quick action; if the drug is mixed with an oil such as peanut oil, the oil is not absorbed rapidly from the injection site. The drug thus diffuses slowly from the oily solution into the muscle's capillaries. This can take a few weeks to occur; this type of injection is known as a depot injection.

Exercise, which causes an increase in skeletal muscle blood flow, improves absorption of a drug after intramuscular injection. This was demonstrated by a footballer who was given phenothiazine, an antipsychotic agent (see Chapter 33), as a depot injection and who subsequently suffered from a fairly serious adverse reaction due to rapid absorption of the drug, brought about by increased muscular activity.

The main danger from intramuscular injection is damage to nerves, especially in the case of gluteal injections, as the large sciatic nerve passes through this region. Knowledge of the anatomical positions of major nerves and blood vessels is necessary in order to avoid irreparable damage or injection into these structures. Apart from pain and irritation to tissues, sterile abscesses can occur with intramuscular injections.

Not all intramuscular injections act faster than using enteral routes; for example, **diazepam** (see Chapter 34) is faster-acting when given rectally or orally. Table 7.15 contains information about the administration of medications by the intramuscular route.

Intravenous injections

The administration of drugs intravenously avoids the process of absorption, resulting in most cases in very fast action. The action of a drug given by this route may take only seconds, as is the case with the injectable general anaesthetics, such as **thiopentone** (see Chapter 41). When extreme speed is

TABLE 7.14 ADMINISTERING DRUGS BY THE SUBCUTANEOUS ROUTE

Action	Rationale
Inspect skin surface; palpate for masses and tenderness; site should be free from infection, skin lesions, scars and bony prominences	Site should be free from abnormalities, which may interfere with absorption
In long-term therapy, such as with insulin, rotate the injection sites	A site used repeatedly can become hardened due to hypertrophy (thickening of skin) and lipodystrophy (atrophy of tissue)
If giving at a 45-degree angle, hold as a dart, palm up and bevel of needle down; if giving at a 90-degree angle (e.g. insulin in an insulin syringe, or heparin), hold as a dart, palm down	Good manipulation of syringe allows for a quick, smooth injection
Grasp the skin with thumb and forefinger of non-dominant hand and lift up; ensure the patient relaxes arm, leg or abdomen	Needle penetrates tight skin more easily than loose skin; relaxation of site reduces discomfort
Only small doses (0.5–1 ml) of water-soluble medications should be given	Subcutaneous tissue is sensitive to oil-soluble medications and large volumes; collection of medications in the tissue can cause abscesses
For a thin, cachectic patient, the abdominal site is best; for an obese patient, pinch skin at site and inject below the fold	Thin patients have insufficient tissue for subcutaneous injections; obese patients have a fatty layer of tissue above the subcutaneous layer

TABLE 7.15 ADMINISTERING DRUGS BY THE INTRAMUSCULAR ROUTE

Action	Rationale
Avoid areas with lumps, bruises and other lesions; note integrity and size of muscle, and palpate for tenderness	Insertion site must be free of abnormalities, which may impede drug absorption; rotate site if frequent injections are given
Position non-dominant hand against skin, spreading it tightly; hold syringe as a dart, palm down	Insertion will be quick and smooth, reducing discomfort
If muscle mass is small, grasp the centre of muscle between thumb and other fingers of non-dominant hand	Ensures injection reaches muscle mass
Ask the patient to lie flat, on the side, prone or sit, depending on the chosen site; slightly flex knee	These positions reduce strain on muscle, minimising discomfort and movement during injection
3 ml of medication can be safely tolerated in larger muscles (vastus lateralis or dorsogluteus); young children and elderly and frail patients tolerate no more than 2 ml	Small muscle can tolerate only small amounts of fluid before causing discomfort
Aspirate for blood before giving the injection	Determines whether a blood vessel has been entered

required, as in an emergency, this is often the method of administration of choice.

Intravenous administration is also used when giving extremely irritant drugs, such as the cytotoxic drugs used in cancer chemotherapy (see Chapter 76). These drugs, which are given intravenously at high concentrations, have been known to leak into the surrounding tissues, either from needle dislodgement or from vein damage caused by faulty

TABLE 7.16 ADMINISTERING DRUGS BY THE INTRAVENOUS ROUTE

Action	Rationale
Observe the patient for the following systemic complications: • Excess fluid volume caused by a too fast flow rate. Treatment: diuretic, oxygen, sit up • Decreased fluid volume caused by a too slow flow rate. Treatment: fluids • Air embolism caused by air in line. Treatment: oxygen, heparin, +/– mechanical ventilation • Infection and febrile reaction caused by contamination of intravenous line or insertion site. Treatment: blood cultures, antibiotics	Potentially life-threatening situations require prompt recognition of manifestations, early intervention and knowledge of preventive measures
Observe the patient for the following local complications: the patient is not receiving the prescribed amount through the vein, and the effect is very uncomfortable: • Phlebitis: vein is inflamed, manifesting as a red, swollen and painful area • Thrombophlebitis: vein is inflamed and has clotted, manifesting as a red, swollen, warm and hard area • Infiltration: the cannula has come out of the vein, manifesting as an oedematous and painful area • Treatment: turn off line, check site with another nurse, remove cannula, set up for reinsertion of line by doctor	Solution must be flowing freely for accurate drug administration
Care of site: • Cover with vapour-permeable adhesive film dressing (e.g. OpSite™) over area; redress only if necessary • Ensure no dried blood is located under the dressing • Splint area if located over a joint • Place plastic bag over arm for shower • Change line and cannula every 48 hours or depending on hospital policy	This route is susceptible to infection because of the break in skin integrity and direct access to bloodstream; strict asepsis is imperative
Flow rate: • Check half-hourly • Fill to required amount for the hour; ensures the patient does not become underhydrated or overhydrated; never overfill burette if it is attached Documentation and drug-checking: • If an additive is placed in the flask, an additive label needs to be filled in and signed by two nurses; if an additive is placed in the burette, an additive label needs to be filled in and placed against the burette for the duration of the drug's administration • Fluid-balance chart needs to be kept up to date, indicating when flasks start and finish, and hourly measures for burettes and volumetric pumps • Intravenous order chart: orders need to be up to date and signed by a doctor; the order also needs to be signed by a nurse at the start and completion of infusion • The nursing notes need to be documented with the type of fluid, additive, duration, volume and dose per hour	Allows the nurse to maintain accountability for actions
If the intravenous drip stops or slows down: • Check roller clamp and reposition if necessary • Check insertion site for infiltration, etc. • Check tubing for kinking and reposition if necessary • If site is over a joint, check limb joint for obstruction; place a splint against the limb • Raise flask on pole	Correct flow rate must be maintained to ensure the patient obtains the prescribed dose

insertion of the cannula. If this happens, severe necrosis of the tissue can result; this has, on occasion, necessitated amputation of the affected limb. (Imagine the result, then, if these drugs were injected directly into the tissues.) When introduced into the bloodstream, drugs are diluted within seconds into the total blood volume; this diluting effect prevents direct damage to the formed elements in the blood.

Another possible advantage of intravenous injections is that, in the case of rapid development of an adverse reaction, injection may be stopped before a critical blood level occurs.

The use of aseptic techniques is of extreme importance when giving intravenous injections, as is the avoidance of intra-arterial injection, which can cause arterial spasm leading to gangrene in the tissues supplied by the artery. Intravenous medications should be examined for particulate material before administration. If such material is found, the drug should be discarded. Table 7.16 contains information about the administration of drugs by the intravenous route.

Other modes of injection

- *Intra-arterial injections* can be used to infuse an organ directly with a drug while more or less avoiding other parts of the body. This may be of use in cancer chemotherapy.
- *Intrathecal injections* are made into the cerebrospinal fluid (CSF), usually at the level of the third or fourth lumbar vertebra in order to avoid the spinal cord. (You may remember that the spinal cord terminates here at the conus medullaris, to become the cauda equina.) These injections are given to get drugs directly into the central nervous system (CNS) by avoiding the blood–brain barrier (see Chapter 13).
- *Epidural injections* are given at the same position as intrathecal injections, but the drug is deposited above the dura mater and not into the CSF. Local anaesthetics are often given in this way during surgical procedures, especially for procedures involving the pelvic and inferior regions, to block pain transmission to higher centres of the CNS.
- *Intra-articular injections* are made into articular joints to obtain high concentrations of, for example, anti-inflammatory corticosteroids in the treatment of inflammatory conditions of a joint.

These are just a few of the more common routes for giving injections, but almost any part of the body can be injected under appropriate circumstances.

NEBULISER AND INHALER ADMINISTRATION

Nebulisers and inhalers are used to administer medications to the lower respiratory passages of the body (refer to Figures 7.5 and 7.6). Metered-dose inhalers deliver medications in an inert propellant gas and require good hand–breath

FIGURE 7.5 NEBULISER UNIT, WITH NEBULISER, OXYGEN TUBING AND MASK

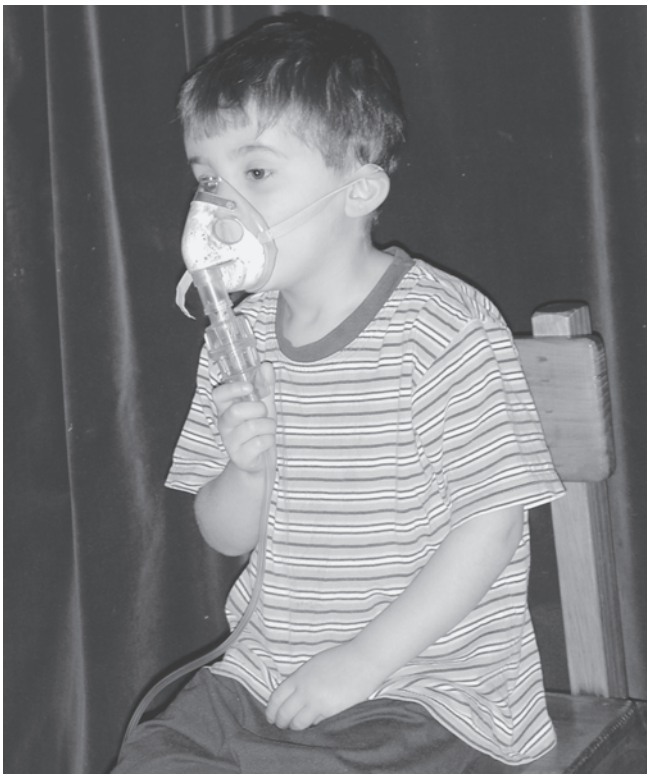
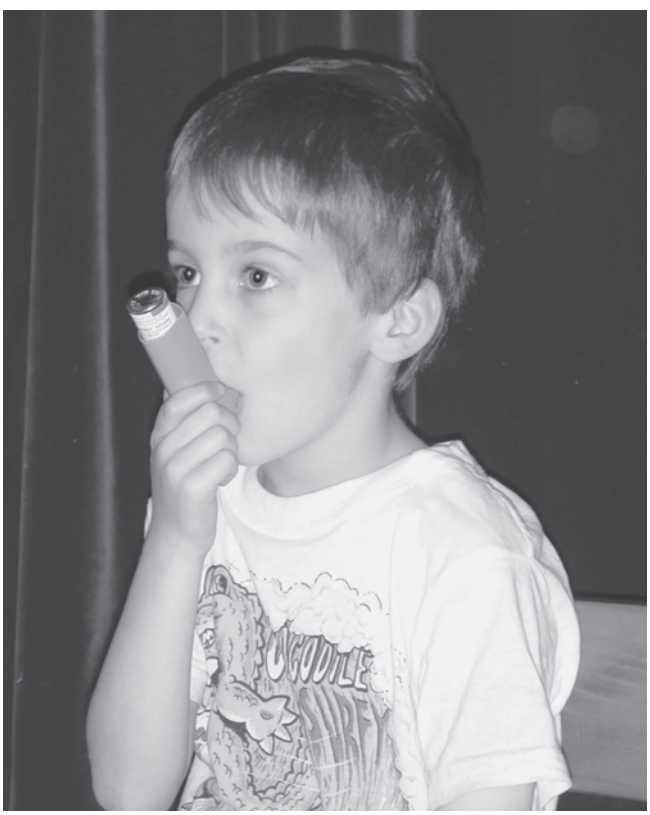


FIGURE 7.6 USE OF A METERED-DOSE INHALER



coordination. They are, therefore, not suitable for children under 5 years. Spacers are devices used in conjunction with metered-dose inhalers and are suitable for individuals who lack hand–breath coordination (see Figure 7.7). Dry-powder inhalers deliver medications in a dry powder form and are activated by a breath. As dry-powder devices require a higher inspiratory flow than metered-dose inhalers, they may not be effective in situations of acute exacerbation of asthma. Nebulisers produce an aerosol by using an air compressor or jet and are able to deliver large doses of medication over a long period. Due to the warmth and moisture associated with using such devices, nebulisers carry the risk of microbial contamination. Tables 7.17 and 7.18 provide information about the administration of medications by inhalers and nebulisers, respectively. Figure 7.5 shows a nebuliser attached to oxygen tubing.

FIGURE 7.7 USE OF A SPACER IN A YOUNG CHILD

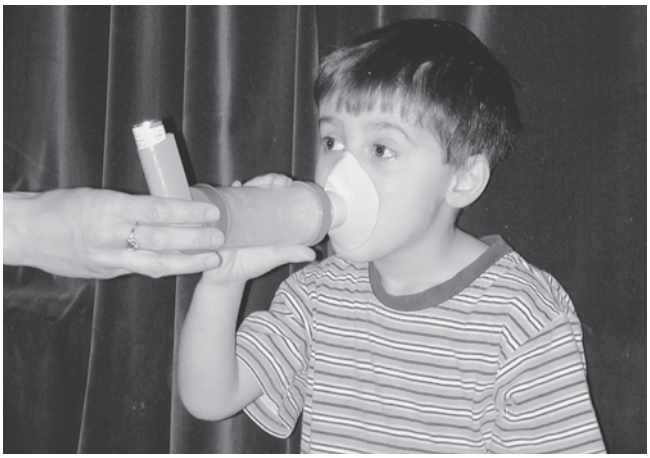


TABLE 7.17 ADMINISTERING DRUGS BY THE RESPIRATORY ROUTE: INHALERS

Action	Rationale
Shake canister vigorously before use	Allows dispersion of contents
With the patient's lips open, instruct the patient to place inhaler in the mouth and direct towards the back of the throat; the mouthpiece is gripped with the teeth; instruct patient to exhale fully and then inhale, breathing deeply through the mouth and depressing the canister fully; hold breath for 10 seconds	Medication is directed towards the respiratory airways and not allowed to escape through the mouth
Wait 5–10 minutes between inhalations	The first inhalation dilates airways, and the second inhalation penetrates more deeply
Drink, eat or brush teeth immediately after use	Prevents oropharyngeal candidiasis, hoarseness and irritated sore throat

TABLE 7.18 ADMINISTERING DRUGS BY THE RESPIRATORY ROUTE: NEBULISERS

Action	Rationale
Place the required amount of medication and diluent in the nebuliser device	Ensures the right proportions of medication and diluent are used
Connect tubing, nebuliser and mask to an oxygen or air source; ensure all connections are tight; turn the flow rate to the required level (e.g. 10 l per minute)	Allows for continuous mist from the mouthpiece
Instruct the patient to sit up as straight as possible; tell the patient to hold the nebuliser upright, and to breathe slowly and deeply until the medication mist stops; turn off oxygen or air source	Allows for maximal chest expansion and efficient use of the nebuliser
For cleaning, dismantle the nebuliser unit and disconnect the tubing; rinse the nebuliser unit and mask in warm water; shake and allow to drain dry; do not wipe nebuliser parts with a towel or tissue	Prevents microbial growth from moisture accumulation; a tissue or towel should not be used to dry the nebuliser unit, as particles may block the nebuliser jet, leading to poor or no misting

STORAGE OF DRUGS

Nurses must be extremely aware of the storage conditions of drugs. Generally, medicines should not be exposed to sunlight, bright light, moisture or extremes in temperature. Some drugs are particularly sensitive and will rapidly deteriorate or become ineffective if subjected to these conditions. The standard storage instructions for labelling pharmacotherapeutical agents are as follows:

- Store below −18 °C.
- Store below −5 °C.
- Store at 2–8 °C.
- Store below 8 °C.
- Store below 25 °C.
- Store below 30 °C.

The temperature conditions of various drugs are often critical. Many drugs, especially those of a biological origin, need to be stored between 0 °C and 4 °C. Common examples are insulin and vaccine preparations. **Amoxicillin** in a reconstituted form with water is extremely unstable and needs to be refrigerated. Amoxicillin in a powder form must be stored at a temperature below 25 °C, although when reconstituted the mixture must be stored at 2–8 °C. Most biological products, such as insulin, vaccine preparations, total parenteral nutrition and blood products, are easily denatured, causing a loss in effectiveness. Denaturation is usually minimal at 4 °C; consequently, this is the temperature selected for storing biological preparations. Preparations must not be frozen, as this may result in crystal formation, with concomitant loss of activity. It is also important not to store preparations in the refrigerator when optimal conditions are considered to be at temperatures greater than 4 °C. For example, crystal growth and separation occurs when **phenoxymethylpenicillin** suspension is stored at 4 °C. Furthermore, many refrigerated preparations need to be kept at room temperature before administration in order to acclimatise to body temperature (e.g. total parenteral nutrition and insulin).

Naturally produced and semisynthetic penicillins possess certain common properties regarding temperature. Except for **ampicillin**, all penicillins will retain at least 90 per cent of their initial potency for a few days when stored at 4 °C in solutions for injection. Chemical reactions, however, do occur when penicillins are in aqueous solution. As the chemical reactions of penicillins may lead to allergic effects, it is recommended that solutions for injections be administered within 24 hours. Excess supplies should not be kept for a prolonged period in the refrigerator. When ampicillin powder is reconstituted with water for injection, it undergoes rapid hydrolysis; such solutions should be used immediately.

Expiry dates should be checked carefully before administering a drug. This information is documented on the container of the product. Certain preparations have a very short shelf life due to chemical instability or the possibility of bacterial contamination. Ophthalmic preparations (see Chapter 79) carry the risk of contamination once the sterile container is opened. The volume of solution placed in eye-drop preparations is often limited to 5–10 ml in order to discourage prolonged storage. Breakdown or loss of preservative, together with incorrect technique of administration, can result in contaminated preparations. Table 7.19 shows the suggested shelf life for various preparations. Some eye drops are presented in individual plastic containers, containing enough drug for only one application to both eyes. This prolongs the shelf life and prevents wastage but is more costly. The package insert should always be consulted for concise information regarding expiry dates.

In addition to observing expiry dates of medications, the nurse should ensure that tablets of different generic names are never put in the same container. Despite the obvious risk of the wrong medication or dose being taken, the drugs may interact and alter their chemical composition. Furthermore, medications of the same generic name (e.g. **digoxin** or glyceryl trinitrate) must never be removed from their individual containers and placed in one container.

TABLE 7.19 SHELF LIFE OF PREPARATIONS AFTER OPENING

Preparation	Shelf life after opening (days)
Penicillin syrups (when reconstituted)	7
Eye preparations (general)	28
Ear preparations	28
Nystatin eye drops	7
Mild silver protein eye drops	14
Corticosteroid eye drops and ointments	7
Insulin preparations	30
Total parenteral nutrition	2
Glyceryl trinitrate tablets	90
Aspirin mixture	7

Different batches of tablets usually indicate a different expiry date, and out-of-date tablets may chemically interact with other tablets, altering the composition and rendering them ineffective.

Exposure to light may also cause changes in a drug's chemical composition. Manufactured preparations will be presented in dark, protective containers if light is an important factor. These containers should be stored away from sunlight (e.g. in a cupboard or on a trolley) and situated away from the bright lights often present in hospital wards and community health centres. Light-sensitive drugs that need to be made up in infusion fluids should have black plastic bags placed over the fluid flasks to provide protection during administration. Examples include **amphotericin**, total parenteral nutrition, **amiodarone** and **sodium nitroprusside** infusions.

Care must also be taken to avoid moisture coming into contact with preparations. Several drugs are broken down by hydrolysis, often rendering them ineffective. Common examples are aspirin and glyceryl trinitrate tablets. The degradation of aspirin is determined easily by the presence of a vinegary smell. In preparations such as paints, pastes, pessaries, suppositories, inhalations and ointments, contact with water makes application or insertion fairly difficult and their therapeutic activity is often nullified. On discharge, patients should be advised to store medications in a cool, dry place and to ensure that containers are always kept airtight. The bathroom and kitchen should be avoided as storage areas, because of their propensity for continuous and excessive humidity and warmth. Due to the possibility of perspiration and sweating, containers should not be carried close to the body.

SUMMARY

- Drugs can be formulated in many different forms, including tablets, capsules, powders and liquids.
- Drugs can be administered to the body by routes involving the gastrointestinal tract.
- Drugs administered avoiding the gastrointestinal tract are termed parenteral drugs.
- Almost any part of the body can be used to administer drugs parenterally.
- Drugs are often unstable and cannot be stored indefinitely.
- All drugs have an expiry date on the package.
- Storage of drugs must be according to the manufacturer's directions.

1. Why should suppositories be inserted with the patient in the left lateral position?
2. Can you think why cocoa butter is sometimes used in the formulation of suppositories?
3. Suggest two reasons why suppositories should not always be inserted high into the rectum.
4. Ibuprofen (an anti-inflammatory analgesic) can be obtained as a solution in gelatine capsules for the treatment of acute painful conditions. In the treatment of rheumatoid arthritis, ibuprofen is usually given in the form of an enteric-coated tablet. Why is there a difference in the two formulations?
5. Why is indomethacin, an acidic drug, absorbed from the rectum at a slower rate than prochlorperazine, a basic drug?
6. What advice should be given to women concerning the administration of pessaries and vaginal creams?
7. Can you think of any reasons why drugs are not normally administered vaginally except for topical treatment? (Think about the gross and microscopic anatomy of the vagina.)
8. Your patient has been ordered enteric-coated aspirin tablets. How do these tablets work to prevent gastric irritation?
9. Bupivacaine is available with adrenaline for use as an epidural anaesthetic. What advantages does adrenaline provide in this preparation?
10. How would you administer an intramuscular injection into the gluteal muscles to prevent damage to the sciatic nerve?

11 Your patient has been ordered aminophylline suppositories for asthma. What advantages has this formulation over theophylline tablets?

12 How would you prepare the skin for a transdermal patch?

13 You, as the administering nurse, are confronted with the following prescription for your patient: enoxaparin 20 mg IM daily. What is wrong with this prescription? Why?

14 Morris Jones, a 50-year-old executive, takes glyceryl trinitrate tablets when he has an attack of angina, and applies a glyceryl trinitrate transdermal pad every morning as a preventive measure against angina. With reference to the formulations (tablet versus transdermal pad), describe how these act to either treat angina or prevent an attack of angina.

15 In caring for a patient with an intravenous infusion, you notice the infusion stops dripping. What action would you take?

THE CLINICAL DECISION-MAKING PROCESS

8

CHAPTER EIGHT

OBJECTIVES

After completing this chapter, the reader should be able to:

- **apply the clinical decision-making process to principles of drug administration;**
- **describe the aspects that are considered in patient assessment;**
- **describe the aspects that are considered under patient diagnosis;**
- **describe the aspects that are considered under care planning;**
- **describe the aspects that are considered under implementation;**
- **describe the aspects that are considered under evaluation.**

KEY TERMS

Clinical decision-making
Patient assessment
Patient diagnosis
Care planning
Implementation
Evaluation

THERE ARE CERTAIN PRINCIPLES OF MANAGEMENT THAT nurses must apply to every facet of drug administration. The principles outlined in detail in this chapter have, as their primary focus, the safe and effective administration of medications and a high standard of patient care. The clinical decision-making process, as it applies to drug therapy, is discussed as an effective means of enabling the nurse to provide individualised care that takes into account all aspects of the patient's condition.

The clinical decision-making process is a means of gathering and organising information and then using this information to plan, administer and evaluate nursing care. Knowledge and skill in the use of the clinical decision-making process are needed for drug administration as in other areas of patient care. The process follows five steps: assessment, diagnosis, planning, implementation and evaluation.

ASSESSMENT

The first step involves the collection of information about the patient that is likely to affect drug therapy. This information forms the basis for an individualised drug regimen. The nurse obtains data by interviewing the patient and family members, collaborating with other health-care professionals, performing a physical assessment, and reviewing diagnostic and laboratory test results. Objective data are information concerning the patient's condition that are observed by others. These data provide unbiased factual information about the patient. Subjective data obtained during the patient interview include the patient's feelings, thoughts, values and expectations, which cannot be observed directly and can be obtained only by questioning the patient.

On admission, the nurse assesses the patient for age, weight, height, acute or chronic disease processes with their associated clinical manifestations, and current health status (particularly concerning cardiovascular, renal and hepatic functions). At this stage, a preliminary determination of developmental level, particularly in children and older people, is essential in planning nursing care. The nurse also considers the family history and personal disease history to determine the patient's risk for various medical conditions. Next, a medication history is taken of past and current use of prescription, non-prescription and recreational (e.g. alcohol, caffeine, tobacco) preparations. Questions that the nurse would consider include the following:

- *What are the current drug orders?*
- *What drugs has the patient taken before?* Include prescription drugs used for chronic conditions such as diabetes mellitus, arthritis and hypertension. Non-prescription (over-the-counter) drug preparations commonly used for headaches, nasal congestion, indigestion and constipation should also be considered, as patients often do not view these preparations as drugs (see also Chapter 2). For the same reason, the nurse should ask about the patient's use of homeopathic and naturopathic medicines, such as tea-tree oil, comfrey, royal jelly, **aloe vera**, **garlic**, special teas and liniments. Homeopathic and naturopathic medicines produce their own therapeutic effects that may ultimately impinge on the current drug regimen.
- *Does the patient know about the actions, adverse reactions and other specific aspects of the drug regimen?* These may include the effect of giving the drug with food (e.g. whether the drug is taken with food or on an empty stomach), the regularity of the dose (same time each day), storage conditions, and the need to avoid alcohol or other drugs.
- *Has the patient had an allergic reaction to a drug?* What clinical manifestations occurred and what date did they occur? This information will prevent the administration of medication that can produce severe, life-threatening reactions (e.g. anaphylaxis with penicillins). Conversely, some patients describe certain effects as allergies when in fact these effects are mild adverse reactions to the drugs. One common example is the side effects of nausea and vomiting associated with **morphine** use, which are not actually allergic reactions.
- *Does the patient follow a special diet?* For example, low-salt, low-protein, low-fat or diabetic. The nurse should also determine whether the patient is following a particular fluid regimen, such as fluid restriction.
- *What immunisations has the patient received?* When did the patient last receive a tetanus injection?
- *What is the patient's attitude to drugs?* Does the patient think the medication is doing what it was originally prescribed to do? What are the patient's concerns about the medications? Concerns could relate to the safety, therapeutic and adverse effects, and the appropriateness for the medical condition being treated. What is the patient's level of willingness to take all prescribed medications according to the required dose, time, route and formulation? This willingness contributes to whether the patient is complying with the drug regimen, taking the drugs reluctantly or abusing the designated orders (see Chapter 5 for further discussion about compliance). Many drugs rely on regular, continuous dosage to maintain a steady response in the patient. Treatments for hypertension, diabetes and epilepsy are only a few examples where missed doses can cause severe problems.
- *Can the patient communicate his or her needs freely regarding drug administration?* This may involve a lack of command of the English language, sensory problems (e.g. loss of vision or hearing), or loss of voice (e.g. postlaryngectomy). It may also involve cognitive deficits such as confusion or dementia.
- *If several tablets are involved, is the patient able to swallow oral medications?* Does the patient possess a sensory or motor deficit that impedes self-administration of drugs (e.g. rheumatoid arthritis, loss of sight)?
- *What sources of objective data are available?* Include the patient's health history, progress notes, laboratory reports and diagnostic tests in formulating data concerning the patient's response to medication. These, together with baseline and ongoing vital-sign measurements and physical assessments, form the basis of monitoring the therapeutic or adverse effects of medications. Laboratory tests of liver function (e.g. serum bilirubin, alkaline phosphatase, gamma-glutamyl transferase levels) and kidney function (e.g. serum potassium, urea, creatinine levels) are very helpful because certain drugs can damage these organs. Furthermore, liver and kidney damage can lead to altered drug excretion and metabolism, thus requiring a decrease in dosage (see Chapter 14). Other important

and common laboratory tests include analysis of microbiology and culture specimens before antibiotic administration, monitoring of serum potassium levels before digoxin therapy, and monitoring of clotting tests before and during anticoagulant therapy.

DIAGNOSIS

The assessment statements describe the patient's actual or potential needs and are based on the analysis and interpretation of assessment data. A diagnosis statement comprises the identification of an actual or potential patient problem, the cause of the problem, and the clinical manifestations of an actual problem.

The following diagnoses are applicable to drug administration.

- *Non-adherence* related to:
  - patient or family misunderstanding of directions;
  - poor vision or hearing of the patient;
  - lack of affordability of the drug;
  - patient's inability to get the prescription dispensed at a pharmacy due to immobility;
  - patient's confusion with medications, leading to administration in incorrect amounts or at the wrong times;
  - patient's inability to manage a new route of administration (e.g. self-injection of insulin);
  - intolerable adverse reactions (e.g. postural hypotension with antihypertensives);
  - patient's inability to accept a particular medical diagnosis (e.g. adolescent with asthma);
  - lack of control of the problem in the doses designated by the doctor's order (e.g. patient experiencing severe pain following a surgical procedure).
- *Knowledge deficit – drug therapy regimen related to:*
  - misunderstanding of the benefits and adverse effects of drug therapy;
  - lack of availability of drug information explained in a simple and thorough manner.
- *Knowledge deficit – safe and effective self-administration related to:*
  - patient's fear of implementing the task associated with self-administration (e.g. self-injection with insulin);
  - lack of explanation at time of discharge involved in practising the task required for self-administration.
- *Potential for injury – adverse drug reactions related to:*
  - central nervous system depressant effects, leading to altered level of consciousness;
  - damage caused to specific organs (e.g. altered levels of magnesium, calcium and potassium causing cardiac damage; nephrotoxic drugs such as **vancomycin** causing kidney damage; ototoxic drugs such as gentamicin causing ear damage).

PLANNING/GOALS

This step involves stating the expected outcomes of drug therapy. These goals are expressed in terms of the patient's behaviour rather than the nurse's behaviour. Goals may be either short-term or long-term. A short-term goal can be achieved very quickly, often during a period of hospitalisation or a home visit. A long-term goal is one that may be achieved in the future. Long-term goals usually focus on health promotion, rehabilitation and health education (see Chapter 5 for further information about teaching and learning strategies for drug therapy). Relevant aspects pertaining to the planning phase of drug therapy include the following:

- The patient will receive and understand relevant education about the drug therapy and will:
  - receive all drugs as prescribed;
  - tend to self-administration of drugs in an accurate and safe manner (if applicable);
  - display a good knowledge of essential drug information;
  - maintain appointments for monitoring and follow-up.
- The patient will receive the safe administration of the drugs and will:
  - display the therapeutic benefits of drugs;
  - avoid the occurrence of adverse drug reactions.

In planning the safe administration of drugs, the nurse will carefully analyse the patient's subjective and objective data. For instance, if the radial pulse is 50 beats per minute, then the patient will not receive cardiotoxic drugs such as **digoxin**; if the patient's international normalised ratio (INR) is four, then a **warfarin** dose will be withheld. A nursing plan will incorporate the five rights of drug administration, which are discussed in detail in Chapter 9.

It is also important to ensure that the correct techniques and equipment are used for drug preparation (e.g. syringes, needles, sterile water, alcohol swab, additive labels for intravenous antibiotics).

IMPLEMENTATION

This step involves putting into action the plan of care. Interventions may be dependent, independent or interdependent. A *dependent intervention* is a nursing activity requiring a doctor's order. An *independent intervention* is one that does not require consultation or collaboration with other health-care professionals. An *interdependent intervention* is one that is implemented in collaboration with the health-care team. Relevant aspects pertaining to the implementation phase of drug therapy include the following:

- The nurse will administer the drugs as prescribed, in the manner required by the agency's policies and procedures.

- Several non-drug interventions can be employed to improve the therapeutic effects or to nullify the adverse effects of drugs. These interventions include:
  - handwashing between patients and maintaining a meticulous aseptic dressing technique to prevent infection;
  - maintaining body alignment of patients when positioning in a bed or chair and turning bed-bound patients at least 2-hourly for pressure-area care;
  - assisting patient to cough and deep-breathe, especially in bed-bound and postoperative patients;
  - assisting and encouraging ambulation;
  - applying heat and cold treatments (e.g. tepid sponge, hot and cold compresses) to relieve pain and itchiness and to lower body temperature;
  - changing the level of sensory stimulation;
  - scheduling nursing activities to allow for adequate periods of rest and sleep.
- The nurse should provide accurate records and interpretations of the effects of drugs on vital signs, fluid intake, urine output and other assessment data. The medication order should be documented promptly immediately after administration.

EVALUATION

This step involves assessing the patient's status in relation to stated goals and expected outcomes. The patient's progress towards goal achievement governs future directions for reassessment, prioritisation, new goal-setting, anticipated outcomes and revision of the care plan. Relevant aspects pertaining to the evaluation phase include the following:

- The nurse determines whether the therapeutic benefits of the drug are apparent. The nurse should, therefore, know the expected effects of the drugs administered and when to expect these effects.
- Adverse and unwanted reactions should be observed. These effects are more likely in patients with severe liver or renal disease, very young and elderly patients, those receiving large doses of a drug, and those receiving several drugs.
- The nurse will observe whether the patient is experiencing any difficulties in compliance.
- The patient is observed for ability to undertake self-administration of the drug.
- The nurse must also be aware of the common drug–food and drug–drug interactions that may occur (see Chapter 15). As most patients often receive two or more medications, a drug interaction may be the cause of an unexpected response.
- Some drugs are potentially toxic or possess a therapeutic range that is close to the toxic dose range (i.e. have a narrow margin of safety). For some antimicrobial drugs, the antibacterial activity is dependent on a relatively high peak level in the blood. The blood levels of these drugs are checked routinely to ensure that the required dose is within the therapeutic range. Common examples include quinolones (e.g. **nalidixic acid**, **ciprofloxacin**) and aminoglycosides (e.g. **gentamicin**, **tobramycin**) (see Chapter 68).
- A patient should be observed for an allergic response to medications. Typically, this reaction does not occur on the primary exposure to the drug, as time is needed to create antibodies required for an allergic reaction (see Chapter 17). Once the patient exhibits an allergic reaction, the nurse documents this information on the patient's identity label, history and drug chart.
- The potential for drug tolerance should also be considered, particularly in patients receiving long-term analgesic cover. Tolerance is the situation where repeated use of the drug creates a lesser response unless the dose is raised. A patient receiving a narcotic analgesic for acute pain is unlikely to become tolerant because, when the pain starts to decrease, then so too does the desire for the drug. As the pain continues to subside, the patient should be weaned off the narcotic gradually and placed on other types of analgesic. Note, however, that patients with severe chronic pain associated with terminal cancer are an exception to this consideration.
- In determining the required dose for a specific patient, much consideration is placed on assessment data so that the potential for toxic effects is low. Certain patients, however, have a greater potential for developing toxic effects and should, therefore, be monitored closely. For instance, patients admitted into emergency departments following a drug overdose would almost certainly exhibit toxic effects. Similarly, administration of drugs with a narrow margin of safety may lead to toxicity if drug levels are not monitored regularly.

SUMMARY

- The clinical decision-making process follows five steps: assessment, diagnosis, planning, implementation and evaluation.
- Assessment involves the collection of information that is likely to affect the patient's medication therapy.
- Diagnosis involves identifying an actual or potential patient problem, the cause of the problem, and the clinical manifestations of an actual problem.
- Planning concerns involve stating the expected outcomes or goals of medication therapy, which are expressed in terms of the patient's behaviour. Goals may be either short-term or long-term.
- Implementation involves putting into action the plan of care through interventions. Interventions may be dependent, independent or interdependent.
- Evaluation involves assessing the patient's status in relation to expected outcomes.

1 Identify the important components of the clinical decision-making process.

2 Maria Bombardi, a patient who has developed a severe chest infection, is commenced on vancomycin therapy. What aspects will you evaluate while the patient is on this therapy?

3 Jane Black has commenced a course of digitalis therapy for congestive cardiac failure. What aspects will you evaluate while the patient is on this therapy?

DRUG ADMINISTRATION STRATEGIES AND DOCUMENTATION

9

CHAPTER NINE

OBJECTIVES

KEY TERMS

Five rights of administration
Trust policy and procedure
Checking procedure
Documentation procedure

After completing this chapter, the reader should be able to:

- **describe the five rights of drug administration;**
- **describe the checking procedures for medication administration;**
- **describe the documentation procedures for various types of medications.**

THE PRINCIPLES THAT ENSURE A HIGH STANDARD OF nursing practice in drug administration are covered in this chapter. These principles include the five rights of drug administration, agency policies and procedures, and checking and documenting strategies.

FIVE RIGHTS OF DRUG ADMINISTRATION

Accurate drug administration centres on the 'five rights': giving the right drug, in the right dose, to the right patient, by the right route and at the right time. Although on the surface it may appear that these five rights should be relatively easy to achieve, each right requires considerable knowledge, skill and concentration.

Right drug

In providing the right drug, the nurse should interpret the doctor's order accurately. If the drug appears to be unfamiliar, the information is checked with an authoritative source, such as pharmaceutical references (e.g. *British National Formulary* (BNF), *MIMS*) or other health-care professionals. To understand whether a particular drug is suitable for a specific patient, the nurse must know and comprehend the patient's health problems and the way in which the drug will assist in providing therapeutic benefit. Careful attention is paid to the labels of drug containers, ensuring that they match up with the drug orders. The prescribing doctor should be questioned about the order if the name of the drug is unclear or if the drug appears inappropriate for the patient's health condition.

Right dose

Providing the right dose is extremely important. Here, the nurse should interpret measurements and abbreviations accurately. Drug calculations should be made carefully and then rechecked for correctness before administration.

The nurse must also determine whether the dose is an appropriate one for the size, age and condition of the patient.

Right patient

In identifying the right patient, the nurse should check the identification bands of institutionalised patients and verify the identity of other patients. This checking procedure must be undertaken every time a drug is administered.

Right route

In ensuring the right route, the nurse must use the correct technique for drug administration. Some drugs can be given only by a specific route, and serious problems may develop if other routes are used. For example, sympathomimetic agents such as **adrenaline**, **noradrenaline** and **dopamine**, which are commonly used in critical-care areas, cannot be given through a peripheral vein, as they can cause necrosis of extremities. Furthermore, the nurse must use appropriate anatomical landmarks in identifying areas for intramuscular injections. If the sciatic nerve is damaged on injection, then paralysis of the limb may occur.

Right time

Providing the patient with the dose at the right time may be difficult to accomplish, particularly in a busy ward, where a nurse is responsible for a number of patients. If this is the case, it is important that the nurse concentrates on providing parenteral medications at the recommended schedule, as time plays a critical role in their therapeutic effects (e.g. subcutaneous **insulin** and intravenous antibiotics).

NHS TRUST POLICIES AND PROCEDURES

A nurse must practise within the policies and procedures of the NHS trust and follow the legal framework of government legislation. Policies relate to general principles by which a trust manages its affairs. A nurse employed by a trust is required to know these policies and to follow the procedures that lead from them. Generally, policies and procedures are developed to complement and integrate with legal guidelines. Although policies and procedures may differ between trusts, most have fairly strict and detailed guidelines on drug administration.

CHECKING PROCEDURES

Guidelines for the administration of medicines are published by the Nursing and Midwifery Council. Some drug administrations require complex calculations, and it may be necessary for a second practitioner to check the calculation in order to minimise the risk of error. It is unacceptable to prepare substances for injection in advance of their immediate use or to administer medication drawn in a syringe by another practitioner.

The administration of controlled drugs requires that two nurses check and sign the controlled drug register. One of these may be a student nurse if he or she feels confident to do so. Student nurses need to be involved with qualified staff when administering medicines. The registered practitioner must remain with the student throughout and is the responsible signatory on the drug sheet. Accountability for patient safety and adherence to local trust policies remains with the registered nurse at all times.

DOCUMENTATION PROCEDURES

An important aspect of drug administration involves careful and accurate documentation. Although several medications require two health-care professionals to check the

information, the documentation usually has space for only one set of initials or signature.

It is important to document the therapeutic and/or adverse effects of a drug on the observation chart, especially if the reaction is of significance or intended to resolve a specific problem. Common examples include pain relief, blood pressure control and alleviation of nausea and vomiting (see Figure 9.1). As an anaesthetic affects the cardiovascular, respiratory and neurological systems, the nurse should conduct routine post-anaesthetic observations for a time after the patient's return to the ward setting (see Figure 9.1).

FIGURE 9.1 OBSERVATION CHART

Routine post-anaesthetic observations taken on a client post-appendicectomy. Note that pethidine and metoclopramide (Maxolon) were given for pain and nausea, respectively, with reference made to dose, route and time of administration. Effects on vital signs and other clinical manifestations are indicated.

OBSERVATION CHART

U.R. Number: 765432
Surname: BLOGGS
Given Names: Cindy Jane
Address: 1 Smith Street
Smithsville
Date of Birth: 1.1.1970 Female

Routine Post-Anaesthetic Observations
(RPAO)

Date	Time	T	P	R	BP	Pupils				Limb move.	Consc. state	Nursing Comments
						Site		React				
						R	L	R	L			
1.1.04	0700	36^{6}_{PO}	70	18	110/70	equal		✓	✓	S	N	Pre-operative obs.
	1/2 hourly obs — 4 hrs											(appendicectomy)
	1030	36^{2}_{PO}	106	16	100/60	equal		✓	✓	N/S	D	Dressing dry and intact
	1100		110	18	140/80					S	D	Dressing dry and intact
	1130		120	22	140/90					S	D/N	c/o abdo. pain & nausea
	1200		108	18	136/84					S	D/N	pethidine 75 mg & Maxolon 10 mg IM @ 1140
	1230	36^{4}_{PA}	100	16	130/80					S	D/N	Pain and nausea relieved
	1300		90	18	120/76					S	D/N	Dressing dry and intact
	1330		76	18	114/72					S	D/N	Dressing dry and intact
	1400		72	18	110/70					S	N	Dressing dry and intact
	1430	36^{8}_{PA}	70	18	110/65					S	N	Dressing dry and intact
		obs. — 4/24										
	1830											

Abbreviations:

Limb movements

S – Spontaneous
NS – Not spontaneous, in response to command
P/S – In response to painful stimuli
N/R – No response to painful stimuli

State of consciousness

N – Normal
D – Drowsy but rousable, will speak and respond to command
SC – Unconscious, responds to painful stimuli only
C – Comatosed, not responding to painful stimuli

SELF-ADMINISTRATION OF MEDICINES

The Nursing and Midwifery Council supports the self-administration of medicines wherever this is appropriate. There must be safety and security of storage and agreed trust procedures in place. If a patient commences a medication while in hospital, it will be advantageous for the patient to self-administer before discharge so that any problems can be dealt with while professional advice is available. Records should still be maintained, and patient education is needed to support their self-administration. Quite often the patient is the most reliable person in ensuring that the medication is taken on time.

CONCLUSION

Although several health-care professionals are involved in patients' drug regimens, nurses possess the major share of the responsibility. In the sequence of events progressing from drug supply leading to patients receiving their medications, nurses are the linchpin. Nurses' duties also involve direct patient care more so than any other health-care professional. Nurses are, therefore, in an ideal position to ensure a high standard of patient care in relation to drug therapy. This chapter has explained the drug administration strategies and documentation that contribute to realising this standard.

SUMMARY

- Accurate medication administration centres on the 'five rights': giving the right drug, in the right dose, to the right patient, by the right route and at the right time.
- A nurse must practise within the policies and procedures of the employing health-care institution and follow the legal framework of government legislation.
- Certain groups of medications need to be checked by two nurses because they are potent, potentially dangerous or addictive.
- Nurses need to document that they have administered a medication immediately following completion of the task. Nurses should also document the therapeutic and adverse effects of medications on the observation chart or medical history.

1 As a nursing student, you are asked to assist in the checking procedure of a morphine ampoule from the locked, dangerous-drugs cupboard. Outline what is involved in this procedure.

2 Describe the checking procedure involved in administering warfarin to a patient.

MEDICATION ERROR

10

CHAPTER TEN

OBJECTIVES

KEY TERMS

Medication error
Right drug
Right patient
Right dose
Right route
Right time

After completing this chapter, the reader should be able to:

- **define the term 'medication error';**
- **describe the five cardinal rights of drug administration;**
- **describe strategies that could be implemented in order to avoid medication errors.**

THE ADMINISTRATION OF MEDICATIONS IS ONE OF THE MOST common duties undertaken by a registered nurse. As some nurses may consider this task a routine procedure, complacency may take over from meticulous and safe practice. Conversely, some nurses may feel overwhelmed and have trouble in keeping up with the sheer number of drugs available. Others may experience extreme pressure in having to handle several important responsibilities with little time to spare.

THE FIVE CARDINAL RIGHTS OF DRUG ADMINISTRATION

There are several causes of errors, but fundamentally they all stem from the five cardinal rights of drug administration (see Chapter 9). The five cardinal rights involve giving the right drug to the right patient, at the right dose, by the right route and at the right time. Some examples that are potentially dangerous or that lead to ineffective medication use are listed here:

- The wrong drug is given, as it is mistaken for another drug of a similar name.
- The wrong dose is ordered on the drug chart.
- An error is made in calculating the mass or volume, so the patient receives the wrong dose.
- The drug is given by an incorrect route.
- The right dose is ordered, but because of illegible writing an incorrect dose is administered.
- The patient's identity is not checked, and subsequently the wrong drug is administered.
- The drug is administered to a patient who is experiencing an adverse reaction that warrants discontinuation of the drug.
- The patient takes the drug by the correct route but consumes the drug in an incorrect way (e.g. enteric-coated tablets).
- The patient takes the drug at the wrong time.
- The patient takes the drug concurrently with another drug that is contraindicated.
- The patient takes two tablets simultaneously that are very similar in action and use, thus leading to a drug overdose.

AVOIDING MEDICATION ERRORS

Although drug administration is one of the most problematic areas of nursing responsibility, the use of guidelines based on common sense will be most helpful in preventing errors. Each drug order should be read carefully, noting whether the particular drug is applicable for the patient at the specific dose. Never assume that, just because the medicine has been dispensed on a previous occasion, it must be correct. If there is any doubt about the information noted down on the drug order, consult one of the doctors, a nursing colleague or a drug reference book. If the writing is unclear, seek clarification from the doctor who wrote the order. The checking procedure for medications involves reading the container on three occasions: The first is when the medication is obtained from the drug trolley; the second is just before it is prepared and administered; and the third is just before the container is returned to the drug trolley.

Always check the patient's identity carefully, even when giving oral drugs. The nurse should check that the patient's name and unit record number match up with those noted on the drug order. This may seem rather time-consuming, especially if several drugs need to be given out to a large number of patients; however, employing this strategy as standard practice before administering any drug is the best way of preventing the drug being given to the wrong patient. As two patients may possess the same name, it is also important to check the unit record number against the drug order. It is also a good strategy to have two patients with the same name positioned next to each other. In this way, all health-care professionals involved in their care will be more aware of the issue. The medication chart and patient wrist labels may also be documented with this information to further alert the health-care professionals.

If a patient takes oral medication regularly, be sure to gauge the technique carefully. For instance, ensure that the patient drinks enough water to swallow the tablets properly. Tablets and capsules may lodge in the oesophagus if little or no water is used, leading to tissue trauma. Other patients make the mistake of chewing or breaking enteric-coated or delayed-action (slow-release) tablets. Destroying an enteric-coated tablet allows exposure of the drug to the stomach lining and may cause gastric irritation. Similarly, crushing a delayed-release tablet allows too much drug to be absorbed at once, which could lead to a toxic drug level.

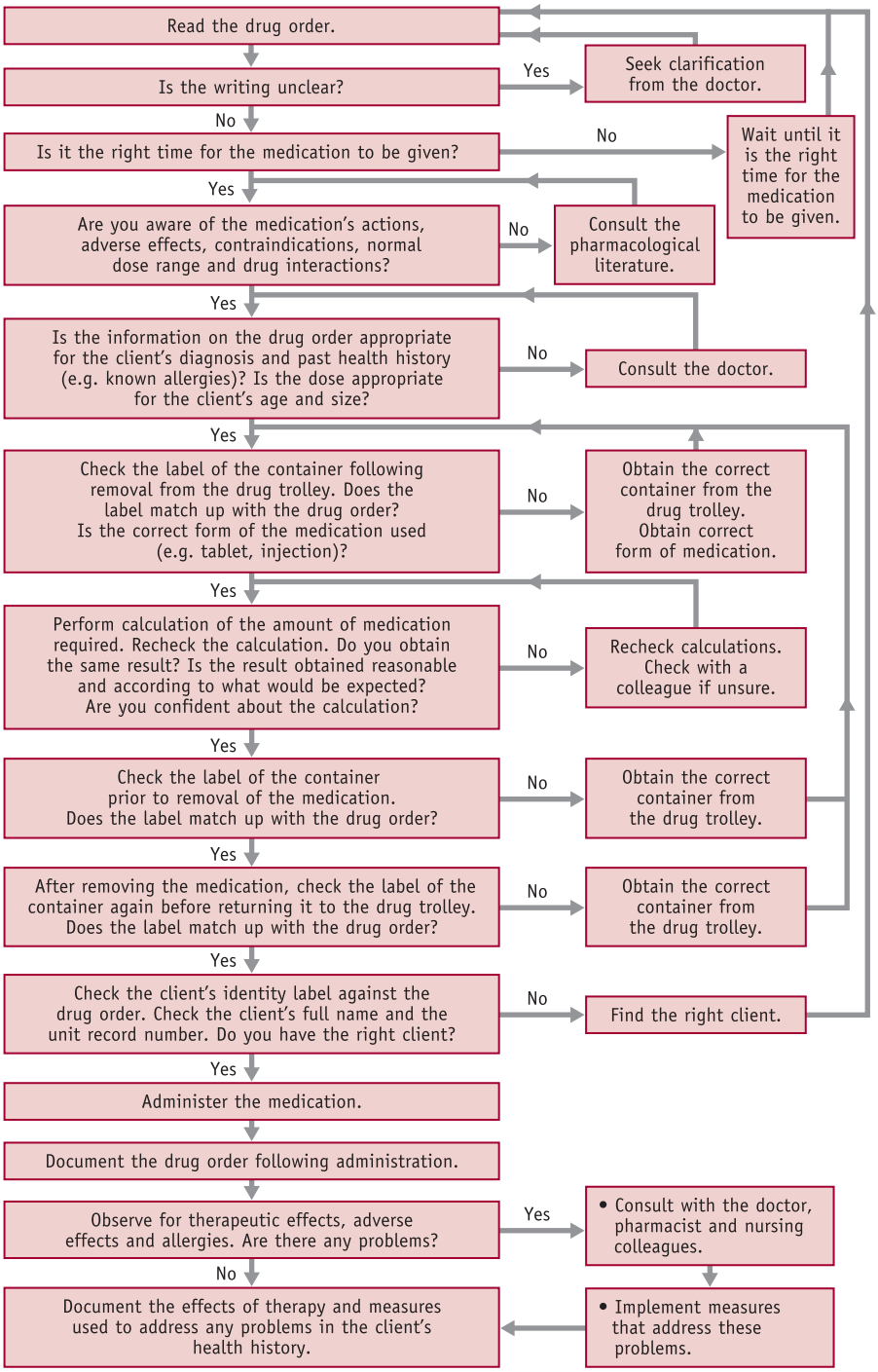
Always take note if patients question their medications, as they tend to become very familiar with their drug regimen, especially if it has remained unchanged for a period of time. Examples include 'What happened to the white pill I usually take in the morning?' or 'I don't normally have this tablet at this time of the day.' If the patient is not present, never leave the medications at the bedside, as you run the risk not only of your patient not taking the medications but also of the wrong patient taking it. Visiting young children may also accidentally consume medications that are left lying around.

Ensure that drug calculations are checked carefully. Where two nurses are required to check a dose (e.g. for parenteral administration of drugs), each nurse should calculate the result separately and then compare it with the other's result. The use of calculators is acceptable, although it is better practice to get into the habit of doing calculations manually. Calculators are not infallible, nor are they always readily available, and manual competence improves mathematical ability for logic. If calculators are used, you need also to be able to estimate the correct amount manually as a further check of the result. Always be very wary of amounts that appear unbelievably large or small (e.g. 1000 drops per minute or 10 tablets per dose). Remember: Always recheck your calculations.

If the doctor orders the drug to be given at particular time intervals, the nurse should never deviate from this time by more than half an hour. For instance, if the doctor orders **erythromycin** every 6 hours, this can be translated to mean

FIGURE 10.1 SEQUENCE OF EVENTS AND CHECKING PROCEDURE FOR DRUG ADMINISTRATION

Flowchart indicating the components of events and sequence for drug administration. The checking procedure involves the five rights of drug administration (right drug, right dose, right patient, right route and right time). Note, in particular, the number of times the medication is checked, and the signing of the drug order following drug administration.



6 a.m., 12 noon, 6 p.m. and 12 midnight (or 8 a.m., 2 p.m., 8 p.m. and 2 a.m.). Either way, the patient would have to be given a dose late in the evening. Attempting to change the midnight dose to 10 p.m. is an unsafe practice: It means therapeutic drug levels will not be maintained as the administration times are no longer regular and consistent.

On administration of the drug, ensure that this is followed up with documentation of the drug order, which is completed after the patient has been observed taking the drug. It is also important to document when a drug is withheld or omitted. This issue is particularly important for as-required, or prn, medications, which are administered depending on the patient's need. The patient's response to the drug should also be documented, especially if a problem develops. In this case, the nurse should document clearly the actions taken to rectify the problem.

Figure 10.1 shows the sequence of events and checking procedure for drug administration. It incorporates the five rights of drug administration and identifies strategies that the nurse should use in order to avoid medication errors.

MANAGEMENT OF ERRORS

The Nursing and Midwifery Council (NMC) emphasises the importance of maintaining an open culture to encourage the immediate reporting of errors and incidents in the administration of medicines. Any error should be reported immediately to the practitioner's line manager. The NMC recommends thorough and careful investigation at the local level with sensitive management that does not discourage future reporting of such incidents. The NMC also supports the use of multidisciplinary critical incident panels, where improvement to local practice can be discussed.

CONCLUSION

Due to the sophistication of current medication regimens and the demands of the health-care setting, it is possible that medication errors will occur. By using a systematic approach to administration, however, problems relating to medication error can largely be avoided.

SUMMARY

- Each medication order should be read carefully, noting whether the particular drug is applicable for the patient at the specific dose, using the specified route and at the indicated time.
- The checking procedure involves reading the container on three occasions. The first is when the medication is obtained from the drug trolley; the second is just before it is prepared and administered; and the third is just before the container is returned to the drug trolley.
- If a patient takes oral medication regularly, be sure to observe the technique carefully.
- Always take note if patients question their medications, as they tend to become very familiar with their drug regimens.
- Ensure that drug calculations are checked carefully.
- If the doctor orders a medication to be given at particular time intervals, the nurse should never deviate from this time by more than half an hour.

1. Graduate nurse Clara Jones has been assigned to care for four patients, two of whom are named Mr Smith. What strategies can Clara implement in order to avoid medication errors relating to these two patients?
2. State the five cardinal rights of drug administration, and give examples of each right.
3. You notice a new nurse on your ward has left the medications for Jack Jones on the bed table. The patient has left the ward to have an X-ray taken. Is this good practice on the part of the nurse? Why or why not?

MANAGEMENT OF COMMON ADVERSE DRUG REACTIONS

11

CHAPTER ELEVEN

OBJECTIVES

After completing this chapter, the reader should be able to:

- **define what is meant by an adverse drug reaction;**
- **identify the two broad classifications of adverse drug reactions;**
- **describe the management of common adverse drug reactions;**
- **describe the Yellow Card System for reporting adverse drug reactions.**

KEY TERMS

Adverse drug reaction
Predictable reaction
Unpredictable reaction

ALTHOUGH THE PRINCIPAL AIM OF DRUG THERAPY IS TO provide maximal therapeutic benefits while minimising adverse effects, adverse reactions continue to be a problem. With some drugs, adverse reactions are very common. It is important to consider the undesirable effects as well as the therapeutic effects following medication administration and the action to take if an individual experiences an adverse drug reaction. In some cases, the dose may need to be reduced or the medication may need to be stopped altogether. The symptoms experienced by the individual also need to be managed in an appropriate manner. Depending on the severity of the disease being treated, the risk associated with an adverse drug reaction may be considered reasonable – as with, for example, medications used in the treatment of cancer and life-threatening dysrhythmias.

DEFINITION AND CLASSIFICATION

Adverse drug reactions are undesirable effects that occur with the administration of medications at normal doses. They can occur as a part of the normal pharmacological profile of the particular drug (type A reactions), or they may be unrelated to the drug (type B reactions). When an adverse drug reaction occurs as a result of the pharmacological profile of the drug, it is known as a predictable effect. Predictable effects take place soon after the drug is initiated or when a medication dose is increased. Examples of drugs that exhibit predictable adverse effects include anticoagulants, which produce bleeding, cardiac glycosides, which produce cardiac dysrhythmias, and **insulin**, which produces hypoglycaemic coma. In most situations, adverse reactions arising from predictable effects are reversible by decreasing the dose or by changing to another drug. In other situations, however, the effect can be fatal.

Adverse drug reactions that are unrelated to the pharmacological action of the drug are classified as unpredictable reactions. These reactions include those that are immunologically mediated effects, those that involve genetic differences in drug metabolism and those whose underlying mechanism is not known. In this case, the onset of the adverse drug reaction is not related to the initiation of the drug or the dose administered and is often delayed. Examples of drugs that exhibit unpredictable effects include the sulphonamides, which are associated with generalised erythema multiforme (Stevens–Johnson syndrome), and **chloramphenicol**, which is associated with aplastic anaemia. As the adverse drug reactions arising from unpredictable effects are not related directly to a particular drug, these reactions are more difficult to manage. Drug hypersensitivity reactions, which are immunologically mediated adverse effects, are described in Chapter 17.

Medication-related problems account for a large proportion of hospital admissions. Drug-related problems account for as many as 5 per cent of all admissions to UK hospitals. Furthermore, for older people the proportion is higher, constituting 10–12 per cent of all acute admissions. Patients over the age of 65 years account for approximately 50 per cent of all those admitted for drug-related causes. More specifically, studies have shown that adverse drug reactions occur in up to 30 per cent of hospitalised patients. Clearly, the incidence of adverse drug reactions is a major concern for all health-care professionals, and great care must be exercised to determine who is at risk of having an adverse drug reaction, the types of drug that cause particular adverse drug reactions, and the management of adverse effects.

COMMON ADVERSE EFFECTS OF DRUGS

Tables 11.1–11.20 identify the most common adverse reactions caused by drugs, and list their associated actions and rationales for management. The actions indicated are of a collaborative nature, which means they are performed in conjunction with all members of the health-care team. The nurse performs some actions autonomously, while other actions require a doctor's authorisation. Common drug groups causing adverse reactions are also indicated.

Respiratory depression

Respiratory depression (see Table 11.1) is a pattern of regular respirations with a rate of fewer than 12 breaths per minute. The respiratory centre regulates breathing, which functions as a coordinated unit in the medulla and pons. A decrease in respiration occurs when there is insufficient cerebral perfusion to activate the neurones of the respiratory centre, when changes in arterial carbon dioxide levels affect chemoreceptor responsiveness, or when neuron responsiveness to changes in arterial carbon dioxide levels is reduced. Medications that commonly affect respiration are the central nervous system (CNS) depressants.

Anaphylactic shock

Anaphylactic shock (Table 11.2) is a dramatic acute reaction characterised by respiratory distress, angio-oedema, cardiovascular collapse, vomiting and urticaria. It culminates as systemic shock and may lead to death (see Chapter 17 for a description of the pathophysiology). The cause of anaphylactic shock is administration of a sensitising drug. The most common cause of anaphylaxis is **penicillin**, which affects approximately 4 in every 10 000 individuals. Penicillin allergy is more likely to occur in people with a familial history of atopic allergy.

Dizziness

Dizziness (Table 11.3) is a sensation of imbalance or faintness, which is also associated with weakness, confusion and blurred or double vision. Episodes of dizziness are usually short, with an abrupt or gradual onset. It is often aggravated by standing up quickly and is improved by lying or sitting down. Dizziness results from an inadequate or irregular blood flow to the brain and spinal cord.

Constipation

Constipation (Table 11.4) involves infrequent and difficult bowel movements. Normal bowel movements vary quite widely between individuals. It is important, therefore, to determine the problem in relation to the individual's particular pattern. The autonomic nervous system is responsible

TABLE 11.1 RESPIRATORY DEPRESSION

Common causes: narcotic analgesics; barbiturates; phenothiazines; general anaesthetics; any of these drugs when given with alcohol will compound the problem

Action	Rationale
(i) Assess the rate of respiration (attempt to maintain above 12 breaths/min for an adult)	(i) To determine effectiveness of intervening measures and to provide an evaluation of the current problem
(ii) Auscultate the chest bilaterally for strength of respiration	(ii) To determine equal air entry on both sides; CNS depression may lead to decreased strength of respiration
(iii) Auscultate abnormal breath sounds (wheezing, crackles)	(iii) Wheezing is associated with decreased diameter of respiratory airways, while crackles occur with fluid in airways; both conditions may accompany respiratory depression
(iv) Assess respiratory status regularly	(iv) Frequent observations are required to determine whether depression leads to apnoea
Be prepared to provide respiratory support in mechanical ventilation and intubation if required	To prevent hypoxia and respiratory failure
Position: (i) If patient is conscious, place in a semi-Fowler's position (ii) If patient is unconscious, place to one side; keep suction source connected and close at hand	(i) To facilitate manual chest expansion and ease of movement of lung muscle (ii) To prevent aspiration of secretions
If patient is drowsy, assess neurological status by checking pupil size and reactivity, ability to obey commands, verbal response and orientation	Allows evaluation of the degree of central nervous system depression
Do not leave the patient unattended; keep the bed in the lowest position, with cot sides up	A decreased level of consciousness can lead to physical injury
If the cause is a suspected overdose from drug abuse, attempt to determine the drug(s) taken, how much, when and by what route; check the patient's arms for track marks; take blood and urine samples for drug identification	Allows determination of the drug abused and the best means of intervention
If a narcotic analgesic is the cause, administer naloxone; assess return of normal respiration and the onset of withdrawal symptoms in addicted patients	Naloxone is a specific narcotic antagonist that reverses the toxic effects within a few minutes
Obtain arterial blood gases and electrolyte levels as ordered	Respiratory depression can manifest as a fall in blood oxygen and a rise in blood carbon dioxide; allows monitoring of the effectiveness of interventions
Oxygen by face mask/nasal prongs as ordered	Provides supplemental oxygen

TABLE 11.2 ANAPHYLACTIC SHOCK

Common causes: antibiotics; aspirin and other non-steroidal anti-inflammatory drugs; angiotensin II receptor blockers; angiotensin-converting enzyme inhibitors; barbiturates; contrast media; transfused blood or blood products; snake/spider antivenom; immunoglobulins

Action	Rationale
Identify the cause and, if possible, discontinue therapy	Limits extent of anaphylactic reaction
If response occurs during blood administration, discontinue transfusion and replace with normal saline; return the unused portion to the blood bank, take a blood sample from patient's other arm and send specimen to pathology	Intravenous access can remain open and is readily available for emergency drug administration; blood specimen allows determination of a hypersensitivity reaction to a specific allergen
Secure intravenous access as soon as possible	Allows for rapid absorption of medications that may need to be administered
In cases where the cause cannot be removed (e.g. injection or ingestion of a drug), measures are needed to reverse the effects of the mediator substances:	
(i) Mainstay of treatment, adrenaline, 0.5 ml of 1 : 1000 solution IM (0.5 mg), repeat every 5 minutes	(i) To restore vascular tone and raise blood pressure
(ii) Antihistamine: chlorphenamine 10–20 mg given after the adrenaline and continued for 24–48 h	(ii) To reverse adverse effects of histamine (vasodilation, bronchospasm)
(iii) In severe cases, hydrocortisone 100–300 mg IV stat	(iii) To reverse effects of immune mediator substances and decrease capillary permeability and, hence, decrease shift from blood vessel to interstitial space; note that antihistamines and corticosteroids have a delayed effect; they may help to reduce the duration of reaction and prevent relapse but they are supportive agents in the management of anaphylaxis and should not be used instead of adrenaline
(iv) Aerosol or nebulised short-acting β-agonist	(iv) To relieve bronchospasm
Assess temperature, pulse (rate, rhythm, depth), respiration (rate and depth) and blood pressure; observe for drop in blood pressure, rising and irregular pulse, increasing rate and depth of respiration and falling temperature	Antibody–antigen reaction causes release of vasoactive substances, leading to massive vasodilation and decreased cardiac output and decreased peripheral vascular resistance; histamine causes bronchoconstriction, leading to difficulty in and rapid breathing; release of vasoactive substances also causes increased capillary permeability and subsequent shift of fluid from blood vessel into interstitial space; pulse may be irregular from cardiac ischaemia
Assess for chest pain (onset, intensity, duration)	Decreased peripheral vascular resistance leads to lowered diastolic blood pressure and hence lowered coronary artery perfusion
Assess peripheries for colour, warmth, pulses, oedema and moistness; observe for pale or flushed, moist, cool skin; take note of any macular or papular rashes	Sympathetic nervous system causes blood to be shunted away from skin to vital organs; increased sweat gland activity causes moistness and clamminess; decreased cardiac output leads to lowered tissue perfusion; shift of fluid from blood vessel to interstitial space causes oedema
Auscultate chest: listen for equal air entry, wheezes, crackles; check for manifestations of respiratory distress: flaring nares, downward movement of trachea, use of accessory muscles, orthopnoea	Due to bronchoconstriction from histamine release; progressive respiratory changes lead to interstitial oedema

TABLE 11.2 ANAPHYLACTIC SHOCK (*continued*)

Action	Rationale
Establish a patent airway: suction secretions, postural drainage, oral airway	Assists in establishing access of air to respiratory passages
Ensure adequate breathing: encourage coughing and deep breathing regularly; if respiratory muscles are fatigued and patient hypoventilates, mechanical ventilation and intubation are indicated	Ensures adequate ventilation and gaseous exchange
Administer intravenous fluids as ordered: crystalloids (normal saline); colloids (Haemaccel, human albumin)	Replaces volume lost in intravascular area (blood vessels)
Administer positive inotropic agents as ordered (e.g. adrenaline)	Contractility usually decreased due to inadequate ventricular filling; positive inotropic effect of adrenaline increases stroke volume and cardiac output
Assess renal function; insert indwelling catheter for accurate urine measurement; accept levels of 30 ml/h or 0.5 ml/kg.	Decreased cardiac output leads to lowered perfusion of kidneys and decreased urine output

TABLE 11.3 DIZZINESS

Common causes: central nervous system depressants; narcotic analgesics; decongestants; antihistamines; antihypertensives; hypertensives; vasodilators

Action	Rationale
Assess frequency, intensity, onset and duration of dizziness; assess associated manifestations: headache, vertigo, drowsiness, blurred vision; aggravating factors: stooping over, standing up quickly; and alleviating factors: lying down, rest	To determine the severity of condition and effectiveness of interventions
Assess vital signs, especially an elevated or lowered blood pressure; take lying, standing and sitting blood pressure	Excessive vasoconstriction leads to an increase in peripheral vascular resistance and thus dizziness; a drop in systolic or diastolic pressure of > 10–20 mmHg between position changes suggests postural hypotension
Assess level of consciousness, motor sensory functions, reflexes, pupil size and reactivity	Dizziness may be associated with a decreased blood supply to the brain
Assess level of emotional stress, irritability, anxiety, insomnia and inability to concentrate	Anxiety can produce continuous dizziness, which may result from inadequate blood flow and oxygen supply to the brain and spinal cord
Institute measures that help the patient cope with stress and anxiety (e.g. relaxation, distraction therapy)	Assists in maintaining blood flow to the brain
If dizziness is experienced in an upright position, advise the patient to lie down, rest for a while and then rise very slowly	Allows opportunity for the baroreceptors and chemoreceptors to become accustomed to changes in position
Ensure the patient wears clothes that are not constricting around the neck; encourage patient to turn the head and body together, rather than just the head alone	Prevents compression of the carotid arteries and promotes central blood flow
Accompany the patient during ambulation; provide with a walking aid if needed	To prevent physical injury

TABLE 11.4 CONSTIPATION

Common causes: narcotic analgesics; antacids containing aluminium or calcium; antimuscarinics; tricyclic antidepressants; excessive use of laxatives

Action	Rationale
Assess size, consistency and frequency of bowel motions; inspect the abdomen for distension and auscultate for bowel sounds; percuss all four quadrants and gently palpate for abdominal tenderness	To determine the extent of bowel activity and severity of the problem
Assess the patient's level of mobility and stress; encourage graded activities and introduce regimens aimed at promoting relaxation; if the patient is bed-bound, reposition at least twice a day and encourage active and passive exercises	Acute emotional stress creates a sympathetic response, leading to decreased intestinal mobility; infrequent activity leads to decreased peristalsis
Ensure the diet contains a lot of high-fibre foods (e.g. fresh vegetables and fruit) and an adequate fluid intake	High-fibre foods and fluids shorten intestinal transit time and promote ease of defecation
Caution the patient not to strain during defecation	To prevent injury to recto-anal tissue
If the patient has not opened bowels for a number of days, the doctor should perform a per rectal (pr) examination wearing a disposable glove and using a lubricant; laxatives or enemas may be required, as ordered	Removes impacted faecal contents and determines the extent of the problem; laxatives and enemas mobilise faecal contents, allowing greater ease of defecation

for controlling bowel movements by sensing rectal distension from the presence of faeces and by relaxing the external rectal sphincters. If untreated, constipation may lead to a lack of appetite and abdominal discomfort.

Hypertension

Blood pressure relates to the force exerted on the blood vessels and is affected by cardiac output, peripheral vascular resistance and blood volume. Raised blood pressure (Table 11.5) generally involves a sustained increase above 140/90 mmHg. With sustained hypertension, arterial walls become thickened, less elastic and resistant to adequate blood flow. Individuals with hypertension may be asymptomatic or experience headaches, especially upon awakening, tinnitus, lightheadedness, fatigue and palpitations.

Hypotension

Low blood pressure (Table 11.6) means inadequate blood pressure to oxygenate the body tissues. Although low blood pressure varies among individuals, a reading below 90/60 mmHg or a drop of 30 mmHg from the baseline level is classified as low blood pressure. Low blood pressure can occur from an expanded intravascular area within blood vessels, such as vasodilation, reduced intravascular volume, such as dehydration and severe bleeding, or decreased cardiac output, such as cardiac failure and dysrhythmias.

Oral candidiasis

Oral candidiasis (Table 11.7) is a mild, superficial fungal infection caused by the *Candida* species. These fungi are part of the normal flora of the mouth and can produce infection when medications alter the balance of the flora. Oral candidiasis produces cream or blue-white patches on the tongue, mouth or pharynx. It is painful only occasionally, but it may cause a burning sensation around the mouth and throat.

Rash

A rash (Table 11.8) is a type of skin eruption. There are three types of rash. A papular rash consists of small, raised circumscribed lesions called papules. A pustular rash involves a collection of vesicles and bullae that fill with purulent exudate. A vesicular rash involves a distribution of singular or multiple vesicles that fill with clear, cloudy or bloody fluid. Medications can lead to the development of any of these types of rash.

TABLE 11.5 HYPERTENSION

Common causes: sympathomimetics; corticosteroids; oral contraceptives; monoamine oxidase inhibitors; central nervous system stimulants

Action	Rationale
Monitor blood pressure regularly and assess for changes in heart rate/pulse (usually tachycardia > 100 beats/min)	To determine the effectiveness of therapy; if blood pressure is consistently above 140/90 mmHg, further therapy may be required
Monitor for associated clinical manifestations: headache, epistaxis, visual disturbances, neck vein distension, peripheral oedema	Inappropriate vasoconstriction leads to signs of increased peripheral vascular resistance
If blood pressure remains consistently high, appropriate forms of treatment should be administered (e.g. α-adrenoreceptor antagonists, calcium antagonists, angiotensin-converting enzyme inhibitors)	Blood pressure reading consistently below 140/90 mmHg demonstrates effectiveness of treatment
Encourage patient not to drink large amounts of fluid (e.g. not > 1.5 l/day) and to avoid adding salt to food	Fluid and salt raise blood volume and potentiate any rise in blood pressure
Encourage stress-alleviating measures: relaxation exercises, massage	Stress stimulates the sympathetic nervous system, aggravating rises in blood pressure
Encourage adequate rest; elevate head of bed	Promotes drainage of fluid via gravity away from the brain
Over-the-counter preparations, such as cough and cold medicines, must be approved by the patient's doctor before use	Several of these preparations contain sympathomimetics, which may raise blood pressure

TABLE 11.6 HYPOTENSION

Common causes: calcium channel blockers; diuretics; antihypertensives; general anaesthetics; narcotic analgesics; monoamine oxidase inhibitors; benzodiazepines; antipsychotic drugs; antidysrhythmics; contrast media

Action	Rationale
Assess vital signs regularly: blood pressure for hypotension, heart rate (pulse) for tachycardia, respirations for tachypnoea; if dizziness or fainting occurs when patient stands suddenly, compare readings when patient is lying, sitting and standing	These manifestations relate to myocardial shock created by low cardiac output and require immediate intervention; a drop in systolic or diastolic pressure of at least 10–20 mmHg between position changes suggests postural hypotension
Check patient's blood pressure regularly; if drop is constant and < 90 mmHg (systolic):	
(i) Fluids may be needed as ordered (e.g. crystalloids such as normal saline or colloids such as Haemaccel, human albumin)	(i) To replace fluid in the intravascular area (blood vessels) after vasodilation
(ii) Vasopressor drugs may be given as ordered (e.g. metaraminol)	(ii) α-Adrenoreceptor stimulation causes vasoconstriction of arteries
Assess conscious state and pupil size and reactivity for decreased conscious state; if patient is conscious, determine associated symptoms: weakness, blurred vision, unsteady gait, chest or abdominal pain, difficulty in breathing, syncope, faintness or dizziness; palpate peripheral pulses, and determine strength and presence; assess peripheries for coolness, pallor and diaphoresis	Determines level of perfusion to vital organs and to peripheries

TABLE 11.6 HYPOTENSION (*continued*)

Action	Rationale
If signs of shock are present:	
(i) Establish intravenous line (e.g. peripheral or central venous catheter)	(i) To replace fluids or blood or administer drugs
(ii) Monitor input/output on fluid balance chart	(ii) For accurate determination of fluid balance
(iii) Insert indwelling catheter and monitor urine output	(iii) For accurate measurement of urine output
(iv) Insert nasogastric tube and place on free drainage	(iv) To prevent aspiration in the comatose patient
If signs of shock are not present:	
(i) Place patient on bedrest; elevate foot of bed	(i) To preserve blood flow to the brain
(ii) Never leave a dizzy patient unattended when sitting or walking; provide with walking aid if needed	(ii) To prevent physical injury
(iii) Instruct patient with postural hypotension to stand from a lying or sitting position very slowly; patient should lie down for 20–30 minutes after the antihypertensive agent is given, and regain an upright position gradually	(iii) To allow adequate time for baroreceptor activation after changes in posture

TABLE 11.7 ORAL CANDIDIASIS (ORAL THRUSH) (SEE ALSO TABLE 11.16)

Common causes: antibiotics; long-term use of corticosteroids; cytotoxic drugs; radiation therapy

Action	Rationale
Hydrogen peroxide solution 3% diluted with equal parts of water or with normal saline	For removal of white plaques coating the tongue
Provide nystatin oral drops as ordered; administer under the tongue or in the buccal cavity; ask patient to hold the solution there for as long as possible before swallowing	This antifungal preparation is most effective if the contact time with the oral mucosa is long

Dry mouth

A dry mouth (Table 11.9), or decreased salivation, involves the decreased production or secretion of saliva resulting from mouth breathing. Several medications can produce this effect, which usually disappears after discontinuation of therapy. Medications are able to produce their effect by inhibition of the muscarinic activity of salivation. Irradiation of the mouth and face produces decreased salivation from salivary gland atrophy.

Nausea

Nausea (Table 11.10) involves a profound aversion to food or an impending desire to vomit. Accompanying symptoms include excessive salivation, diaphoresis, tachycardia, pallor and increased breathing. Medications tend to produce this effect by stimulating the vomiting centre in the medulla oblongata or by irritating the gastrointestinal system.

Drowsiness and sedation

Drowsiness and sedation (Table 11.11) involve a decreased level of consciousness, which can manifest as quiet, calmness or sleep. It may occur following the use of medications that depress the central nervous system.

TABLE 11.8 RASH

Common causes: antibiotics; benzodiazepines; lithium; gold salts; allopurinol; isoniazid; aspirin

Action	Rationale
Assess rash, noting colour, shape, location, time of eruption, presence of itching, burning, pain, tenderness or bleeding; determine changes since rash first appeared	To determine the cause and assess the effectiveness of actions implemented to resolve the problem
Ensure patient keeps the skin clean and dry; dry well between skin folds following washing; instruct patient to wear loose-fitting gowns and to avoid scratching the rash	Moist skin leads to maceration, and perspiration can harbour the growth of microorganisms; wet bed linen/clothes interfere with skin through convection and conduction; loose-fitting clothes are less irritable on a rash; scratching often encourages pain, bleeding, tenderness and exacerbates the itchiness
Encourage the patient to avoid direct sunlight and to apply sunscreen before going outdoors	The skin's outermost barrier, the epidermis, is interrupted by the presence of the rash
Apply antipruritic lotion (e.g. calamine) as ordered	Reduces the desire to scratch and thus aids the healing process; continued scratching leads to inflammation and infection
Wash the area thoroughly; warm soaks or cool compresses can be applied to the rash	Assist in relieving inflammation and itching
Avoid too-frequent baths, excessive use of soap and the use of harsh alkaline soap	May aggravate the rash
Following identification of the drug causing the allergic reaction, the patient should avoid any further contact with the drug	To prevent recurrence of the rash and, more importantly, to avoid the occurrence of an anaphylactic reaction

TABLE 11.9 DRY MOUTH

Common causes: antimuscarinics; antihistamines; phenothiazines; clonidine; narcotic analgesics; excessive irradiation of mouth or face

Action	Rationale
Inspect inner oral mucosa by gently pulling the lower and upper lips away from the teeth; inspect tongue by asking patient to stick out tongue; view buccal mucosa by gently retracting the cheeks with a tongue depressor; inspect for colour, hydration, texture, lesions (e.g. ulcers and cysts) and abrasions	To evaluate the effectiveness of oral hygiene and to determine incidence of mouth infections
Encourage patient to consume fluids and foods with a high fluid content (e.g. oranges, watermelon, apples, soups, casseroles)	To moisten the mucosal membranes and prevent the development of thick encrustations
Encourage the patient to avoid carbohydrates, especially sweets, between meals	Sweet or starchy foods tend to adhere to tooth and gum surfaces
Maintain strict dental hygiene, e.g. clean teeth/dentures immediately after meals; floss teeth	Saliva keeps the mouth moist and clean through physically mobilising particles in the mouth; if saliva content is decreased, dental hygiene needs to be meticulous to remove food particles

TABLE 11.10 NAUSEA

Common causes: narcotic analgesics; antineoplastic agents; ferrous sulphate; levodopa; oral potassium chloride supplements; oestrogens; progestogens; oral contraceptive pill; sulphasalazine; antibiotics; quinidine; anaesthetic agents; digoxin (overdose); theophylline (overdose)

Action	Rationale
Keep patient's room fresh and clean by removing bedpans and emesis dishes promptly after use; reduce food odours from the patient's environment by ensuring meal trays are collected promptly	Removal of irritants will prevent the stimulus of nerve endings leading to nausea
Ensure patient is pain-free (e.g. after surgery) by administering pain relief promptly as ordered	Pain can precipitate or intensify nausea
Administer antiemetic such as metoclopramide or prochlorperazine as ordered	Prochlorperazine and metoclopramide act by inhibiting the effects of the chemoreceptor trigger zone in the brain; metoclopramide also acts peripherally by increasing the rate of gastric emptying through peristalsis
When providing causative agent, administer clear fluids or give on an empty stomach; if possible, give the preparation in an enteric-coated form	Presence of food in the gastrointestinal tract stimulates the release of secretions, intensifying the nausea; enteric preparations break down in the small intestine instead of in the stomach
Assess onset, duration and intensity of nausea, and precipitating and alleviating factors; assess for associated complaints: vomiting, abdominal pain, anorexia, weight loss, changes in bowel habits, bloating, excessive flatus; auscultate for bowel sounds; palpate for rigidity and tenderness; inspect for abdominal distension	To determine the effectiveness of intervening measures

TABLE 11.11 DROWSINESS AND SEDATION

Common causes: overdose or overuse of central nervous system depressants; overuse of aspirin; general anaesthetics; tricyclic antidepressants; use of alcohol with central nervous system depressants; antihistamines

Action	Rationale
Assess conscious state: orientation, motor and sensory responses, pupil size and reactivity	To determine neurological status of patient and effectiveness of measures implemented
Assess for associated manifestations: headache, dizziness, nausea, vertigo, visual or hearing disturbances, weakness, fatigue, changes in personality, memory or temperament	Presence of these associated manifestations indicates the need to alter the medication regimen
Turn the patient's head to one side and have suction source on hand	Prevents aspiration of oral secretions into lungs
If cause is due to the use of hypnotic drugs, implement the following: • Administer, as ordered, short-acting hypnotics (temazepam) in preference to longer-acting hypnotics (nitrazepam) • Administer hypnotics soon after bedtime rather than waiting until later in the night • Limit treatment to no longer than 6 weeks	Hypnotics are habit-forming, producing physiological and psychological dependence with prolonged use
When patient is in bed, put cot sides up	To prevent physical injury

TABLE 11.12 FEVER

Common causes: hypersensitivity reactions (antibiotics, blood transfusion, contrast media, antitoxins); chemotherapy; drugs that impair sweating (antimuscarinics); inhalational anaesthetics; muscle relaxants; toxic doses of aspirin; central nervous system stimulants; tricyclic antidepressants

Action	Rationale
Measure temperature regularly, at least four times daily; rectal temperature is most accurate, but uncomfortable for patient; also assess onset and duration of shivering	To determine effectiveness of measures implemented
Provide frequent tepid sponges	To reduce body's surface temperature
Administer antipyretics, as ordered: paracetamol 500 mg–1 g four times daily oral or p.r.; aspirin 300–600 mg three or four times daily oral if temperature is > 38.5 °C	Prevent the hypothalmus from synthesising prostaglandin E, inhibiting the setpoint of temperature from rising further
Keep room temperature at 18–20 °C unless shivering develops; aim to provide cool circulating air; maintain light clothing and bed clothes; ensure not to induce chills	Assists in stabilising body temperature through conduction and radiation
Provide dry clothes and bed linen; change as often as required	To increase heat loss through conduction and convection
Provide at least 3000 ml fluids daily; input must exceed output; measure input/output on fluid balance chart	To replace fluids lost through insensible water loss and sweating and to ensure a positive balance is maintained
Maintain strict oral hygiene twice daily (e.g. mouth rinse, clean teeth/dentures)	Oral mucosal membranes are easily dried through dehydration
Encourage well-balanced meals (e.g. high complex carbohydrate, high energy)	To meet increased metabolic needs that occur with fever

Fever

Fever, or pyrexia (Table 11.12), can arise from any medical condition affecting any body system. This symptom must be considered in light of other clinical manifestations. With respect to medications, fever often accompanies a rash that results from drug hypersensitivity.

Photophobia

Photophobia (Table 11.13) is an abnormal sensitivity to light. Many drugs produce photophobia from ocular dilation and reduction in aqueous humour drainage.

Stomatitis

Stomatitis (Table 11.14) is characterised by recurrent painful ulcerations of the oral mucosa, often involving the gingiva, hard palate and top of the tongue. Medications can cause these effects by direct activity on the mucosa or by an allergic reaction.

Diarrhoea

Diarrhoea (Table 11.15) is an increase in the frequency and fluidity of bowel motions compared with the individual's normal bowel habits. With the fluid and electrolyte imbalances that occur with severe diarrhoea, it is important to protect against life-threatening dysrhythmias and hypovolaemic shock. Diarrhoea may result from ingestion of poorly absorbed material, such as bulk-forming laxatives, local lymphatic or venous obstruction, stimulation of mucosal intracellular enzymes, decreased integrity of the small-intestinal mucosal wall, and increased intestinal motility.

Anogenital candidiasis

Anogenital candidiasis (Table 11.16) is a mild superficial fungal infection caused by the *Candida* species, affecting the vaginal, anal and penile areas. The infection is caused by an overgrowth of the fungus, which can lead to white or yellow discharge, pruritus, excoriation and inflammation.

TABLE 11.13 PHOTOPHOBIA

Common causes: mydriatics; ophthalmic viral drugs

Action	Rationale
Ask patient whether eye pain is present, and to describe its location, duration and intensity; discontinue drug if eye pain occurs, as ordered	Mydriatics reduce aqueous humour drainage and are contraindicated in patients with glaucoma, as they may cause an abrupt rise in intraocular pressure
Examine pupils regularly following administration into eye; assess other changes such as blurred vision and tearing; examine conjunctiva and sclera, noting their colour; characterise the amount and consistency of discharge	To evaluate the effectiveness and time course of drug therapy; mydriatics typically accommodate for distant vision
Darken the room and avoid patient contact with bright lights; if discomfort continues, encourage patient to close eyes or wear dark glasses; discourage watching television and reading after administration of mydriatics	Dilated pupils are unable to constrict in response to light, leading to eye discomfort

TABLE 11.14 STOMATITIS

Common causes: cytotoxic drugs; radiation therapy; penicillins; sulphonamides; quinine; streptomycin; phenytoin; aspirin; gold salts; barbiturates

Action	Rationale
Assess the lesion: determine onset, pain, odour, discharge; note the lesion site and character; examine the tongue, buccal mucosa, gums and upper/lower lips for colour, texture and contour; inspect teeth and gums, recording missing, broken and discoloured teeth and debris; note also bleeding, inflamed, swollen and discoloured gums; assess also for signs of infection: inflammation, pain, discharge	Determines effectiveness of measures implemented; oral impairment provides a portal of entry for microorganisms
Maintain strict oral hygiene regimen after every meal (e.g. saline rinse, dilute hydrogen peroxide rinse, use of soft toothbrush or mouth swab); avoid mouth rinses that contain alcohol	These prophylactic measures prevent infection; alcohol-containing mouth rinses dry out the mouth and may cause pain on contact with lesions
Encourage bland diet; instruct patient to avoid spicy foods, citrus fruits and alcohol	These can irritate the condition, leading to pain and loss of appetite
Assist patient to avoid stress and anxiety through relaxation, distraction therapy and a quiet environment	Stress- and anxiety-provoking situations can aggravate the condition and delay healing
Topical anaesthetics such as lidocaine and benzocaine preparations can be massaged into the affected areas, as ordered	These local anaesthetics provide temporary pain relief

TABLE 11.15 DIARRHOEA

Common causes: several antibiotics; antacids containing magnesium; colchicine; allopurinol; lactulose; laxative abuse; ethacrynic acid; digoxin (high dose); quinidine (high dose); methotrexate; nasogastric/enteric feeds

Action	Rationale
Assess hydration status: check skin turgor, mucous membranes, urine output, blood pressure (lying, standing, sitting); assess abdomen: inspect for distension, palpate for tenderness, auscultate bowel sounds; characterise the onset, frequency and intensity of diarrhoea; collect and measure resultant diarrhoea; submit faecal specimen for microbiology and culture; explore any associated complaints, such as nausea, vomiting, abdominal pain, anorexia, weight loss, excessive belching and bloating	To determine severity of the condition, to diagnose the causative agent and to prevent the onset of hypovolaemic shock
Ensure patient's privacy during defecation; empty pans promptly	To maintain patient's dignity and avoid embarrassment
Advise the patient to avoid spicy and high-fibre foods (e.g. fruit and vegetables), caffeine and fatty products (e.g. milk, butter); organise smaller, more frequent meals	To promote ease of digestion and to prevent incidence of excess osmotic load in small intestine
Cleanse perineum thoroughly and promptly; offer pans regularly; avoid use of a rectal tube unless the diarrhoea is extremely severe despite conservative measures	To prevent the breakdown of skin; a rectal tube is extremely uncomfortable for a conscious patient and may cause recto-anal trauma if inserted incorrectly
Maintain accurate input/output record on a fluid balance chart; ensure patient remains in a positive or at least even balance; encourage oral fluids (at least 2 l/day) and administer intravenous fluids as ordered	To monitor the effects of dehydration and to prevent the patient becoming dehydrated
Antidiarrhoeal agents such as loperamide may be required, as ordered	To slow gut peristalsis
If the patient is receiving nasogastric/enteric feeds, slow down the rate; monitor nasogastric aspirate four times daily	To facilitate a more acceptable absorption

Vomiting

Vomiting (Table 11.17) is the expulsion of gastric contents by the mouth and results from the coordinated contraction of abdominal muscles and reverse oesophageal peristalsis. Medications can cause vomiting by irritating the gastric intestinal mucosa or by stimulating the vomiting centre in the medulla oblongata.

Blistering

A blister is a small, thin-walled raised vesicle containing clear, serous, purulent or bloody fluid. Medications may produce blistering (Table 11.18) as a result of an allergic or immunosuppressant reaction.

Photosensitivity

Photosensitivity (Table 11.19) is an increased reactivity to sunlight. Brief exposure to sunlight or an ultraviolet lamp may lead to urticaria, oedema, papules or burns.

Postural hypotension

Postural hypotension (Table 11.20) is a fall in blood pressure precipitated by moving from a lying or sitting position to standing. It is often associated with medications that block the α-adrenoreceptors.

TABLE 11.16 ANOGENITAL CANDIDIASIS

Common causes: see Table 11.7; also oral contraceptives; other oestrogen-containing preparations

Action	Rationale
• **Female patient**: identify onset, colour, consistency, odour and texture of vaginal discharge; determine how discharge differs from usual vaginal secretions and whether onset relates to menstrual cycle; ask about associated manifestations, such as dysuria, perineal pruritus and burning; examine external genitalia; observe vulvar and vaginal tissues for redness, oedema and excoriation • **Male patient**: examine anogenital area for erythematous, weepy, round lesions; these are often present under the prepuce; note location, size, colour and pattern of lesions; ask about associated manifestations such as dysuria, perineal pruritus and burning	Observations determine course of infection and effectiveness of interventions
Instruct patient to wear loose-fitting clothes, cotton underwear, and to avoid nylon underwear and tight clothes	Moist, warm environments created by tight clothes and nylon underwear encourage growth of *Candida albicans*
Instruct patient on the use of antifungal vaginal pessaries/cream (females) and cream (males); preparations are usually applied/inserted at bedtime; sexual partners also need to be treated; advise patient to take prescribed medication even if the symptoms clear or menstruation occurs; advise patient to avoid intercourse until symptoms clear, and thereafter for the male partner to use condoms until the course of medication is completed	Reduce chances of reinfection

TABLE 11.17 VOMITING (SEE ALSO TABLE 11.10)

Common causes: see Table 11.10

Action	Rationale
Characterise onset, frequency and intensity of vomiting; collect and measure resultant vomitus; explore any associated complaints such as nausea, abdominal pain, anorexia, weight loss, changes in bowel habits, excessive belching and bloating	To determine severity of condition; it is important to diagnose the underlying cause, as antiemetics will provide only symptomatic relief
Monitor vital signs, input/output and clinical manifestations of dehydration (e.g. decreased skin turgor, dry mucous membranes, decreased urine output, cool skin)	To determine onset of dehydration, which occurs with severe vomiting
Ensure patient maintains an adequate intake of fluids; aim to maintain an even or slightly positive fluid balance	To prevent onset of dehydration
If vomiting continues, obtain blood tests as ordered to determine fluid, electrolyte and acid–base balance	Prolonged vomiting can lead to dehydration, electrolyte imbalance and metabolic acidosis
If vomiting is caused by: (i) Theophylline or digoxin: take blood specimen to determine blood levels (ii) Narcotic analgesics: this will generally subside with continuous administration	 (i) Toxic levels of theophylline or digoxin can lead to vomiting (ii) Stimulation of the chemoreceptor trigger zone to produce nausea and vomiting is only a transient effect
Elevate the patient's head or position on the left side	To prevent aspiration of vomitus

TABLE 11.18 BLISTERING

Common causes: antibiotics; allopurinol; aspirin; barbiturates; cytotoxic drugs; hypoglycaemic agents; gold salts; phenytoin

Action	Rationale
Inspect distribution of blisters, noting their exact location, colour, shape and size; observe for presence of crusts, scales, macules, papules, wheals and scars	Determines severity and nature of the condition, and allows evaluation of the effectiveness of measures implemented
Ensure fluid status is well maintained; if necessary, commence intravenous administration	Blisters that cover a large area can cause substantial fluid and electrolyte loss through weeping lesions
Keep patient's environment warm; cover patient with blankets as necessary	Warmth may be lost through breaks in the skin barrier caused by the blisters
Obtain swabs for microbiology and culture as ordered, if the temperature is > 38.5 °C or if purulent exudate and swelling are present; report presence of a secondary infection to the doctor	Infection occurs easily due to loss of protective skin barrier; increased inflammation and immune response lead to hyperthermia
Instruct patient to wash hands regularly and not to touch the lesions	Burst blisters are predisposed to infection through the exposure of denuded skin
Cover blistered area with occlusive dressing or non-adhesive covering	Provides artificial barrier to area, protecting it against infection
Apply antimicrobial cream to the area (e.g. silver sulfadiazine cream) prophylactically and therapeutically; give systemic antibiotics according to results of skin cultures	To prevent and treat infection; silver sulfadiazine acts as a bactericidal against several Gram-positive and Gram-negative organisms

TABLE 11.19 PHOTOSENSITIVITY

Common causes: amiodarone; anticancer drugs; phenothiazines; nalidixic acid; griseofulvin; quinine; chloroquine; tetracyclines; tricyclic antidepressants; antihistamines; thiazide diuretics; loop diuretics; carbonic anhydrase inhibitors; sulphonamides; oral contraceptives; quinidine; dantrolene; vitamin A derivatives; clofibrate; carbamazepine; non-steroidal anti-inflammatory drugs

Action	Rationale
Assess sunburn that develops after sun exposure, such as blisters, red skin, pain or discomfort over the skin surface	Determines severity and nature of reaction to the sun, and allows for evaluation of effectiveness of measures implemented
Limit outdoor activities during the middle part of the day, between 10 a.m. and 2 p.m.	This is the warmest part of the day and has the potential to cause the severest effects
When patient is outside, advise them to wear a wide-brimmed hat, a long-sleeved shirt or jacket and long trousers; ensure feet remain covered	It is important that the patient wears clothes and shoes that will maintain maximum protection from the sun; a hat also protects the face from exposure
Advise patient to use a sunblock with maximum protection (sun protection factor (SPF) 18+). Ensure sunblock is applied to exposed skin surfaces and the application is repeated every 1–2 h	Sunblock provides protection against the sun's ultraviolet rays; regular application is required to maintain effectiveness of sunblock

TABLE 11.20 POSTURAL HYPOTENSION

Common causes: sympatholytics; phenothiazines; antihypertensives

Action	Rationale
Assess for dizziness, light-headedness, weakness, fainting	Determines severity of problem and allows evaluation of the effectiveness of measures implemented
Advise patient to tighten calf muscles regularly while standing or to walk around on the spot	Promotes blood circulation around the body and facilitates brain perfusion
Advise patient to consider sitting rather than standing	Standing requires greater effort for the body to pump blood to the head
Advise patient to move slowly from a lying to sitting or standing position and to hold on to something while moving from a lying to a sitting or standing position	Allows body to bring into play regulatory mechanisms in adjusting to changes in blood pressure; holding on to an object while moving provides support and prevents falls
Advise patient to avoid the use of alcohol	Alcohol causes dehydration and may lower blood volume
Encourage patient to maintain adequate fluid intake, especially if sweating profusely	Avoid dehydrations, which may decrease blood volume

REPORTING ADVERSE DRUG REACTIONS

A spontaneous adverse drug reaction reporting scheme is run in the UK by the Medicines and Healthcare Products Regulatory Agency (MHRA) and the Commission on Human Medicines (CSM). This Yellow Card Scheme has been in place for several decades. The scheme acts as an early-warning system for the identification of previously unrecognised reactions to prescription medicines, herbal remedies and OTC medicines. Yellow forms are available in the back of the BNF and may be filled in by health-care professionals. Forms are also available online for submission electronically at the MHRA website (www.mhra.gov.uk). Changes to the system now allow and encourage not only nurses, doctors and allied health workers but also patients, parents and carers to use the Yellow Card Scheme.

When a health-care professional reports a suspected adverse drug reaction using the Yellow Card Scheme, an acknowledgement letter is sent and a unique identification number assigned to the report. A copy of the report is provided for inclusion in the patient's notes. The case is entered on to the MHRA's Adverse Drug Reactions database, which facilitates monitoring of the reports. Reports are studied by the Pharmacovigilance Group of the MHRA to assess possible causal relationships and risk factors. This information is studied alongside other available evidence, e.g. case reports and clinical trials; and regulatory action, where necessary, is taken. The CSM advises the MHRA on drug safety issues. Rarely, a drug may be withdrawn from the market. Other possible regulatory actions include restrictions in use, reduction in dosage and provision of special warnings and precautions. An example of the dosing schedule of a drug being changed is Zyban™ (bupropion), a drug licensed as an aid to smoking cessation. Following Yellow Card reports of an increased incidence of seizures being a dose-related risk, a lower starting dose was recommended with a slower increase to the maximum dosage. To further reduce the risk of seizures, Zyban was contraindicated in certain categories of patient.

SUMMARY

- Adverse drug reactions are undesirable effects that occur with the administration of medications at normal doses.
- Adverse drug reactions can occur as a part of the normal pharmacological profile of the particular drug (type A reactions), or they may be unrelated to the drug (type B reactions).
- When a reaction is part of the pharmacological profile of the drug, it is known as a predictable effect. Predictable effects take place soon after the drug is initiated or when a medication dose is increased.
- Adverse drug reactions that are unrelated to the pharmacological action of the drug are classified as unpredictable reactions.
- Unpredictable reactions include those that are immunologically mediated effects, those that involve genetic differences in drug metabolism and those whose underlying mechanism is not known.
- Unpredictable reactions are more difficult to manage than predictable reactions.
- Medication-related problems account for a large proportion of hospital admissions.
- The Yellow Card Scheme is used in the UK to report new adverse drug reactions.

1 Chui Yuit Ming, a 60-year-old patient with severe peripheral vascular disease, returns from theatre following a femoropopliteal bypass operation. She has been placed on an epidural infusion containing bupivacaine for analgesic relief. On checking her vital signs, her respiration rate has dropped from 16 to 10 breaths per minute over 1 hour. What would you suspect? What would you do?

2 Marissa Bombaso, a patient admitted for severe anaemia, is cross-matched for 2 units of packed cells. During the first hour of the blood transfusion, you notice her oral temperature rises to 38 °C. What would you do?

3 After 1 week of receiving digitalis therapy for congestive cardiac failure, Madga Borishev complains of diarrhoea and feeling very nauseated. What would you suspect? What would you do?

4 Jane Blake, who has asthma, is ordered timolol eye drops to treat acute closed-angle glaucoma. What is the problem associated with this order?

5 John Hall, a 45-year-old male, has been ordered co-trimoxazole (sulfamethoxazole and trimethoprim) tablets over a 21-day period to treat a mild *Pneumocystis carinii* pneumonia infection. What counselling would you offer Mr Hall in reducing the risk of photosensitivity?

CASE STUDY III.1 Ms JT accompanies her 3-year-old son, Master M, to the doctor. Over the past week, M has suffered an upper respiratory tract infection, with symptoms including a runny nose, sore throat and coughing. Over the past 24 hours, however, the symptoms have become progressively worse. Master M has developed laboured breathing, with pronounced wheezing and increased coughing. The child also has difficulties in speaking due to his symptoms.

The local doctor diagnoses that Master M is experiencing an episodic asthma attack caused by the respiratory tract infection and promptly prescribes the bronchodilator salbutamol to be administered as a metered-dose inhaler, using a mask and spacer device. Antibiotic treatment is not required as the infection is of viral origin. The doctor asks Ms JT to return with Master M within 24 hours to check that his respiratory symptoms have improved. He also indicates to Ms JT that the child could possibly experience similar symptoms again with future respiratory tract infections and to administer salbutamol prophylactically at the first sign of an infection. On the following day, Ms JT visits the doctor with Master M, whose symptoms are considerably improved.

QUESTIONS

1. *Why were the spacer device together with the mask recommended for Master M, rather than a metered-dose inhaler on its own?*
2. *What instructions would be provided by the doctor and pharmacist to Ms JT in administering salbutamol using a spacer device?*
3. *Using the clinical decision-making process, what aspects would be evaluated to determine that the child's respiratory symptoms had improved?*

CASE STUDY III.2 Ms HD is a 19-year-old physiotherapy student who visits her doctor after developing a sticky and red left eye, with a yellow discharge. The doctor diagnoses bacterial conjunctivitis and prescribes a week's course of chloramphenicol eye drops. He also asks her to return to see him if the symptoms do not improve in 48 hours. Ms HD is relieved that her symptoms have begun to improve after 1 day, and she continues to administer the eye drops for the remainder of the week.

QUESTIONS

1. *How should the eye drops be administered to ensure maximum benefit from the antibiotic therapy?*
2. *Where should the eye drops be stored?*
3. *When should the eye drops be discarded, and why?*

CASE STUDY III.3 Ms LT, aged 72 years, is admitted to the emergency department with chest pain. After her heart condition is stabilised, the emergency nurse attempts to work out the cause of the problem. According to her medical history, Ms LT has been taking sublingual glyceryl trinitrate (GTN) for 4 months to treat ischaemic heart disease. Ms LT indicates to the nurse that she stores the bottle of GTN on the windowsill of her bathroom and that she initially opened the bottle about 4 months ago.

QUESTIONS

1. *How should glyceryl trinitrate be stored in order to ensure maximum effectiveness of therapy?*
2. *When should a bottle of glyceryl trinitrate be discarded after opening?*
3. *What would the emergency nurse look for in checking Ms LT's method of administering the sublingual dose of glyceryl trinitrate?*

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WEB RESOURCES

Institute for Safe Medication Practices www.ismp.org

Medicines and Healthcare Products Regulatory Agency (MHRA) www.mhra.gov.uk

National Prescribing Centre www.npc.co.uk

Prescribing Support Unit www.psu.nhs.uk

Prescribing and Medicines Management www.pharmj.com/MedicinesManagement/CurrentContents.html

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GENERAL ASPECTS OF PHARMACOLOGY

Work on,
My medicine, work!

WILLIAM SHAKESPEARE – *OTHELLO*

Pharmacology is not only a science concerned with the use of drugs to treat diseases, their dosages and other relatively mundane facts but a dynamic science that deals with all aspects of drug usage.

Drugs must first be prepared by either chemical synthesis or extraction from a plant, bacterium or other natural source. The system by which drugs are named is explained in Chapter 12.

After a drug is given to a patient, a number of events occur before any observable effect is produced. This branch of pharmacology is divided into two aspects: pharmacokinetics (Chapters 13 and 14) and pharmacodynamics (Chapter 16). These topics are of the utmost importance to all who deal with drugs. In the succeeding chapters, much of the text regarding drug groups will concentrate on these aspects of pharmacology. An understanding of these basic concepts enables one to grasp more easily many seemingly complicated aspects of drug therapy.

Drug therapy can have many problems, and all health-care professionals involved should be aware of the factors that can influence treatment outcomes. This book explores how drugs can interact with one another (Chapter 15) and how the genetic disposition, pregnancy and lifestyle of patients can alter their handling of a drug (Chapters 18 and 19). Special reference is made to issues related to paediatric and geriatric pharmacology (Chapter 20). These issues, as well as some other important considerations concerning drug development and safety (Chapter 17), are dealt with in appropriate detail.

IV

SECTION IV

DRUG NOMENCLATURE

12

CHAPTER TWELVE

OBJECTIVES

KEY TERMS

Nomenclature
Chemical names
Generic names
Proprietary names
Drug classes

After completing this chapter, the reader should be able to:

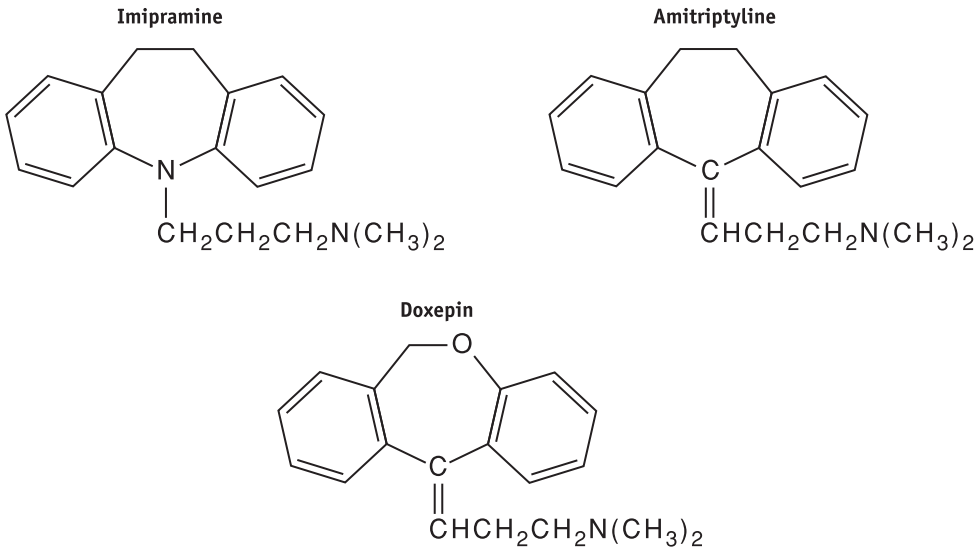
- **differentiate between the chemical, generic and proprietary names of drugs;**
- **differentiate between the following three drug classifications: therapeutic, mode of action, and molecular structure.**

THERE ARE THREE WAYS USED WITH ALMOST EQUAL frequency to name drugs. Even among informed laypeople you may find some of these names being used. A good example is the expression 'beta-blocker'. It is doubtful that most laypeople who use this term have the faintest idea what it means, even though they may know that beta-blockers have something to do with the treatment of high blood pressure.

As far as the health-care professional is concerned, the way in which a drug is classified depends on the prevailing circumstances. For example, in considering what type of antidepressant (*therapeutic use*) to give to a patient, the doctor may consider giving a monoamine oxidase inhibitor (*mode of action*) or a tricyclic antidepressant (*molecular structure*).

The *therapeutic use* of a drug is determined by the conditions the prescriber wants to treat. The therapeutic use for drugs can vary, and many examples will be given in this book. For example, the drug *clonidine* can be used to treat high blood pressure (see Chapter 44) and migraine (see Chapter 29) and as an adjunct to relieve some of the symptoms associated with the withdrawal of addictive drugs (see Chapter 23). Thus, clonidine has at least three different therapeutic uses.

FIGURE 12.1 MOLECULAR STRUCTURES OF THREE TRICYCLIC ANTIDEPRESSANTS



The *mode of action* describes how the drug exerts its effect on the body. For most drugs, there is often one principal mode of action, and clonidine, no matter what its therapeutic action, probably acts only by interfering with the way in which certain neural messages are conducted (see Chapter 44). Some drugs may act by differing mechanisms (see **amantadine** in Chapters 36 and 73) to produce their therapeutic effects.

The *molecular structure* of a drug often shows great similarity to other drugs, usually with similar action. Chemists and pharmacologists tend to group drugs according to their basic structure, the different drugs being made by altering only slightly the additions to the basic structure. This is analogous to changing the chimney shape on one of two identical houses or by having different numbers of chimneys present on each house. Figure 12.1 shows three tricyclic antidepressant drugs. If you examine each structure, you should be able to see the slight differences in overall structure, with the basic tricyclic (three-ringed) structure being similar in all cases. These sometimes apparently trivial changes can lead to huge changes in therapeutic effects, to the point of completely negating them in some circumstances.

NAMING OF DRUGS

Most drugs have at least three different names by which they can be recognised. These are their chemical, generic (non-proprietary) and trade (proprietary) names.

Chemical names of drugs can be extremely cumbersome to use and remember that they are almost never used except by chemists and pharmacologists. Imagine telling a patient that the drug he or she is receiving is 7-chloro-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one. To circumvent using these long-winded names, a simplified method has evolved whereby the original makers of the drug, in conjunction with the appropriate drug authorities, derive, for example, a simplified chemical name from the full name. This simplified name is meaningless, chemically speaking, and the derivation is usually made by the random extraction of bits and pieces of the chemical name to make an easier-to-recall name. The above-mentioned compound is known as **diazepam**, which is a lot easier to remember. There are other methods whereby simpler names are derived. For example, **aspirin** is a derivative of a chemical found naturally in a plant with the Latinised name *Spirea*. **Morphine** is derived from the Greek god of sleep, Morpheus. **Salbutamol** is derived from its chemical name, which includes **sal**icylyl, **but**yl, **am**ine and alcoh**ol** groups. Other names are more or less contrived, such as the antiplatelet drug **abciximab**. How many words do you know that start with 'abc'? This name is not completely contrived, as 'mab' stands for monoclonal antibody (see Chapter 46).

This simplified name is the *generic name*, or *non-proprietary name*, and is the drug name that is generally used throughout this book. Even generic names are not standard; this can become confusing when using foreign textbooks and has led to the development of internationally approved names.

You may notice that many generic names of drugs have another name attached to them. For example, morphine is rarely used as such because of its insolubility in water for injection. Instead, it is used as a salt, such as hydrochloride,

sulphate or tartrate. The type of salt used may alter morphine's solubility and, therefore, absorption, but generally the salt names are not used in drug descriptions. Some manufacturers use complex organic acids to form salts with drugs; these acids have their own generic name, which is often used with the drug's generic name. An example of this is found in the drug sometimes termed mycophenolate mofetil (see Chapter 75, where the drug is discussed as simply **mycophenolate**); mofetil is a generic form of 'morpholino methyl ester'. In this book, these salt and ester names are not used in either the full or simplified form, unless there is a particular reason to do so, but you may come across them in other books and references. The reason for using these unusual derivatives is generally to improve the drug's bioavailability (see Chapter 14). For example, **betamethasone** dipropionate is much more potent than the valerate ester when applied topically, thus accelerating skin penetration.

Occasionally, the chemical name for a drug is so simple that it is of no advantage to create a generic name. Common examples are **lithium carbonate** (see Chapter 35) and **potassium chloride** (see Chapter 49). Occasionally, the chemical names are shortened by creating an abbreviation; for example, the antianginal drug **glyceryl trinitrate** is abbreviated to GTN.

Once a generic name has been given, the manufacturer gives the drug a name by which to sell it. This is the *proprietary name*, or *trade name*; like a trademark, this name is the property of the company manufacturing the drug and can be used only by that company. When drugs are first sold by their manufacturers and discoverers, they are usually sold under patent; hence, they can be sold only by the company holding the patent. When the patent expires, other companies may want to market the drug, but if they do they must use a different proprietary name. With widely sold unpatented drugs, there may be several different proprietary names. These names can change rapidly and vary greatly between countries. This makes the use of proprietary names cumbersome, and the medical, nursing and allied professions are being encouraged to use generic names wherever possible. The policy of this book is to use the generic name where possible; at the end of some chapters, the drugs mentioned are listed with the proprietary names used. Trade names are always written with an initial capital letter, while generic names use lower case.

Another trend that may add to confusion among health professionals and the public is to use proprietary names for one drug to concoct new proprietary names for similar drugs. For example, Canesten™ has been a trade name for **clotrimazole**, an antifungal preparation, for more than 30 years. The manufacturer has now released another antifungal called **bifonazole**, with the trade name Canesten Once Daily Bifonazole Cream™. Perhaps a textbook is not the place to complain about nomenclature, but it must be pointed out that very often confusion with drug names can cause mistakes and that health professionals should know the potential pitfalls. Appendix F lists some drug names that are commonly mixed up.

SUMMARY

- Most drugs have at least three names: chemical, generic and proprietary. In most cases, it is better to refer to drugs by their generic name.

1. Beta-blockers generally have the suffix '-olol', but two end in '-alol', namely labetalol and sotalol. Is there a reason for this? You will have to refer to Chapters 44, 45 and 48 to answer this question.
2. Many benzodiazepines have a common suffix. What is this suffix? (Refer to the drug summary table in Chapter 34.)
3. Some benzodiazepines do not have the suffix referred to in question 2, but can you identify any commonality in their generic names? (See Chapter 34.) (N.B. The similarity in names of drugs cannot be relied on, as there are many exceptions to this supposed 'rule'. For example, chlorpropramide and chlorpromazine are completely different drugs, the former being used in type 2 diabetes mellitus and the latter being an antipsychotic.)
4. Give the correct therapeutic classification for the following:
   (a) water pills;
   (b) blood-thinning drugs;
   (c) headache tablets.
5. Can you develop an argument for and against the lay terms used in question 4?

PHARMACOKINETICS: ABSORPTION AND DISTRIBUTION

13

CHAPTER THIRTEEN

OBJECTIVES

KEY TERMS

Absorption
Lipophilic
Lipophobic
Distribution
Protein binding
Blood–brain barrier
Volume of distribution

After completing this chapter, the reader should be able to:

- **explain the principles of pharmacokinetics;**
- **describe the distribution of drugs within the body, and the factors that can affect this;**
- **name the various naturally occurring barriers that exist in the body, and their importance in drug distribution.**

PHARMACOKINETICS LITERALLY MEANS THE MOVEMENT OF drugs inside the body. (The administration of a drug, described in Chapter 7, could be considered to involve the movement of a drug by the administrator and is sometimes classified as belonging to pharmacokinetics.) The metabolism of drugs, which involves the movement of molecules and their chemical transformation, is often considered to be a branch of pharmacokinetics. Excretion of a drug from the body, being a movement out of the body, is undoubtedly a branch of pharmacokinetics. As excretion and metabolism are related closely, they are dealt with in Chapter 14. This leaves two remaining aspects of pharmacokinetics to deal with in this chapter: the absorption of a drug, and its distribution within the body. These two processes are of great importance in pharmacology, and their study can be extremely complicated. This is because there are so many factors that can affect these processes and, ultimately, the action of a drug.

DRUG ABSORPTION

Generally, when a drug is administered, absorption has to take place before the drug gains access to the interior compartments of the body. The exceptions are parenteral injections, apart from those administered by the intradermal, subcutaneous and intramuscular routes. In most cases, a drug has to cross one or more membranes to gain access. In the case of a swallowed drug, there are layers of protective mucus in many parts of the gastrointestinal tract, which must be traversed before the drug reaches the cell membranes of the epithelial cells lining the tract. Several membranes may have to be penetrated before the drug eventually reaches the bloodstream.

The chemical nature of the drug determines how this absorptive process takes place. With the majority of drugs, the process is simple diffusion. Before this can take place, however, the drug must be present in a state that enables it to penetrate the cell membranes. As cell membranes consist mainly of lipid materials, only lipid-like, or *lipophilic*, substances cross through easily and rapidly. The molecular size of the drug is important, as small molecules diffuse more rapidly than large molecules. Some drugs have comparatively low molecular weights but are *hydrophilic* in nature (i.e. highly ionised) and will not diffuse through the gastrointestinal wall. An example of this was known to the native South Americans, who realised that animals killed with the arrow poison **curare** could be eaten safely. Curare is a highly ionised molecule that causes death by paralysis when injected into the bloodstream, but it can be ingested safely. Compounds similar to curare are still used today to paralyse patients during surgery (see Chapter 27).

Lipophilic means 'fat-loving'. When olive oil is mixed with sunflower oil, the two oils are completely miscible. This is true for all oils, or lipids. Substances that can be mixed with oils are termed lipophilic. When lipids are mixed with aqueous media, two phases are produced: the lipid phase and the aqueous phase. In other words, they are immiscible. (This is seen easily when one tries to wash greasy dishes in water without the addition of a detergent.) As lipids 'do not like' water, they are termed hydrophobic. The terms lipophilic and hydrophobic are more or less synonymous. The word used is determined by the context. For example, we say that safflower oil is lipophilic when it proves to be completely miscible with palm kernel oil but hydrophobic when it proves to be immiscible with water.

To be absorbed effectively, ideally drugs should be lipophilic. The gastrointestinal tract has a variable pH; this variability is especially great between the stomach and duodenum, where the pH gradient is steep, from about pH 3 to about pH 8. The pH of the medium can affect the nature of a drug. Weakly acidic drugs are lipophilic when present in acidic surroundings, whereas weakly basic drugs are lipophilic when present in basic or alkaline surroundings.

The equations below show what happens to weak acids and weak bases when present in a low pH. For an acidic drug:

$$R.COOH \rightleftharpoons R.COO^- + H^+$$

The R group is lipophilic, as is the un-ionised COOH group. This makes R.COOH a lipophilic compound. The carboxylic anion COO^- is lipophobic, making the carboxylic acid lipophobic when ionised. This occurs predominantly when the pH is basic, the equilibrium then being towards the right; when the pH is below 7, however, there is a preponderance of hydrogen ions and the equilibrium lies towards the left. For a basic drug:

$$R.NH_2 + H^+ \rightleftharpoons R.NH_3^+$$

Again, the R group is lipophilic, as is the NH_2 group. When the pH is low, the hydrogen ions unite with the NH_2 group to convert it into the NH_3^+ anion, which is lipophobic. The converse is true when the pH is above 7.

In theory, this will mean that acidic drugs such as **aspirin** will be absorbed best in the stomach, whereas basic drugs such as **morphine** will be absorbed better in the small intestine. This would be quite true if it were not for the fact that the time a drug spends in the stomach is limited. The surface area of the stomach is also comparatively small compared with the intestinal surface area, which has been described as equivalent to a singles tennis court. So, even though more aspirin molecules will cross through each square centimetre of stomach wall than through a similar area of small intestine, there are many more square centimetres of small intestine. Thus, for most drugs, absorption takes place mainly in the intestines.

This can be a problem if a basic drug is taken for fast action and is given orally after a meal. Depending on the nature of the meal, it may take quite some time for the drug to reach an absorptive surface. If an acidic drug is taken after a meal, a therapeutic effect may be noticed much more quickly, owing to gastric absorption. This has another advantage: Acidic drugs are often gastric irritants, and the presence of food will lessen the irritation to the gastric mucosa.

For a drug, even if it is lipophilic, to be absorbed in the intestine, some portion of the drug needs to be dissolved in the intestinal juices, which are primarily aqueous. Few substances are completely insoluble in water, and if only a small portion is soluble at one point in time this amount will be absorbed. An equivalent amount will then be dissolved from the undissolved portion. Thus, the process of absorption will continue until either complete absorption

takes place or the drug still remaining in the tract has passed by the absorptive surface. The presence of bile salts in the intestine will aid in the solvation of drugs and their resultant absorption.

Some drugs may be amphipathic; that is, they have both lipophilic and hydrophilic properties. Absorption of this type of compound poses no problem; a common example is ethanol (what we commonly call alcohol).

A few drugs are so hydrophobic that absorption would be very difficult and they would be present in the gastrointestinal juices like globules of oil floating in water. Again this poses no problem: The bile salts will emulsify these drugs, rendering the drugs into particles that are small enough for absorption to take place. The fat-soluble vitamins are examples of this type of compound.

A few drugs are similar to naturally occurring substances that can be absorbed by active transport. **Thyroxine**, one of the thyroid gland hormones used in the treatment of hypothyroidism, is formed from an iodinated amino acid. Amino acids are absorbed by active transport. **L-Dopa**, used in Parkinson's disease, is also a naturally occurring compound in humans and is absorbed by active transport.

When drugs are given by injection into muscle or subcutaneous tissue, absorption still has to take place. This time, the chemical nature of the drug is not so important because absorption is by entry into the circulation through small pores in the capillary walls.

DRUG DISTRIBUTION

After absorption, a drug enters the circulation, which is itself an aqueous medium, and travels to its site of action. As the drug has to be lipophilic for absorption to take place, solubility in plasma may be limited. This is normally of no consequence. Some drugs use plasma-transport systems such as protein binding. Many drugs are also prevented from entering particular body compartments due to the presence of natural barriers.

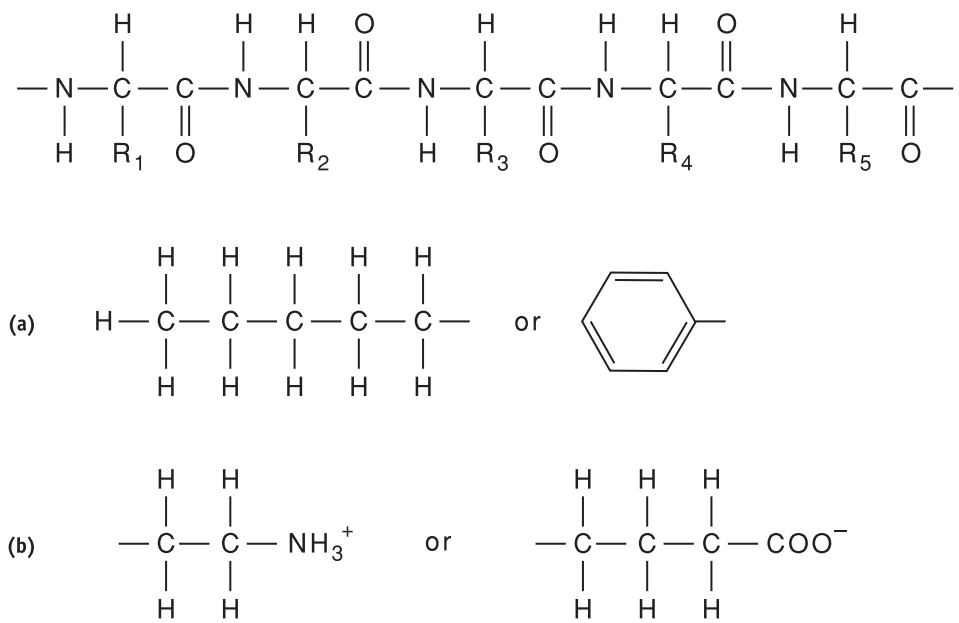
Protein binding

The bloodstream has the ability to transport relatively insoluble substances. Many naturally occurring substances, such as the sex hormones, are hydrophobic and yet are transported efficiently in the blood. They are transported attached to blood proteins (they are then said to be 'protein-bound'). A simplified structure of a protein is shown in Figure 13.1.

Protein binding confers amphipathicity to many drugs. The hydrophilic groups render the molecule soluble in water (or plasma). Lipophilic compounds are attracted to the lipophilic groups and become loosely bound to the protein molecule, hence the term protein-bound. This binding is only temporary and, as there is always some free drug present in the plasma, the protein-bound drug is in equilibrium with the free drug. This is shown in the

FIGURE 13.1 SIMPLIFIED PROTEIN STRUCTURE

The protein consists of a backbone of peptide linkages. From this backbone protrude various groups, some of which are lipophilic, as shown by structures similar to (a), and some of which are hydrophilic, as shown by structures similar to (b).



equation below, where P represents a protein, such as albumin, and D represents a drug:

$$P + D \rightleftharpoons [PD] \rightleftharpoons P + D$$

Acidic drugs are usually bound to albumin and basic drugs to some of the globulins. As the concentration of globulins increase with age, this factor has to be taken into account when using highly protein-bound drugs in elderly patients. Under normal circumstances, proteins do not leave the bloodstream and enter the tissues. For drugs to act on the body, entry into the tissues is usually required. This means that protein-bound drugs will not leave the bloodstream, but the free drug can. As the system is in equilibrium, if the free drug leaves the bloodstream, more drug will be released from the protein in order to maintain the equilibrium. The stronger the protein binding, the less of the free drug that will be present in the plasma. This will prolong the time that a drug remains in the plasma. **Suramin**, a drug used to treat trypanosomiasis (sleeping sickness), is so highly protein-bound that it can stay in the blood for 3 months or more.

Protein binding can have other important clinical implications. If two drugs that bind at the same site of a protein molecule and are administered together, there could be problems. This can occur if the anticoagulant **warfarin** (see Chapter 46) is administered with aspirin. Both of these drugs are protein-bound, but aspirin binds more strongly than warfarin to similar protein sites. Hence, aspirin can displace the warfarin from its binding site. Warfarin is therapeutically active only when it is in the free state; when warfarin is taken together with aspirin, there is more than the usual amount of free warfarin in the plasma.

Warfarin alone is readily protein-bound and is present in equilibrium with free (active) warfarin. This is shown below:

$$W + P \rightleftharpoons [WP] \rightleftharpoons W + P$$

Aspirin alone is readily protein-bound and is present in equilibrium with free (active) aspirin:

$$A + P \rightleftharpoons [AP] \rightleftharpoons A + P$$

Taking warfarin and aspirin together results in aspirin being protein-bound at the expense of warfarin, which remains mainly unbound and is thus present in a free (active) form:

$$W + A + P \rightleftharpoons [PA] + W$$

This is effectively like giving an increased dose of warfarin. Warfarin is a very toxic drug (it is used as rat poison), and thus its administration with aspirin could prove fatal. Aspirin also significantly displaces **diazepam** from proteins and can greatly potentiate the sedative action of this drug. When blood proteins are deficient, as can occur in kwashiorkor (dietary protein insufficiency) and other causes of hypoproteinaemia, there may be insufficient protein to provide for normal transportation. This can lead to an increase in the amount of free drug, leading to an enhanced effect of the drug. This type of reaction is often seen in patients with chronic liver diseases and those with severe burns. Chronic liver disease can lead to a decrease in protein synthesis, while following the tissue damage caused by burning, proteins can be lost by exudation through the damaged tissues.

The converse is also true: Various tumours secrete excessive amounts of plasma proteins. An example is multiple myeloma, in which there is rapid synthesis of an immunoglobulin. This protein can bind to some drugs and necessitate an increase in dosage as less free drug is available.

Tissue proteins can also be involved in drug binding. This can be very important for drugs that show selective binding for certain tissues; for example, the antimalarial and anti-inflammatory drug **chloroquine** binds to retinal proteins and can lead to blindness.

The role of the liver in drug distribution

After a drug is absorbed from the gastrointestinal tract, it is taken up by the part of the bloodstream called the hepatic portal system. This is true for most substances that are absorbed from the gastrointestinal tract. The exceptions are lipids, which normally enter the lymphatic system and are eventually deposited in the blood via the thoracic duct into the superior vena cava.

The hepatic portal system is designed to take digested foodstuffs to the liver, where they can be processed. In some cases, they are stored before being distributed to the rest of the body. When this happens to drugs, they may be metabolised before reaching the rest of the body. This means that an analgesic taken for a headache could, in theory, never reach the structures in the head, the drug never making it past the liver. Such a drug is said to have 'a high hepatic first pass'.

This phenomenon can be illustrated by comparing orally administered drugs with those given by a parenteral method. **Pethidine**, for example, when given parenterally, may require injection of only 25 mg to produce an analgesic effect equivalent to 100 mg taken orally.

Some drugs are metabolised so completely during their hepatic first pass that they cannot be given orally to produce a therapeutic effect. An example is **glyceryl trinitrate**, used to treat angina pectoris. Once absorbed by the oral mucosa (i.e. sublingually), glyceryl trinitrate will not be carried to the liver via the hepatic portal system but will reach the other areas of the body long before the

liver, where drug metabolism usually takes place. Glyceryl trinitrate is almost 96 per cent destroyed by the liver on its first journey through – it has a high hepatic first pass. Drugs that have a high hepatic first pass are better given by a route other than oral in order to obtain therapeutic blood levels.

(Hepatic first pass has led to the manufacture of many drug dosage forms that are dealt with in Chapter 7.)

The blood–brain barrier

The capillaries of most of the cerebral circulation are structurally different from those of the rest of the body. The endothelia of most blood capillaries have small pores (fenestrations) present at intervals between the cells. These pores allow materials dissolved in plasma water to cross to and from the tissues and the blood. The pores are not big enough to permit the passage of larger molecules such as proteins. The set-up in the cerebral circulation is rather different: Here, the endothelial cells are closer together and some of the connective tissue cells of the central nervous system (CNS) create a barrier between the capillaries and the brain tissue. This effectively prevents many molecules from traversing from the blood to the brain tissue. Only substances that are very lipophilic or are actively transported across this barrier can pass from the bloodstream into the CNS. This barrier, referred to as the blood–brain barrier, is protective of the CNS. The barrier prevents harmful substances that may be present in the blood from entering the brain. Not all of the brain is protected by this barrier: The chemoreceptor trigger zone (CTZ) present in the fourth ventricle is an example (see Chapter 55 for further explanation and the function of the CTZ).

The blood–brain barrier is sometimes useful in drug therapy, as it can prevent some drugs from crossing into the CNS and causing a deleterious effect. The neuromuscular blocking agents (see Chapter 27) are examples of this. These substances completely block the action of acetylcholine at neuromuscular synapses. If they were to block the action of acetylcholine completely in the CNS, death could ensue. On the other hand, drugs such as **penicillin** do not cross the blood–brain barrier, and in CNS infections this may be problematic. The penicillin in these cases has to be given by intrathecal injection (into the cerebrospinal fluid). In meningitis, the blood–brain barrier, being in the meninges, is often damaged, allowing some antibiotics to cross over to treat the infection.

Very often the blood–brain barrier allows the passage of drugs, resulting in unwanted effects. A good example of this occurs with many of the antihistamines. The administration of most antihistamines invariably results in a certain amount of drowsiness, an effect not usually required when treating cases of allergy-induced runny noses and itching. Drug manufacturers have developed several antihistamines that are not lipophilic enough to cross the blood–brain barrier and so can be used in cases where drowsiness could be problematic (see Chapter 29).

Other barriers

Other barriers to drugs in the body are the placental and the testicular barriers. The placental barrier is not very efficient, and most drugs will cross over into the fetus and may cause congenital malformations. In general, most drugs should be withheld in pregnancy unless they are needed for life-saving purposes. Drug reference books usually detail drugs that are known to harm the fetus and categorise them according to their safety. Placental drug transfer is explored further in Chapter 17.

The testicular barrier, which protects spermatogenesis from some blood-borne chemicals, is little understood. Not much is known about the adverse effects that may occur when drugs cross this barrier.

VOLUME OF DISTRIBUTION

The approximate volume of plasma in a 70-kg adult is 3 l. When a drug is administered and its concentration measured in the plasma, the figure obtained usually does not correlate with the amount of drug given. This is not unexpected, as drugs can diffuse from the blood into the tissues. It is useful to know how much of a drug does get distributed into the tissues. To do this, a known amount of drug can be injected intravenously and its concentration measured. If the drug stayed wholly in the plasma, the concentration would be equivalent to the amount dissolved in 3 l of liquid. If the drug was distributed evenly in the body, the concentration would be equivalent to the drug being dissolved in 40 l (the total volume in the body's fluid compartments). If the drug is concentrated in certain tissues, as is iodine by the thyroid gland, by being tightly bound to receptors in the nervous system or, by being highly lipophilic, is concentrated in the adipose tissue, then the concentration could be equivalent to the drug being dissolved in a greater volume than the total body volume (i.e. much greater than 40 l). This figure is known as the apparent volume of distribution, or *Vd*. The word 'apparent' is used as the drug only *seems* to be distributed in this volume. For some drugs, the *Vd* may have seemingly astronomical values: **nortriptyline**, an antidepressant, has a *Vd* of ~1000 l, while chloroquine, used in the treatment and prophylaxis of malaria, has a *Vd* of ~13 000 l. In both cases, these very high figures are due to extensive tissue binding of the drug. **Heparin**, an anticoagulant, on the other hand, has a *Vd* of ~5 l, signifying that this drug is totally contained in the bloodstream. Apart from giving an idea of the amount of distribution of a drug in the body, the *Vd* of a drug, if low, is helpful in determining whether, in cases of poisoning, the drug can be cleared from the body by haemodialysis. If the *Vd* is low, then this procedure will usually be successful.

SUMMARY

- With most methods of delivery to the body, drugs must be absorbed into the internal environment in order for them to exert their pharmacological effects.
- After delivery to the internal environment, the drug has to be distributed to its site(s) of action.
- Both the rate and the efficiency of absorption can greatly affect the drug's final pharmacological response.
- The mechanisms of distribution can affect the magnitude and duration of the pharmacological response.

1 Why do you think the blood–brain barrier exists?

2 Why may a patient suffering from kwashiorkor (protein deficiency) respond badly to some drugs?

3 Oestrogens are sometimes administered transdermally to combat menopausal symptoms. There are fewer adverse effects when the drugs are administered in this way. Why?

4 It has been noted that oestrogens administered transdermally have less effect on blood lipoprotein levels than when given orally. Can you suggest why?

5 Theoretically, aspirin is better absorbed in the stomach. In actual fact, most is absorbed in the small intestine. Why?

6 Sipping whisky or taking beer through a straw is said to make one intoxicated faster. Could there be any scientific explanation for this?

7 Explain the following terms and derive a sentence for each word:
(a) lipophobic;
(b) lipophilic;
(c) hydrophobic;
(d) hydrophilic.

8 Why would you advise a patient who is taking glyceryl trinitrate tablets not to swallow the tablets but rather to allow them to dissolve under the tongue?

9 Insulin is a protein that cannot be given orally. Why is this so?

10 Iain O'Grady is admitted to hospital with 35 per cent burns to his body. He develops a deep vein thrombosis and is placed on a heparin infusion. Would the dose be higher, lower or the same as the dose used for a patient without burns? Why?

11 You are confronted with the following drug prescription for your patient: warfarin 2 mg nocte; aspirin 100 mg mane. Explain what will happen with drug distribution in protein binding following administration of these medications.

12 Levodopa (L-dopa) has been ordered for Michael Ng, who suffers from Parkinson's disease. Why is dopamine ineffective in treating Mr Ng's condition?

PHARMACOKINETICS: METABOLISM AND EXCRETION

14

CHAPTER FOURTEEN

OBJECTIVES

After completing this chapter, the reader should be able to:

- **identify the sites of drug metabolism;**
- **describe the mechanisms of metabolism and the factors that can affect the metabolism of drugs;**
- **identify the sites of excretion of drugs and their metabolites;**
- **describe the bioavailability of a drug and the factors that affect this mechanism.**

KEY TERMS

Drug metabolism
Phase I metabolism
Phase II metabolism
Enzyme induction
Enzyme inhibition
Bioavailability

HUMANS, AND INDEED MOST, IF NOT ALL, LIVING SPECIES, ingest many chemicals for which there are no physiological uses. To counteract this, the organisms concerned have developed various ways to deal with these chemicals so that they can be removed from the body. Drugs are chemicals and are dealt with in the same way as unwanted chemicals in food. It is reasonable to think that the body will simply excrete unwanted chemicals via the bile or urine in an analogous fashion to the removal of natural wastes such as urea or bile pigments. With many chemicals, however, this may not be as simple as it sounds.

DRUG METABOLISM

Remember from Chapter 13 that in order for a drug to be absorbed efficiently from the gut, it is better to be in a lipophilic state. If the drug remains in the same lipophilic state and is either filtered at the glomerulus or excreted via the bile, then most will be reabsorbed and thus will remain in the body for prolonged periods. This is why metabolic processes are available in the body to metabolise drugs: not so much to detoxify them but to make them more hydrophilic in order that they will not be reabsorbed into the system during the excretory process.

The insecticide DDT was used prolifically for many years, especially in the eradication of mosquitoes in certain parts of the world. Consequently, individuals in the areas where DDT was used ingested some of the compound. Humans have no enzymes available to metabolise DDT; as DDT is a very lipophilic compound, when filtered at the glomerulus it is quickly reabsorbed into the peritubular capillaries and redistributed in the body. Eventually, most of the compound is taken up by the adipose tissues. In individuals exposed to DDT, the insecticide remains in their bodies in measurable quantities to this day.

If this happened with all chemicals, we would quickly become saturated with chemicals and probably die from their toxicity. Thus, metabolism is a way of making chemicals more hydrophilic. With some drugs, instead of metabolism leading to detoxification, the metabolites are more active than the original drug. This is true for many of the anxiolytic benzodiazepines (see Chapter 34).

Why is it that, in the majority of instances, a new chemical never met by the human body can be metabolised by enzymes? Enzymes have, after all, specificity for certain substrates. In many instances, this specificity is absolute, which means only one compound can be acted on by a given enzyme. Glucose dehydrogenase, for instance, will act only on glucose; it does not act on galactose, even though both have a more or less identical structure when represented on paper. Spatially, however, the arrangement of one hydroxyl (-OH) group is different in the two molecules; this slight variation in structure makes all the difference to the action of the enzyme.

The enzyme pepsin, which is found in the stomach, does not have this absolute specificity. Pepsin acts on most soluble proteins and breaks them down into polypeptides and perhaps some amino acids. It does not matter whether the protein is muscle protein from a piece of steak or the globin part of haemoglobin found in black pudding – the breakdown is similar. The reason for this is that amino acids are joined together by chemical bonds called peptide bonds. The peptide bond formed when most amino acids combine with each other is identical; it is these bonds, rather than the individual amino acids, that pepsin and other proteolytic enzymes break down.

In organic chemistry, there are a vast number of different compounds, but all these compounds are created using similar bonds and groupings. For example, many compounds and drugs have amino groups (-NH_2) and only one enzyme may be needed to react with this group; therefore, one enzyme can deal with many different drugs. This means that there need be only a limited number of enzymes present in the body to be capable of metabolising a large number of compounds.

There are two types of enzyme involved in metabolism. The first type is involved in phase I metabolism. These enzymes modify the drug chemically by processes such as oxidation, reduction and hydrolysis, or by removal or addition of an active group. Phase I metabolism is of tremendous importance in drug use and is dealt with more fully in Chapter 15 when we discuss liver actions and drug interactions.

The second type is involved in phase II metabolism, which includes the conjugation of a drug or phase I metabolite with a polar molecule to render the product soluble for excretion. Note that some drugs that are readily water-soluble are often excreted largely unchanged. Substances that are commonly used in conjugation reactions are sulphates and glucuronides. Glucuronides are derived from an acidic compound made from glucose, called glucuronic acid. These conjugation reactions are used not only in the removal of drugs and unwanted chemicals from the body but also in the removal of natural substances, such as steroid hormones and the bile pigments.

The antibiotic **chloramphenicol** (see Chapter 68) is conjugated before removal from the body. In newborn babies, this conjugation process is often defective; if chloramphenicol is administered to young babies, death can result from chloramphenicol toxicity, as blood levels continue to rise with each administration. In the early days of antibiotic therapy, many babies died from circulatory collapse resulting from the use of this drug. This phenomenon is called ‘grey baby syndrome’.

A less serious problem involving conjugation can occur with the common laxative **phenolphthalein**, found in many aperients. Phenolphthalein is conjugated in the liver and is partly excreted, via the bile duct, into the duodenum. Bacterial enzymes in the small intestine can deconjugate the hydrophilic conjugated phenolphthalein, converting it back into the lipophilic base. The base is therapeutically active and causes further laxative effect on the bowels, maybe when it is not wanted. If large doses are taken, the laxative effect continues for several days.

This reabsorption from the gastrointestinal tract of compounds that have been excreted via the bile can occur naturally. This happens with the bile salts, used in fat emulsification, and allows them to be reutilised (see Chapter 43). This process is known as the enterohepatic cycle.

Deconjugation of drug conjugates by bacterial enzymes in the gut can sometimes lead, indirectly, to unforeseen circumstances. The hormones in the contraceptive pill are partially metabolised by conjugation, and it is expected that there will be significant enterohepatic recycling. This means that less of the hormones needs to be given in order to maintain adequate blood levels. A problem may arise, however, when women on oral contraceptives take antibiotics concurrently. This concurrent use leads to lack of bacterial deconjugation and hence lower blood levels of the hormones. Clearly this can lead to failure of the oral contraceptive pill, and unwanted pregnancies have occurred due to women taking antibiotic therapy concurrently with the pill.

Drugs can be metabolised in most cells of the body, but the principal sites are the liver and the kidneys.

Once a drug has been metabolised to render it hydrophilic, under normal conditions it can then be excreted in the bile or urine without significant reabsorption.

Factors that affect metabolic processes involving drugs are the basis for many drug–drug interactions. These can cause problems during drug therapy, although occasionally the alteration of metabolic processes can be used to beneficial effect. Some of these phenomena are now examined.

Enzyme induction

Under normal circumstances, the enzymes involved in drug metabolism are present only in small quantities. When a drug is present in the body, especially for prolonged periods, the amount of enzyme can increase and thus speed up the metabolism of that drug. This is very noticeable with the metabolism of alcohol: Habitual drinkers metabolise alcohol at a faster rate than light or non-drinkers, and therefore alcohol appears to have less effect on the habitual drinker. Alcohol stimulates the production of several hepatic enzymes – not only those involved in its metabolism per se but also enzymes involved in the metabolism of other drugs. For example, the barbiturates (a group of hypnotic drugs) are needed in greater doses to produce a pharmacological effect in alcoholics than in teetotallers. Likewise, the barbiturates themselves are potent enzyme inducers. Patients with epilepsy and on **phenobarbitone** (a barbiturate) may need higher than normal doses to achieve a therapeutic effect if they need treatment with another drug. Barbiturates have been used in late pregnancy to induce hepatic enzyme production in the fetal liver in order to increase bile pigment metabolism; in some cases, this helps to prevent neonatal jaundice. Alcohol in moderate amounts may have a similar effect.

It is not only standard drugs that can act as enzyme inducers: Other substances, including tobacco smoke, barbecued and smoked foods, and even Brussels sprouts, can act similarly.

Enzyme induction may require an increase in drug dosage with long-term therapy in order to maintain its therapeutic effect. This is one explanation for the development of tolerance with some drugs. With drugs such as **warfarin**, an anticoagulant whose blood levels must be strictly controlled, a knowledge of drug enzyme induction is of extreme importance.

Enzyme inhibition

Very often, as mentioned in Chapter 16, drugs that are enzyme inhibitors are used therapeutically to moderate enzyme activity and slow down body processes. Some drugs that are not used specifically for their enzyme-inhibitory properties nevertheless can cause enzyme inhibition, which may lead to accumulation of other drugs in the body. The commonly used H_2-receptor antagonist, antiulcer drug **cimetidine**, inhibits some liver enzymes involved in the metabolism of other drugs. When, for example, the antihypertensive beta-blocker **propranolol** is given with cimetidine, the metabolism of propranolol is slowed down, and higher than usual blood levels are attained. This can lead to propranolol toxicity. The antiepileptic drug **phenytoin** inhibits its own metabolism, and after prolonged therapy the dose may have to be reduced in order to avoid toxicity. This type of drug action is the converse of enzyme induction and is another example of a drug–drug interaction.

Many drug–drug interactions result from enzymic interference, and awareness of these, along with many other types of interaction, is important when more than one drug is prescribed. As there are so many possible drug–drug combinations, it is useful to remember those that affect liver enzymes and be wary about prescribing them together. When in doubt, drug reference books listing these interactions should be consulted.

Drug interactions are dealt with more fully in Chapter 15.

DRUG EXCRETION

We have already mentioned that the majority of drugs are excreted either unchanged or as metabolites in the urine or bile. Some drugs, such as **penicillin**, can be actively secreted from the peritubular capillaries of the nephron directly into the lumen of the nephron. This phenomenon can be used therapeutically. To maintain higher blood levels of penicillin, this process can be inhibited by the antigout drug **probenecid** (see Chapter 59), which inhibits tubular secretion. In some patients, the route of excretion is important in therapy. In patients with hepatic problems, it would normally be advantageous to administer a drug excreted by the kidneys; in patients with renal problems, it is usually advantageous to give a hepatically excreted drug. This is applicable only when similar therapeutic drugs that fall into the correct category are available.

These are not the only routes by which drugs may be excreted: Drugs can leave the body by any natural route, including saliva, sweat, tears and breath. The excretion of alcohol by the lungs is well known by the police, and hence random breath testing is used to detect drunk drivers.

Apart from the lungs (with gaseous anaesthetics), the majority of drugs are excreted in the bile and urine. This is why patients with liver and kidney problems need special consideration during drug therapy and often require reduced dosages. Hepatic disorders can cause additional problems by reducing the rate of drug metabolism.

This leads to the concept of blood levels and drug action. In order for a therapeutic effect from a drug to be achieved, a certain blood level has to be obtained. Drugs are generally poisonous, and at higher blood concentrations these poisonous effects are more apparent and can lead to serious consequences, including death. It is important to keep blood concentrations as near as possible to the non-toxic level. This crucial aspect of pharmacology is concerned with dosages of drugs and when and how often drugs should be administered to patients.

Drug dosage and blood levels

The faster the metabolism and/or excretion of a drug, the less time the drug will remain in the circulation and, as a consequence, the less drug will be available to the tissues. A rapidly metabolised or excreted drug thus has to be given more often than a drug that stays in the circulation for a longer period. It is not appropriate to state the time for which a drug remains in the circulation, as this figure is almost impossible to derive at, for reasons that will become apparent later. It is much more useful to talk about a drug's *half-life* – that is, the time required for the concentration of a drug to decrease by one-half.

For example, if the blood concentration of a drug is 1000 µg/l at a certain time and this level drops to 500 µg/l after 4 hours, then the drug's half-life is 4 hours. After another 4 hours, the concentration would be 250 µg/l, and so on. If you continue to halve these figures, you soon see why it is not appropriate to use 'whole lives' of drugs. Half-lives are useful for calculating when repeat doses of a drug should be given. Look at Figure 14.1, which shows the progression in blood levels, giving a drug at an interval of every half-life.

If you continued Figure 14.1 ad infinitum, you would find that the concentration of the drug, if given at half-life intervals, would never reach a value of 2000 µg/l. This means that you can reach a steady-state concentration of the drug in the blood after approximately five half-lives have passed.

Invariably, the intention is to attain *steady-state concentrations* of a drug during therapy. For drugs with long half-lives of, say, 48 hours, this would take 2 weeks to achieve, whereas drugs with short half-lives of, say, 2 hours would need less than a day. This can create problems, as drugs with long half-lives may take considerable time to reach therapeutic concentrations in the blood. With drugs that must be given to attain therapeutic levels quickly, long half-lives can be problematic. A way around

FIGURE 14.1 DEVELOPMENT OF A STEADY-STATE CONCENTRATION

The mec represents the minimum effective concentration of a drug that is therapeutically beneficial.

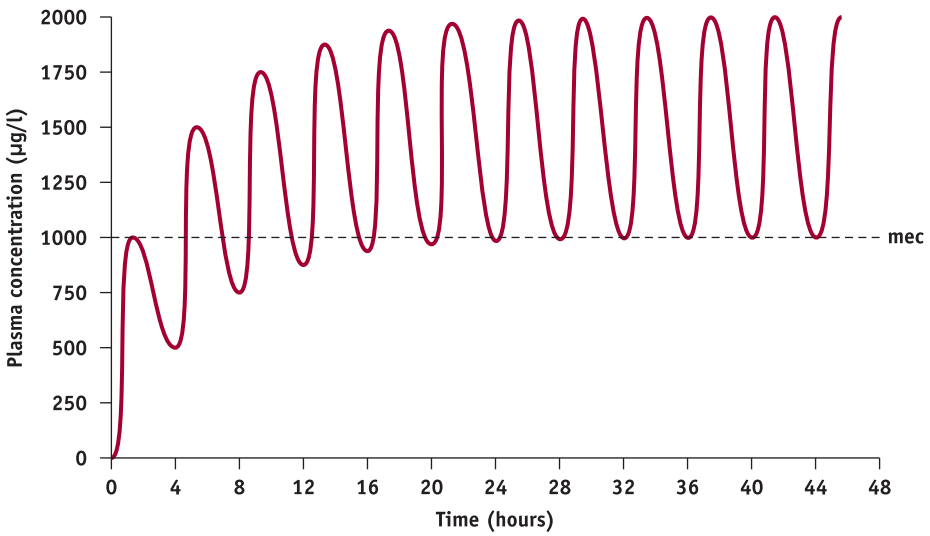
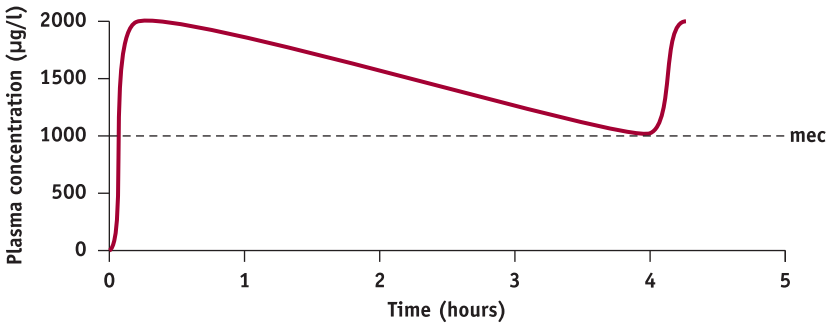


FIGURE 14.2 EFFECT OF A LOADING DOSE ON PLASMA CONCENTRATION

In this example, a loading dose produces a plasma concentration well above the minimum effective concentration (mec).



this is to give what is known as a 'loading dose' or 'priming dose'. This dose is normally twice the usual dose. Many readers will have been told at some time to take two tablets of a drug initially and then to follow this dose with one tablet at half-life intervals. A similar dose of the drug may be given by injection and given initially in place of the tablets.

Look at Figure 14.2 to see what happens with a loading dose. This cannot be done with all drugs, as adverse effects can occur more frequently with loading doses than with normal dosages.

One reason why there are many drugs in a therapeutic group is because of differences in their half-lives. For example, a hypnotic with a short half-life will be better for patients with difficulty in falling asleep, whereas a hypnotic with a longer half-life will be more suitable for patients with insomnia due to early-morning awakening. (The foibles of this are discussed in Chapter 34.) Another reason is that drugs with longer half-lives are taken less often. The patient often prefers this but, as pointed out above, a steady state is not achieved quickly. Drug manufacturers artificially increase the half-lives of some drugs by using sustained-release preparations, partly in order to improve patient compliance.

When looking at values given for half-lives, you will see that a range is usually given. This is because the half-life of a drug varies from individual to individual, with factors such as age and weight, which are discussed fully in Chapters 19 and 20.

The concentration of drug in the plasma is of the utmost importance, and knowledge of this is sometimes critical with very toxic drugs.

For all drugs, there is a minimum effective concentration (mec), below which there will be no therapeutic effect. Likewise, there is usually a concentration of drug in plasma that, if exceeded, will result in the development of toxicity. This is the maximum safe concentration (msc). With many drugs, it is important that the concentration of the drug in the blood does not fall below the mec; therefore, the drug must be given at regular intervals once steady-state conditions have been attained. The further apart the mec and the msc, the safer a drug is. The safety of drugs can also be expressed in terms of the therapeutic index (TI), which is the ratio of the toxic dose to the therapeutic dose; the larger the TI, the safer the drug:

$$\text{TI} = \text{toxic dose}/\text{effective dose}$$

Some drugs have such a low therapeutic index that their plasma levels must be monitored during therapy in order that toxic levels are not reached. Common examples are **lithium** (Chapter 35), **digoxin** (Chapter 48) and **gentamicin** (Chapter 68). On the other hand, some drugs have such a high therapeutic index that the normal clinical dose is probably much higher than is actually needed in order to achieve a therapeutic effect. Penicillin is an example of this (as long as the patient is not allergic to it).

Bioavailability

The bioavailability of a particular drug is perhaps the most important aspect of pharmacokinetics. Bioavailability is quite easily defined: It describes the amount of drug that is available to the body to produce a therapeutic effect. There are two parameters in pharmacokinetics that determine this: absorption and hepatic first pass. The only way to ensure 100 per cent bioavailability is to give a drug intravenously, remembering that the majority of other methods used to deliver drugs still involve absorption even though the hepatic first pass can be avoided. It is important to know the bioavailability of a drug so that the dosage can

be calculated. An extreme example of this is with the drug **etidronate**, used in the management of osteoporosis (see Chapter 58), which has a bioavailability of 0.5 per cent due to poor absorption. This means that 99.5 per cent of this fairly expensive drug is, literally, flushed down the toilet. As the formulation of a drug (mainly the excipients) can affect the absorption of a drug, any variation in the manufacturing of this drug could result in a large change in bioavailability, with the consequence of either over- or underdosing. Before the real importance of the factors that can affect bioavailability were taken into account, a serious error occurred: A manufacturer of **digoxin**, a drug with a low TI, changed its tableting machine, but nothing else; the tablets produced by the new machine gave a greater bioavailability of the drug, which had some serious consequences for patients being prescribed this manufacturer's brand of digoxin.

Kinetics of drug metabolism

Drugs that are metabolised in such a way that a fixed half-life, which is more or less a constant figure, can be measured are said to undergo *first-order reactions* or to follow *first-order kinetics*. Most drugs used at therapeutic dosages tend to follow this pattern and thus fit into the preceding section on drug metabolism. A few drugs, however, do not follow first-order kinetics. Instead, these drugs undergo *zero-order kinetics*. In this case, metabolism takes place at a constant rate, and the metabolic process is measured as the amount of drug metabolised per unit time; for example, alcohol (**ethanol**) is metabolised at a rate of approximately 10 ml/hour. This is quite different from dealing with half-lives. This type of kinetic process is due to the body having a limited amount of enzymes for metabolic processes, which consequently can quickly become saturated with excess quantities of substrate. Ethanol, if consumed at a rate of less than 8 g/hour (about half a glass of wine), follows first-order kinetics in an average-sized man (the rate is a quarter of a glass for an average-sized woman). This explains why a person can still be over the legal limit of blood alcohol concentration in the morning after a night's heavy drinking.

As ethanol is rarely used therapeutically (see Chapter 23), what is the relevance of zero-order kinetics in clinical pharmacology? Several drugs if taken in excess, whether intentionally or accidentally, may, because of enzyme saturation, change their rate of metabolism from first-order to zero-order kinetics. This makes them considerably more toxic and often delays recovery from overdose. Two common examples of such drugs are **aspirin** and phenytoin (an antiepileptic drug). The blood concentration at which first-order kinetics changes to zero-order kinetics can change due to enzyme induction (which we discussed earlier). This is common with alcohol, where regular heavy drinkers can stay apparently sober after an evening's drinking. The same amount of alcohol consumed by light or non-drinkers would place them in an extremely inebriated state. Note that other factors can cause this; for example, genetics and sex are important determinants of the kinetics of alcohol metabolism (see Chapter 23).

Missed doses

A common question asked regarding drug dosages is what to do when a dose is missed. There is no single answer to this question, as it depends on the drug and what the drug is being administered for. A general rule is if the drug has a long half-life, it should be given as normal; in the case of short half-life drugs, double the dose should be given at the next dosage time. The second option should normally be utilised only with drugs with a high margin of safety. If in doubt, and if the situation seems to warrant it, a pharmacist should be consulted or the manufacturer contacted. Most large drug companies have telephone hotlines to deal with such queries. Any deviation from the norm should be recorded in the patient's notes.

SUMMARY

- Drugs are metabolised in the body by various organs, but principally by the liver.
- Drugs are metabolised to assist in their excretion by converting a lipophilic substance into a hydrophilic substance.
- There are two phases of drug metabolism: oxidation/reduction and conjugation.
- Drugs are excreted by numerous routes from the body, but principally by the liver via the bile and the kidneys via the urine.

1. Explain the significance of the enterohepatic cycle.
2. Why is it sometimes dangerous to administer drugs to patients with renal failure?
3. When alcoholics are given normal doses of some hypnotics, sleep is not induced. Why?
4. When the antibiotic gentamicin is administered, blood levels of the drug are often monitored. Why?
5. What other drugs commonly have their blood levels monitored?
6. The following statement was taken from a well-known journal (Neu HC (1978) 'A symposium on the tetracyclines: a major appraisal', *Bulletin of the New York Academy of Medicine*, 54, 141–55): 'Approximately 20% to 50% is unabsorbed and eliminated through the gut or the biliary tract.' Discuss this statement.
7. From the same article as question 6 is taken this sentence: 'After an enterohepatic circulation the drug [tetracycline] is chelated with the divalent ions [calcium or iron] in the stool and excreted.' Explain what is meant by 'enterohepatic circulation' and 'chelated'. Discuss the validity of this statement.

DRUG INTERACTIONS

15

CHAPTER FIFTEEN

OBJECTIVES

KEY TERMS

Pharmaceutical interactions
Food interactions
Synergism
Summation
Cytochrome P450
Enzyme induction
Enzyme inhibition

After completing this chapter, the reader should be able to:

- **list the various types of drug interaction that can occur**
  - **outside the body;**
  - **in the gastrointestinal tract;**
  - **after absorption;**
  - **with liver enzymes.**

DRUGS ARE CHEMICALS, AND CHEMICALS OFTEN INTERACT with one another. When this happens, a drug's action may be suppressed, rendered completely inactive or enhanced. These chemical interactions can occur even in the stage when drugs are being prepared for administration, such as when mixing in a syringe. Another type of interaction is seen when the therapeutic action of one drug interferes with the therapeutic action of another drug. This interaction could be a cancelling out of effects or an amplification of an effect. Such interactions are sometimes of therapeutic value or in many cases deleterious to the patient, but they are usually impossible to predict. In these days of polypharmacy (many drugs given at the same time; see Chapter 2), this type of reaction can occur often. With so many drugs available, no one can know all of the potential interactions; it is of great importance then that when multiple drug therapy is instituted, any adverse reaction is reported to the appropriate authorities for publication in the *Adverse Drug Reactions Bulletin* or equivalent. Most pharmacology handbooks contain lists of known interactions, and these lists should be consulted before drug mixtures are given.

A representative sample of the types of drug interaction that can occur is given below and, where appropriate, in the subsequent text.

INTERACTIONS AND INACTIVATION BEFORE ADMINISTRATION

The most common effect is due to storage conditions, in which the drug can decompose due to the action of light, oxygen and moisture (see also Chapter 7). Drugs are usually fairly complex organic chemicals and are prone to degradation. The antihypertensive agent **sodium nitroprusside** (see Chapter 44) is very light-sensitive and must be kept in darkened glass ampoules, wrapped in black plastic and preferably in a cupboard. It is a good rule to store all liquid medicines, whether or not they are in dark-glass bottles, away from light. **Glyceryl trinitrate** (see Chapter 45) is so prone to oxidation that its shelf life is only about 3 months after the bottle has been opened. **Aspirin** hydrolyses readily to acetic acid and salicylic acid in the presence of moisture, so beware of vinegary-smelling aspirin tablets.

Hydrolysis of drugs due to moisture is of the utmost importance, as people have a habit of storing drugs in the dampest room in the house, the bathroom. Being complex chemicals, most drugs have a limited shelf life after manufacture. This is marked on the container as the expiry date. After this date, drugs should be discarded, as their potency will no longer be guaranteed and, with some drugs, toxic degradation products can be formed. This can happen with the tetracycline antibiotics. **Penicillin** in its solid form is relatively stable, but in the presence of water it has a very limited shelf life; hence, liquid preparations of penicillin are made up fresh and stored in a refrigerator for no more than 2 weeks. Likewise, many injectable preparations must be reconstituted with diluent immediately before being injected.

There have been rare cases of drugs reacting with the so-called inert ingredients used as fillers in tablets and capsules. An instance of this happened when people with epilepsy taking the same brand of the antiseizure drug **phenytoin** developed what was eventually diagnosed as toxic symptoms of phenytoin overdose. Their dose had not been altered, but the manufacturer had changed the capsule filler from a calcium compound to lactose. Unbeknown to the manufacturers, calcium complexed with some of the phenytoin, rendering that proportion of it unavailable to the client; when lactose was substituted, more phenytoin was available for absorption. This then resulted in higher blood levels, giving rise to toxicity. Another reaction known to occur with phenytoin is its ability, in dilute solution, to react with glass; thus, when phenytoin is added to glass infusion bottles, much of the drug remains stuck to the glass and does not reach the patient. This is not a problem with phenytoin in glass vials, as the surface area is small and the concentration of the drug is high.

Drugs may also interact with the container. The hypnotic **paraldehyde** is a liquid that dissolves plastics, and so it must be administered parenterally using a glass syringe.

Mixing of a drug in a syringe for injection can, occasionally, precipitate a chemical reaction. For example, the neuromuscular blocking agent **suxamethonium** reacts with the intravenous anaesthetic **thiopentone** to form an insoluble derivative, which it would be inadvisable to inject. As these two drugs are usually given together during anaesthesia, they must be injected separately.

Caution is required when administering different forms of insulin. A reaction that commonly occurs is between the rapid-acting and the slower-acting forms of insulin (see Chapter 57). Slow-acting insulins consist of **insulin** bound to various compounds, such as **protamine**, which slows down the insulin's absorption from the injection site. Rapid-acting insulins consist of relatively pure insulin. If the two forms are mixed, some of the rapid-acting insulin can combine with the protamine, rendering the insulin slow-acting. If a patient with diabetes injects this, most of the benefit of the rapid-acting insulin will be lost, which could have serious consequences. Fortunately, this reaction is slow, and in practice both forms can be mixed for immediate injection. The problem has arisen in elderly patients with diabetes when a visiting nurse has mixed the insulins in the same syringe the night before, ready for the patient to inject the next morning.

In practice, we recommend that drugs are not mixed before injection in case there is any reaction between them, resulting in inactivation of one or more of the drugs.

INTERACTIONS IN THE GASTROINTESTINAL TRACT

The amount of drug that is absorbed from the gastrointestinal tract into the bloodstream determines the subsequent plasma levels of the drug and, hence, its therapeutic action. The amount absorbed is termed the drug's bioavailability (see Chapter 14). The pharmaceutical formulation dictates to some extent the bioavailability of a drug. For example, slow-release tablets are specially formulated to decrease the bioavailability of a drug. Many other factors, however, can lead to a decrease in the bioavailability of the drug and can interfere with the absorption of the drug. This leads to a decrease in blood levels, with the minimum effective concentration (mec) not being reached, resulting in the drug not doing what is intended. Sometimes the converse is also true.

Food consists of innumerable chemicals, and it is not surprising that some foodstuffs react with drugs. It is perhaps more surprising that there are not many of these reactions. One of the most common food–drug interactions is between calcium ions and some of the tetracycline group of antibiotics. Calcium is present in many foods, especially dairy products; swallowing a **tetracycline** capsule with milk will render the tetracycline unabsorbable. Ideally, tetracyclines should be taken an hour before or

2 hours after a meal in order to avoid the formation of tetracycline–calcium complexes. Tetracyclines react with other divalent ions such as magnesium and iron and with trivalent aluminium; therefore, consumption of antacids (except **sodium bicarbonate**) or iron salts with tetracyclines is contraindicated.

Iron is best absorbed in the ferrous (Fe^{2+}) state. Ferrous iron is easily oxidised to the ferric (Fe^{3+}) state by oxidants in food; ferric iron is not absorbed well. This would seem to suggest that iron tablets should be given on an empty stomach to ensure reliable absorption, but as iron salts can be irritant to the gastrointestinal tract it is better to take iron tablets with food, perhaps in combination with an antioxidant such as **vitamin C** (see Chapter 61).

A problem with some drugs in the gastrointestinal tract is their ability to prevent absorption of some of the fat-soluble vitamins. This can happen with liquid paraffin and the antihypercholesterolaemic agent **cholestyramine**.

Another indirect reaction with drugs and vitamins involves some of the broader-spectrum antibiotics, which can kill off some of the natural flora of the intestine. Some of this flora makes **vitamin K**, and deficiencies of this vitamin have occurred with antibiotic therapy. Tannin, which is present in tea, can bind to many drugs, and it is recommended that clients be instructed not to swallow medications with tea.

INTERACTIONS AFTER ABSORPTION

Most of the known drug interactions take place after absorption, usually when two or more drugs are administered concurrently. Sometimes interactions occur between compounds absorbed from food and drugs. These compounds can be vitamins, as is the case with vitamin K and its interference with the action of **warfarin** (see Chapter 46) and **isoniazid** with **vitamin B6** or **pyridoxine** (see Chapter 61).

A potentially fatal reaction can occur between a group of drugs used in the treatment of depression and amines found in some foodstuffs. These drugs, called monoamine oxidase inhibitors (MAOIs), act by inhibiting the metabolism of noradrenaline in the central nervous system. Similar enzymes to those involved in normal catecholamine metabolism are found in the gut and liver, which metabolise amines in food such as tyramine to biologically inactive compounds. MAOIs may be either selective or non-selective in their activity against these enzymes. Non-selective MAOI drugs prevent these enzymes from working in the gut and liver, so that bioactive amines such as tyramine get into the general circulation and can cause a hypertensive crisis by potentiating or mimicking the effect of high levels of noradrenaline. Patients taking non-selective MAOIs should be warned not to eat foods high in monoamines, such as yeast products (e.g. Marmite™), red wine, cheese and broad beans. People on non-selective MAOIs have been known to commit suicide by consuming such products. (See Chapter 35 for more details on MAOIs.)

TABLE 15.1 INTERACTIONS AFTER ABSORPTION: DRUGS AFFECTED BY GRAPEFRUIT JUICE/GRAPEFRUITS (THIS LIST IS BY NO MEANS EXHAUSTIVE)

Amlodipine
Cisapride
Nimodipine
Warfarin
Oestrogens
Terfenadine
Nifedipine
Verapamil
Felodipine
Benzodiazepines
Cyclosporin

An unusual drug–food interaction has been noted to occur with the antihypertensive **felodipine** and many other drugs (see Chapter 44). When consumed with grapefruit juice, its bioavailability is increased by a factor of about 250 per cent. This does not happen with other citrus fruit juices, except bitter Seville oranges. The suggested mechanism for this interaction is that substances present in grapefruit, namely some flavonoids, suppress intestinal cytochrome P450 enzymes (see below) but not the hepatic isoform of these enzymes. Since this chance finding, many other drugs have been shown to be affected adversely by grapefruit juice; these are shown in Table 15.1. There are probably innumerable drug–food interactions, not only with grapefruit, and they may take many forms. It should be noted that this effect of grapefruit on drug metabolism can last for up to 3 days.

As mentioned previously, drug–drug interactions are numerous, making vigilance a necessity when new combinations of drugs are used in treatment. Many of these effects are due to interactions between drugs and enzymes in the liver, which can alter the length of time that a drug remains active in the body. Some drugs interfere with the excretion of other drugs, which, like metabolic effects, can alter the length of time that a drug remains active in the body. (Both of these effects are dealt with in Chapter 14.)

Sometimes drug interactions can be put to good use, when a combination of two or more drugs may lead to an increased beneficial therapeutic effect. The most important example of this type of interaction is *synergism*, which can be subdivided into two kinds: addition or summation, and potentiation.

Summation occurs when two types of drug work by altering different physiological or biochemical activities to produce an additive effect: that is, analogous to 1 + 1 = 2.

There are many examples of this type of effect in therapeutics, a common one being in the treatment of hypertension (high blood pressure), where two or more drugs are given concurrently to produce a larger drop in blood pressure than that which could be obtained by using one drug alone (see Chapter 44).

Potentiation occurs when two drugs act on different physiological or biochemical activities to produce an effect that is more than additive: that is, as if 1 + 1 = 3. Again, there are many examples of this, which can usually be explained by examining the drugs' modes of action. In the combination of the two antibacterial drugs **trimethoprim** and **sulfamethoxazole** (this combination being so commonly used that it has its own generic name of **co-trimoxazole**), for example, the antibacterial activity of the mixture is much better than that which can be explained simply by an additive effect.

LIVER ENZYMES AND DRUG INTERACTIONS

Phase I metabolism has already been referred to in Chapter 14, but we consider it in more detail here as this type of interaction is perhaps one of the most important in clinical therapeutics. Most of the known drug–drug interactions occur in the phase I steps of drug metabolism. Inside the liver cells, organelles/vesicles known as microsomes contain the relevant enzymes for metabolism. There has been an explosion in knowledge in recent years concerning 'one' enzyme in particular – cytochrome P450. Although described as 'one' enzyme, this enzyme is actually present as several hundred isoforms. Isoforms are the same enzyme but structurally slightly different and with a different range of substrate specificity. This specificity is low, and this is why these several hundred forms of cytochrome P450 have the ability to metabolise literally millions of different chemicals, drugs, toxins and so on. It is only in recent years that technology has been advanced enough to study these enzymes, and this is now an essential part of any drug-screening protocol. Some of these enzymes are constitutive, while others are inducible. In cases where one drug taken with one or more other drugs cause a decrease in half-life of the other drug(s), the likelihood is that there has been an enzyme induction. This will lessen the therapeutic effect with normal dosing schedules. Any drug monograph or detailed description, such as that found in the larger drug reference books, such as Martindale or the MIMS Annual, now details the effect of drugs on this enzyme system and lists those drugs that may be affected. The knowledge of these cytochrome enzymes and their inducers enables pharmacologists to predict the many potential drug–drug interactions that may occur. Before the development of knowledge of this enzyme system, many of these interactions were seen only during therapy using different drugs. Further discussion of these cytochrome enzymes can be found in Chapter 18.

Similarly, some drugs can inhibit an isoform and thus decrease the metabolism of another drug metabolised by the same isoform. This can lead to drug toxicity. Inhibition can occur with both constitutive and inducible enzymes.

SUMMARY

- Drug interactions can occur before the actual delivery to the patient, for example by mixing two drugs in a syringe barrel.
- Drugs can be affected by food intake.
- Drugs taken together have the potential to lead to many adverse effects.
- Drug–drug interactions can be related to all pharmacokinetic parameters.
- Most drug–drug interactions are probably related to enzyme inhibition or potentiation.

1 Why should thiopentone and suxamethonium, two drugs often administered at the same time, not be given as one injection?

2 Which of the following foods should not be eaten by a patient on non-selective monoamine oxidase inhibitors (MAOIs)?
   - broccoli;
   - broad beans;
   - cabbage;
   - Cheddar cheese;
   - red wine;
   - Marmite;
   - steak.

3 Why should a patient on MAOIs not use preparations such as nasal decongestants for a common cold?

4 Why is aspirin not normally available as an elixir or syrup?

5 Why should tetracyclines not be swallowed with milk?

6 Why should tetracyclines not be given to young children or during pregnancy?

7 What advantage does the sublingual spray of glyceryl trinitrate have over the sublingual tablets?

8 How would you advise a patient on the storage requirements for glyceryl trinitrate tablets?

9 Jacqui Quick, a 21-year-old student, is on a 21-day course of amoxicillin to treat a chest infection. Two days after completion of the course of the antibiotic, she notices an unpleasant taste and white coating on her tongue. Her doctor diagnoses this condition as oral *Candida* infection (thrush). How might a course of amoxicillin treatment lead to the development of oral thrush?

10 With reference to your area of clinical practice, provide two examples of drug summation and potentiation.

11 Jason Jacob, aged 4 years, is ordered amoxicillin syrup for otitis media. His mother, following the directions, reconstitutes the amoxicillin powder with water. How would you advise Jason's mother about the storage requirements of amoxicillin syrup? Why should these storage recommendations be followed?

PHARMACODYNAMICS

16

CHAPTER SIXTEEN

OBJECTIVES

After completing this chapter, the reader should be able to:

- **define the term 'pharmacodynamics';**
- **describe the chemical, physical and physicochemical modes of action of some drugs;**
- **explain the nature of competitive and non-competitive inhibitors of enzymes;**
- **describe the use of competitive inhibitors of enzymes in therapeutics;**
- **describe the concept of receptors and their significance;**
- **differentiate between agonists and antagonists and their action on receptors;**
- **list the uses that enzymes can have in therapeutics.**

KEY TERMS

Pharmacodynamics
Chemical action
Physical action
Non-competitive enzyme inhibition
Competitive enzyme inhibition
Agonism
Antagonism
Second messengers

PHARMACODYNAMICS IS THE MECHANISM WHEREBY DRUGS exert their effect on the body; that is, what the drugs do to the body in order to produce the therapeutic and other effects resulting from administration. To exert these effects, drugs usually act on physiological processes. Disease results from an alteration in the normal physiological functioning of the body. The aim of drug therapy is to counter any changes so that the body returns to the homoeostatic state. Bear in mind that a drug does not confer absolute changes on physiological processes but, rather, modifies those processes. This modification can be

either an increase or a decrease in a specific process. All bodily functions are a result of complex interactions between various molecules; drugs act by interfering with these interactions. To do this, the drug usually combines with a particular molecule, thereby modifying its effect on the body. This combination is in most cases only temporary and reversible. In a few instances, the combination is permanent. Molecular targets for drug action are often enzymes and associated compounds, from coenzymes to the complex receptors found on cell membranes, in cells and on DNA. It is these receptors that are part of the mechanisms responsible for the normal physiological control of body functions. They are stimulated either directly by the nervous system through the production of neurotransmitters, or indirectly by the endocrine system through the production of hormones, which travel in the blood to the receptor site.

With a few exceptions, we can state that all drugs act on receptors in the body or, in the case of antimicrobials, microorganisms. In practice, it is convenient to divide receptors into groups, depending on their characteristics. This is the approach taken here.

In this book, in each chapter that deals with drug groups, the mode of action of the relevant drugs is mentioned, if it is known. To facilitate an understanding of these different processes, a description of each category is detailed below.

The reader is advised to consult certain sections of this chapter when reading about the pharmacodynamics of drug families dealt with in many of the later chapters of this book. A small proportion of material dealt with in this chapter may not be understood fully until later chapters are studied.

DRUGS THAT WORK BY CHEMICAL ACTION

Although almost all drugs work by a chemical process, it is convenient to consider those that act on simple chemical processes in the body under this heading. These chemical processes involve simple inorganic compounds or non-complex organic compounds.

A few commonly used drugs have what can be termed a direct chemical action on the body. If we consider a very common drug such as **magnesium hydroxide** (a component of many antacid preparations), the action is simple chemistry, as all this drug is required to do is to neutralise stomach acid in the treatment of indigestion, among other conditions. This type of action can be represented by using simple chemical equations:

$$Mg(OH)_2 + 2HCl \rightleftharpoons MgCl_2 + 2H_2O$$

Another example of a group of drugs that exert their effects through chemical action are the chelating agents, used to remove heavy metal ions from the body in cases of poisoning and in disorders of heavy metal ion handling by the body (see Chapter 21).

DRUGS THAT WORK BY PHYSICAL ACTION

Few drugs act by a physical mechanism, principally because there are not many purely physical processes occurring in the body. One of these physical activities, which is very common and occurs all over the cellular milieu of the body, is osmosis. Osmosis results when two differing concentrations of molecules are separated by a semipermeable membrane. A semipermeable membrane is, theoretically, permeable only to water. In practice, there is no such thing as a perfectly semipermeable membrane, and so the term 'selectively permeable' is more correct. When a solution of high molecular concentration is separated from one of low concentration, water from the more dilute solution (with respect to solute) will pass through the membrane into the strong solution until the concentrations on both sides of the membrane are equal (see also Chapter 49). In this example, the more dilute solution actually has a higher concentration of water molecules (the solvent). Instead of talking about water concentration, it is perhaps easier to talk about water potentials. Pure water has a higher water potential than a dilute solution, and a dilute solution has a higher water potential than a concentrated solution. In other words, water will flow from a region with a higher water potential to that of a lower water potential. Solutions that are at a higher solute concentration or osmolarity than others are termed *hypertonic*; those at a lower concentration are *hypotonic*. Solutions at the same concentration are *isotonic*. A common example of an isotonic solution is normal saline, a 0.9% solution of sodium chloride used for irrigations and formulating injections. Osmosis is an important factor in preserving fluid balance between body compartments. Any upset in osmolarity in these compartments will result in an imbalance. Changes in osmolarities can be brought about by using drugs to correct imbalances or to cause a change in normal osmotic balances in order to produce a therapeutic effect. Examples of this type of drug can be found with the osmotic laxatives discussed in Chapter 54 and the osmotic diuretics discussed in Chapter 47.

Another example of a physical mechanism of action is with drugs that lower the surface tension of gastrointestinal fluids in order to relieve conditions in which excess gastrointestinal gases are causing problems. (The drug used in such conditions, **simethicone**, is dealt with in Chapter 53.)

A further example of a physical action is with **activated charcoal**, which is used to relieve flatulence and to treat some cases of poisoning. Its action is as an adsorbent in both cases. The charcoal has a large surface area, which can physically bind to many materials, including gases.

DRUGS THAT WORK BY PHYSICOCHEMICAL ACTION

An example of this are most inhalation anaesthetics, which appear to act by altering the lipid part of cell membranes, especially in brain tissue. This alteration results in a change in the movement of ions (Na^+ and K^+), which causes a change in nerve-cell responsiveness, leading to a loss of consciousness. As most general anaesthetics are very lipophilic, this is thought to be one possible mechanism of their action. **Halothane**, a commonly used anaesthetic, could substitute as a expensive stain remover because of its lipophilicity. (Anaesthetics are discussed in more detail in Chapter 41.)

DOSAGE AND ACTION

In general, drugs that act according to the last three principles can be identified by their dose or, more particularly, by the effective concentration of the drug at the site of action. This is considerably higher than that required by drugs that act by the methods that follow in this chapter. Antacids are usually given in gram quantities and anaesthetics are given in large volumes for considerable periods of time, whereas many drugs that act on receptors often act with a total administered dose of micrograms or milligrams. This type of categorisation when applied to drug dosage cannot always be relied on, as there are exceptions to the rule; for example, the normal dose of paracetamol for an adult is 1 g.

DRUGS THAT ACT ON ENZYMES

Enzymes are biological catalysts and carry out countless reactions in the body. A catalyst is a substance that is involved in a reaction but remains unchanged itself at the conclusion of the reaction. An enzyme reacts with a substrate; the generalised reaction is shown in the following equation:

$$E + S \rightleftharpoons [ES] \rightleftharpoons E + P$$

where E is the enzyme, S the substrate and P the product or products; ES is an enzyme–substrate complex. The arrow going in both ways indicates that enzyme reactions are reversible; the direction of action is determined by the conditions under which the reaction occurs. The arrows also show that enzyme reactions are equilibrium reactions. At equilibrium, the rates of the forward and backward reactions are balanced. An important aspect of equilibrium reactions in pharmacology is that if the product is removed, more enzymes will combine with the substrate in order to form more product.

Another important concept to consider with enzymes is that they are relatively or, sometimes, completely specific for a certain substrate. Pepsin, an enzyme found in the stomach, is classed as a proteinase, as it breaks down proteins into polypeptides and amino acids. Thus, although pepsin is specific for proteins; as it will break down a globulin in a similar fashion to a muscle protein, therefore, it is relatively non-specific in its action. In reality, pepsin is more specific than this statement implies, as it hydrolyses only peptide bonds associated with some amino acids.

Some enzymes are much more specific as they will act on only one compound and are therefore completely specific to that compound. An example is glucose dehydrogenase, which will act only on glucose and not on the closely related sugar mannose.

The specificity of enzymes in biological reactions is often likened to that of a lock-and-key mechanism. Generally, only one shape of key will unlock a door, and likewise only one substrate will fit into the active centre of an enzyme. This is shown in Figure 16.1.

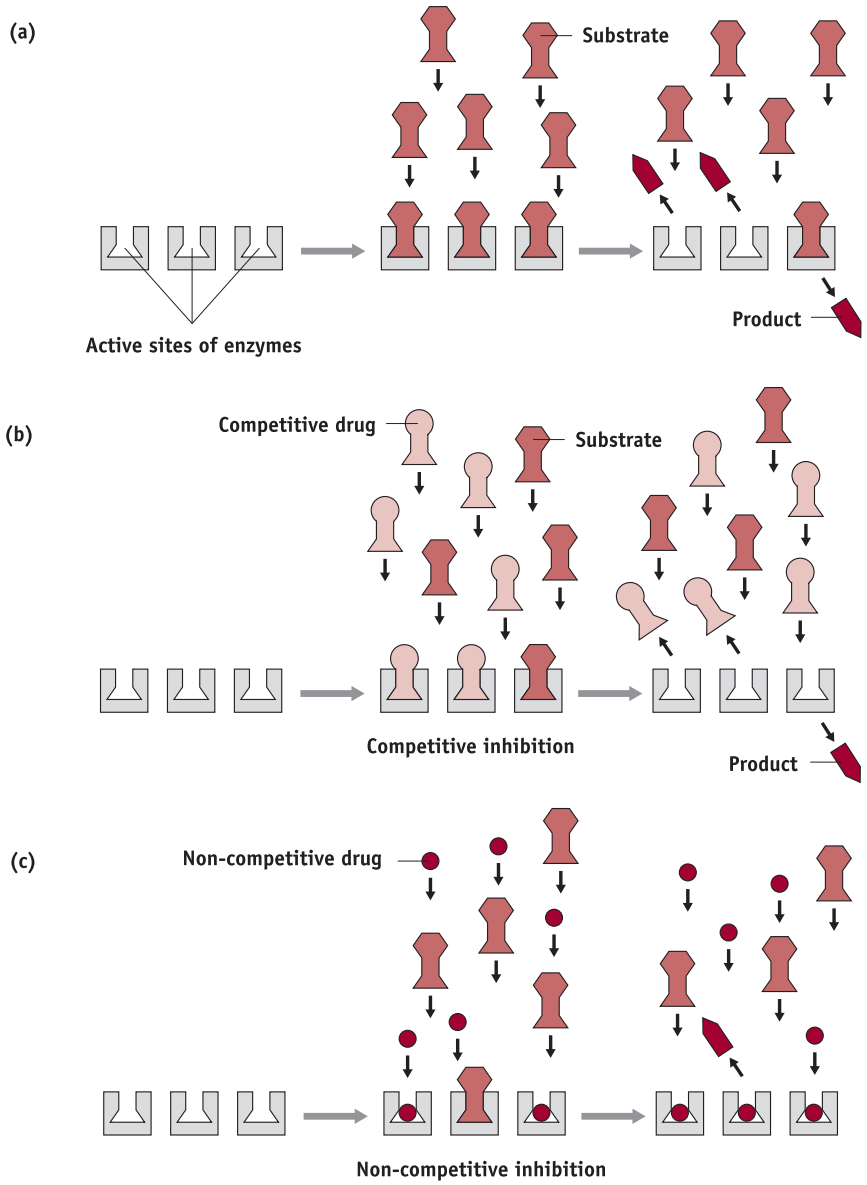
Competitive inhibition

You may have experienced the situation in which a key fits into a lock, starts to turn and then sticks; the key then has to be withdrawn. If you have a bunch of keys and only one fits a given lock, it takes time to find the correct key. Consider the case where an enzyme meets look-alike substrates and binds to them by its active centre; because the enzyme cannot do anything with the look-alike, the look-alike is discarded unchanged. Another look-alike may then be taken up by the enzyme, and the process is repeated until the correct substrate is met. Like searching through a bunch of keys, this process takes time and thus the rate of an enzyme reaction is slowed down. This slowing is even greater in the body than with a person with a bunch of keys, who has the advantage of knowing which keys he or she has tried previously. An enzyme has no memory and may continuously bind with the same look-alike. These look-alikes can be drugs used to slow down enzyme reactions. This type of action is known as competitive inhibition, as the drug is competing with the natural substrate for the active centre of the enzyme. The more drug that is present with an enzyme, the slower the enzymic reaction that will take place. Drugs that act in this way can be counteracted by increasing the substrate concentration, and this process is the basis of some antidotes. (See Chapter 46 for a description of the treatment of **warfarin** overdose.)

Competitive inhibition occurs when an enzyme combines with a substance that has a very similar structure to that of the normal substrate; because it is not the normal substrate, the enzyme does not know what to do with it, and so it discards it to 'look' for another molecule of

FIGURE 16.1 EFFECT OF COMPETITIVE AND NON-COMPETITIVE DRUGS ON ENZYME–SUBSTRATE REACTION

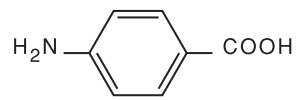
(a) The enzyme converts the substrate into a product or products without interference.
(b) A competitive drug is present and competes with the substrate for the active centre of the enzyme. If the drug binds to the enzyme site, it prevents binding of the normal substrate. The drug then leaves the active centre unchanged and another drug molecule or normal substrate can then take its place. Note that the enzyme is still active and enzyme action is still occurring but at a much slower rate.
(c) A non-competitive drug has bound permanently to the active site, blocking any further activity. This binding may not be at the active centre but could be at a remote site. When this happens the three-dimensional shape of the enzyme can be distorted, preventing any binding to the substrate.



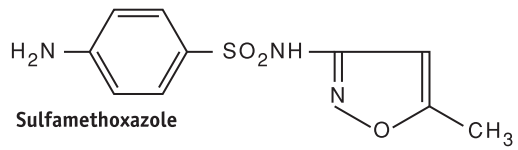
substrate – or it could be another molecule of inhibitor if there are plenty available. From this, it should be clear that if the inhibitor is present in excess, then the enzyme will meet the inhibitor more often than the normal substrate, and the normal reaction that should occur will be slowed down greatly or, in some cases, completely inhibited.

Many drugs work like this. A good example occurs in the class of antimicrobial drugs known as sulphonamides

FIGURE 16.2 STRUCTURES OF 4-AMINOBENZOIC ACID AND SULFAMETHOXAZOLE, A SULPHONAMIDE



4-Aminobenzoic acid



Sulfamethoxazole

(see Chapter 67). These drugs are very similar in structure to a compound called 4-aminobenzoic acid, which is an essential component in the synthesis of folic acid, one of the B group of vitamins. The structures of 4-aminobenzoic acid and a sulphonamide are shown in Figure 16.2. Bacteria cannot use ready-made folic acid; instead, they must synthesise it intracellularly for their own use. Humans, on the other hand, can use only preformed folic acid. Sulphonamides are competitive inhibitors of the enzyme that uses the 4-aminobenzoic acid in the synthesis of folic acid, and thus the bacteria are starved of folic acid. Consequently, when the bacteria are exposed to these antimicrobials, they will die. Other examples of competitive inhibitors will be met in later chapters.

Non-competitive inhibition

Think back to the lock-and-key description given earlier. Sometimes when a key is inserted in a lock it turns and then sticks, and you have to get a locksmith to extract the key. A similar thing can happen with enzymes – but there are no 'enzyme locksmiths'. Therefore, the enzyme is effectively rendered non-functional. When this happens, a stop is put to all competition; this type of inhibition is called non-competitive and is usually irreversible. Note that non-competitive inhibition can also occur when the inhibitor binds to a site distinct and often remote from the active centre. This causes a conformational change in the tertiary structure of the enzyme, rendering it inactive. Non-competitive inhibitors bear no resemblance to the normal substrate but combine with the enzyme in a permanent fashion. Many non-competitive inhibitors are simple metal ions such as arsenic and mercury. Arsenic compounds were used as some of the first antimicrobials against *Treponema pallidum*, the causative agent of syphilis, but they are now only of historic interest. Mercury is still used occasionally in the treatment of superficial skin infections, usually in an organic form such as **mercurochrome**; this is less toxic than the inorganic forms of mercury, but still fairly toxic to bacteria. It is, of course, too toxic to be used internally.

The action of an irreversible non-competitive inhibitor can be represented by the following equation:

Enzyme + non-competitive inhibitor → [enzyme–non-competitive complex]

When this happens, the enzyme is incapacitated and, under most circumstances, will never again carry out an enzymic reaction; that is, the reaction is not reversible, and hence the use of a unidirectional arrow. There are not many examples of drugs that act like this, as compounds that act as non-competitive inhibitors are not usually selective in their action, will destroy all enzymes and thus will be very toxic to life in general. The nerve gases and garden insecticides are examples of fairly specific non-competitive enzyme inhibitors, which inactivate the enzyme acetylcholinesterase, which is essential at the synapse. A nerve gas type of drug has occasionally been used in the treatment of glaucoma by topical administration (the non-competitive anticholinesterase **ecothiopate**). Few drugs are available that act as non-competitive inhibitors. Common examples are **aspirin** when used as an antiplatelet drug and some of the monoamine oxidase inhibitors (MAOIs) used in the treatment of severe endogenous depression. The biochemical pathways affected by these drugs can be taken over by involving other pathways, and therefore the consequences of completely inhibiting essential enzymes can be bypassed to some extent. Nevertheless, the use of these drugs can have severe consequences, even after the drug has been withdrawn, owing to inactivation of enzymes that the body needs time to manufacture. This is important with the MAOIs and is discussed in more detail in Chapter 35.

Sometimes enzymes with similar substrates are different in some tissues from others. You may know that clinical laboratories can determine whether lactate dehydrogenase in plasma is of heart or skeletal muscle in origin. This type of difference in enzymes has been exploited recently in pharmacology. The enzyme monoamine oxidase (MAO) that is present in the gut and liver is different from some MAO enzymes in the central nervous system. The antidepressant **moclobemide** is an MAOI that is relatively specific for the brain enzyme, and thus its use avoids many of the problems associated with the other MAOIs.

DRUGS THAT ACT ON RECEPTORS

Many processes in the body are controlled by a range of molecules, including hormones and neurotransmitters. These chemicals carry out their actions usually by binding to receptors on the cell membrane or receptors present in the cell's cytoplasm or nucleus. This action is analogous

in many ways to the lock-and-key mechanism discussed above. When receptors are bound to a certain substance, this directs a change to occur in the cell, which then alters an activity of the cell. In a way, it can be considered analogous to a key opening a lock, in a similar way to enzyme action. The lock will not open by itself as it needs the key. Receptors are like locks that need a specific key: they need a specific chemical in order to be activated. Substances that bind to receptors are referred to as ligands. Many cellular processes will not happen without the presence of a certain ligand on the cell membrane or without being bound to a receptor in the cell's cytoplasm. Many drugs are similar to or have similar chemical groups to the naturally occurring chemical and have the ability to bind to a receptor, where one of two things can happen – either the receptor will respond or it will be blocked (i.e. the drug binds to the receptor but nothing happens). When a drug stimulates a receptor, it is known as an *agonist* and mimics the endogenous transmitter. When a drug blocks a receptor, it is known as an *antagonist* and blocks the action of an endogenous transmitter; as a result, the effects observed are often the opposite to those following stimulation of a receptor. When a drug acts as an antagonist, it prevents the natural chemical from acting on the receptor. If the drug leaves the receptor soon after binding, the action will be similar to competitive inhibition with enzymes. There will be a competition between the drug and the natural stimulus to the receptor. The more drug that is present, the less chance of the natural stimulus having an action. As with competitive inhibition in enzymes, this type of antagonism can be reversed by increasing the amount of natural stimulatory chemical at the receptor sites. Occasionally, drugs bind firmly to receptors; in these instances, antagonism continues until the drug is destroyed. There can be no antidote to this type of antagonism. Figures 16.3 and 16.4 show examples of agonism and antagonism at a synapse.

A good example of drug antagonism happens at the synapse of cholinergic nerve fibres. At the synapse, acetylcholine is released from the vesicles of one nerve cell and binds to receptors on the next nerve or effector cell, where it sets up an action potential and the message is transmitted down the axon of this fibre or an effector response is triggered. These receptors are fairly specific for acetylcholine, but various drugs can act here and interfere with the normal transmission of the nerve impulse. The drug atropine can bind to some of the acetylcholine receptors and block the binding of the natural acetylcholine (see Chapter 27 for a fuller explanation of acetylcholine receptors). No message can be transmitted, and therefore the atropine can be said to be a cholinergic antagonist. The action of atropine could, theoretically, be overcome by the addition of more acetylcholine. This is easily explained: Imagine you have a board with thousands of holes (receptors) into which round balls can be fitted, and you have both black (acetylcholine) and white (atropine) balls. When you drop the balls on to the

FIGURE 16.3 COMPETITION BETWEEN AGONISTIC DRUG AND NEUROTRANSMITTER

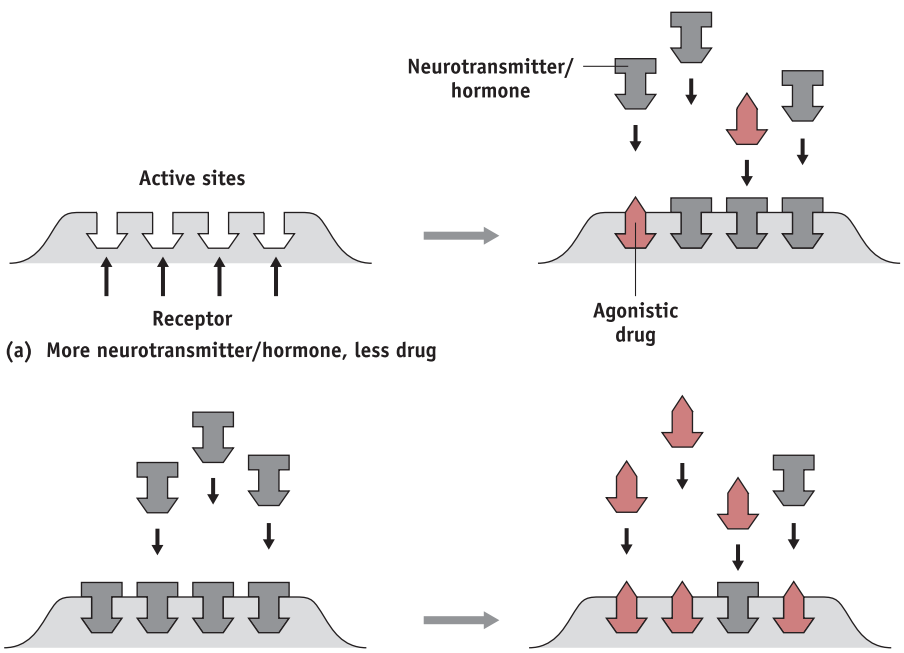
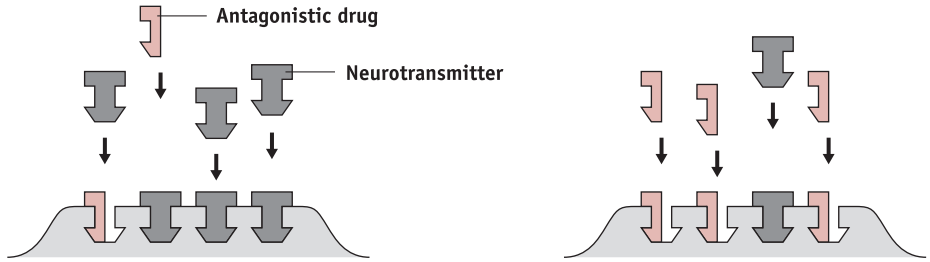


FIGURE 16.4 COMPETITION BETWEEN ANTAGONISTIC DRUG AND NEUROTRANSMITTER



(a) More neurotransmitter, less drug

(b) More drug, less neurotransmitter

board, both colours will fill the holes, and the colour that is in excess will fill more of the holes. Thus, if acetylcholine is in excess, an action potential will be generated; but if atropine is in excess, none will be forthcoming.

Partial agonists

Sometimes drugs act like the natural stimulus but to a lesser extent than the natural agonist. When a transmitter binds to a receptor, bonding occurs between the drug and the receptor. For normal action to proceed, there has to be complete congruity between the drug and the receptor in this bond formation. This is known as receptor fit. Some drugs do not fit exactly on the receptor site but still form some of these bonds – this binding is therefore not a 100 per cent fit but is enough to initiate some response. These types of drug are termed partial agonists. As their action is less than the natural stimulus, a decrease in receptor response is achieved, but not to the same extent as when using an antagonist.

Mixed agonist/antagonist drugs

Another type of drug that acts at receptors is the so-called agonist/antagonist. These drugs can work either as an antagonist or as an agonist, depending on the receptor involved. At one receptor, these drugs antagonise; at another receptor, they agonise. An example of this type of drug is the narcotic opioid **pentazocine**. If a **morphine** addict is given pentazocine, the morphine is displaced from certain receptors in the central nervous system. This displacement results in antagonism on some receptors and leads to withdrawal symptoms. The receptors associated with pain will still be stimulated, as pentazocine is agonistic to them. (This is discussed in Chapter 39.)

Affinity, specificity, efficacy and potency

There are many receptors for acetylcholine scattered about the body. These receptors are discussed in detail in Chapter 27. Pharmacologically speaking, there are several types of acetylcholine receptor found in the body, which respond differently to drugs. This phenomenon is extremely useful in drug treatment, as very often drugs can be designed to act to a greater extent on only one type of receptor and not on others. This makes drugs selective in their action, and thus their effects on the body are decreased. This phenomenon is being exploited more and more in pharmacology, with the number and type of receptors identified increasing yearly. Some terms often used to describe a drug's action at a receptor site are 'affinity', 'specificity', 'efficacy' and 'potency'. *Affinity* is defined as the extent of binding of a drug to a receptor; the greater a drug's affinity, the greater the binding and, consequently, the greater the action at that site. *Specificity* is defined as the ability of a drug to produce an action at a specific site. *Efficacy* is the ability of a drug to produce an effect at a receptor; for example, an agonist has an affinity for a receptor and has efficacy; an antagonist has affinity but no efficacy. *Potency* is the relative amount of drug that has to be present in order to produce a desired effect; the more potent a drug, the less that has to be administered.

Inverse agonists

The concept of inverse agonism or negative efficacy is a relatively new one in pharmacology. Some drugs, instead of blocking a receptor, stimulate the receptor in such a way that the opposite effect to the normal agonistic effect is seen. This type of action may apply to some existing so-called antagonists. Much research is being undertaken to develop drugs that, theoretically, will be more efficacious than plain antagonists. Put simply, if an inverse agonist is used to control high blood pressure, then the drug will actually cause a direct decrease in the blood pressure rather than simply block the intrinsic mechanisms that cause a rise in blood pressure.

First and second messengers

Receptors mediate their physiological action through a linkage to an effector system. There are at least four types

of receptor linkage that produce the resulting physiological effect. Receptors may be linked to:

- ion channels;
- G-proteins;
- tyrosine kinases;
- DNA interactions (steroid receptors).

Endogenous substances that stimulate receptors are generally termed 'first messengers', as they are often implemental only in causing an effect. This stimulation cannot be likened exactly to a switching on or off, but receptor stimulation produces conformational structural change in the receptor, which then initiates sequences of other biochemical changes. For example, when acetylcholine stimulates the nicotinic receptor complex in motor-nerve synapses, the change in receptor complex structure allows ions to flow through the synaptic membrane in order to initiate the muscle response. This happens in milliseconds.

When a first messenger acts on a receptor, it sometimes acts on what are known as transducer substances called G-proteins. The sequence of events that takes place in the cell depends on which G-protein is activated. A common action of a G-protein is to stimulate or, in some cases, inhibit the enzyme adenylate cyclase. Adenylate cyclase in turn converts adenosine triphosphate (ATP) to 3′,5′-cyclic adenosine monophosphate (cAMP). cAMP can then activate many cellular functions, including the activation of enzymes involved in energy regulation, cell division, cell differentiation, ion transport and ion-channel function. As the cAMP causes the effect, it is known as a 'second messenger' (see Chapter 26). There are several different types of G-protein, each of which can interact with different receptors and control different effectors, such as phospholipases, which produce the second messenger inositol trisphosphate (IP_3), an important regulator of calcium movement from intracellular stores. Thus, G-proteins can also be involved in ion channels, but the response here is slower than that described above, where receptors are linked directly to ion channels. The series of actions with the G-proteins amplifies the response to receptor stimulation, not unlike that associated with the blood clotting or complement cascades. Some drugs can act through a direct effect on the second messenger system; an example is **theophylline**, a common drug used in the treatment of asthma (see Chapter 51), which inhibits cAMP metabolism. G-protein-associated receptors generally produce a very rapid response (seconds), whereas those linked to DNA interactions are quite slow, taking hours.

Tyrosine-kinase-linked receptors are involved in growth and differentiation; the biochemical response time is measured in minutes, but the observable response is much slower. For example, **insulin** initiates the biochemical processes involved in controlling blood glucose levels in minutes, but the observable response in blood glucose levels could take hours. Similarly, the observable response to the activity of **growth hormone** could take weeks or longer. Tyrosine-kinase-linked receptors are not as important in pathology and pharmacology as the other types of receptor mechanisms. For example, in diabetes mellitus, serious and irreversible damage to the body develops slowly, and therefore the prompt use and action of drugs is not as immediately important as, say, following cardiac arrest, when immediate response to a drug such as **adrenaline** is vital.

Many other hormones, for example **thyroxine**, steroids and some vitamins, interact with DNA. Two processes are involved here that slow down this type of receptor action. The interacting molecule must first enter the cell and then be transported to the nucleus. When in the nucleus, the binding of the molecule to the DNA results in gene expression and, as a result, secondary transduction can result in a decrease or increase in protein synthesis, which can then cause physiological changes. This takes hours. For example, in anaphylaxis, prompt treatment to cause an immediate reversal of bronchoconstriction and hypotension is essential. Adrenaline can achieve this by being mediated through the G-proteins; however, (cortico)steroids are also usually given concurrently, which, even though the response takes several hours, can prevent secondary sequelae from developing.

Ion channel blockers

As indicated in the previous section, receptors may be associated with the transport of ions to and from cells. Ions such as calcium, sodium and potassium are transported into and out of cells in order to cause various physiological events. Opening or closing these channels is known as gating, and drugs can affect this gating phenomenon. The initiation of these transport mechanisms often involves enzymes (as is the case with sodium/potassium transport) or neurotransmittable stimuli (in the case of calcium). If enzymes are directly involved, then an enzyme inhibitor can block the transport. The cardiac glycosides (see Chapter 48), for example digoxin, act by inhibiting enzymes involved with the ATPase enzyme involved in the interchange of sodium and potassium ions. In other cases, drugs that react with the receptors in the channels can prevent the transport of the ions. In most of these cases, the receptors are not known, but it is assumed that this is one of the main mechanisms of action of the ion channel blockers used widely today. Like other receptors, these ion channel receptors vary in different parts of the body; this enables drugs to be made that have selectivity for specific channels. For example, the calcium channel blocker **nifedipine** has an action on arterioles but little action on the myocardium, whereas another calcium channel blocker, **verapamil**, has exactly the opposite effect (see Chapters 44, 45 and 48). Neither of these drugs has an affinity for calcium channels in skeletal muscle.

ENZYMES AS DRUGS

Many enzymes are used as drugs, their action being biochemical rather than chemical. There are several different uses of enzymes in therapeutics, of which the following are representative examples. Others will be dealt with in subsequent chapters.

In some conditions, there may be a deficiency of a natural enzyme, particularly digestive enzymes. These enzymes can be replaced orally and are usually taken with food. An example is **pancreatin**, which is a mixture of pancreatic enzymes (see Chapter 54).

Enzymes can also be used to increase the speed of absorption of injected drugs. An example of this is the enzyme **hyaluronidase**, which acts on hyaluronic acid, a component of tissue cement. This helps to keep cells 'glued together'. If a drug is injected together with this enzyme, especially by subcutaneous injection, the drug will be absorbed faster and cause less discomfort to the patient when large volumes are injected.

Sometimes enzymes are used to destroy unwanted materials in the body. An ancient example of this is the application of leeches to bruises. When a leech bites, it injects some of its saliva, containing a mixture of proteins and enzymes, which prevent blood clotting. Enzymes can also destroy preformed blood clots, such as those found in bruised tissue. Many of these substances have now been identified and will probably be used to treat blood-coagulation disorders in the future. Examples are hirudin, which inactivates thrombin; destabilase, which depolymerises fibrin; and haementin, which cleaves aggregated platelets. There has been an upsurge of interest in these substances, and a firm in Wales is currently breeding thousands of leeches for medical use.

Finally, an unusual use of an enzyme is to destroy a substrate within the body. There is only one example of this known to the authors, and that is the enzyme **asparaginase** or **colaspase**, used in some types of cancer (see Chapter 76).

Note that the action of a drug is its effect at the cellular or biochemical level, whereas therapeutic action is the end result of a drug action. For example, the action of aspirin is as an enzyme inhibitor, but its therapeutic action is in the production of analgesia.

SUMMARY

- The general term for the mechanism of action of drugs on the body is 'pharmacodynamics'.
- Pharmacodynamics can, in a few instances, be due to physical or chemical changes induced by drugs.
- Most pharmacodynamic activity is due to the action of drugs on enzymes or receptors within the body.
- Drugs can inhibit enzymic activity irreversibly, but most drugs that act on enzymes reversibly inhibit enzyme activity.
- Irreversible inhibition is non-competitive and may be irreversible.
- Reversible inhibition is competitive.
- Drugs that act on receptors can either stimulate the receptor or inhibit (block) receptor activity.
- Drugs that stimulate receptors are termed 'agonists' and those that block receptors 'antagonists'.
- In most cases, drugs that act on receptors compete with the neurotransmitter/hormone that usually stimulates the receptor.
- Receptor stimulation involves a cascade of events at the cellular level.
- Some drugs are enzymes.

1. Atropine is used as an antidote for anticholinesterase poisoning. Can you give the reason for this?
2. What is meant by 'receptor affinity'?
3. Neostigmine is a competitive inhibitor of cholinesterase. Look up the disease myasthenia gravis and suggest why this drug is used in its treatment.
4. Streptokinase is a bacterial enzyme used as a thrombolytic agent. Why would this enzyme be better if it were of human origin? (You need to know some basic immunology to answer this.)
5. Explain the terms 'potency' and 'efficacy'.
6. Simethicone lowers the surface tension of the gastrointestinal fluids. In one word, what is its mechanism of action?

7 Naloxone is used as an antidote for morphine poisoning. Morphine binds to receptors in the brain. Suggest how naloxone exerts its effect.

8 Iodine is a good oxidising agent and is used topically as a disinfectant. By what mechanism will it kill microorganisms?

9 The drug fluorouracil is used in the treatment of some forms of cancer. It is very similar to the compound uracil, which is an essential component of RNA. Suggest how this drug exerts its effect.

DRUG DEVELOPMENT, EVALUATION AND SAFETY

17

CHAPTER SEVENTEEN

OBJECTIVES

After completing this chapter, the reader should be able to:

- **outline briefly the process of evaluation and approval of new drugs;**
- **define what is meant by a drug's margin of safety;**
- **outline briefly how unwanted drug effects arise, and differentiate between predictable and unpredictable reactions;**
- **describe the underlying pathophysiology of drug allergy, and state examples of differing degrees of allergic severity;**
- **describe the pharmacological properties that influence drug transfer across the placenta and into breast milk;**
- **describe the factors that determine the teratogenic potential of drugs once they enter the embryonic/fetal circulation.**

KEY TERMS

Adverse drug reactions
Drug development
Drug safety
Drug teratogenicity
Drugs in pregnancy
Hypersensitivity
Lactaction and drugs
Margin of safety
Placental drug transfer

IN THIS CHAPTER, AN OVERVIEW OF THE PROCESS OF NEW drug testing and evaluation is presented. The drug-development process not only involves a determination of the effectiveness of a new drug but also includes an assessment of its toxicity. A potential clinical drug must be judged not only on its clinical benefit but also on the harm it might do. The discussion of aspects of drug safety involves the nature of adverse drug

reactions, drug hypersensitivity, and placental and breast-milk transfer. For many drugs, there is a wide margin between the dose that is therapeutically effective and the dose that is toxic. For others, there is a fine line between safe and unsafe dosage; these agents are considered highly toxic. In such instances, the costs of crossing this line have to be weighed against the benefits to the patient. One example is in the cytotoxic therapy of people with cancer (see Chapter 76); another is the use of certain antimicrobial agents in the treatment of serious infection (see Section XIV).

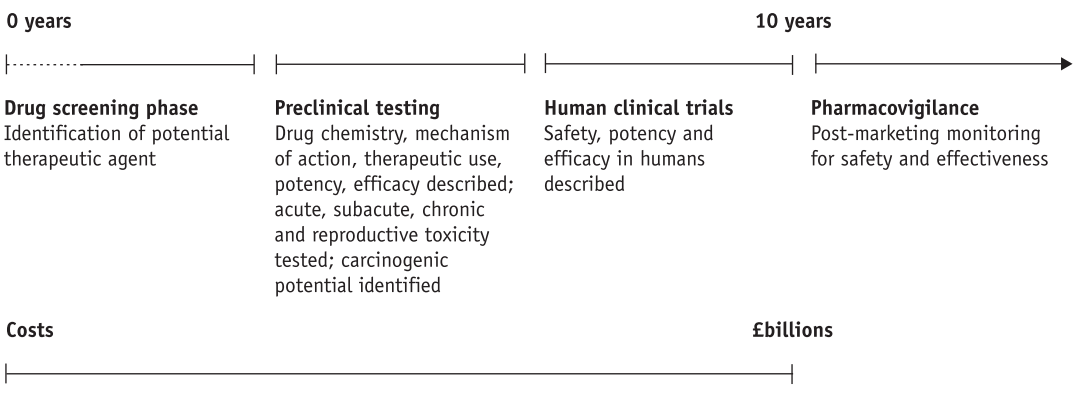
NEW DRUG EVALUATION AND APPROVAL

Drug manufacturers commit a considerable amount of time, money and other resources to the development of new therapeutic agents. In Chapter 1, the nature of screening chemicals isolated from plants, animals and other sources for therapeutic effects is outlined. Once a potential medicine is identified, it is subjected to a battery of assays and other tests in living biological systems. A timeline of the drug evaluation process is represented in Figure 17.1. Before any human testing can commence, potential drugs are tested on cells in tissue culture and on a variety of animal species in order to establish a chemical and pharmacological profile. The agent is described in terms of its chemistry, its probable physiological mechanism of action, whether it is antagonistic or stimulatory on its physiological system, its therapeutic uses, its potency and efficacy, and its toxicity.

The safety tests determine a drug's acute toxicity (indicating tissue targets for damage resulting from high single doses), subacute toxicity (repeated doses given over a prolonged period of days in order to reveal tissue targets for damage and the potential for toxicity resulting from drug accumulation) and chronic toxicity (repeated doses for a period of months in order to assess the safe therapeutic and toxic dose ranges). These tests should also assess the effects of the drug with respect to carcinogenic potential and reproductive toxicity (affecting fertility, implantation, embryonic and fetal development, and its effects on the breast-fed infant). The drug is then ready for testing on humans.

Approval for human clinical trials is granted by government authority after a thorough examination of all of the known data about the drug. The Medicines for Human Use (Clinical Trials) Regulations (2004) regulate clinical trials in the UK. Pharmacology studies in healthy human volunteers (phase 1 studies) require authorisation from the Medical and Healthcare Products Regulatory Agency (MHRA), which acts on behalf of the UK licensing authority. Each trial must have an identified sponsor, who takes responsibility for its management. The procedures and protocols of the intended clinical trials are also subjected to scrutiny by independent ethics committees, and there is a requirement that all clinical trials are conducted in accordance with the internationally recognised principles of good clinical practice (GCP). The latter helps to ensure that all UK trials are conducted at a high standard, thus minimising the risks to patient volunteers. In addition, the investigators must obtain written informed consent from all the participants in the study before the study can proceed. Clinical trials proceed in stages. First, the effects of the drug in healthy humans are evaluated; then the drug is tested on patients with a disease for which the new drug is intended. The latter tests are usually of a double-blind experimental design, where neither the participants nor the investigators know at the time of administration whether the test agent or a placebo has been administered. Until recently, clinical trials were the elusive domain of doctors and scientists; nowadays, however, it is more likely than not that the investigation team includes nurses and other health professionals.

FIGURE 17.1 TIMELINE AND COSTS FOR DEVELOPMENT AND EVALUATION OF NEW DRUGS



On completion of a clinical trial, a final report is submitted and the licensing authority, acting through the MHRA, may issue a product licence, which gives approval to market the drug. The health ministers of the UK make up the licensing authority.

The work of the MHRA and the expert advisory bodies does not finish once the drug is approved. They are also responsible for receiving and assessing pharmacovigilance reports from the market authorisation holders of the product. This ongoing monitoring of safety and usage is applicable not only to newly introduced drugs but all drugs available on the market, particularly through the Yellow Card reporting system. The authorities must also approve any changes to existing products. With the growth in community use of complementary medicines, there will be a need to include the evaluation and regulation of complementary health-care products.

DRUG EFFECTIVENESS

The aim of therapeutics is to maintain the plasma drug concentration within its known effective range and thus avoid the extremes – ineffective at one end and toxic at the other. The dose range that places the plasma concentration within this effective level (between the minimum effective concentration and the maximum safe concentration) is called the margin of safety (see Figure 17.2). Another measure of drug safety is the therapeutic index (see Chapter 14).

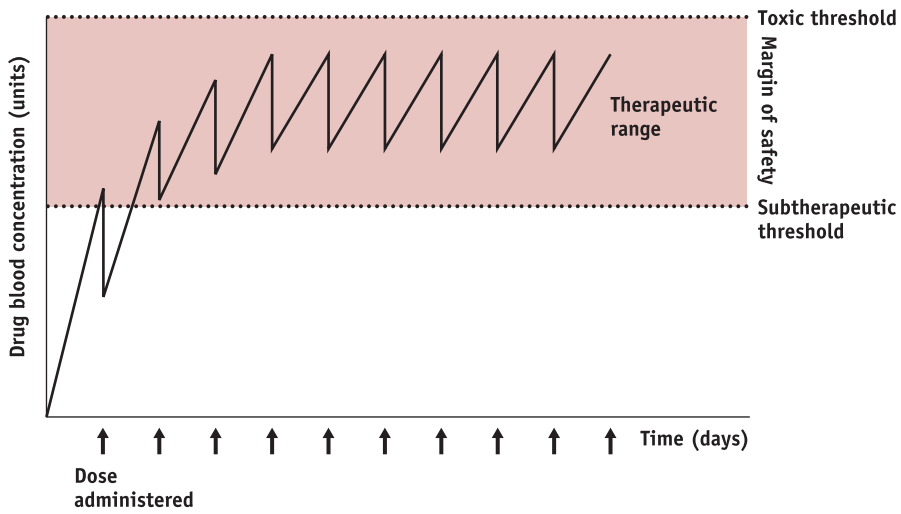
For a number of drugs, the margin of safety can be so narrow that individual variations in pharmacokinetics can lead to toxic plasma concentrations being achieved in some patients. Examples of agents with narrow margins of safety are **digoxin**, the cardiac glycoside used in the treatment of congestive cardiac failure and dysrhythmia (see Chapter 48), and the aminoglycoside antibiotics **gentamicin** and **tobramycin** (see Section XIV). For other drugs, such as the **penicillins**, the margin of safety is very broad, offering the clinician a choice of a wide range of doses considered both safe and therapeutic.

ADVERSE DRUG REACTIONS

Another consideration is the frequency and nature of the adverse reactions or unwanted effects observed after the administration of drugs. Side effects usually arise out of an alteration of similar physiological processes at sites distant from the primary site of action. Consider the instance when a drug is administered for the purpose of altering the heart rate. The drug does this by stimulating a population of receptors on the myocardium. It will also induce an undesirable alteration in gut motility, however, because the same type of receptor is also located on gut tissue. As Sir Derrick

FIGURE 17.2 GRAPH OF BLOOD DRUG CONCENTRATION, SHOWING THE MARGIN OF SAFETY

The graph shows the range of blood concentrations that are considered therapeutic for any drug. Concentrations above the toxic threshold (maximum safe concentration) would cause serious harm to the patient, while concentrations below the subtherapeutic threshold (minimum effective concentration) would be inefficacious. Blood concentrations between these thresholds would be the most effective therapeutically. The range of doses that would produce blood concentrations lower than the toxic threshold but above the subtherapeutic threshold represents a drug's margin of safety.



Dunlop, Chair of the Committee on the Safety of Drugs between 1964 and 1969, said: 'Show me a drug with no side effects, and I'll show you a drug with no actions.'

Unwanted effects can manifest as either side effects or idiosyncratic effects. In this book, a clear distinction is made between these types of adverse reaction. A side effect is an unwanted effect of the drug related to its action at other sites in the body. It is predictable (a type A reaction), and its intensity often relates to drug dosage. Side effects are context-specific: For a patient with bradycardia taking an antimuscarinic agent such as atropine, urinary retention is a side effect; for an incontinent person taking the same drug, the urinary retention may be considered therapeutic.

More unpredictable and variable are allergic reactions and idiosyncratic drug effects (type B reactions). These reactions do not occur in every patient who receives the drug, and the seriousness of the reaction is sometimes unrelated to the dose administered. An example of such a reaction is the potentially fatal allergic reaction called anaphylaxis (discussed below). Idiosyncratic drug effects occur infrequently, affect a very small proportion of people and are related to the individual's genetic constitution. (Such reactions are discussed in detail in Chapter 18.)

DRUG HYPERSENSITIVITY

Hypersensitivity reactions to drugs are characterised by inappropriate immune responses of an allergic type to the administered therapeutic agent. There are four types of drug hypersensitivity reaction: type I (anaphylaxis), type II (cytotoxic), type III (serum sickness) and type IV (delayed).

Known hypersensitivity to a particular drug is always a contraindication for its use. Therefore, asking a patient whether they are allergic to the drug you are about to administer is an important part of the general role of the nurse in regard to drug therapy.

Type I hypersensitivity

The most severe form of type I hypersensitivity is a life-threatening reaction called anaphylactic shock. On entering the body for the first time, either the drug itself or the drug in combination with an endogenous protein such as a hapten acts as an antigen and triggers the production of antibodies. An immune response is triggered on the second or subsequent re-exposure to the antigen through interaction with immunoglobulin E (IgE) antibodies, causing the systemic release of chemical mediators (see Figure 17.3). This induces a widespread vasodilator response, which consequently produces a state of circulatory shock. The mediators also trigger spasms of bronchial and gastrointestinal smooth muscle, resulting in severe respiratory distress and abdominal cramping. The treatment of anaphylaxis involves placing ice packs over the injection site to reduce systemic absorption and administering the adrenergic agonist **adrenaline**, which produces vasoconstriction and bronchodilation and relaxes the gut muscle (see Chapter 26).

The intensity of the reaction varies from individual to individual and often depends on the access of the antigen to the bloodstream. If the antigen remains confined to one region, it will produce only a localised anaphylactoid reaction, simply called an allergy. Hayfever is an example of a localised allergic reaction confined to the upper respiratory tract. A localised anaphylactic reaction confined to the skin usually manifests as an urticarial rash.

Type II hypersensitivity

Type II hypersensitivity reactions occur when an absorbed drug binds to the surface of blood cells and consequently induces antibody production. On subsequent exposure to the drug, the antibody–drug combination triggers blood-cell lysis through complement fixation. Depending on the type of blood cell involved, this reaction leaves the affected individual in a state of anaemia, thrombocytopenia or agranulocytosis. Antimicrobial drugs such as the penicillins and sulphonamides (see Section XIV) have been reported to produce type II hypersensitivity.

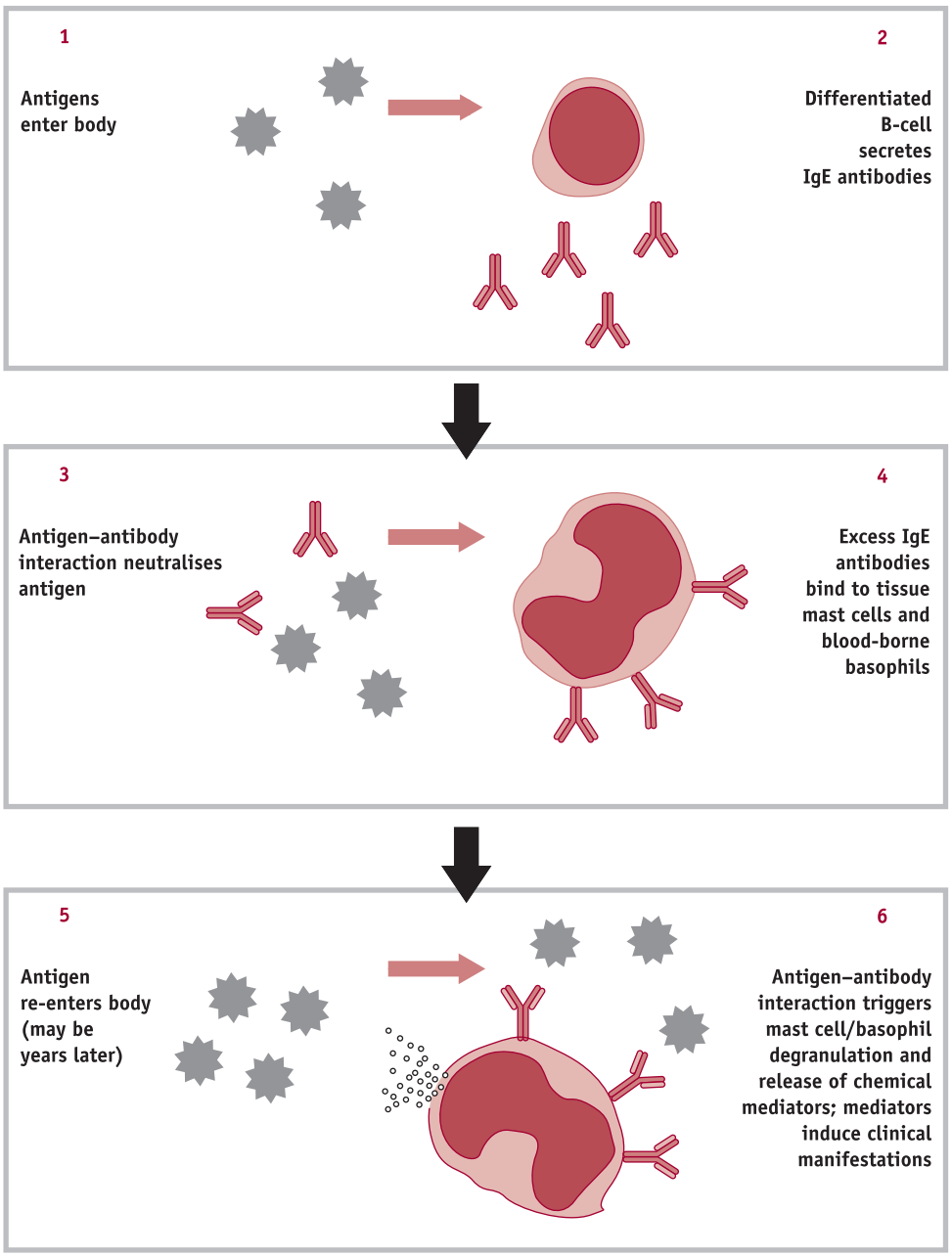
Type III hypersensitivity

Type III hypersensitivity involves an interaction between circulating antibodies to the therapeutic agent while it is present in the plasma. The antibody–antigen interaction leads to the formation of an insoluble complex that precipitates out of the blood and into the tissues. Within the tissues, the complex elicits an inflammatory reaction that severely damages the surrounding tissue. Common sites of deposition include the skin, kidneys and joints. The manifestations usually include fever, rash, protein in the urine and swollen lymph nodes. Immunostimulants such as antivenoms (see Chapter 21), antitoxins and other antisera raised in non-humans (see Chapter 75) are associated with this form of hypersensitivity.

Type IV hypersensitivity

Type IV hypersensitivity reactions depend on an interaction between the drug and T-lymphocytes rather than an antibody reaction. The underlying response is delayed at least 12 hours after exposure to the drug and is characterised by an inflammatory skin reaction. Manifestations of delayed hypersensitivity may include redness, induration, blistering and scaly skin. Drug-related contact dermatitis and eczema are common examples of this form of hypersensitivity. Another type of delayed hypersensitivity reaction is photosensitivity. In this condition, ultraviolet light from the sun enhances the antigenic quality of the drug. This is of particular importance to people living in regions where they are exposed to the sun for much of the year and pursue an outdoor lifestyle. Agents that induce photosensitivity include

FIGURE 17.3 ANTIGEN–ANTIBODY INTERACTION LEADING TO A TYPE I HYPERSENSITIVITY REACTION



IgE, immunoglobulin E.

some antibiotics (see Section XIV) and the phenothiazine antipsychotic drugs (see Chapter 33).

PLACENTAL TRANSFER TO THE FETAL CIRCULATION

The transfer of drugs from the maternal circulation across the semipermeable placental barrier into the embryonic/fetal circulation is dependent on two factors: the physicochemical properties of the drug itself, and the dose of the drug.

Physicochemical drug properties

The physicochemical properties of the drug determine the nature of the interaction at the placental interface. Molecular size, solubility, degree of ionisation and affinity for

plasma proteins influence the rate and extent of absorption into the embryonic/fetal circulation. (To some degree, this has already been discussed in Chapters 13 and 14, which cover pharmacokinetics.) The size of the drug is determined by its molecular weight. Drugs with molecular weights under 500 Daltons (Da) cross readily into the fetal circulation. Drugs with molecular weights between 500 and 1000 Da can still cross the placenta, but more slowly. Drugs with higher molecular weights are restricted to the maternal circulation and generally do not pass into the fetus unless they are lipid soluble.

Lipid-soluble drugs readily cross the placenta and exert their effects on the developing conceptus. By nature of this property, however, their effects are short-lived, as they rapidly move back into the maternal circulation. The amounts of lipid-soluble drug in the embryonic/fetal circulation are determined largely by placental blood flow. Water-soluble drugs cross the placenta less easily because they readily form ions. Drugs cross membranes most efficiently when they are in a non-ionised form. For acidic drugs, the greatest proportion of non-ionised drug occurs at acidic pH values; for basic drugs, this occurs at alkaline pH values (see Chapter 13). That is not to say that the ionised portion cannot transfer across the placenta, but, relative to that of the non-ionised portion, the transfer rate is slow and the extent marginal. Furthermore, drugs that are highly ionised at physiological pH tend to bind to maternal plasma proteins. This impedes placental transfer further, as only the unbound fraction, a relatively small portion of the total blood drug concentration, is free to cross into the embryonic/fetal circulation.

Effect of drug dose

The second contributing factor to placental transfer is the drug dose. The higher the plasma drug levels in the maternal circulation, the greater the magnitude of the concentration gradient across the placenta. Therefore, under these circumstances, one would expect higher drug concentrations within the embryonic/fetal circulation.

DRUG TERATOGENICITY

Having discussed the rate and extent of placental transfer, in terms of drug safety a most important consideration, once a drug has entered the circulation of the developing conceptus, is whether it will cause harm in the form of birth defects. Agents that cause morphological defects in the developing human in utero are called teratogens.

Tissue growth and development are dependent on the rate of cell division occurring. Therefore, drugs that affect cellular proliferation are most likely to cause major morphological abnormalities in the developing fetus if they can cross the placenta. Examples of drugs to avoid during pregnancy because they impair cell division are certain antimicrobial agents and the drugs used in cancer therapy.

Not all organ systems and structures develop at the same time. The nervous system and heart develop first, followed by the sense organs, digestive system and limbs. Irrespective of which structure develops first, all tissues are most susceptible when they are undergoing optimal rates of proliferation. It follows, therefore, that the timing of drug exposure determines the extent of damage. The conceptus is most susceptible as an embryo during the first trimester (i.e. the first 3 months of pregnancy), when body structures are forming. After this time, all structures undergo further development, but no new structures form. Some drugs need to be avoided only during one trimester (usually the first), while other drugs are so toxic that they are contraindicated throughout pregnancy. Additionally, there is the issue that some women may be unaware that they have conceived in the first trimester.

Many studies have been conducted on both animals and humans to determine the risk of drug teratogenicity. Drugs may be usefully categorised on the basis of the evidence ranging from no evidence of increased teratogenicity to demonstrable teratogenicity (see Table 17.1).

DRUGS AND LACTATION

Most drugs administered during lactation will pass into the breast milk. The factors that determine placental transfer also contribute to entry into breast milk: drug molecular size, solubility and affinity for plasma protein. Final drug concentrations in the infant's blood are also influenced by the maternal dose, the amount of milk consumed and the time interval between maternal absorption and when the infant was fed.

The effects on the breast-feeding infant vary greatly from drug to drug. Narcotic analgesics, antianxiety agents and hypnotics can have profound effects on the breast-feeding infant, whereas the effects of many antibiotics, **aspirin** and **caffeine** are relatively insignificant at this time of life (although this exposure may sensitise the child for drug hypersensitivity reactions later in life). The problem is that for many drugs, the effects on breast-feeding infants are not yet known. Clearly, more studies need to be performed in this area. The potential risk to the child must be weighed carefully against the benefits of taking the drug. Clinical references such as the *British National Formulary* include a section with available data on the potential risks of specific medications to an infant during breast feeding.

TABLE 17.1 CATEGORISATION OF MEDICINES IN PREGNANCY

Category	Description	Examples
A: drugs taken by large numbers of pregnant women and women of childbearing age	No proven increase in occurrence of fetal damage or other proven harmful effects on fetus	Penicillin G and V (Ch. 68), erythromycin (Ch. 68), paracetamol (Ch. 40)
B: drugs taken by a limited number of pregnant women and women of childbearing age	No proven increase in occurrence of fetal damage or other harmful effects on fetus	
B1	Animal studies have not produced evidence of increased incidence of fetal damage	Oestrogens (Ch. 58), ipratropium (Ch. 51)
B2	Animal studies may be inadequate, but available data have not produced evidence of increased incidence of fetal damage	Mefloquine (Ch. 72), aciclovir (Ch. 73)
B3	Animal studies have shown evidence of fetal damage, but significance to humans is unclear	Carbamazepine (Ch. 37), dopamine (Ch. 26)
C	Drugs that have caused or are suspected of causing fetal harm without causing malformations; harmful effects may be reversible	Antipsychotics (Ch. 33); benzodiazepines (Ch. 34)
D	Drugs that have caused or are suspected of causing higher occurrences of fetal malformations or irreversible damage	Aminoglycosides (Ch. 68), cytotoxic antibiotics (Ch. 76), antiseizure drugs (Ch. 37)
X	Drugs with a high risk of causing irreversible damage; they should not be used during pregnancy or when there is a possibility of pregnancy	Isotretinoin (Ch. 78)

SUMMARY

- New drugs are submitted to an evaluation and approval process by an appropriate governmental body.
- Any new drug is submitted to an evaluative process that describes its chemistry, physiological effects, therapeutic uses and toxicity. The new agent is then subjected to human clinical trials. Even after a drug is approved for marketing, it is still subjected to ongoing monitoring of safety and effectiveness.
- The margin of safety defines the plasma drug concentrations that are therapeutically effective and safe and those that are considered toxic.
- Adverse drug reactions are unwanted drug effects that may derive from the drug's action in other body tissues (side effects), allergic reactions, and those that are idiosyncratic (derive from differences in genetic makeup).
- Drug hypersensitivity reactions are characterised by inappropriate immune responses to the presence of a drug. There are four distinct types: type I (anaphylaxis), type II (cytotoxic), type III (serum sickness) and type IV (delayed).
- Placental transfer of drugs into the fetal circulation is determined largely by the drug's physicochemical properties and the drug dose.
- Some drugs may damage the developing human in the womb; this property is called teratogenicity. The risk of damage is represented as an alphabetical category (A, B, C, D, X). Different tissues and organs are more susceptible at certain times during pregnancy. Therefore, some drugs are contraindicated only during certain periods in pregnancy.
- Most drugs administered during lactation will pass into the breast milk. The effect on the infant varies from drug to drug. For a significant number of drugs, the effects on the breast-feeding infant are unknown.

1 Determine whether the following drug effects should generally be regarded as predictable or unpredictable effects:
   (a) rash;
   (b) bradycardia;
   (c) dry mouth;
   (d) anaphylaxis.

2 Comment on the factors that will influence the absorption of drug X, a water-soluble drug that is 90 per cent bound to plasma proteins and has a molecular weight of 450 Da.

3 For each of the following reactions, indicate the type(s) of hypersensitivity to which it belongs:
   (a) haemolytic anaemia;
   (b) joint pain and swollen lymph nodes;
   (c) contact dermatitis;
   (d) photophobia;
   (e) rash.

4 Indicate the margin of safety (broad or narrow) for each of the following:
   (a) penicillin V;
   (b) aminoglycosides;
   (c) digoxin.

5 Explain why a double-blind experimental design is appropriate in human clinical drug trials.

6 Differentiate between acute and chronic toxicity drug tests.

7 Name the government drug regulatory bodies that oversee the evaluation of new drugs.

PHARMACOGENETICS

18

CHAPTER EIGHTEEN

OBJECTIVES

After completing this chapter, the reader should be able to:

- **define the terms 'pharmacogenetics' and 'genetic polymorphism';**
- **describe how genetic polymorphism can affect drug responsiveness at the population level;**
- **outline how genetic polymorphism can be tested for diagnostically;**
- **in terms of the effects on drug treatment, compare responders and non-responders;**
- **outline the relationship between genetic polymorphism and ethnicity;**
- **outline the ethical considerations associated with pharmacogenetics.**

KEY TERMS

Cytochrome P450 enzymes
Drug stratification
Fast metabolisers
Genetic polymorphism
Pharmacogenetics
Slow metabolisers

THERE CAN BE SIGNIFICANT VARIATION IN INDIVIDUAL responsiveness to drug therapy. For some people, standard drug regimens induce inappropriate drug concentrations at the site of action (due to pharmacokinetic variability) or unsuitable effects at appropriate drug concentrations (due to pharmacodynamic variability). The clinical consequences of such variability can range from poor effectiveness of treatment to serious injury or death caused by adverse drug reactions.

At the population level, responsiveness to a particular drug is considered to be *distributed normally*. That is, drug responsiveness can be represented as a bell-shaped curve, where the most frequent level of response corresponds to the mean or average (see Figure 18.1). The level of responsiveness decreases as we move to the left or right of this average value.

The differences in drug responsiveness can be due, at least in part, to a person's genetic makeup. Pharmacogenetics is a branch of pharmacology established to investigate how genetic variation contributes to variable drug responsiveness. In this chapter, we provide an overview of pharmacogenetics and some clinical considerations associated with this field of study.

FIGURE 18.1 NORMALLY DISTRIBUTED DRUG RESPONSIVENESS AT THE POPULATION LEVEL

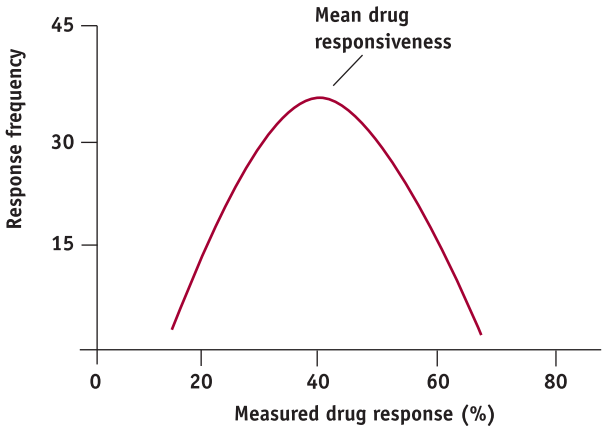
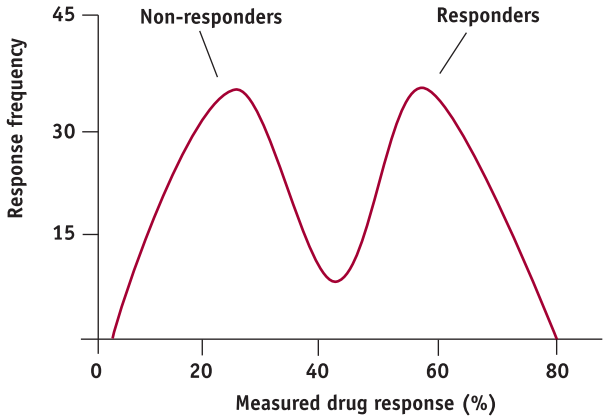


FIGURE 18.2 BIMODAL DRUG RESPONSIVENESS AT THE POPULATION LEVEL



OVERVIEW OF PHARMACOGENETICS

Our genes are responsible for the coding of enzymes, receptors, ion channels, drug transporter molecules and other physiological systems involved in observable drug responses. Some of these proteins are located at the drug's site of action, while others are involved in the metabolism of drugs. Within the human population, genetic variation causes individuals to express different forms of these proteins. This phenomenon is known as genetic polymorphism. Genetic polymorphism occurs when a genetic trait (e.g. coding for the synthesis of a particular enzyme) can be expressed within the population in two (or more) different forms, or phenotypes. It is this type of polymorphism that can lead to differential drug responses.

Responders and non-responders

In pharmacogenetics, gene sequences are examined and differences in DNA noted. These sequencing differences are, in effect, genetic markers that can be used to predict the probability of a particular drug response. Broadly speaking, a patient will be likely either to respond (i.e. be a responder) or not respond (i.e. be a non-responder) to a therapy. At the population level, responsiveness of this kind fits a *bimodal distribution*, where there are two peak frequencies of responsiveness (see Figure 18.2). This is in contrast to a normal distribution, where there is only one peak.

Tailor-made drug therapy

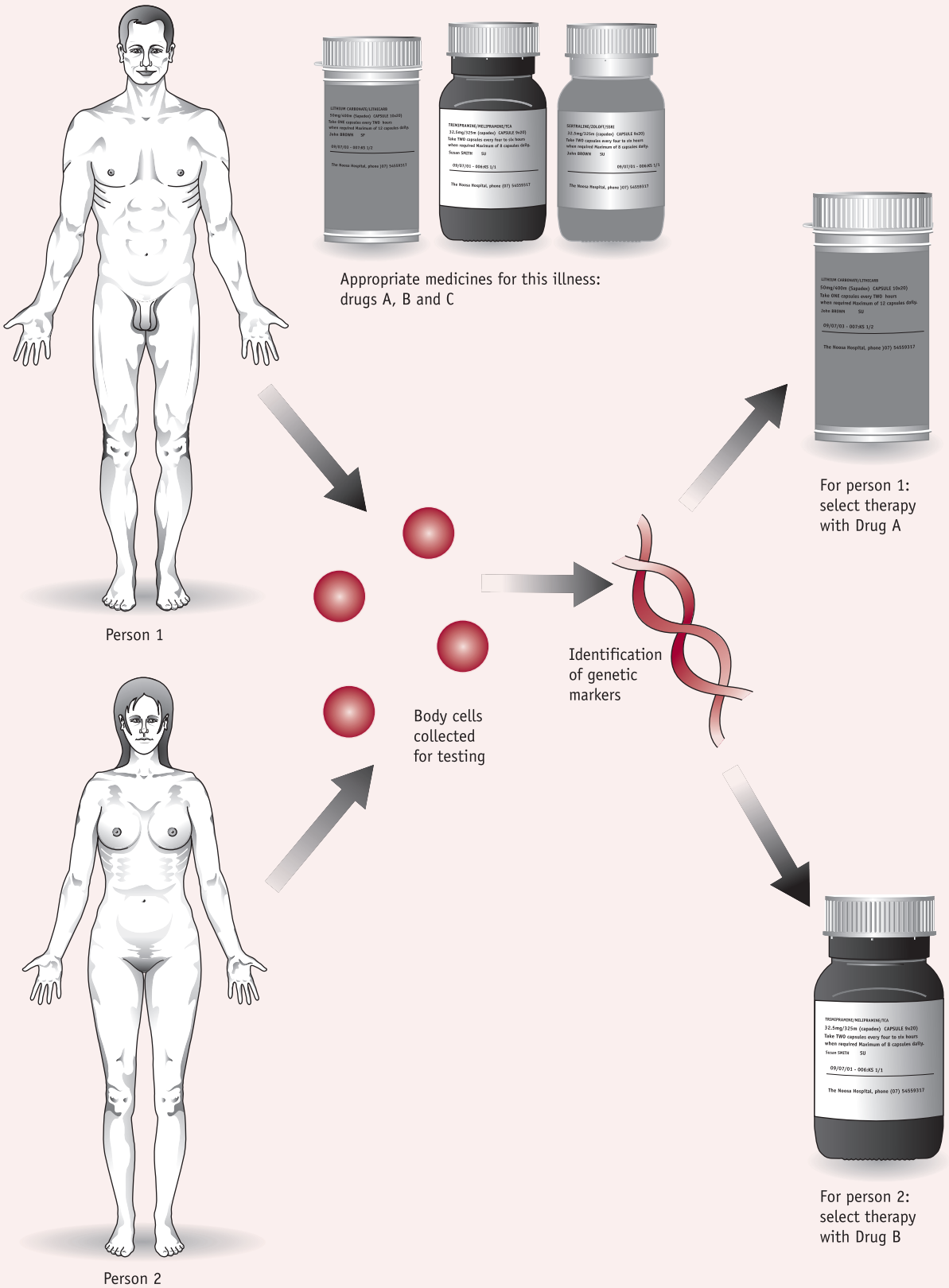
Clinically, the presence of these genetic markers can be tested for using a suitable diagnostic procedure, and then individualised drug treatment could commence. This is not so new a concept, as diagnostic testing for specific genetic markers is done routinely when a patient requires a blood tranfusion. In this case, the genetic markers are the different blood groups, and it is this that determines the type of blood the person receives. An individualised pharmacogenetic-based therapeutic approach is known as *drug stratification*, where the dose and/or choice of drug is determined by the person's genetic status. The goal of such an approach is to tailor the safest and most appropriate drug treatment to the needs of the individual (see Figure 18.3).

Diagnostic testing

A relatively sophisticated example of pharmacogenetic screening has recently been adopted in clinical practice and is seen to be the way of the future with regard to drug stratification. In cases of primary breast cancer, 25–30 per

FIGURE 18.3 TAILORING DRUG TREATMENT TO THE INDIVIDUAL

Drug stratification is achieved by tailoring the safest and most appropriate treatment to the needs of the individual.



cent of patients overexpress a cancer-related gene called *HER2*, the product of which forms an HER2 receptor on the cancerous cells. These tumours tend to grow aggressively. The HER2 receptor represents a genetic marker whose overexpression can be tested for. If the marker is overexpressed, the choice of drug treatment is a monoclonal antibody against the HER2 receptor, called **trastuzumab** (see Chapter 76). In this way, the test result determines the appropriateness of drug treatment.

Currently, pharmacogenetic testing is not used widely. It is limited to some hospitals and specialist centres. Until recently, phenotyping high-risk individuals before or during therapy was the only way of assessing pharmacogenetic factors. This involved the administration of a test substance, collection of samples (e.g. from urine or breath tests) and laboratory analysis of the ratio of active drug to inactive metabolites. Simpler, more convenient diagnostic techniques to detect genetic markers will ensure more widespread testing of the population in clinics and hospitals. DNA tests using small amounts of tissue (such as hair follicles or buccal cells) could rapidly provide the information about a person's genetic status required for drug stratification.

POLYMORPHISM AND DRUG METABOLISM

In pharmacogenetics, genetic polymorphism is studied most widely in relation to drug metabolism. More than 20 human enzymes associated with drug metabolism have polymorphisms. In addition, ethnicity plays a role in the frequency of these polymorphisms.

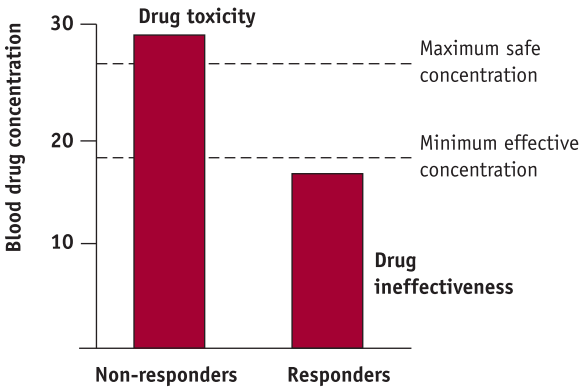
A number of important enzymes are involved in drug metabolism, including N-acetyltransferase and some of the cytochrome P450 family of oxidative enzymes. For these enzymes, human populations can be divided into two groups based on their ability to metabolise particular drugs: responders (extensive metabolisers) and non-responders (poor metabolisers). In this section, some well-documented examples of this bimodal distribution of drug responsiveness are outlined.

From a clinical perspective, non-responders are of great importance. If, during therapy, plasma drug concentrations remain high because of an inability to degrade the active agent, then non-responders are at risk of developing serious adverse drug reactions. Such individuals may require a reassessment of the dose regimen or choice of drug in order to avoid toxicity. For the responders, the worst scenario is that the drug will be less effective because the plasma concentration is subtherapeutic. This could be redressed by altering the choice of drug or dosage (see Figure 18.4).

Fast (effective) and slow (poor) acetylators

The process of metabolic acetylation is where inactive metabolites are created in the liver by the attachment of a two-carbon acetyl group donated by acetyl coenzyme A, a component of the citric acid cycle. The hepatic enzyme N-acetyltransferase is involved in the acetylation of drugs such as the sulphonamide antibiotics, the antituberculotic agent **isoniazid**, the antidysrhythmic **procainamide**, the hydrazines (such as the peripheral vasodilator **hydralazine** and the antidepressant **phenelzine**) and **caffeine**.

FIGURE 18.4 POTENTIAL CLINICAL CONSEQUENCES OF GENETIC POLYMORPHISM



A slow acetylator is a non-responder who inactivates the drug more slowly than the general population, leading to an accumulation of the drug in the blood and possible toxicity. As a consequence, a reassessment of dosage or drug may be required.

A fast acetylator is a responder who degrades the active drug into its acetylated metabolite effectively. Some individuals, however, can achieve this too effectively, ending up with lower than normal blood concentrations of the active drug. Such individuals may require a change in the standard dose regimen for these drugs (i.e. more frequent or higher dosage) in order to compensate.

In terms of ethnicity, recent studies indicate that for this enzyme 50–60 per cent of Caucasians and 10–20 per cent of Asians are poor metabolisers. This suggests that as a significant proportion of the community are at risk of toxic adverse reactions, testing genetic status would be very worthwhile.

The underlying problem is related not to a defect in the enzyme responsible for acetylation but rather the amount of enzyme present in the liver. The pattern of inheritance is thus: Fast acetylators are either homozygous or heterozygous for the autosomal dominant gene (*R*), which programmes for higher enzyme levels, while slow acetylators are homozygous for the recessive gene (*r*).

Caffeine has been used as a safe phenotyping probe to determine fast and slow acetylators. As indicated above, the ratio of caffeine to its metabolites in the urine indicates to which group a person belongs. High levels of caffeine metabolites indicate fast acetylation.

Polymorphism involving cytochrome P450 enzymes

Cytochromes are haem proteins that catalyse important physiological reactions involved in energy production and phase I drug metabolism (see Chapter 14). The cytochrome P450 enzymes represent a family of enzymes responsible for the oxidation of a number of important clinical agents. The term 'P450' represents the wavelength of the colour, a 'pink' colour near 450 nm, which characterises the chemical properties of this family. Between 20 and 200 different genes encode the cytochrome P450 family. The current naming system (nomenclature) for the family members is CYP, and there are three main groups of this family involved in drug metabolism in the liver: CYP1 (cytochrome P450 1), CYP2 and CYP3. Each specific enzyme in these groups is represented by a further letter and numeral, which is its unique identification. For example, cytochrome P450 1A1 would be CYP1A1.

Genetic polymorphism is associated with a number of enzymes in this family, including CYP2D6 and CYP2C9, which together account for around 24 per cent of the total human liver cytochrome P450 content. This means that for each of these enzymes, the population is distributed into responders and non-responders. CYP2D6 is involved in the breakdown of more than 100 drugs used in psychiatric, neurological and cardiovascular diseases. CYP2C9 is necessary for the breakdown of at least 60 drugs, including the benzodiazepine **diazepam**, the aspirin-like anti-inflammatory drug **ibuprofen** and the anticoagulant **warfarin**. Associated with many of the drugs affected by this polymorphism is a narrow margin of safety, and so the consequences of being a non-responder may be serious toxicity. Interestingly, the polymorphic states of one enzyme have no bearing on that of the other.

On the other hand, for CYP2D6, a subgroup of responders are ultra-extensive metabolisers. For them, the *CYP2D6* gene is amplified, and so they metabolise enzyme-dependent drugs very rapidly. The consequence is that it may be difficult to produce a therapeutic effect at standard doses of such drugs in these patients.

Some interesting data have been published with respect to cytochrome P450 activity and ethnicity. In Caucasians, poor metabolisers of CYP2D6 represent 5–10 per cent of the population and poor metabolisers of CYP2C9 represent 1–5 per cent. While the percentages sound small, this translates to many thousands of people who could be seriously injured during drug treatment. In Asians, poor metabolisers of CYP2C9 represent up to 18 per cent of the population and poor metabolisers of CYP2D6 1 per cent. For CYP2C9, this fits well with the observation that physicians working in Hong Kong routinely prescribe lower than standard doses of diazepam for Chinese patients. With regard to the amplification of the *CYP2C9* gene, 20 per cent of Ethiopians are so affected.

The possibility of having to produce different clinical drug regimens for people from different ethnic groups is posing some interesting problems for multinational pharmaceutical companies. Over recent times, these companies have become more interested in exploring the genetic status of participants in clinical trials in order to account for variation in drug responsiveness. These data are then used to inform decisions related to the development of new drugs.

Poor suxamethonium metabolism

The role of acetylcholinesterase as the highly specific degradative enzyme responsible for the inactivation of the neurotransmitter acetylcholine is covered in Chapter 27. The relatively non-specific cholinesterases, the pseudocholinesterases, are present in blood and other tissues. They appear to be involved in the local modulation of the response to acetylcholine.

Pseudocholinesterases are important in the breakdown of the neuromuscular blocking agent **suxamethonium**. About 1 in 2000 of the population show phenotypic variation for pseudocholinesterase synthesis. Non-responders break down suxamethonium more slowly; in these individuals, such treatment leads to prolonged paralysis lasting for about 24 hours. There is no antidote to suxamethonium. Paralysis, when it occurs, requires that the patient be mechanically ventilated and maintained in deep sedation for the duration of the facilitated respiration. When this idiosyncrasy is already known, suxamethonium should be avoided.

Erythrocyte reactions

Individuals who have an inheritable defect in the stability of erythrocytes may be more susceptible to haemolysis or structural changes in haemoglobin during therapy with a number of common clinical agents. Drugs such as the sulphonamides, antimalarials, some non-steroidal anti-inflammatory agents and the antimicrobial **chloramphenicol** are known to induce these changes.

Another condition that can manifest during drug therapy is porphyria, a disorder of haem synthesis. A haem group is formed in either the liver or bone marrow from the combination of a ferrous ion with a pigment called a porphyrin. In porphyria, haem synthesis is abnormal, resulting in the deposition of porphyrins into body tissues such as the skin.

There is evidence of a genetic predisposition to porphyria, which can be precipitated by drug treatment. In these individuals, the hepatic level of the enzyme that converts the precursor substance aminolaevulinic acid (ALA) into a porphyrin, ALA-synthetase, is high. Certain drugs induce more ALA-synthetase, producing porphyria. These drugs include **ethanol**, the sulphonamides, **oestrogen** and the barbiturates.

PHARMACOGENETICS AND DRUG PHARMACODYNAMICS

It appears that genetic variation in drug metabolism is not the only inheritable factor to affect drug responsiveness. Genetic variation in the mechanism by which drugs act has also been found to affect the observed responses.

Variations in receptor structure

Studies have shown that there is genetic variation in the programming of receptor structure and that this affects the observed responses to drugs. An example of this is the β_2 receptor. Molecular variants of this receptor show normal binding of agonist drugs but a three- to five-fold reduction in the response to agonist activation. The clinical consequence is that the bronchodilator effect associated with β_2 agonist therapy will be reduced.

There is also some evidence that central dopamine receptor variation may play a role in altered responsiveness to the antipsychotic drugs used in the management of schizophrenia.

Reactions to mydriatics

It is also interesting to note that certain drug effects are enhanced in individuals with a particular family background. Drugs that dilate the pupil (i.e. mydriatics) produce stronger effects in people with blue eyes than in those with a more deeply pigmented iris. This must be a genetic predisposition, because eye colour is an inheritable trait.

Reactions to corticosteroids

Another example involving the eye relates to the use of topical corticosteroid therapy (see Chapter 79). Some individuals with a family history of glaucoma have shown increased intraocular pressure in response to eye drops/ointments containing corticosteroids. Individuals with such a background should be monitored for this during such therapy.

ETHICAL CONSIDERATIONS ASSOCIATED WITH PHARMACOGENETICS

The use of this treatment approach raises some ethical issues that are worth considering. First, once the pharmacogenetic data are collected, there are questions of who is entitled to access the information and how patient confidentiality is protected. These issues need to be worked out by the patient and the health-care professionals associated with the person's care before the data are collected.

Another issue relates to the insurance risk associated with the genetic data. For some patients, screening before treatment may reduce the risk because there will be a lower incidence of serious adverse reactions associated with individualised therapy. For patients shown to be poor metabolisers, however, the risk may increase. Will these individuals be refused insurance or pay a significantly increased premium if there is no alternative treatment available?

It is interesting to speculate about the not too distant future in health care. There is tremendous potential in pharmacogenetics to individualise drug therapy for maximal effectiveness and negligible toxicity. A time may come when genetic screening and drug stratification are routine procedures associated with the management of illness. It is then possible that a decision not to use these procedures will be considered an unethical and a significantly less cost-effective strategy in clinical practice.

SUMMARY

- Pharmacogenetics is the study of how genetic variation contributes to differences in drug responsiveness.
- Genetic variation contributes to differences in the structure and function of proteins involved in drug metabolism, receptors and other physiological systems involved in drug responsiveness. This represents genetic polymorphism.
- Differences in gene sequences can be identified as genetic markers.
- Where genetic polymorphism exists, drug responsiveness at the population level is divided broadly into responder and non-responder groups. In terms of drug metabolism, this is expressed as extensive and poor metabolisers, respectively.
- Genetic markers can be screened for in diagnostic tests to determine whether a person is a responder or a non-responder.
- Examples of genetic polymorphism have been determined for a number of enzymes involved in drug metabolism, such as N-acetyltransferase, the cytochrome P450 family and pseudocholinesterases.
- Genetic polymorphism also exists in the structure of receptors and the responses to certain clinical agents.
- There are ethical considerations associated with pharmacokinetics as to who has access to a person's genetic data and how this information might be used to assess insurance risk.

1 Define the following terms:
(a) pharmacogenetics;
(b) polymorphism.

2 What are the consequences of being a non-responder with regard to drug effects?

3 What is the clinical management of someone who metabolises suxamethonium poorly?

4 With respect to drug therapy, suggest ways in which a person's genetic status could be assessed.

5 For the following drugs, indicate an idiosyncratic reaction that can occur as a result of an unusual genotype:
(a) β_2 agonists;
(b) corticosteroids;
(c) mydriatics;
(d) sulphonamides.

6 Halle Zingiber has been granted refugee status in this country. He has had to leave his wife and two children in Ethiopia. He is severely depressed and is receiving treatment with the tricyclic antidepressant nortriptyline. No effects were reported when standard doses of the drug (25 mg t.i.d.) were used. His doctor has increased the dose many-fold to 200 mg/day, a dose that is inducing effects. Can you account for Halle's unusual response to therapy?

7 Camilla De Rosa is on the antidepressant phenelzine. It is soon discovered that Ms De Rosa is a slow acetylator of drugs. What change would the doctor make to her prescription?

8 Jack Smith has a genetic makeup that involves a deficiency of pseudocholinesterases. How would this affect the metabolism of the neuromuscular blocking agent suxamethonium?

9 With respect to metabolism of a particular drug, what does it mean when a patient has a high ratio of active to inactive metabolites present in a urine sample?

10 On examination of your patient's history, you notice that she is a poor metaboliser of certain medications. How could this affect the patient's proposed drug therapy?

PHARMACOKINETIC FACTORS THAT MODIFY DRUG ACTION

19

CHAPTER NINETEEN

OBJECTIVES

After completing this chapter, the reader should be able to:

- **describe the ways in which drug absorption is altered by disease, diet, exercise and pregnancy, and the consequent effects on drug action;**
- **name the ways in which drug distribution is altered by disease and pregnancy, and the consequent effects on drug action;**
- **list the ways in which drug metabolism is altered by disease, occupation and diet, and the consequent effects on drug action;**
- **describe the ways in which drug excretion is altered by disease, and the consequent effects on drug action.**

KEY TERMS

Drug absorption
Drug distribution
Drug effects
Drug excretion
Drug metabolism
Occupational effects
Pharmacokinetics
Pregnancy

IN CHAPTERS 13 AND 14 YOU WERE INTRODUCED TO pharmacokinetics, the study of how the human body processes a drug once it has been administered. There are four stages of pharmacokinetics: drug absorption, distribution, metabolism and excretion. During drug development (see Chapter 17), the appropriate formulation, dosage and route of administration for humans are determined, taking into account the medicine's pharmacokinetics. In this way, if the dispensing instructions are followed, the drug should reach the site of action in an appropriate concentration that is both safe and therapeutically effective.

Unfortunately, a number of factors can affect the drug concentration at the site of action. If the concentration is higher than expected, the drug may exert a stronger, possibly toxic, effect. If the concentration is lower than expected, then the drug may not be therapeutically effective. In Chapter 18, we saw an example of this, where genetic variability can affect the process of drug metabolism. Disease, diet, occupation and pregnancy are other states that can affect the efficiency of pharmacokinetic processes and ultimately induce stronger or weaker drug effects than expected. The nature of these influences is discussed in this chapter. The effects of age on pharmacokinetics are discussed in Chapter 20.

ABSORPTION AND DRUG ACTION

The rate and degree of drug absorption into the blood (bioavailability) are dependent on the route of administration. Effective absorption from the oral route depends on both the chemical properties of the drug and the functional efficiency of the gastrointestinal tract. Parenteral absorption depends on the extent of the blood supply through the tissue where the drug was injected.

Effects of disease

Gastrointestinal illness can affect the rate and degree of oral absorption. Conditions affecting gastrointestinal peristalsis, such as severe vomiting, diarrhoea and constipation, and the rate of gastric emptying may significantly alter the degree to which drugs are absorbed. Inflammatory conditions that cause changes to the structure and function of the gut wall may also impede drug transit into the blood, but this is dependent on the region of the tract affected and the usual site of drug absorption. Fortunately, the problem of poor oral absorption under these circumstances can be overcome by administering the drug parenterally.

The pharmacokinetic behaviour of drugs can also be affected indirectly by gastrointestinal illness. A number of nutrients are essential for normal liver function. Nutritional imbalances brought about by gastrointestinal diseases can affect normal drug metabolism, resulting in unexpected drug effects. The effects of diet on drug metabolism are discussed in detail below.

The rate of drug absorption from a parenteral site can be affected greatly by disease. As stated earlier, absorption here is determined by the vascularity of the tissue. Diseases such as circulatory shock, congestive cardiac failure and peripheral vascular disease often profoundly reduce the perfusion of tissues with blood. As a result, the blood levels may be lower than expected while the drug concentration at the injection site remains high. In effect, the injection site becomes a drug reservoir. If, under these circumstances, tissue perfusion were to increase suddenly, the levels of circulating drug might rise accordingly, leading to increased drug activity and possible toxicity.

Effects of exercise

Tissue vascularity greatly affects the rate of drug absorption. This can be illustrated by comparing the rate of absorption from skeletal muscle with that from the subcutaneous layer of the skin.

Circumstances that result in tissue blood-flow changes can certainly influence the absorption of a drug from an injection site. An example of this is when a person receives an intramuscular drug injection and participates in vigorous exercise shortly afterwards. Increased blood flow to the muscle will enhance drug absorption. This may result in quicker drug absorption and higher levels of circulating drug than expected.

Effects of diet

The presence of food in the gut around the time of drug administration can greatly affect the degree of absorption. Nutrient molecules compete with drugs for sites of absorption. As a result, peak plasma concentrations are lower than expected and the drug action is more prolonged. Drug solubility, however, has a significant influence on the degree of absorption. Lipid-soluble agents are less affected by this competition than are water-soluble drugs.

For some drugs, it is not only a matter of competition for binding sites that impedes absorption. Drugs such as the more water-soluble tetracycline antibiotics are chelated by calcium salts, predominantly found in milk products but also present in some antacid preparations. Drug bioavailability is then lowered greatly as the conjugated antibiotic is mostly excreted in the faeces.

As a rule, unless it is stated explicitly that a drug can or should be given with food, medications must be administered either 1 hour before or 2 hours after food.

Effects of pregnancy

The function of the gastrointestinal tract may be altered greatly by hormonal action during pregnancy. Peristalsis and gastric emptying may be slowed to such a degree as to affect the amount of drug absorbed from the gut. Gastric-acid secretion is also more erratic in pregnancy, which can affect the degree of absorption of acidic agents. Because of individual differences in the effects of pregnancy, however, the observed effects on absorption can vary greatly and are difficult to predict. Nevertheless, an awareness of the kinds of pharmacokinetic effect to expect during pregnancy is valuable, even if these effects do not occur every time.

DISTRIBUTION AND DRUG ACTION

The factors that determine distribution include plasma protein concentration and affinity for the drug, body fluid levels, drug solubility, pK_a (the ionisation constant for a weak acid; see Glossary), body fat content and tissue blood flow. Some of these characteristics are intrinsic properties of the drug; however, conditions that influence body fluids, fat content, tissue perfusion/permeability and plasma proteins can also affect drug distribution.

Effects of disease

Any condition that decreases the concentration of plasma proteins (e.g. kidney disease, severe burns, malnutrition) will affect the activity of drugs that bind strongly to these proteins. While the plasma drug levels may be within the normal therapeutic range, the proportion of unbound drug will be higher. As a result, the drug effects will be greater in these individuals. Examples of drugs that bind strongly to plasma proteins are **diazepam**, **phenytoin**, the sulphonylureas, the sulphonamides and **warfarin**. The margins of safety of some of these drugs are narrow under normal physiological conditions, and therefore the consequences of such a change would be expected to be toxic.

Diminished synthesis of plasma proteins can occur in severe liver disease. For drugs that bind strongly to plasma proteins, there will subsequently be a higher proportion of unbound drug in the blood. As a result, the drug effects will be stronger and potentially more toxic. These effects are compounded by the fact that in severe liver disease, hepatic drug clearance is reduced greatly.

Another physiological imbalance affecting the plasma protein binding of drugs is a sudden and dramatic rise in plasma bilirubin levels. Plasma bilirubin levels will rise as a result of haemolytic anaemia or serious internal haemorrhage. Bilirubin is transported to the liver attached to the plasma protein albumin. Drugs that bind to plasma proteins can be displaced by the competing bilirubin molecule, leading to a higher concentration of unbound drug. Again, the consequences are greater drug effects and increased toxicity.

Drugs are distributed to their sites of action via the body fluids, particularly extracellular fluids. Indeed, body fluid levels ultimately determine the concentration of a drug at its receptor sites. Oedematous states reduce the drug concentration around its receptors, diminishing the magnitude of the effect. Conversely, dehydration concentrates the drug at this location, causing stronger, potentially more toxic effects.

Effects of pregnancy

There is little evidence of altered drug effects as a result of changes in drug distribution. With the expanded plasma volume that occurs during pregnancy, however, one would expect some drugs to be distributed to their receptors differently. Subsequently, the concentration of drug at the receptor site would be presumed to be lower than normal.

METABOLISM AND DRUG ACTION

The major site of metabolism in the body is the liver. Therefore, any condition that affects hepatic function will alter the rate and/or degree of drug metabolism. More specifically, drug metabolism is determined by the activity of microsomal oxidative enzymes dependent on cytochrome P450 (as we saw in Chapter 18) and the liver's capacity for conjugation (see Chapter 16).

Effects of disease

Diseases of the liver can lead either to the accumulation of pharmacologically active agents to toxic levels or to prolonged drug effects, or both. The consequences vary from drug to drug and depend on the pharmacokinetic characteristics of the drug. The impact is greatest for those drugs that must be mostly metabolised before excretion. Examples of specific agents in this category are the narcotic **morphine** and the non-specific beta-blocker **propranolol**. Drugs excreted unchanged from the administered form are handled normally under these circumstances.

Health-care professionals are advised to consult a clinical reference such as the *British National Formulary* (BNF) for the relevant pharmacokinetic information pertaining to specific drugs ordered for patients with hepatic disease. The BNF now includes an appendix dedicated to drug dosages in liver disease.

Metabolic processes can also be influenced indirectly by other diseases, even when liver function is normal. Congestive cardiac failure significantly reduces hepatic blood flow. As a result, drug clearance through the liver is thus diminished, prolonging the drug action. Conditions characterised by deficient levels of plasma proteins produce a higher proportion of unbound drug. Only this component is susceptible to metabolic degradation and so even though drug effects are stronger under these conditions, the duration of action will be shorter than normal.

Effects of occupation

There are a number of chemical agents such as insecticides and pesticides that are known to induce microsomal enzymes in the liver. Occupational exposure to these chemicals in agriculture and chemical manufacturing industries would be expected to result in altered drug metabolism in these workers. The inactivation of drugs dependent on the action of microsomal enzymes would be quicker than expected in these individuals.

Furthermore, chronic exposure to such chemicals has been linked to the onset of a number of diseases, such as cancer and pulmonary disease, which would be expected

to affect drug pharmacokinetics (see the specific sections on the effects of disease on drug action in this chapter).

Effects of diet

The most important consideration in regard to the influence of nutrition on metabolism is that microsomal enzyme activity is dependent on the presence of certain vitamins and minerals. Deficiencies in the levels of **vitamins A**, **B_1** and **B_2**, essential fatty acids, protein and the minerals **copper**, **zinc** and **calcium** result in ineffective metabolism. Blood drug levels will be higher than expected for those agents metabolised by these enzymes.

EXCRETION AND DRUG ACTION

The principal site of drug excretion is the kidneys. Conditions that affect kidney function, either directly or indirectly, will alter drug concentrations in the body and the observed clinical effects.

Effects of disease

Renal diseases affect the blood concentrations of most drugs. The impact of this on the drug effects depends on whether the drug is mostly metabolised in the liver, producing inactive metabolites that are eliminated via the kidneys, or whether the drug is excreted mostly unchanged from its administered form. The latter agents will produce stronger, potentially more toxic effects in patients with renal disease. Examples of specific agents in this group are the penicillins, the aminoglycosides and **digoxin**. Renal drug clearance can also be affected indirectly by diseases that impede blood flow through the kidneys, such as congestive cardiac failure.

Health-care professionals are advised to consult an appropriate clinical reference for pharmacokinetic information on specific agents when required. Tables of the drug dosage adjustments recommended in renal disease are included in the appendices of the BNF.

SUMMARY

- Factors that affect pharmacokinetic processes can alter drug concentrations at the site of action. This may result in unexpected drug effects.
- Drug absorption may be altered in gastrointestinal and cardiovascular diseases and by the presence of food or exercise.
- Drug distribution may be altered by conditions that affect the availability of plasma proteins (e.g. kidney disease, malnutrition, severe burns), body fluid balance and pregnancy.
- Drug metabolism may be altered in liver disease, hepatic blood flow, conditions that affect hepatic enzyme levels and diet.
- Drug excretion may be altered by kidney disease and renal blood flow.

1. Name some conditions that would tend to decrease the level of drug absorption.
2. Name some conditions that would tend to increase the amount of free drug molecules in the blood.
3. Name some conditions that would tend to decrease the rate of drug metabolism.
4. Name some conditions that would tend to decrease the rate of drug excretion.
5. Given the physiological changes that occur during pregnancy, list the expected effects on absorption, distribution, metabolism and excretion. If all of these effects did occur, what would you expect the net change in drug action to be (increased or decreased action)?
6. Mary Wolstencort is suffering from acute renal failure following a very severe bleeding episode. How would this condition be expected to alter the effects of any medications she may take during this time? How would drug treatment have to be modified to minimise these effects?
7. Cecilia Fong is a teenager who has been prescribed tetracycline for her acne. Why would you recommend that she avoid taking dairy products with this medication?
8. Your next-door neighbour, who is pregnant, complains to you that in the past week she has been experiencing severe heartburn. How would you explain the reason underlying this condition?

9 Richard Kriochek suffers from severe end-stage liver failure. How would the dosage of his medications be modified? Why?

10 Despina Stamatopoulous is a 65-year-old widow with congestive cardiac failure. She is taking the angiotensin-converting enzyme (ACE) inhibitor enalapril for her cardiac failure and the penicillin ampicillin for a respiratory infection. How would her condition affect the excretion of ampicillin?

11 Sinead O'Donald, an 18-year-old student, is brought to your community hospital. Her mother is concerned that she does not eat a balanced diet. Ms O'Donald is on amoxicillin for a respiratory infection. How would Ms O'Donald's diet affect the metabolism of amoxicillin?

PAEDIATRIC PHARMACOLOGY AND PHARMACOLOGY IN OLDER PEOPLE

20

CHAPTER TWENTY

OBJECTIVES

KEY TERMS

Clinical decision-making process
Drug actions
Elderly care
Non-compliance
Paediatric care
Paediatric dosage calculation
Pharmacokinetics and age

After completing this chapter, the reader should be able to:

- **list the ways in which drug absorption, distribution, metabolism and excretion are altered by age, and the consequent effects on drug action;**
- **describe the means by which adult doses must be adjusted for paediatric administration;**
- **describe the principles involved in paediatric and elderly clinical management;**
- **discuss the issue of non-compliance with drug treatment and elderly people.**

THE EFFICIENCY AND EFFECTIVENESS OF THE PHYSIOLOGICAL processes involved in drug absorption, distribution, metabolism and elimination change across the lifespan. Because the body systems of young children are still developing and maturing, the manner in which their bodies handle drugs can be quite different from that of adults. The effects of drugs in children may be either stronger or weaker than those observed in adults given the same treatment. At the other end of the lifespan, elderly people experience age-related changes in body structure and function that alter the behaviour of drugs after administration. The effect of these altered pharmacokinetic processes on drug action is examined in this chapter. The principles involved in the clinical management of paediatric and elderly patients is also outlined, as is the issue of non-adherence with drug treatment and the older person.

ABSORPTION AND DRUG ACTION

The function of the gastrointestinal tract is quite different in very young and very old people compared with a young adult. Common problems in both age extremes are slowed peristalsis and gastric emptying; both can lead to a greater degree of drug absorption than normal and, subsequently, higher plasma drug levels than expected. The activity and concentration of digestive secretions is lower in the newborn infant; low levels of bile may lead to impaired absorption of some fat-soluble drugs.

Another problem in early infancy is that gastric acid secretion is erratic; this may result in reduced bioavailability of acidic substances best absorbed in the stomach. In this case, parenteral administration may be indicated. For some drugs, however, lower stomach acid levels can be turned to clinical advantage. In the adult, penicillin G is absorbed poorly from the gut because it is degraded by stomach acid. In the infant, because of lower gastric acid levels, absorption is significantly better and produces effective plasma drug levels; this permits the oral administration of penicillin G to young infants.

Parenteral absorption is also influenced by age. Both very young and elderly patients have poor peripheral tissue perfusion and reduced skeletal muscle mass compared with young adults. These differences may influence the rate of drug absorption from the injection site.

There is also a consideration regarding the topical administration of drugs to very young patients. Young infants are thin-skinned; the absorption of some topically applied agents may, therefore, be greater than expected.

DISTRIBUTION AND DRUG ACTION

The concentration of plasma proteins is lower in very old and very young people, leading to a higher proportion of unbound drug in the blood. Drug activity and potential toxicity are thus increased, even though total drug concentration in the plasma is within the expected range. Compounding this problem is the fact that the capacity of plasma proteins to bind with drugs is well below adult levels for the first 2 years of life.

Bilirubin can be displaced from albumin by drugs that bind strongly to plasma proteins. This is of particular concern during the neonatal period, when the blood–brain barrier is not fully developed. At this time, bilirubin can enter the developing brain and cause a profound degree of damage, resulting in severe mental retardation. This condition is known as kernicterus.

It is interesting to compare the levels of body fluid and fat tissue across the lifespan and the consequences of these differences on drug effects. The levels of body fluid fall with age, while the amount of fatty tissue increases. Such variation has an impact on the behaviour of drugs. For a given plasma drug concentration, the amount of drug actually present at the receptors, and the magnitude of the subsequent drug effect, depends on the level of extracellular fluid. Therefore, in neonates, there will be a lower concentration of drug around its specific receptors and a diminished response, while in elderly people, there will be a higher drug concentration and greater effects than expected.

Some fat-soluble drugs are distributed into adipose tissue, which acts as a reservoir, reducing the amount of free drug readily available to its receptors and prolonging the duration of action. Altered adipose tissue levels can cause unexpected drug effects. Young children, having less adipose tissue, may have stronger but more short-lived responses to fat-soluble drugs, whereas drug effects in elderly people may be reduced in magnitude but more prolonged.

METABOLISM AND DRUG ACTION

The activity of microsomal enzymes and conjugative ability do not reach adult levels until approximately 3 years of age. Before this, the capacity of neonates and young children to metabolise drugs is poor. Hepatic clearance of drugs is slowed and as a consequence drug half-lives are prolonged. Some drugs, however, have the ability to induce higher cytochrome P450 levels, which enhance the activity of microsomal enzymes. Antiseizure drugs, barbiturates, glucocorticoids and some antibiotics are examples of enzyme inducers. If a woman receives treatment with one of these agents in late pregnancy, enzyme induction could occur in the fetus, resulting in a greater capacity to metabolise certain drugs as a neonate.

Metabolic processes alter with increasing age. In elderly people, the ability to metabolise certain drugs deteriorates. It appears that drugs that depend on the action of microsomal enzymes are most affected (e.g. barbiturates, some benzodiazepines, methylxanthines, some tricyclic antidepressants), whereas drugs inactivated by conjugation are relatively spared.

EXCRETION AND DRUG ACTION

The rate of glomerular filtration and the extent of renal blood flow are substantially lower in neonates than in adults. Therefore, the clearance of drugs dependent on renal means is completed more slowly in neonates. Fortunately, this is a concern only for a relatively short period, because renal function usually reaches adult levels within the first year of life.

A significant proportion of the elderly population show a deterioration in the renal clearance of drugs. Clearly, the action of drugs will be prolonged under these circumstances and may accumulate to toxic levels if no adjustment of dosage is considered.

PAEDIATRIC DOSAGE CONSIDERATIONS

In young children, many organ systems are yet to reach maturity, including the kidneys, liver and circulation. Muscle mass is lower in children than adults, but the body water percentage is higher. As discussed, these factors can affect the absorption, distribution, metabolism and elimination of drugs.

The physiological differences between adults and children mentioned above suggest that the pharmacokinetic behaviour of some drugs will vary greatly across age. Indeed, the dose of a drug administered to a child is never equivalent to that given to an adult. One cannot, however, simply regard a young child as a small adult and scale down the dose accordingly: It is important to stress that the relationship between paediatric and adult doses is not linear.

Although for many clinical agents the recommended paediatric dose has been calculated by the manufacturer, this isn't always the case. Age and body weight have been used to calculate paediatric dosage, but it is generally agreed that body surface area is a more reliable indicator. Most drugs used in paediatric practice follow the 'unit mass per kilogram body weight' method of dosage calculation. Several paediatric hospitals have their own lists of tables indicating the appropriate level in amount per kilogram. With knowledge of the child's weight, this unit dose is multiplied by the number of kilograms to determine the amount that needs to be given. For example, a unit dose of 10 mg/kg for a 20-kg child would result in a dose of 200 mg being administered. In September 2005, the *British National Formulary for Children* was launched. This has been developed to meet the clinical requirements of general practitioners, pediatricians, pharmacists, nurses and other health-care professionals involved in paediatric drug prescribing, dispensing and administration. This formulary provides reliable advice on the use of medicines in children from birth to adolescence. The resource is freely available on the Internet via www.bnfc.org following registration. Advice in this formulary goes beyond the marketed authorisations because the licensed indications often do not cover the needs of children. The formulary should now supersede the numerous paediatric formularies that are available.

Drug therapy in children requires special consideration because of their constantly changing size, body composition, developmental level and organ functions. The principles relating to drug administration are covered below with regard to the use of the clinical decision-making process.

Assessment

The height (or length) and weight of the child are documented to assist in the calculation of accurate doses of drugs. For a child whose weight varies considerably from the ideal weight for a particular age group, it is more appropriate to calculate the required dose using the actual body weight rather than the ideal body weight. When examining drug information to determine dosage requirements, take care to interpret whether the dosage is expressed as mg/kg/dose or mg/kg/24 hours.

The child's physical development, motor activity, social interactions with other children, vocabulary and ability to conceptualise are all assessed. These aspects are very important as they determine the extent to which the child can be included in the drug-administration process. Furthermore, as the family plays a major supportive role in a child's experiences, it is important to determine the family's response to illness and treatment and their knowledge of the child's drug therapy.

Planning

The child should be provided with information appropriate to his or her age and level of development. Written instructions should be given to the child's parents. Interpreters should be used where possible for families from a non-English-speaking background.

Parents should be encouraged to keep a drug diary for their child, which includes information on the drugs used, dosage, anticipated effects and any adverse reactions.

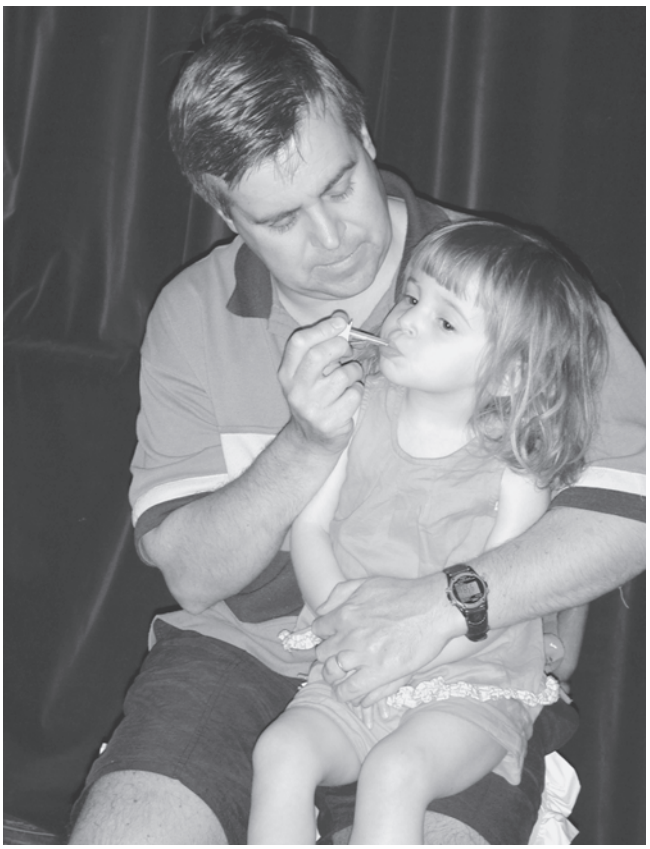
Implementation

It is important to include the child in the drug-administration process as much as possible. Children should be involved in decisions about taking medicines and encouraged to take responsibility for their use. The degree of involvement will depend on the child's age, understanding and personal circumstances. Including the child will promote a sense of independence and achievement.

The oral route of drug administration is used where possible. Many young children need to have the medicine placed directly into the mouth. This can be accomplished with a syringe, dropper, small spoon or medicine cup. The child should be held in an upright position with the hands kept away from the medication container. The tip of the dropper or syringe is placed midway along the side of the mouth, rather than towards the back of the throat. In this position, the child is less likely to gag or aspirate when the medicine is administered (see Figure 20.1).

If medications are available in tablet or capsule form, it is important to assess the child's ability to swallow these preparations. If the medication does not have an enteric coating and is not in a delayed-release form, the child may chew or the nurse may crush or dissolve the medication. Crushed medications and the contents of capsules can be mixed with food or drink, using the smallest possible amount of food or fluid to ensure that the child takes the entire dose. For this reason, medications should not be added to a bottle of milk feed in case the child does not drink the entire bottle.

FIGURE 20.1 ADMINISTERING MEDICATION TO A YOUNG CHILD USING A DROPPER



Identification of the right child is essential. As young children may not be verbally competent or reliable, the identification label must be checked and verification from the parent, if present, obtained.

A firm and confident approach should be used and the drug administered promptly. Distraction methods (e.g. toys) are often effective during the procedure. Following administration, reassurance and positive reinforcement should be offered. Medications should be prepared out of the child's sight to prevent added anxiety and distress.

Be honest about the purpose of and necessity for medication (e.g. tell the child that the medicine will reduce pain or stop infection). The sensations that will be felt should be explained. For instance, the child should never be told an injection will be painless but rather that the duration of discomfort is short. Likewise, the child must be informed if a drug will leave a bitter taste in the mouth or cause blurred vision for a few minutes. Psychological preparation will promote the child's confidence in you and facilitate cooperation.

When giving an injection, one practitioner should administer the injection while another holds the child still to immobilise the injection site. For an intramuscular injection, the vastus lateralis (anterolateral thigh) is the preferred site. Because of underdevelopment of the gluteal muscles, they are not recommended for use in children under 3 years of age. Likewise, the deltoid muscle is not well developed in children, and so it is not a preferred site. The Royal College of Paediatrics and Child Health in 2002 issued a position statement on injection technique in children, and this is available via the Royal College of Nursing website. Parents should be involved as much as possible in the administration of injections to help pacify the child.

Safety is an extremely important issue in paediatrics. Medications should never be left on a child's bedside locker. Drug trolleys, cupboards and fridges should be locked when not in use, and the keys should always be in the nurse's possession.

Adherence is a significant concern in children, especially those with chronic illness or entering adolescence. Commonly, demanding or complex schedules may contribute to non-adherence. Where possible, it is desirable to maintain once- or twice-daily schedules.

Evaluation

The therapeutic and adverse effects of the drug and any drug interactions should be monitored. The effect of therapy is also gauged, based on the child's emotions and behaviour. The ultimate aim is to establish a trusting relationship, build self-esteem, instil acceptance and receive cooperation.

CLINICAL MANAGEMENT IN OLDER PEOPLE

There are a number of important issues related to the use of medications by elderly people that must be emphasised. People over the age of 65 years represent approximately 12 per cent of the population but account for over half of the prescriptions written and about 30 per cent of the total hospital admissions. In Chapter 2, the sociocultural aspects of drug therapy in elderly people, including polypharmacy, are examined. In this section, issues related to non-adherence with drug treatment and the principles relating to drug administration, with regard to the use of the clinical decision-making process, are covered.

Non-adherence with drug treatment and elderly people

The issue of non-adherence with drug therapy was addressed in general terms in Chapter 8 and has the potential to arise in any patient. In elderly people, the likelihood of non-adherence with drug treatment is probably greater. The reasons for this relate to the biological effects of ageing, the social circumstances of elderly people, the perceptions of elderly people about their medications, and health-care professional-related issues.

BIOLOGICAL EFFECTS OF AGEING

As we age, we are more prone to developing disease. A disease may affect a person's ability to process information and instructions related to prescribed medicines, leading to poor compliance. Disease states and ageing can affect cognitive processing, which may result in confusion, memory loss or dementia. Forgetting when to take medicines or remembering whether the medicine was taken at the correct time are common problems in elderly people. There may also be deterioration in eyesight and hearing, which may affect the reading of medication labels and listening to information about drugs. Some elderly people develop depression, which may further affect their capacity to comply with therapy.

SOCIAL CIRCUMSTANCES OF ELDERLY PEOPLE

Many elderly people live alone and lack social support from neighbours, family and friends. Older people may have depleted finances and poor access to transportation. These factors can affect a person's ability to purchase medicines or to travel to their local pharmacy or hospital to pick up their medications. Other social issues are the patient's literacy level and whether he or she comes from a non-English-speaking background. These factors can affect a patient's capacity to read medication labels and comprehend educational material received in hospital.

PROBLEMS CAUSED BY THE HEALTH-CARE TEAM

Adherence problems caused by the team of health-care professionals caring for their elderly patients include prescribing complicated drug regimens (where a number of drugs need to be taken often or at various times during the day), overprescribing or multiple prescribing of medications, poor preparation of patients for self-administration of medicines, and insufficient communication between health-care professionals about the management of therapy. Some elderly people may have the perception that the medication they have been prescribed will not help their condition and/or that the adverse effects are intolerable. The reasons for non-compliance with therapy are summarised in Table 20.1.

TABLE 20.1 REASONS FOR NON-COMPLIANCE WITH TREATMENT IN ELDERLY PEOPLE

Category	Description
Biological effects of ageing	More prone to disease Altered cognition (confusion, memory loss, dementia) Altered special senses (poor hearing, poor eyesight, depression)
Social circumstances	Living alone Lack of social support Depleted finances Poor access to transportation Low literacy Non-English-speaking background
Health-care team-related	Complicated drug regimens Overprescribing Multiple prescribing Poorly prepared for self-administration of medicines Insufficient communication between team members
Perceptions about medications	Medicines not seen to be helpful Intolerable adverse effects

CONSEQUENCES OF NON-COMPLIANCE AND POSSIBLE SOLUTIONS

Non-compliance with drug treatment usually leads to increases in the number and magnitude of adverse effects induced, prolonged illnesses and hospital stays, readmissions to hospital, decreased therapeutic effectiveness of treatment, increased wastage of drugs, and growing costs to the health-care system. There are a number of ways in which adherence with drug therapy by elderly patients can be improved. Wherever possible, the drug regimen should be simplified in order to minimise error (e.g. if possible, fewer medications per day given at common times). Patient assessments should be comprehensive and include learning ability, manual dexterity, cognition, eyesight, hearing and social circumstances. The use of medication aids such as dosette boxes should be discussed with patients. The medicine education provided to patients should be individualised, recognising what the patient wants to know about their medicines. The knowledge retained by patients following information sessions should be evaluated. In addition, there should be better communication between members of the health-care team (doctors, nurses, pharmacists, other health professionals) about what information has been given and will be given to patients regarding their drug therapy. Ways of improving compliance with therapy are summarised in Table 20.2.

Principles of drug administration and elderly people

ASSESSMENT

The patient's distribution of fat and muscle and condition of skin should be assessed. Neurological status and parameters relating to renal, liver, cardiac and respiratory function should be noted. The patient's level of knowledge about

TABLE 20.2 IMPROVING COMPLIANCE WITH DRUG TREATMENTS

Suggestion	Examples
Simple drug regimens	Fewer medications per day Medications given at common times during the day
Comprehensive patient assessment	Includes learning ability, cognitive function, hearing, eyesight, social circumstances
Use of medication aids	Dosette boxes or drug diary
Individualised medication education	What do patients want to know about their medicines? Evaluate retained knowledge
Improved communication between health-care professionals	Noting what patients have been told and what further information they need

the disease process, current medications, sensory problems (hearing, vision, touch), memory, mobilisation and level of independence should also be considered. It is important to have detailed information about these issues to determine how they may be influenced by medications. For instance, several medications can increase the incidence of falls and fractures (e.g. antiemetics, antipsychotics, benzodiazepines), thus further debilitating a patient's mobility.

Acute illnesses, such as myocardial infarction and urinary tract infection, can lead to a rapid decline in renal function and affect the elderly patient's ability to eliminate drugs. Health-care professionals should assess regularly the renal function of elderly patients with an acute illness and make adjustments to chronic medication treatments based on the findings.

It is important to determine the number of medications taken by the elderly patient and their indications. Some of these medications may be self-prescribed and others may be taken for forgotten reasons. With the growing number of drugs in therapy, adverse drug reactions are much more likely to occur. Furthermore, the patient may be under the care of a number of doctors, each of whom prescribes medications for various reasons and may not communicate with each other. Also, it is important to acknowledge that presenting symptoms may be a result of existing medications rather than the result of advancing age.

PLANNING

Encourage the patient to learn about their medications while in hospital, so that this will not pose a significant problem at discharge. Medication cards can be made out for each drug, indicating the name, strength, dose, time to be taken, and purpose of administration (e.g. 'blood pressure', 'heart', 'infection'). Ensure that the patient practises self-administration of medications before discharge (e.g. subcutaneous **insulin** or inhaled bronchodilator administration). If necessary, a district nurse may need to be organised for home visits to enable the elderly patient to practise under supervision before safe self-administration is possible. A medication clock may be a useful mechanism for helping older patients to take their medications. In making the clocks, two large clock faces are drawn, each one a different colour. One is marked 'a.m.' and the other 'p.m.'. The names of the patient's medications are then placed beside the appropriate times (see Figure 20.2).

Be sure that the patient can open their drug containers. Child-proof containers are difficult for an elderly person with arthritic hands to open and should therefore be avoided.

An elderly patient who has taken several drugs over the years may have developed a specific routine for drug administration. This may involve the time of day or the sequence in which medications are taken. When introducing or removing drugs to or from the regimen, attempt to maintain the same or a similar routine. It is also advisable to keep the regimen as simple as possible at all times.

IMPLEMENTATION

The patient should be sitting upright when taking tablets to prevent oesophageal erosion and aspiration of tablets into the lungs. Generally, medications should be taken one by one, with water. Tablets are not to be crushed if they are enteric-coated or delayed-release. This information is noted on the container. As these tablets are usually somewhat larger than the normal scored tablets, the patient may have trouble in swallowing them. In this instance, effervescent tablets or mixtures may be more palatable alternatives. Table 20.3 contains information about the types of tablet and other preparations that should not be crushed. Capsules can be opened and the contents given to the patient as long as the release properties are built into the small pellets and are not part of the capsule casing. It is, however, important that the pellets themselves are not crushed. When tablets and capsules are to be given together, crush the tablets first. Then add the pellets or the powder contents of the capsules to the crushed tablets. In this way, it is possible to maintain the integrity of the sustained-release or enteric-coated contents of the capsules. Film-coated, uncoated and sugar-coated tablets can be crushed without problem.

In some cases, non-drug measures can be used to decrease the need for or dependence on drugs. For an elderly person who experiences sleep disturbance, avoiding caffeine

FIGURE 20.2 SAMPLE MORNING AND AFTERNOON MEDICATION CLOCKS FOR USE BY AN OLDER PERSON

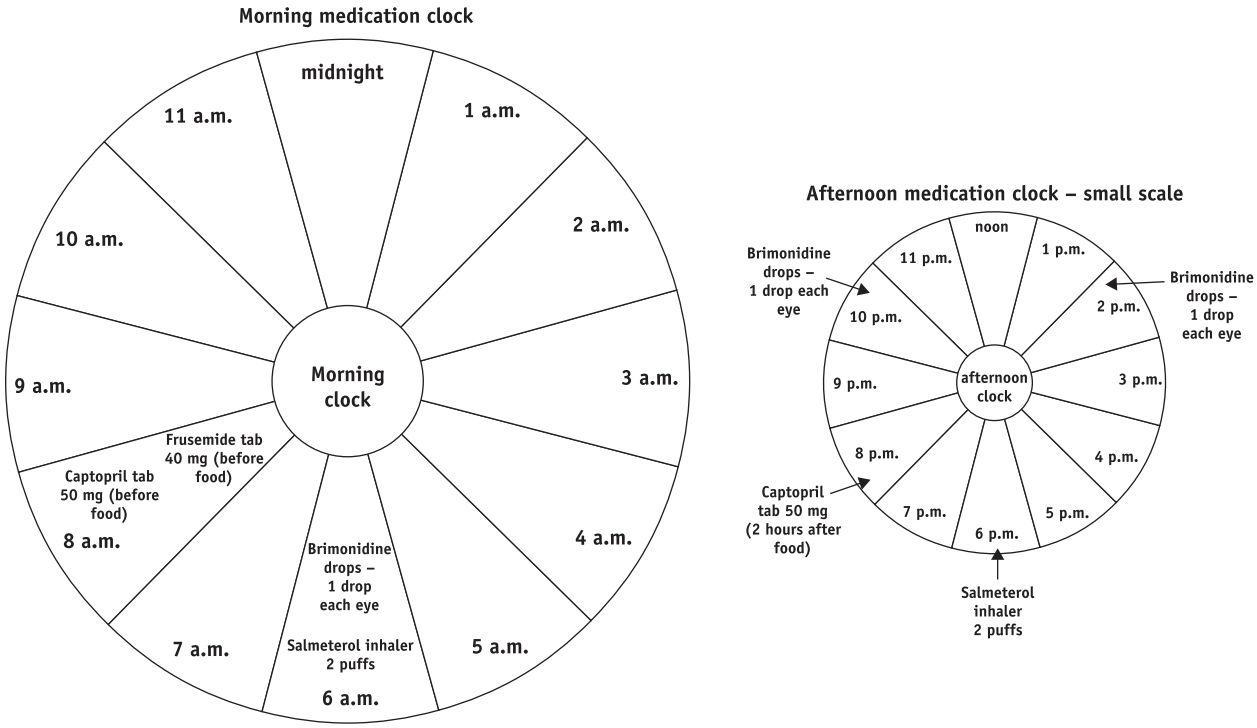


TABLE 20.3 PREPARATIONS THAT ARE NOT SUITABLE FOR CRUSHING

Type of preparation	Explanation
CD	Controlled-dissolution
CR	Controlled-release
EC	Enteric-coated
ER	Extended-release
HBS	Hydrodynamically based system (floating capsules that gradually release drug)
LA	Long-acting
MR	Modified-release
OROS	Osmotic release oral system (two-layered tablet with drilled hole in casing; water enters to allow gradual release of drug)
Repetabs	Two-stage release (immediate and delayed release)
Retard	Delayed-release
SA	Sustained-action
SR	Slow-release
XR	Extended-release

and daytime naps and taking light exercise may decrease the need for sedatives. All drugs should be given for the shortest possible time, and using the smallest number of doses. Typically, an elderly patient requires less than half of the adult dose of a preparation. These adjustments allow for less disruption of normal activities and promote patient compliance.

The deltoid and vastus lateralis muscles should be avoided as intramuscular injection sites in patients with muscle wasting; the dorsogluteal muscle is a more suitable option. If repeated doses are required, consider alternative routes of administration (e.g. intravenous or rectal routes).

The health-care team should also regularly review the effectiveness and need for chronic medications. It may be

TABLE 20.4 MEDICATIONS CAUSING SEVERE ADVERSE DRUG REACTIONS IN ELDERLY PEOPLE

Medication or medication group	Adverse reaction
Anticholinergic agents (e.g. atropine)	Confusion, delirium, dry mouth, blurred vision, constipation, impaired thermoregulation, urinary retention
Antiemetics (e.g. metoclopramide, prochlorperazine)	Drowsiness, confusion, postural hypotension (prochlorperazine), dizziness (metoclopramide), extrapyramidal manifestations
Antipsychotic agents (phenothiazine group)	Postural hypotension, confusion, oversedation, extrapyramidal manifestations, blurred vision, urinary retention, permanent tardive dyskinesia
Benzodiazepines	Confusion, oversedation, memory impairment, poor muscle coordination
Chlorpropamide	Prolonged hypoglycaemia
Digoxin	Nausea, vomiting, confusion, loss of appetite
Flucloxacillin	Hepatotoxicity
Histamine H_2-receptor antagonists (especially cimetidine)	Confusion, dizziness, tiredness, multiple drug interactions
Non-steroidal anti-inflammatory agents (especially non-selective agents)	Sodium and water retention, renal dysfunction, peptic ulceration
Co-trimoxazole	Blood dyscrasias, severe skin reactions (e.g. Stevens–Johnson syndrome)
Theophylline	Confusion, dysrhythmia, tremor

possible to stop the medications or to reduce the dose if renal or liver function declines.

EVALUATION

Always evaluate the therapeutic effects, adverse reactions and drug interactions of the drug. If new or unusual clinical manifestations occur, they may be drug-related. Sometimes such manifestations are attributed to the ageing process. Consequently, they may be ignored or dealt with by prescribing a new drug, when stopping the original drug would have been the correct intervention. Changes to body systems, especially to renal and liver functions, should also be noted. Some medications are particularly problematic for older people and should be avoided altogether. Table 20.4 lists the types of preparation to be avoided, and their adverse effects.

SUMMARY

- The efficiency of pharmacokinetic processes varies across the lifespan. In very young and very old people, the manner in which the body handles drugs can be quite different compared with young adults.
- The differences in pharmacokinetics can lead to stronger or weaker drug effects in children and elderly people compared with young adults.
- The physiological processes that influence pharmacokinetics in children and elderly people include gastrointestinal function, tissue blood flow, body fluid levels, plasma protein concentrations, liver function and renal function.
- Paediatric doses can be based on body surface area, age and body weight.
- Children should be included in the planning and implementation of drug treatment as much as possible. The explanations and degree of involvement depend on their age and level of development. Parents provide important verification of drug treatment and can participate in the monitoring of drug effects.
- Non-adherence with drug therapy in elderly people is a significant problem. The reasons for this relate to the ageing process, the patient's social circumstances, prescribing patterns and the level of communication between health-care professionals.
- The problem of non-adherence can be addressed by an appropriate assessment of the patient, simplified drug regimens, patient medication education and improved communication between health professionals.

1. Outline all the possible pharmacokinetic effects on the actions of drugs in very young patients.
2. Outline all the possible pharmacokinetic effects on the actions of drugs in elderly people.
3. A 20-kg child is to receive a dose of 12.5 mg/kg paracetamol. Your stock solution of paracetamol is 120 mg/5 ml. How many millilitres of paracetamol are required?
4. Summarise the key aspects of paediatric clinical management with respect to each part of the clinical decision-making process.
5. State one reason for non-adherence with drug treatment for each of the following categories, and indicate how the effect of each reason on compliance could be minimised:
   (a) social circumstances;
   (b) biological effects of ageing;
   (c) health-care team-related problem.
6. Summarise the key aspects of clinical management in the elderly patient with respect to each part of the clinical decision-making process.
7. Name five types of drug formulation that are not suitable for crushing before administration.
8. Aaron Skeled is 2 years old and is being hospitalised for a respiratory condition. His father is present at the bedside. Aaron requires an intramuscular injection of a drug. Outline the procedure you would take in managing the administration of this medication.
9. Aldo Tagliatelli is 71 years old and migrated to this country from Italy with his wife 10 years ago. He is in hospital having treatment for a minor stroke. The stroke has affected his speech and the movement of his right arm and hand (he is right-handed). He is recovering well, and it is expected that he will be discharged home, where his 68-year-old wife, Mary, will care for him. He is taking, and will continue to take, the diuretic bendroflumethiazide and the beta-blocker atenolol for hypertension. Added to this will be the anticoagulant warfarin. Discuss the factors, both positive and negative, affecting Aldo's compliance with his drug therapy.

CASE STUDY IV.1

Mr HK, aged 81 years, was admitted to hospital with chest pains. An electrocardiogram (ECG) was carried out, which showed he was suffering from congestive heart failure. He was treated with various drugs to reduce the work of his heart, and normal cardiac output was maintained using an angiotensin-converting enzyme (ACE) inhibitor and a diuretic.

After stabilisation, he was discharged from hospital. After a week at home he became confused, with concomitant nausea. He was prescribed prochlorperazine for his nausea. The confusion, being put down to senility, was left untreated. This seemed to correct the nausea, but he then developed an intermittent tremor of his hands, rather like Parkinson's disease. This was recognised as an adverse effect of the prochlorperazine, and he was given benzatropine to correct this. Constipation resulted, and he was given docusate tablets to alleviate this. His confusion increased, and he became progressively more agitated and restless; he was then prescribed the antipsychotic chlorpromazine, which calmed him down remarkably. Depression set in, however, and he was given imipramine, an antidepressant. Sadly, Mr HK died soon afterwards from ventricular tachycardia.

QUESTIONS

1 *Do you think it is possible that Mr HK's death was preventable?*

2 *In light of what you have learned from this section, what may have gone wrong? (Note that scenarios not unlike the above do happen occasionally.)*

CASE STUDY IV.2

Ms HH is a 28-year-old pregnant woman who visits her midwife for her antenatal check-up. She is 8 months pregnant and speaks to her midwife about clotrimazole 2% vaginal cream prescribed by her local doctor for vulvovaginal candidiasis. Clotrimazole cream is a topical antifungal preparation. Her symptoms, which include vulval irritation, itching and a yellow discharge, have been very uncomfortable, but Ms HH is very concerned about the possible harm of the medication to her baby. She is also unsure about how to use the vaginal cream.

QUESTIONS

1 *Is clotrimazole likely to cause any harm to the fetus? Explain your answer.*

2 *When are medications likely to cause more harm during pregnancy – during the early or late stages? Explain your answer.*

3 *Describe how Ms HH should administer the vaginal cream.*

CASE STUDY IV.3

Mr JM, aged 42 years, visits the community health centre to obtain manipulation therapy from the physiotherapist. He sometimes experiences flare-ups from a chronic back problem, which is greatly relieved by physical manipulation. After the therapy session, the physiotherapist asks Mr JM if he is doing anything else to help with his back problem. Mr JM replies that he has started taking soluble aspirin, which decreases the pain he experiences. From the patient's medical history, the physiotherapist discovers that Mr JM also suffers from epilepsy, which is treated with sodium valproate. The physiotherapist knows that both aspirin and sodium valproate are highly bound to plasma proteins.

QUESTIONS

1 *What is the drug interaction that may occur here?*

2 *What is the potential end result?*

3 *What alternative to aspirin could the physiotherapist recommend to the patient?*

FURTHER READING

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WEB RESOURCES

Association of the British Pharmaceutical Industry (ABPI) www.abpi.org.uk

BNF for Children www.bnfc.org

Prescriber Journal www.escriber.com

Trials Central: On-line Register of US Clinical Trials www.trialscentral.org

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TOXICOLOGY

O, I die, Horatio!
The potent poison quite o'ercrows my spirit . . .

WILLIAM SHAKESPEARE – *HAMLET*

Many people ingest poisons for one reason or another and, as for Hamlet, the consequences can be fatal. It is often the case, however, that the body has sufficient time to neutralise, or at least attenuate, the effects of many toxic substances if we act promptly.

In this section, the effective management of poisoning is the primary objective. Chapter 21 covers the general management of poisoning by non-therapeutic substances, such as household and environmental agents, and the management of envenomation by poisonous animals. Specific antidotes are discussed when applicable. Chapter 22 examines the management of poisoning due to overdosage of therapeutic substances. As you will see, there is some overlap between strategies across the two chapters.

Chapters 23 and 24 examine drugs used mainly for social rather than therapeutic purposes. In some instances, these drugs are taken to gain an unfair competitive advantage in sport. Tobacco, alcohol, marijuana, hallucinogenic agents, anabolic androgenic agents, stimulants and hormones are covered. In many cases, their use is better described as abuse. We have included them in this section because their effects can be toxic to the body.

V

POISONING AND ENVENOMATION

21

CHAPTER TWENTY-ONE

OBJECTIVES

After completing this chapter, the reader should be able to:

- **outline the mechanisms of action of agents used in the treatment of poisoning;**
- **identify contraindications for use of specific antidotes;**
- **outline how the effectiveness of emetics and adsorbents is influenced by the manner in which the substance is administered;**
- **define envenomation and outline the management of this condition;**
- **define an antivenom;**
- **outline the common adverse effects of antivenoms.**

KEY TERMS

Patient assessment
Cyanide poisoning
Decontamination
Envenomation
Life support
Metal poisoning
Methanol poisoning
Neutralisation
Organophosphate poisoning
Venomous animals

THIS CHAPTER EXPLORES POISONING AS A RESULT OF THE ingestion, usually accidental, of non-therapeutic chemicals such as heavy metals, pesticides and domestic agents (e.g. household cleaners, disinfectants). In some cases of poisoning, specific antidotes are available. It is common, however, for a more general approach to be adopted, especially when the identity of the poison is unknown (see Figure 21.1). The management of overdose of medicines is covered in Chapter 22.

Although there are a number of venomous animals in the world, including species of snakes, spiders, jellyfish, molluscs and octopus, in the UK the adder is the only venomous snake. Envenomation is the infusion of venom into another creature by the means of biting or stinging. The emergency management of envenomation in humans is briefly discussed here.

FIGURE 21.1 PRINCIPLES ASSOCIATED WITH THE MANAGEMENT OF POISONING

MANAGEMENT OF POISONING

The main principles associated with the emergency management of poisoning are:

- life support and stabilisation;
- patient assessment;
- decontamination;
- elimination or neutralisation of the poison (see Figure 21.1).

In this way you can see that the priority is on the treatment of the poisoned person rather than identifying the chemical poison.

Life support

Life support is concerned with ensuring a clear airway, maintaining an effective respiration and circulation, and addressing any fluid or metabolic imbalances.

Patient assessment

A thorough patient assessment is vital. The principles of patient assessment were described in Chapter 8. In order to implement an appropriate treatment, you need to gather as much information as possible about the poisoning episode. Important data include the time of poisoning, the number of

chemicals involved, the route of administration, the circumstances surrounding the episode and any first aid that has been administered. A physical examination may reveal a set of clinical manifestations that suggests a particular chemical. This may inform the subsequent treatment.

Decontamination and detoxification

In the first instance, the purpose of decontamination is to reduce the amount of poison absorbed systemically. For instance, it is important to cleanse the skin of any poison residues or, if the poison was inhaled, move the patient to where effective ventilation can occur.

If the poison was ingested and the patient has an intact gag reflex, an adsorbent, e.g. activated charcoal, may be administered. Use of ipecac-induced emesis is no longer recommended, and gastric lavage has been superseded by activated charcoal in most situations. Gastric lavage may be considered occasionally if the ingested drug is not adsorbed by charcoal.

Induction of emesis with ipecacuanha is no longer recommended in the UK because there is no evidence that it affects absorption and it may increase the risk of aspiration. **Ipecacuanha** (ipecac syrup) is an extract from the root of the *Caephalis* plant. One of the active principals in ipecac syrup is the alkaloid **emetine**. Emetine has both central and peripheral emetic actions, but after oral administration the peripheral action is predominant. Vomiting is triggered by intense irritation of the mucosal layer of the intestinal wall. The central action comprises stimulation of the vomiting centre, via the chemoreceptor trigger zone, in the medulla.

Emesis is contraindicated after ingestion of corrosive chemicals (e.g. petroleum products, dishwasher powder) because these can cause further damage to the oesophageal and buccal cavity walls if they are ejected from the stomach. This is also why the practice of giving a glass of milk to a conscious poisoned person, to neutralise the ingested chemical, has been abandoned.

ADSORBENTS

■ MECHANISM OF ACTION

Activated charcoal is used as an adsorbent in poisoning. Charcoal particles bind to molecules of the ingested poison and reduce its absorption into the blood through the gut wall.

✚ CLINICAL CONSIDERATIONS

The problem with using activated charcoal is that the dose necessary to effectively neutralise the poison is often underestimated. A dose ratio of at least 10 parts charcoal to 1 part estimated dose of poison is recommended. Charcoal has proven effectiveness in the treatment of overdosing with clinical drugs such as the cardiac glycosides and the methylxanthines, but it is ineffective in cases of poisoning with heavy metals or corrosive chemicals.

Elimination and neutralisation

The elimination and neutralisation of poisons is an important part of the management of poisoning. This aspect of management is covered in some detail in Chapter 22. If the poisonous chemical can be identified, then there are a number of specific antidotes that can be used. In this section, the use of antidotes in the management of poisoning associated with a number of environmental chemicals (e.g. heavy metals, methanol, cyanide, organophosphate sprays) is considered.

METAL POISONING

Many metal ions, such as iron and zinc, are essential for normal body function. Body requirements are such, however, that only small amounts – mere traces – are sufficient. In excess, these metal ions produce widespread systemic toxic effects. Other metals, such as lead, arsenic, bismuth, gold, antimony, thallium and mercury, do not play a role in normal physiological processes. On entering the body, these cause deleterious effects by displacing essential trace elements and accumulating in tissues such as the brain, kidneys, skin, bone and blood.

There are a number of substances that bind strongly to metal ions, forming a ring structure around the offending substance. These are called *chelating agents* because they latch on to the ion firmly, just as a crab grabs something with its claws (chelae); by virtue of this bond, they facilitate the elimination of the heavy metal. The main chelating agents, their specificities and adverse effects are listed in Table 21.1.

METHANOL POISONING

Methanol, or methyl alcohol, has a number of industrial and domestic uses (e.g. as a solvent in photocopier and window-cleaning solutions, and as a domestic heating material). Methanol causes features of intoxication but is far more toxic to the human body than **ethanol** because it is metabolised into formaldehyde and formic acid. Intoxication with methanol can lead to permanent disability and sometimes death. Onset of metabolic toxic features may be delayed for several hours, especially if methanol is ingested alongside ethanol.

Like ethanol, methanol is a central nervous system (CNS) depressant. Clinical manifestations of intoxication include nausea, vomiting, abdominal pain, visual disturbances, bradycardia, coma, metabolic acidosis, respiratory depression and seizures. Ingestion of methanol and its metabolites can lead to blindness due to permanent damage to the retina and optic atrophy.

Gastric aspiration is useful if the patient presents within 1 hour of methanol ingestion. Charcoal is of no use as it does

TABLE 21.1 CHELATING AGENTS

Chelating agent	Specificities	Adverse effects
Calcium disodium edetate	Lead, plutonium, yttrium	Renal necrosis, gastrointestinal upset, muscle cramps, malaise
Desferrioxamine mesylate	Iron, aluminium	Allergic reactions, gastrointestinal upset, visual/hearing disorders, liver/kidney impairment
Dicobalt edetate	Cyanide	Rare
Dimercaprol	Arsenic, gold, mercury, bismuth, antimony, thallium, lead (with versenate)	Hypertension, gastrointestinal upset, paraesthesias, muscle pain, headache
D-Penicillamine	Lead, copper, zinc, gold, mercury	Allergic reactions, liver/kidney impairment, gastrointestinal upset, hearing/taste impairment, blood dyscrasias

not adsorb methanol. The rate of conversion of methanol into more toxic metabolites can be slowed by the intravenous administration of a 10% solution of ethanol. Alcohol dehydrogenase is the hepatic enzyme responsible for the catabolism of both methanol and ethanol. By saturating this enzyme with ethanol, the degradation of methanol is competitively inhibited. Much of the methanol will then be eliminated via the lungs and kidneys. Haemodialysis, discussed in Chapter 22, is also effective in assisting the clearance of methanol from the body.

CYANIDE POISONING

On entering the body, cyanide has a strong affinity for iron, particularly in the ferric form (Fe^{3+}). This leads to an impairment in the function of the tissue cytochrome system. As a result, cellular adenosine triphosphate (ATP) formation is greatly diminished. An impairment of cellular metabolism is a life-threatening situation. Functionally, it is the same as a complete lack of oxygen within body cells.

The treatment of this condition involves two steps: reactivation of the cytochrome system, and the administration of a binding agent that will inactivate cyanide and promote its excretion. In order to achieve the first step, the nitrites, vasodilators used in the treatment of angina pectoris (see Chapter 45), are put to good use. Nitrites act to rapidly convert haemoglobin (Fe^{2+}) into methaemoglobin (Fe^{3+}). As a result, a proportion of the cyanide will be drawn off the cytochromes on to methaemoglobin. Cellular cytochromes responsible for the energy production necessary for survival will function again. **Amyl nitrite** may be administered by inhalation, followed by intravenous administration of **sodium nitrite** or **sodium thiosulphate**. Alternatively, intravenous sodium nitrite is immediately followed by intravenous administration of sodium thiosulphate.

Cyanide's excretion from the body is facilitated by the intravenous administration of **dicobalt edetate** (see Table 21.1), but this is recommended for use only in cases of severe poisoning. Owing to its own toxicity, it should be used only when the patient is tending to lose, or has lost, consciousness. Dicobalt edetate should not be used as a precautionary measure. This chemical forms non-toxic complexes with cyanide by displacing a cobalt ion for a cyanide molecule. Side effects include hypotension, tachycardia and vomiting. Adverse reactions are relatively rare and are associated with either cobalt toxicity or allergy.

ORGANOPHOSPHATE POISONING

The organophosphate sprays are used as agricultural and domestic pesticides. They are present in crop sprays, pet flea collars and some fly sprays. When absorbed into the body, the toxic effects arise out of the ability of the organophosphate to bind irreversibly to the enzyme acetylcholinesterase (AChE), permanently disabling it. As a consequence, synaptic acetylcholine levels rise, leading to overstimulation of muscarinic and nicotinic receptors (see Chapter 27). The action of organophosphate pesticides is similar to that of the therapeutically valuable anticholinesterases, e.g. **neostigmine** and **physostigmine**, except that the interaction between cholinesterase and the latter drugs is reversible.

The manifestations of pesticide poisoning derive from this action and include pupil constriction, excessive sweating, drooling, diarrhoea, abdominal cramps, either bradycardia (if muscarinic stimulation is dominant) or tachycardia (if nicotinic stimulation is dominant), agitation, and skeletal muscle twitching followed by flaccidity (the latter leading to respiratory paralysis). Treatment involves respiratory support, blockade of cholinergic receptors, and reactivation of the enzyme cholinesterase. The blockade of receptors is

achieved through administration of the antimuscarinic agent **atropine**, and the reactivation of cholinesterase by intravenous injection of **pralidoxime iodide**. When reactivation is delayed, phosphorylated enzyme may become 'aged' or inactive and dephosphorylation of inhibited AChE then does not occur to any clinically significant degree. This means that pralidoxime is effective only if administered within 24 hours; repeated intravenous doses may be required in severe cases. This depends on the erythrocyte cholinesterase activity; advice should be sought from the National Poisons Information Service. If the enzyme becomes 'aged', resynthesis of new AChE is needed in order to restore the enzyme activity to normal; this may take days.

Poisoning with nerve agents, which are organophosphates, requires similar treatment; in the UK, ambulance service trusts have protocols for decontamination and the administration of antidotes. If the patient is not responding to pralidoxime, a second-line antidote is **obidoxime**, which is held by the National Blood Service. This is also a cholinesterase reactivator.

ENVENOMATION

There is only one indigenous poisonous snake in the UK – *Vipera berus* or adder. Other types of poisonous snake may be found in zoos and private collections. Snake bites are uncommon in the UK, and the majority of patients will have been bitten by non-venomous snakes. In other countries, such as Australia, there are many venomous snakes, and the toxins contained within these venoms have the potential to cause profound tissue damage (cytolysis), neurological injury, clotting disorders, muscle injury and cardiovascular collapse, particularly after absorption into the bloodstream.

The aims of the emergency care of a patient who has been stung or bitten by a poisonous creature follows the same principles associated with the management of poisoning; that is, to maintain life support, to minimise systemic absorption of the venom and to facilitate the neutralisation of the venom.

Life support involves maintaining a clear airway, initiating artificial ventilation in the event of respiratory collapse, and monitoring cardiovascular function.

The adder

Adder venom causes local damage; immobilisation rather than pressure-immobilisation is required. Most adder bites occur in the summer in people walking through heathland or long grass. The last recorded fatality was in 1972, but the bite may cause significant morbidity. Pain is felt immediately at the site of the bite, and local swelling will occur. Treatment before hospital transfer is simply immobilisation and reassurance; no bandage should be applied. In severe cases, antivenom treatment in hospital may be required. The contents of one vial of European viper venom antiserum is given by intravenous injection over 15 minutes or as an infusion diluted in sodium chloride 0.9%. Systemic effects include early anaphylactoid symptoms, transient hypotension with syncope, angioedema, urticaria, abdominal pain, diarrhoea and vomiting for which adrenaline may be administered.

The weever fish (*Echiichthys vipera*)

This fish is found in the coastal waters off the UK. It is about 14 cm in length, with a stout body. It has about six spines in its dorsal fin and one on each gill that contain venom. The fish move to shallow waters and bury themselves in the sand in summer with only their eyes and mouth protruding; this enables the fish to attack any passing prey. The venom remains potent for hours after the fish has died. The sting is excruciatingly painful but usually a full recovery occurs, although occasionally there may be swelling for up to 24 hours. A sharp stabbing pain is felt as the sting penetrates the skin. The pain increases in severity, usually reaching its height after about 30–60 minutes, and then gradually subsides over 2–24 hours. There is a small risk of secondary infection, for which antibiotics may be needed.

Treatment is to immerse the affected foot in water as hot as can be tolerated for about 30 minutes. The intense pain should ease, but applying anything cold may make the pain worse.

POISONOUS PLANTS

A useful website for the identification of poisonous plants is www.realgardeners.co.uk with colour photographs for identification of dangerous species. The reader is referred to this list for a more detailed description. Three plants that have the potential to be fatally toxic are described below. Ingestion of inedible plants with lower toxicity often causes nausea, vomiting and diarrhoea; active treatment is not usually required, although fluid replacement may be needed. The plant should always be identified and expert advice sought.

Deadly nightshade (*Atropa belladonna*)

All parts of this plant are toxic. The berries and some other parts of the plant contain atropine and other alkaloids, all with an anticholinergic effect. This means that they block the effects of cholinergic transmission and the parasympathetic nervous system. The fatal dose in children is reported to be as low as two to five berries. Severe poisoning with this plant is rare, but the effects are often prolonged and may be frightening. The effects are similar to those of atropine – dry mouth, dilated pupils, blurred vision, tachycardia, hallucinations, pyrexia with no sweating, restlessness and convulsions.

Treatment includes the administration of activated charcoal and supportive measures such as rehydration

and cooling measures. Diazepam may be given for the convulsions. Physostigmine has occasionally been used in severe cases of deadly nightshade poisoning.

Laburnum (*Laburnum anagyroides*)

This tree has attractive yellow flowers sometimes known as golden rain. It produces seeds in a pod. All parts are poisonous, but especially the bark and seeds. These contain cytosine, which has a similar effect to nicotine. It is usually the seeds that are eaten by children; severe cases of poisoning are uncommon, perhaps because of the emetic action of the seeds. Vomiting, drowsiness and tachycardia may occur within 30 minutes to 2 hours. In severe cases, there may be convulsions, respiratory depression and coma. Activated charcoal is the recommended treatment, along with observation with supportive treatment if needed.

Yew tree (*Taxus baccata*)

This is an evergreen shrub with leaves that are needles. The seed is brownish purple. All parts of the plant, including dried clippings, are toxic. The poisonous alkaloid is taxine, which is cardioactive. Serious yew poisoning is rare, but vomiting and diarrhoea usually develop after about an hour. Other effects include dilated pupils, dizziness and lethargy. In severe cases, bradycardia and hypotension may occur. Death is usually due to respiratory or heart failure.

Activated charcoal is the treatment, together with observation for at least 4 hours, with monitoring of pulse and blood pressure. Convulsions may be controlled with diazepam; cardiac pacing may be needed in severe cases.

INSECT STINGS

Local pain and swelling may be caused by stings from ants, wasps, hornets and bees. They only rarely cause severe direct toxicity, unless many stings are inflicted at the same time.

Bee stings should be removed as quickly as possible and any anaphylactic reaction should be treated with adrenaline. A short course of an antihistamine may help to relieve itching and reduce the inflammatory response.

SUMMARY

- There are four main principles associated with the management of poisoning:
  - life support;
  - patient assessment;
  - decontamination;
  - elimination or neutralisation of the poison.
- Life support involves maintaining a clear airway, respiration and circulation.
- Patient assessment consists of a process of gathering information to guide management. It involves taking a good history and completing a thorough physical examination.
- The purpose of decontamination is to reduce systemic absorption of the poison. Emetics, adsorbents and cathartics represent important treatments in this phase.
- There are some antidotes available that neutralise or promote the elimination of selected poisons.
- Envenomation is the infusion of venom from a poisonous animal by biting or stinging. Venoms can cause extensive tissue damage and are potentially fatal.
- The management principles in cases of envenomation are similar to those associated with poisoning.
- Antivenoms are very effective against a range of venoms and act to neutralise the toxins in the venom.

1 Indicate the circumstances under which each of the following antidotes should not be administered:
(a) sodium sulphate;
(b) activated charcoal;
(c) salts of magnesium;
(d) penicillamine.

2 What is a chelating agent?

3 Name the agent(s) used in the treatment of poisoning by each of the following substances:
(a) cyanide;
(b) lead;
(c) mercury;
(d) pesticides.

4 Define the term 'envenomation'.

5 State the three aims of emergency care when someone is bitten or stung by a poisonous animal.

6 Your neighbour visits you in an extremely distressed state. Joey, her 3-year-old son, has just swallowed an unknown quantity of paracetamol tablets. What would you advise her to do? Why?

7 Mario Malodoro, a 60-year-old farmer, is brought into the emergency department with organophosphate poisoning. How would this form of poisoning be treated?

21 DRUG SUMMARY TABLE: POISONING AND ENVENOMATION

FAMILY NAME	GENERIC NAME	TRADE NAME(S)
Adsorbent	Activated charcoal	Carbomix, Charcodote
Methanol intoxication antidote	Ethanol	
Cyanide antidote	Amyl nitrite Sodium nitrite Sodium thiosulphate	
Organophosphate antidotes	Atropine sulphate Pralidoxime iodide	 PAM injection

MANAGEMENT OF CLINICAL OVERDOSE

22

CHAPTER TWENTY-TWO

OBJECTIVES

After completing this chapter, the reader should be able to:

- **state the four principles underlying the management of clinical drug overdose;**
- **identify the clinical manifestations of poisoning that require life support;**
- **outline the ways in which drugs are identified in cases of overdose;**
- **describe the general approach used to detoxify a poisoned patient;**
- **identify the specific antidotes available, their common adverse effects, and important clinical considerations when using them.**

KEY TERMS

Antidote
Patient assessment
Decontamination
Detoxification
Drug overdose
Haemodialysis
Haemoperfusion
Gastric lavage
Life support
Neutralisation

IN CHAPTER 21, THE TREATMENT OF POISONING BY THE ingestion of household and industrial chemicals was discussed. In this chapter, the management of overdosage of clinical agents, whether deliberate or accidental, is described.

The importance of this area of pharmacology is self-evident. A significant proportion of hospital admissions results from serious adverse reactions to drugs – some following inappropriate therapeutic use. Serious illnesses arising from these reactions are termed **iatrogenic** (induced by a physician or by medical treatment) conditions. Deliberate abuse of drugs is also common, and a drug overdose may be unintentional or purposeful.

FIGURE 22.1 PRINCIPLES ASSOCIATED WITH THE MANAGEMENT OF OVERDOSE

There are four principles underlying the management of clinical overdosage:

- life support;
- patient assessment;
- drug decontamination and detoxification;
- drug neutralisation and elimination.

These principles and their components are summarised in Figure 22.1.

LIFE SUPPORT

Drug overdose often manifests itself as an acute clinical emergency. Failure to act quickly may result in the death of the patient. Indeed, immediate supportive measures may take precedence over the identification and detoxification of the offending agent.

The kinds of life-threatening emergency that can be induced by drugs include seizures, cardiac dysrhythmias, circulatory shock and, often as a consequence of coma,

airway obstruction and respiratory arrest. Massive damage to vital organs such as the liver, lungs and kidneys caused by drug toxicity can also lead to death within a relatively short period of time.

The management of these conditions is the same, no matter what specific drug is the cause. The management of such medical emergencies can be found in suitable clinical references and will not be duplicated here.

PATIENT ASSESSMENT

If the overdose occurs within the confines of a controlled clinical setting, then it is relatively easy to determine the offending agent and the dose administered. On the other hand, if a person is admitted with a suspected drug overdose, such information may not be available. Drug identification and dosage may have to be deduced from a combination of patient history, clinical manifestations and laboratory findings.

A thorough physical examination of the patient will reveal a syndrome of clinical manifestations of drug overdose. A knowledge of the manifestations that characterise a particular therapeutic agent is useful and usually comes with clinical experience and drug familiarity. It is also most helpful to know that there is a section at the front of the *British National Formulary* (BNF) detailing the emergency treatment of poisoning and an online information service for health-care professionals, but not members of the public, called TOXBASE. There is also a UK National Poisons Information Service (NPIS) comprising six poisons centres (Belfast, Birmingham, Cardiff, Edinburgh, London and Newcastle) providing a year-round 24-hours-a-day service, for health-care staff on the diagnosis, treatment and management of patients who may have been poisoned. TOXBASE should be the first line for any enquiries and is regarded as the most authoritative source of information available. Users have to register to use the website. The database is contributed to, and constantly updated by, all NPIS centres. The latter should be contacted only for more specialised information in complex cases.

The most powerful diagnostic tool is detection of a drug in the blood by laboratory testing. Indeed, blood drug levels may be necessary to guide the detoxification process. Laboratory testing provides information concerning pH changes, electrolyte imbalances and the extent of damage to the liver and kidney. These values will also determine the supportive measures necessary to restore homoeostasis.

DRUG DETOXIFICATION

No matter what the route, once an overdose has been noticed, continued administration must cease until the crisis is under control. Irrespective of whether life support takes precedence over detoxification, this is the first action.

The general approach employed to reduce systemic absorption of an ingested poison referred to in Chapter 21 (such as the use of **activated charcoal**) has application in clinical overdose if the drug was administered orally. Indeed, this form of treatment, if initiated quickly, is particularly effective for oral poisoning with agents such as the cardiac glycosides, angiotensin-converting enzyme (ACE) inhibitors and methylxanthines.

DRUG NEUTRALISATION AND ELIMINATION

Within the clinical environment, this general approach can be broadened to include more invasive medical procedures, such as gastric lavage and haemodialysis, which facilitate the elimination of the drug from the body. An antidote to the drug may also be available to neutralise its effects.

Gastric lavage

Gastric lavage is rarely required and should be considered only if a life-threatening amount of a drug has been ingested within the preceding hour. It should be carried out only if the airway can be protected adequately. It may occasionally be considered in patients who have taken drugs that are not adsorbed by charcoal, such as iron and lithium. A large-bore tube is passed directly into the stomach; a solution of tepid water is instilled into the stomach and then suctioned out. This is repeated a number of times until the aspirated solution is clear. The first sample of aspirate is usually sent to the laboratory for identification.

The necessity for a large-bore tube restricts the use of this procedure in children (who have a smaller-diameter oesophagus), and there is a risk of metabolic alkalosis due to excessive loss of chloride ions from the gastrointestinal tract. Figure 22.2 demonstrates the positioning of an unconscious patient for gastric lavage.

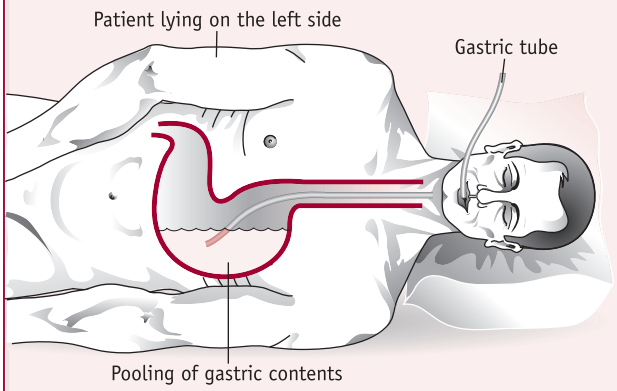
Haemodialysis and haemoperfusion

Haemodialysis involves passing the poisoned patient's blood through a dialysis medium, where the drug and/or its metabolites are removed and electrolyte imbalances corrected. The detoxified blood is then recirculated to the patient. Only a limited number of drugs can be removed effectively by this method. Evidence indicates that haemodialysis can be used effectively in **lithium** and salicylate poisoning.

Haemoperfusion is a filtering system in which the patient's blood is passed through a medium containing adsorbent beads. The offending agent, and/or its metabolites, adheres to the beads and remains within the medium, while the filtered blood returns to the patient. Like haemodialysis, haemoperfusion has limited use because it is effective for only a handful of drugs, e.g. **carbamazepine**, **theophylline**, **digoxin** and **phenobarbitone**. Its disadvantage compared

FIGURE 22.2 PATIENT POSITIONING DURING GASTRIC LAVAGE

During gastric lavage, the unconscious patient is positioned on the left side to facilitate pooling of gastric contents and to hinder their passage to the duodenum.



with haemodialysis is that it cannot correct electrolyte imbalances.

Special antidotes

There are few specific detoxifying agents available for use in situations of clinical overdosage. Antidotes neutralise, antagonise the effects of or facilitate the elimination of the clinical agent. They are available against poisoning with the following substances: **paracetamol**, anticholinesterases, antimuscarinic agents, iron, narcotics, benzodiazepines, **heparin**, **warfarin** and **digoxin**. The advantage of specific antidotes is that other interventions, such as gastric lavage, artificial ventilation and brain scans, are unnecessary if an antidote is used.

PARACETAMOL (ACETAMINOPHEN) OVERDOSE

The mechanism of toxicity of paracetamol is complicated and can be found in any toxicology textbook, but it is worth relating here briefly as it indicates some of the intricacies of drug metabolism. Normal doses of paracetamol are handled well by the liver's metabolic processes. Most paracetamol (90–93 per cent) is conjugated to glucuronide and sulphate conjugates and the conjugates excreted directly; around 2 per cent of paracetamol is eliminated unchanged by the kidneys and the remainder (about 5 per cent) is metabolised to a highly reactive intermediate compound, N-acetyl-p-benzoquinone-imine (NAPQI), which is then bound to glutathione and detoxified. Unfortunately, the body's stores of glutathione are limited. If excess paracetamol is consumed, then the normal routes of conjugation are saturated and NAPQI is produced in excess. NAPQI has an affinity for liver cells and their enzymes, to which it binds, slowly destroying them and leading to hepatic necrosis. Once this process has started, it becomes irreversible and death may follow.

It takes only a relatively low dose of paracetamol for hepatotoxicity to occur. Two 500-mg tablets (1 g) is considered a toxic dose in a 10-kg child. For an adult, 8 g (16 500-mg tablets) is sufficient to produce a toxic reaction. As little as 10–15 g (20–30 tablets) within 24 hours may cause severe liver necrosis and occasionally renal necrosis.

TREATMENT OF PARACETAMOL OVERDOSE

Treatment must be commenced as soon as possible after the overdose and is aimed at increasing body stores of glutathione. Glutathione is incapable of crossing into cells, but compounds that stimulate its production can cross into cells. The drugs that can do this are the amino acid **methionine** and the amino acid derivative **acetylcysteine**. Both of these drugs are utilised in the synthesis of glutathione. Acetylcysteine is the preferred drug, being more potent than methionine, but has to be given intravenously. Both agents are effective if given within 10–12 hours of the ingestion of paracetamol. Depending on the circumstances, acetylcysteine may be beneficial if used more than 12 hours post-ingestion but is most effective if administered within 8 hours.

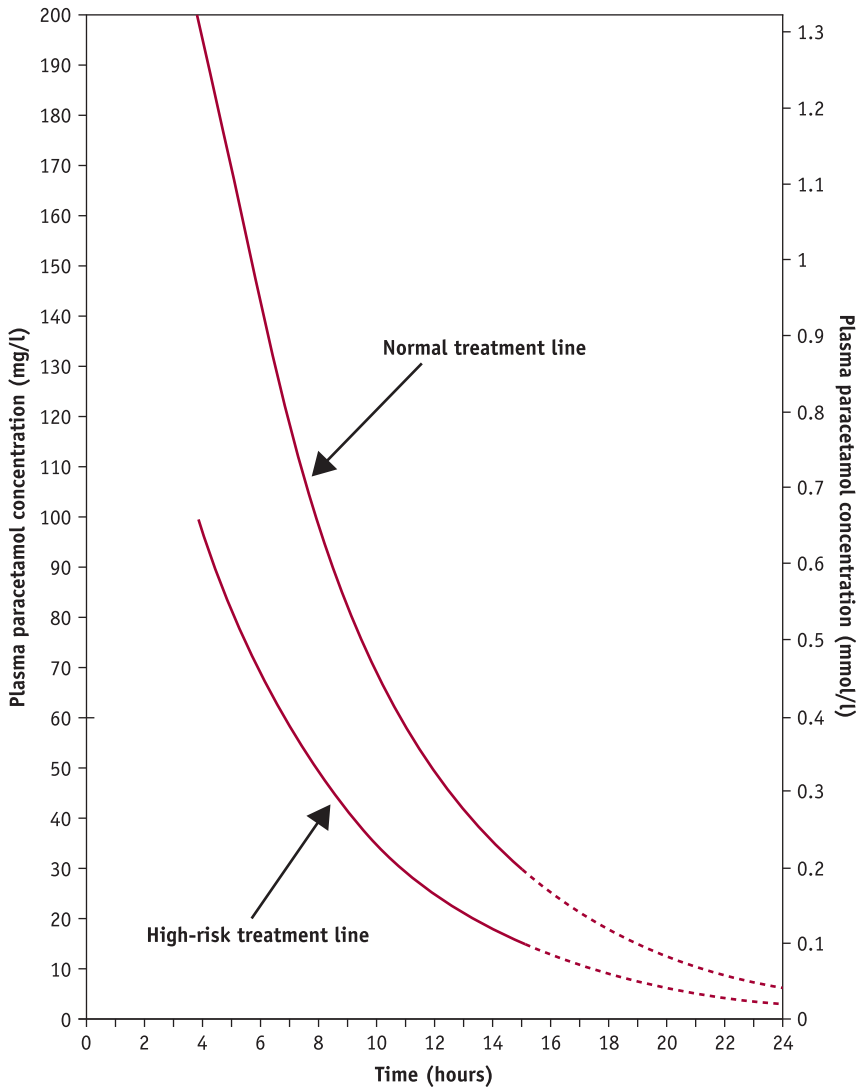
Hypersensitivity-like reactions have been reported after administration of acetylcysteine. Mild reactions are treated by stopping the infusion or reducing the infusion rate of acetylcysteine until the reaction has settled. Antihistamines may also be given. More severe anaphylactoid reactions may present with a rash, flushing, bronchospasm, nausea, vomiting, angioedema, tachycardia and hypotension. It is recommended in the BNF that a poisons information centre be contacted if the reaction is severe. In patients with asthma, hypersensitivity is more likely and bronchospasm may result. The drug is not withheld in patients with asthma, but the administration of nebulised salbutamol may be necessary.

Alcoholics and heavy alcohol drinkers are more susceptible to paracetamol poisoning, possibly due to the fact that the enzyme-inducing properties of ethanol raise the rate of conversion of paracetamol to its toxic metabolite. Patients are treated according to their plasma paracetamol concentration and the time since the overdose was taken. A chart is used to assess the need for administration of acetylcysteine (see Figure 22.3). Note that there are two treatment lines – a normal line and a high-risk line.

At high risk would be:

- patients taking enzyme-inducing drugs such as phenytoin, rifampicin and St John's wort;

FIGURE 22.3 TREATMENT LINE FOR USE OF ACETYLCYSTEINE IN PARACETAMOL POISONING



Patients whose plasma paracetamol concentrations are above the normal treatment line should be treated with acetylcysteine by intravenous infusion (or, if acetylcysteine cannot be used, with methionine by mouth, provided the overdose has been taken within 10–12 hours and the patient is not vomiting).

Patients on enzyme-inducing drugs (e.g. carbamazepine, phenobarbital, phenytoin, primidone, rifampicin, alcohol, St John's wort) or who are malnourised (e.g. anorexia, alcoholism, HIV-positive) should be treated if their plasma paracetamol concentration is above the high-risk treatment line.

The prognostic accuracy after 15 hours is uncertain, but a plasma paracetamol concentration above the relevant treatment line should be regarded as carrying a serious risk of liver damage.

Source: Graph reproduced courtesy of University of Wales College of Medicine Therapeutics and Toxicology Centre

- patients who are malnourished, e.g. in anorexia, alcoholism;
- patients who are HIV-positive.

The plasma paracetamol level is unreliable if measured less than 4 hours after ingestion, and the prognostic accuracy of the chart is uncertain more than 15 hours after ingestion.

CLINICAL FEATURES OF PARACETAMOL POISONING

Anorexia, nausea and vomiting are the only early features of poisoning; these usually settle within 24 hours. There is often a delay of up to 24 hours before the patient becomes truly symptomatic. This is dangerous and hospital admission may not occur until liver damage is already under way. Persistence of symptoms beyond 24 hours, especially

TABLE 22.1 TIME COURSE OF PARACETAMOL TOXICITY

Time after ingestion	Clinical features
Up to about 24 hours	Anorexia, nausea, vomiting, liver enzymes (transaminases) start to rise
24–72 hours	Right subcostal pain develops, bilirubin levels and prothrombin times are raised, transaminases peak
72–96 hours	Necrosis of liver cells causes jaundice, bleeding, encephalopathy, acute renal failure and death
96 hours–14 days	Resolution and healing of liver

with the onset of right subcostal pain, is usually due to the onset of liver damage, which is greatest after 3–4 days and may lead to acute liver failure and death. A liver transplant may be needed; if necessary, the patient will have been transferred to a specialised liver unit. If the patient survives this period, the liver has great powers of regeneration. The time course of paracetamol toxicity is shown in Table 22.1.

The danger of paracetamol means that even if there are no early symptoms, a person who has taken a paracetamol overdose needs urgent transfer to hospital.

In the UK, the introduction of legislation in 1998 limiting the number of paracetamol tablets sold produced a reduction in the number of deaths from paracetamol overdose. Suicidal deaths from paracetamol and salicylates were reduced by 22 per cent in the year after the change in legislation.

ANTICHOLINESTERASE OVERDOSE

The antidotes for overdose of the anticholinesterases **neostigmine**, **physostigmine** and **pyridostigmine** are **atropine** and **pralidoxime iodide**.

Atropine is a competitive antagonist for acetylcholine at the muscarinic receptor. The synaptic activity of acetylcholine is prolonged by the anticholinesterases (see Chapter 27). Common adverse effects of atropine are antimuscarinic in nature and include dry mouth, blurred vision, constipation, tachycardia and urinary retention. Atropine is contraindicated in obstructive and atonic conditions of the gastrointestinal tract and urinary bladder and in cardiospasm.

Pralidoxime iodide activates cholinesterase, the acetylcholine degradative enzyme. It is used as an adjunct to atropine in this type of poisoning and its action is described elsewhere (see Chapter 21) when used in the reversal of organophosphate insecticide poisoning.

ATROPINE OVERDOSE

When a patient has been poisoned by atropine administration, it would appear to make sense to use an agent that stimulates muscarinic receptors (see Chapter 27). The recommended drug used to be the anticholinesterase physostigmine. Many of the more serious manifestations of atropine overdose are of central nervous system (CNS) origin, and physostigmine readily crosses the blood–brain barrier. Physostigmine is no longer recommended for anticholinesterase poisoning due to the severity of its side effects. Common adverse effects of physostigmine result from excessive cholinergic stimulation and include muscarinic reactions (CNS stimulation, nausea, vomiting, diarrhoea, sweating, drooling, bradycardia, miosis) and nicotinic reactions (muscle cramps, fasciculations).

In the case of an oral overdose of anticholinergics, activated charcoal should be considered if the patient presents within 1 hour of ingestion. Usually, specific treatment is not needed, and observation for 6 hours is all that is required. In the case of a more serious overdose, it may be necessary to artificially ventilate the patient if the arterial carbon dioxide levels are raised, to correct hypoxia and hypotension, and to treat hypothermia. Convulsions may occur and are treated with intravenous diazepam. Antiarrhythmic drugs are not given, but sodium bicarbonate may be used to treat acidosis.

IRON POISONING

Iron poisoning is usually accidental and is most common in children. Nausea, vomiting, abdominal pain, diarrhoea, haematemesis and rectal bleeding are all possible symptoms. Later, hypotension and coma may occur, with liver necrosis. Gastric lavage is still recommended within 1 hour of ingestion of a significant quantity of iron or if X-ray shows that iron tablets are still in the stomach. Advice should be sought from a poisons information centre. Mortality from acute iron poisoning may be reduced by the use of **desferrioxamine**, which chelates iron and enhances excretion by forming a water-soluble complex called ferrioxamine. The serum iron concentration is measured, but in severe cases intravenous desferrioxamine may be given immediately without waiting for the laboratory results (following advice from the NPIS). Adverse effects of desferrioxamine include allergic reactions, gastrointestinal disturbances, alterations in vision and hearing, dizziness and hypotension. Desferrioxamine is contraindicated if hypersensitivity is apparent.

Desferrioxamine is also used in the treatment of iron overload, as may occur in aplastic anaemia and other anaemias due to repeated blood transfusions. It may also be given at the time of blood transfusion, but not through the same line as the blood. Inappropriate iron therapy in thalassaemia major may also result in overload. In these cases, desferrioxamine is given as a subcutaneous infusion over 8–12 hours. Ascorbic acid 200 mg daily enhances iron excretion by desferrioxamine.

Deferiprone has been approved for use in patients with thalassaemia major experiencing iron overload. This is an oral chelating agent that promotes iron excretion. Deferiprone is particularly useful for patients who are unable to take desferrioxamine or in cases where the latter treatment is ineffective. Common adverse effects include nausea, vomiting, arthalgia and abdominal pain. A reduced white cell count has occurred in some patients and so the neutrophil count should be monitored weekly.

NARCOTIC OVERDOSE

Narcotic drug overdose can be treated effectively using the full antagonist naloxone (see Chapter 39). Opioids (narcotic analgesics) cause respiratory depression, pinpoint pupils and coma. Naloxone is indicated if there is bradypnoea or coma.

Naloxone has a much stronger affinity for opiate receptors than most of the agonists and can be used to reverse their action in cases of overdose. The result is quite dramatic: One can have a comatose patient with respiratory depression and, following intravenous injection of naloxone, see an immediate recovery to more or less normality. There is one problem: Naloxone has a half-life of about 1 hour, which is much shorter than that of most opioid agonists. Repeat doses of naloxone may be necessary, depending on the dose, duration of action and time interval since administration of the offending narcotic. Care must be taken to keep cases of overdose under observation for a considerable time, especially with the longer-half-life narcotics, as recovery may occur after a single dose of naloxone but the patient may relapse into a coma in 1–2 hours. When repeat doses of naloxone are needed, the drug may be given by continuous intravenous infusion and the rate of infusion adjusted according to the patient's vital signs.

Naloxone works antagonistically with most of the narcotics, but with **buprenorphine** there is only partial reversal (see also Chapter 39). Larger doses of naloxone may also be needed with codeine and fentanyl derivatives.

When administered quickly, naloxone can induce narcotic withdrawal symptoms, such as nausea, vomiting, tachycardia, tremor and sweating. The drug may be given intramuscularly for a slower effect, and paramedics often use this route in non-life-threatening situations in patients who take opioids regularly; this avoids immediate acute withdrawal symptoms.

BENZODIAZEPINE OVERDOSE

The benzodiazepines, such as diazepam, are among the safest of all CNS drugs. It has been suggested that, even following ingestion of large amounts, the patient is easily roused. Deaths have occurred, however, when benzodiazepines are taken in excess with alcohol, a common combination.

Benzodiazepines commonly cause drowsiness, slurring of speech and ataxia. Occasionally, coma, hypotension and respiratory depression may occur following overdose, but these are not usually serious if the drugs are taken alone – the coma usually lasts only a few hours, but may be longer in elderly patients.

Flumazenil is a specific antagonist to the benzodiazepines that is useful in the treatment of life-threatening situations. It is rarely required in benzodiazepine overdose and should not be used in a mixed overdose or as a diagnostic test to see whether benzodiazepines have been taken. This may be dangerous and can precipitate convulsions in patients with epilepsy and arrhythmias with some other drugs, such as tricyclic antidepressants. Flumenazil is used mostly as a reversal agent when benzodiazepines have been used as sedation in endoscopy and other diagnostic procedures. Its use enables the patient to recover quickly from the sedation and be discharged sooner.

Flumenazil is usually tolerated well, although agitation, shivering, nausea and vomiting have been reported following its use. It is important to remember that most benzodiazepines are characterised by long durations of action. Therefore, the patient may lapse back into a state of sedation after the antidote wears off (average elimination half-life of flumazenil is around 1 hour). This effect has implications for patients discharged from hospital shortly after treatment. Hypersensitivity is a contraindication for use.

HEPARIN OVERDOSE

Excess heparin results in the risk of haemorrhage. Toxicity is related to the size of the dose injected. Bleeding may present in many ways, for example as epistaxis, gastrointestinal blood loss or haematuria. An intracerebral bleed is also possible.

A protein derived from the sperm of salmon is the rather bizarre-sounding medium for neutralising a heparin overdose. The protein **protamine sulphate** combines with the heparin molecule to form a complex that suppresses the pharmacological activity of the anticoagulant.

Adverse cardiovascular effects such as hypotension, bradycardia and facial flushing can occur, but these are minimised by giving the drug as a slow intravenous infusion. Rapid injection can cause an anaphylactic reaction. In order for protamine sulphate to be effective, it must be given within 3 hours of the heparin injection. For every 100 units of heparin in the blood, 1 mg of protamine is administered; however, no more than 50 mg of protamine can be infused at any one time.

WARFARIN OVERDOSE

An excessive anticoagulant effect brought about by warfarin overdose is best treated by **vitamin K_1** administered either orally or parenterally. In cases where serious bleeding is observed, the usual dose for slow intravenous injection is 5 mg. In an emergency, where severe haemorrhage is present, a transfusion of fresh frozen plasma or prothrombin complex concentrate may also be necessary. In more minor cases, the warfarin is stopped, the international normalised ratio (INR) monitored and 0.5 mg vitamin K_1 given by slow intravenous injection or 5 mg given orally.

DIGOXIN OVERDOSE

High doses of digoxin and related cardiac glycosides can be fatal, even if life support is provided. The fatal dose is variable and death has occurred after ingestion of 4 mg, although some patients have survived the ingestion of 20–40 mg with treatment. Death usually occurs from ventricular arrhythmias, heart failure or conduction impairment. Clinical features of overdose usually occur within 6 hours of ingestion. Chronic toxicity may also occur, resulting in anorexia, headaches, blurred vision and altered colour perception. With both acute and chronic toxicity, any type of arrhythmia may occur. Digoxin-specific antibodies with a strong affinity for digoxin are available as Digibind™. Manifestations of digoxin poisoning are reversed rapidly, and clinical improvement is usually seen within 30–60 minutes of commencing treatment with specific antibodies. Adverse effects are rare, but rashes and low platelets have been reported. Digoxin levels are unreliable for 5–7 days after treatment with digoxin-specific antibodies.

The preparation consists of antibody fragments specific to the digoxin molecule, which have been raised in sheep. Antibody fragments have been found to be less immunogenic than whole immunoglobulin. Nevertheless, being a protein derivative from an animal source, its most common adverse reactions are of an allergic kind.

When this preparation is not available, life-support measures have to be relied on. Atropine may be used in marked bradycardia and atrioventricular block.

TRICYCLIC ANTIDEPRESSANT OVERDOSE

Tricyclic antidepressants interfere with the reuptake of noradrenaline and serotonin within the nervous system. They are used to treat depression, but they are extremely dangerous if an overdose is taken and are potentiated by alcohol ingestion. Amitriptyline and dosulepin (dothiepin) are particularly dangerous – less than ten times the therapeutic dose is toxic. Selective serotonin reuptake inhibitors (SSRIs), such as fluoxetine, are alternative drugs for depression and have a much safer profile.

Early signs and symptoms of overdose are due to the anticholinergic effects of the drugs. They include dry mouth, hot dry skin, blurred vision, sinus tachycardia, urinary retention and dilated pupils. The real danger of the drugs lies in their cardiovascular effects; a patient taking an overdose may present anywhere on the spectrum from mild signs of anticholinergic syndrome to unconsciousness, life-threatening seizures and arrhythmias with hypotension. The patient may present following recent ingestion of the tablets and have no symptoms. Deterioration can occur within 1 hour, and all patients having taken an overdose of these drugs require immediate attention and assessment. Activated charcoal is given and the heart rhythm monitored. Convulsions are controlled with intravenous diazepam. Electrocardiogram (ECG) changes include prolongation of the QRS interval and a variety of ventricular dysrhythmias. It can be dangerous to treat the dysrhythmias with drugs, but correction of hypoxia and acidosis are useful.

There are no suitable antidotes to tricyclic overdose. Physostigmine previously was used to reverse the anticholinergic effects, but this has been shown to precipitate convulsions and asystole and is now contraindicated.

SUMMARY

- The main principles associated with the management of clinical drug overdose are:
  - life support;
  - patient assessment;
  - drug decontamination and detoxification;
- drug neutralisation and elimination.
- Life support is concerned with maintaining a clear airway, respiration and circulation. It is also important to treat any seizures, cardiovascular and respiratory disturbances and any significant damage to any other organ system as part of these supportive measures.
- Patient assessment involves a thorough physical examination, taking a good history and performing any appropriate laboratory tests.
- During the detoxification phase, the systemic absorption of the drug is reduced, the agent is neutralised and the elimination of the substance is facilitated. Emetics, adsorbents, cathartics, haemodialysis/haemoperfusion and specific antidotes may be used to achieve detoxification.

1. Briefly describe the four principles underlying the management of clinical drug overdose.
2. Identify the procedures available that form the general approach in drug detoxification. Indicate when each procedure should be used and any problems associated with its use.
3. Name the specific antidote(s) for overdose of the following drugs:
   (a) morphine;
   (b) iron;
   (c) paracetamol;
   (d) atropine.
4. (a) For which examples of overdosage do the antidotes have shorter half-lives than those of the overdosed drug?
   (b) What is the impact of the relative differences in half-lives on the treatment of overdose?
5. Why are the specific antidotes for overdose of heparin and warfarin different, even though both drugs are anticoagulants?
6. Phillip Jones, who sustained a deep vein thrombosis 5 days ago, is on a heparin infusion to prevent the development of further clots. As his nurse, you notice haematuria following a urinalysis test, bleeding gums and a bleeding nose. What would you suspect? How would this condition be treated?
7. Martin Cairns, 27 years old, is receiving treatment for a heart condition. Martin complains of marked dryness of the mouth, a burning sensation and nausea. You note that he has tachycardia, facial flushing, tremor, restlessness and confusion. Is this a case of anticholinesterase or atropine poisoning (you may need to refer to Chapter 27 for help)? What is the antidote for this overdose?
8. Baby Anna Riali is admitted to the emergency department after the ingestion of iron tablets. What antidote will be administered? What information would you provide to Anna's mother about this antidote?
9. Katrina Markowitz, a 22-year-old student, is admitted to the emergency department after an overdose of diazepam and paracetamol. She was lying unconscious in her flat for at least 20 hours before she was found by friends and transferred to hospital. What treatment will be administered? Is it likely that Ms Markowitz will sustain any permanent organ damage from the overdose?
10. John Roberts, an 18-year-old unemployed youth, is brought into the emergency department by a friend after a heroin overdose. A dose of naloxone is administered. He suddenly regains consciousness and begins to tremble and sweat. How would you explain this phenomenon?
11. Jack Daniels is a 50-year-old business manager with a past history of rheumatic fever and a mechanical mitral valve replacement. He takes warfarin to prevent clots forming associated with the valve replacement. While showering one day, he notices extensive bruising on his abdomen and thighs. He visits his general practitioner, who determines that the warfarin dose is too high. What drug could be administered to rectify this problem?

22 DRUG SUMMARY TABLE: CLINICAL OVERDOSE

FAMILY NAME	GENERIC NAME	TRADE NAME(S)
Adsorbent	Activated charcoal	Carbomix Charcodote
Paracetamol overdose antidote	Acetylcysteine Methionine	Parvolex
Anticholinesterase overdose antidote	Atropine Pralidoxime iodide	
Atropine overdose antidote	Physostigmine	
Iron poisoning antidote	Desferrioxamine	Desferal
Narcotic overdose antidote	Naloxone	Narcan
Benzodiazepine overdose antidote	Flumazenil	Anexate
Heparin overdose antidote	Protamine sulphate	
Digoxin overdose antidote	Antidigoxin antibodies Atropine	Digibind
Warfarin overdose antidote	Vitamin K_1	

CONTEMPORARY DRUGS OF ABUSE

23

CHAPTER TWENTY-THREE

OBJECTIVES

After completing this chapter, the reader should be able to:

- **describe the problems associated with alcohol;**
- **describe the drugs used to treat alcoholism;**
- **describe the problems associated with nicotine and smoking tobacco;**
- **describe the drugs used to treat nicotine addiction;**
- **describe the problems associated with caffeine;**
- **describe the problems associated with hallucinogens;**
- **describe the problems associated with marijuana;**
- **describe the problems associated with cocaine;**
- **describe the problems associated with volatile substances.**

KEY TERMS

Drug addiction
Drug abuse

ALCOHOL, NICOTINE AND CAFFEINE ARE THE MOST WIDELY used of all drugs – so much so that most people would not consider them to be drugs at all, as they are used mainly for social rather than therapeutic purposes. Each of these substances has pronounced pharmacological effects on the body, however, and all have been used at some time as therapeutic substances. Today, their pharmacological use is very limited. In the case of nicotine, the pharmacological use is almost non-existent, except as a research substance, occasionally as an insecticide and in some substitute forms to aid smoking cessation. As these

substances are used a great deal in society for their pleasurable effects, a short discussion on them is appropriate. The other drugs addressed in this chapter have no distinct clinical use and are used recreationally rather than therapeutically. With most of these drugs, harmful rather than beneficial effects are the norm. The abuse of drugs related to enhancing performance in sportspeople is dealt with in Chapter 24.

ALCOHOL

When most people talk about alcohol, they are referring to ethanol rather than the numerous other organic compounds classed as alcohols. **Ethanol** has been known since antiquity (~3000 BC) as an ingredient of fermented products of both plant and animal origin. It is best known today as an ingredient of fermented grapes (in wine), fermented barley (in beer) and, in a more concentrated form, in the distilled liquors such as whisky, gin and brandy.

The mechanism of action of alcohol is probably not unlike that of the general anaesthetics (see Chapter 41), in that it disrupts the lipids in nerve-cell membranes, altering their permeability and thus altering the neural transmission. There is also some evidence that alcohol augments the action of gamma-aminobutyric acid (GABA) at its receptor (see Chapter 34), hence the unofficial and inadvisable use of alcohol as an anxiolytic.

Contrary to popular belief, alcohol is a central nervous system (CNS) depressant and not a stimulant. The reason that many people think of it as a stimulant is that, in depressing some of the higher centres of the brain, it suppresses inhibitions and stimulates people to do things that they would not do normally.

Pharmacologically, ethanol is classified as an anaesthetic; small amounts lead to a sense of wellbeing and relaxation; more leads to a loss of inhibition, and even more leads to a complete lack of coordination, which is commonly called drunkenness, until eventually a stage of unconsciousness may be reached. Very large amounts of alcohol can lead to coma and death due to respiratory depression. There have been several cases of people dying after drinking a whole bottle of spirits. Apart from being poisonous in excess, one of the more important aspects of alcohol is its potential to cause addiction.

Alcohol addiction is one of the most common of the serious addictions; it can wreck not only an individual's life but also that of his or her family. This can happen for three main reasons: Alcoholic drinks are expensive and can destroy a large part of a family's budget; the effect on the addict's mind can lead to inadequate job performance; and loss of inhibitions can lead to violent outbursts against family members. These factors have led to some people wanting alcohol banned completely, as it can be classified as a dangerous drug. This happened early in the twentieth century in the USA during the infamous period known as Prohibition. Far from eliminating alcohol completely, however, this drove the sale of alcohol underground and in the process led to an increase in organised crime with its involvement in the illicit sale of alcohol.

Conclusive evidence is mounting that taken in moderation, alcohol can be beneficial. There is evidence that when alcohol is consumed in moderation, it can lengthen the lifespan compared with that of teetotallers. The beneficial effects of alcohol were known to St Paul, who states in one of his letters to Timothy 'No longer drink only water, but use a little wine for your stomach's sake and your frequent infirmities.' It has taken 2000 years for this statement to be medically proven.

Effects of alcohol

The exact mechanism of how alcohol in moderation may be beneficial is still unclear, but it appears to be related to the metabolism of cholesterol and its associated lipoproteins. High-density lipoprotein (HDL) (see Chapter 43) levels are raised in people who drink alcohol, and this reduces their chances of developing atherosclerosis. Atheroma formation is infrequent in these individuals, which tends to confirm this observation. Alcohol may also decrease intravascular clotting, thus helping to prevent thrombotic episodes. This action works synergistically with the decrease in atheroma formation, as atheromatous plaques can increase the formation of thrombi. It must be pointed out, however, that individuals with an alcohol problem have a very high chance of dying from other cardiovascular diseases, such as hypertension and cardiac dysrhythmias. Alcohol increases plasminogen activator activity, which in turn strengthens the body's fibrinolytic system, thus decreasing the likelihood of thrombus formation. Stress may play an important part in the development of cardiovascular diseases; alcohol, due to its relaxing effects, may counteract stress and so aid in prolonging life.

The amount of alcohol that should be taken in order to obtain maximum benefit is unclear, and there is probably not much difference between an ideal amount and a deleterious amount. The current consensus of opinion is that a man should drink no more than four standard drinks per day and a woman no more than two. A standard drink is approximately 400 ml beer, 100 ml wine or 30 ml spirits. There are at least two reasons why women should not drink as much alcohol as men. First, there is a lack of alcohol dehydrogenase (an enzyme that destroys alcohol) in the gastrointestinal tract of women. This is not the case in men, and therefore women absorb more alcohol than men. Second, alcohol is taken up only slowly by adipose tissue; in general, women have more adipose tissue than men

compared with their body weight. Alcohol, being very soluble in water, is distributed well in body water and as, weight for weight, women have proportionally less body water than men, the concentration of alcohol in the body fluids of women is higher. This also makes for higher blood levels in women and consequently a more pronounced effect. This so-called drink-safe limit may be on the high side, as evidence exists that even this amount may lead to higher blood pressure. There seems to be no doubt that moderate consumption of alcoholic drinks is without risk under most circumstances and may have its advantages, but teetotalism is also a healthy lifestyle. There is always the danger that drinkers may start to go over the drink-safe limit, use alcohol as an escape from reality, and finish up as heavy drinkers or with serious alcohol problems.

The dangers of alcohol are numerous. They include alcoholism, which is a true addiction, and the cardiovascular problems mentioned above. Symptoms of having too much to drink may include making a fool of oneself due to the complete discarding of one's usual standards and a hangover the following morning. A hangover results from alcohol's irritant effect on the stomach, leading to acute gastritis, often with nausea and vomiting. There is no reliable cure for a hangover, although many people recommend obscure remedies such as Worcestershire sauce with raw egg. **Domperidone** (see Chapter 55) and H_1-receptor antagonists (see Chapter 29) may help the nausea and gastric problems, respectively. Alcohol inhibits the production of antidiuretic hormone (ADH) from the pituitary gland, leading to excessive urine output and dehydration. Dehydration of the cranial tissues leads to the typical malaise and headache of a hangover.

Alcohol addiction

It is sometimes difficult to determine the point at which a heavy drinker becomes an alcoholic, the usual definitions of alcoholism being based on the following three premises:

- physical dependence on alcohol;
- physical damage caused by excessive drinking;
- social problems attributed to alcohol abuse.

The true alcoholic conforms to all three statements, the heavy drinker only to the second and third. It is probable that most heavy drinkers eventually descend slowly into true addiction. Physical dependence on alcohol results in withdrawal symptoms, which manifest after about 12 hours' abstinence. The symptoms of withdrawal, apart from an overwhelming urge for a drink, are initially 'the shakes'; in a long-term alcoholic, this deteriorates into delirium tremens (DTs). DTs can last for several days and can present with epileptiform seizures accompanied by severe nightmarish hallucinations. Death from respiratory failure can occur. With proper medical care and the willingness of the patient, these symptoms can be avoided using anxiolytic drugs such as **oxazepam** or the hypnotic **chlormethiazole**.

The physical problems associated with heavy drinking and alcoholism are many. The most widespread is liver damage, which can lead to cirrhosis, eventual liver failure and death. Stomach ulcers and gastritis are common. Pancreatitis often occurs, and this can lead to diabetes mellitus. The incidence of cancer of the mouth, oesophagus, breast and colon is higher in alcoholics than in the general population. CNS deterioration occurs, with actual brain shrinkage. In men, the part of the CNS controlling libido may be destroyed permanently. Many individuals with an alcohol problem have a limited food intake and below-average absorption of vitamins, and suffer from a vitamin B group deficiency leading to Wernicke–Korsakoff's syndrome, which results in multiple cerebral haemorrhages, confusion and amnesia.

In pregnancy, heavy drinking can result in congenital damage to the fetus, known as fetal alcohol syndrome. Alcohol is officially recognised as a teratogen. Some authorities suggest that alcohol should be avoided completely in pregnancy, although many people dispute this, with one or two drinks per day being regarded as acceptable. In the USA, there have been cases of obviously pregnant women being refused alcoholic drinks by waiters in restaurants, who considered the consumption of such to be child abuse. There is some evidence that small amounts of alcohol in late pregnancy may help prevent postnatal jaundice, perhaps by stimulating the fetal liver to metabolise bile pigments at a greater rate.

Drug treatment of alcoholism

DISULFIRAM

■ MECHANISM OF ACTION

Disulfiram is an inhibitor of the enzyme aldehyde dehydrogenase, an enzyme involved in the metabolism of ethanol. Normally, ethanol is converted into acetaldehyde (ethanal) by alcohol dehydrogenase, the acetaldehyde in turn being converted to carbon dioxide and water. Disulfiram blocks the degradation of acetaldehyde, causing it to accumulate in the blood and tissues.

◆ ADVERSE EFFECTS

Acetaldehyde is a very noxious substance and causes many adverse symptoms, including a massive vasodilation that results in flushing and, in many cases, severe headache. Respiratory difficulties, vomiting, vertigo, confusion and chest pain are a few of the other symptoms – altogether not a pleasant experience, considering that the symptoms can last for several hours. If a patient taking disulfiram has as little as 7 ml ethanol, these symptoms occur and are intended to discourage alcoholics from drinking. This type of therapy is called avoidance therapy and has been successful in many instances in the treatment of individuals with

alcohol problems. Unfortunately, the 'disulfiram reaction' has led to some fatalities, which limits its use.

ACAMPROSATE

■ MECHANISM OF ACTION

Two neurotransmitters in the brain associated with alcoholism are GABA and glutamate (see Chapter 32). Alcohol causes GABA transmission to be decreased and glutamate activity to be increased. When alcohol is withdrawn, these neurotransmitters remain inhibited and increased, respectively, but without the moderating effect of alcohol, withdrawal symptoms occur. Benzodiazepines are valuable in the treatment of alcoholism because they increase GABA activity (see Chapter 34). **Acamprosate** is thought to decrease glutamate activity by a complex series of modulating steps at the glutamate receptor complex.

◆ ADVERSE EFFECTS

There are no serious or rate-limiting adverse effects associated with acamprosate. Diarrhoea affects about 10 per cent of patients. Rash and fluctuations in libido may also be associated with acamprosate. Other adverse effects are typically mild and transient.

Therapeutic uses of alcohol

The only common medical use for alcohol is as a skin antiseptic (see Chapter 70). As a 70% solution, it is also used to partially disinfect bench tops and implements such as tweezers in cosmetic salons. Alcohol can be used as a rubbing agent on skin to prevent decubitus ulcers. Many lotions and astringent solutions use alcohol as a solute. Some drugs for injection can be dissolved in alcohol, e.g. **diazepam**.

As an internal medication, alcohol has limited use in the clinical situation. Injected directly into the proximity of nerves or ganglia, it destroys the neural tissue and can be used to treat intractable pain, such as that in carcinoma. Pure ethanol has been used with limited success in the palliative treatment of small tumours of the liver. The ethanol is injected directly into the tumour under ultrasound or computed tomography (CT) scan control, causing the tissues to become coagulated immediately.

In cases of methanol (wood alcohol) poisoning, ethanol is an effective antidote (see Chapter 21). Methanol is occasionally produced by home distillation of various fermentation products, in the hope of escaping excise duty. This is common in parts of the world where alcoholic drinks are expensive. For example, home distillation is relatively common in India, and occasionally one reads in Indian newspapers about many wedding guests dying after drinking home-distilled liquor. This type of poisoning has also resulted in hospitalisations following the mistaken addition of methanol instead of ethanol to a party punch. Methanol is much more toxic than ethanol because when methanol is acted on by alcohol dehydrogenase, formaldehyde (methanal) is produced. Formaldehyde in dilute solution is called formalin and is used to permanently fix tissues by denaturing proteins. The optic nerve is particularly sensitive to formaldehyde and even if the patient does not die from methanol poisoning, permanent blindness can result. Ethanol competes with methanol for alcohol dehydrogenase and, if present in excess, allows the methanol to be excreted unchanged, thus preventing toxic results.

An outdated use for alcohol is as a tocolytic (a drug that inhibits labour). Its mechanism of action is in the inhibition of oxytocin release by the posterior pituitary. Today, other drugs such as **terbutaline** have superseded this use of alcohol.

Muscular tremors of unknown aetiology are occasionally amenable to the consumption of various spirits, but long-term treatment is not advised because of the risk of addiction.

Lastly, many people swear that whisky or brandy taken with hot water, sugar or honey, and lemon is just the thing for a head cold. This is known as a 'hot toddy' and may give a good night's sleep due to the hypnotic effect of the alcohol. An old English saying suggests: 'At the first inkling of a cold, hang one's hat from the bedpost, drink from a bottle of good whisky until two hats appear, and then go to bed and stay there.'

NICOTINE

When tobacco is used in any form, from snuff to cigars and cigarettes, the active substance to which a craving develops is probably nicotine. **Nicotine** is a very powerful drug, which, as mentioned in Chapter 27, is a potent agonist at the nicotinic receptors in the nervous system. In the brain it acts mainly as a stimulant, but on other receptors in the nervous system it can act as a depressant. Its central action leads to its addictive properties. The action of nicotine on the adrenal medulla, stimulating the release of catecholamines, is partly responsible for causing a rise in blood pressure in some smokers. This may be one of the factors involved in the higher incidence of cardiovascular disease in smokers.

Nicotine, although a nicotinic agonist, has few therapeutic uses, except as an adjunct in smoking-cessation programmes (see below) and perhaps in the treatment of Tourette's syndrome. Smokers tend to weigh less than non-smokers, and this may be due to the appetite-suppressing properties of nicotine. This fact was used therapeutically in Italy in the 1950s, when cigarettes were prescribed to teenagers with weight problems. Such use of cigarettes today would create an outrage – and rightly so! Despite its dangers, however, the appetite-suppressing properties of

nicotine are one of the reasons why so many young people, especially women, smoke.

Another problem with cigarettes is the several thousand other ingredients of tobacco smoke, known collectively as tar. These ingredients include cyanide and many hydrocarbons, which are proven carcinogens. Carbon monoxide in cigarette smoke can contribute to some of the cardiovascular problems of smoking, the incidence of which is greatly increased in women who both smoke and take the oral contraceptive pill. The evidence today is overwhelming that tobacco smoke is one of the leading causes of cancer and cardiovascular diseases. A person does not have to smoke to be at risk: passive smoking also increases the risk of all smoking-related diseases, including emphysema and chronic bronchitis. Smoking in pregnancy increases the risk of spontaneous abortion, and resulting offspring may be born with a lower birth weight and lower intelligence.

Unlike alcohol, which can have some beneficial effects, smoking has no significant redeeming features, although the incidence of Parkinson's disease, Alzheimer's disease and ulcerative colitis is lower in smokers than in non-smokers. Whether this is due to the smoking habit is unclear, but it should not be considered as a reason to smoke. The rather paradoxical suggestion has been made that a very low intake of tobacco smoke may prevent lung cancer; the evidence for this is based on purely theoretical grounds and is rather tenuous. Small amounts of tobacco smoke can activate lung phagocytic cells. These activated cells are known to be involved in immune surveillance and can destroy incipient cancer cells. This has not been demonstrated in vivo. Too much tobacco smoke inactivates these cells, and it is almost impossible to predict how much tobacco smoke would have to be inhaled for optimum effect, if indeed the effect does exist. This would not, of course, avoid other smoking-related illnesses. Consequently, smoking is a dangerous habit – not only to the smokers themselves but also to the people around them who have to breathe in the noxious fumes. Smokers should be regarded as drug addicts whose habit is sanctioned by society. Pharmacologically speaking, nicotine is more addictive than heroin and vastly more addictive than alcohol.

Drug treatment in the cessation of smoking

Various drugs have been used in an attempt to treat tobacco addiction. These include (with moderate success) the antihypertensive **clonidine** and the tricyclic antidepressants.

The most widely used drug at present is nicotine itself, which is available as an ingredient of a chewing gum. This type of therapy is simple replacement therapy and involves substituting one form of nicotine with another form that is less dangerous, and then slowly weaning the patient off the chewing gum. This gum works occasionally in true addicts, but it is not very successful for people in whom smoking is more of a habit than an addiction. Transdermal delivery systems of nicotine are available, the use of which maintains blood levels of nicotine for long periods and suppresses the desire for a cigarette, sometimes effectively. The dreadful taste of nicotine is avoided with this method of administration. Many smokers abuse these patches and use them on long-haul flights in which smoking is banned to avoid discomfort during the journey. See Chapter 27 for a further discussion of nicotine replacement therapy.

The other drug used to help smokers cease their addiction is **bupropion**, which is used in some countries as an antidepressant and appetite suppressant and in the treatment of attention deficit hyperactivity disorder (ADHD).

BUPROPION

■ MECHANISM OF ACTION

The exact mechanism of action of bupropion in smoking-cessation treatment is unknown but may be related to an increase in dopamine levels in the nucleus accumbens area of the brain, a region associated with reward and addictive behaviours. The effect of this drug is to decrease the desire to smoke. When used together with nicotine replacement therapy, the efficacy is increased.

◆ ADVERSE EFFECTS

The most common adverse effects are dry mouth, insomnia, headache and rash.

Bupropion should not be prescribed to patents with a history of seizures, eating disorders or acute symptoms of alcohol or benzodiazepine withdrawal, as it has been associated with the occurrence of seizures (see also Chapter 11).

CAFFEINE

Caffeine, found in many products, is one of the most widespread drugs used in society. It is present in tea, coffee, cocoa products and cola drinks. Even decaffeinated tea and coffee contain small amounts of caffeine. Weight for weight most teas contain more caffeine than coffee, but when made into drinks most cups of coffee contain more caffeine than similar-sized cups of tea.

Caffeine belongs to the group of biochemicals known as purines and therefore is related closely to such biochemicals as adenine and uric acid. The drugs **theophylline** and **aminophylline** (see Chapter 51) are related closely to caffeine. Theophylline is found in tea, from which its name is derived: it literally means 'tea leaf'. Caffeine is a CNS stimulant and acts on adenosine receptors throughout the body. Its action is antagonistic at these receptors. **Adenosine** generally causes lethargy, lowers the heart rate and blood pressure, and diminishes gastrointestinal functions. Caffeine therefore reverses all of these processes, causing wakefulness, high blood pressure, increased heart rate and an

increase in gastric secretions. Many people are so sensitive to the action of caffeine on the cardiovascular system that they experience palpitations after drinking a cup of coffee. Caffeine and other methylxanthines have another important inhibitory action on the enzyme phosphodiesterase, which is discussed in Chapters 26 and 51.

So are people who consume caffeine-containing products addicted to a potentially harmful drug? The answer is, most likely, yes. This does not imply that the ingestion of such products actually does one harm, but the potential for harm is there, especially if large amounts are taken. Unless adverse effects accompany the taking of caffeine-containing products, moderate consumption for the majority of the population is not harmful. If adverse effects do occur, then the consumption of caffeine-free or decaffeinated products may be advocated if one can accept the change in taste. Some researchers have produced evidence that the incidence of cardiovascular disease is higher in drinkers of decaffeinated coffee than in drinkers of coffee containing caffeine. Tea-drinkers in Scotland have been shown to have a lower incidence of cardiovascular disease than non-tea-drinkers. Until more evidence appears to validate this research, it could, perhaps, be considered spurious.

Even people who consume only moderate amounts of caffeine are very often dependent on it. Withdrawal effects are commonly seen at weekends in such people, apparent as 'weekend headaches'. This is due to excessive coffee-drinking at work during the week but less coffee-drinking at home during the weekend, hence the withdrawal symptoms. In view of the large amounts of caffeine products consumed, this addiction cannot be considered to be of significant importance. The only conclusive evidence that implicates caffeine as contributing to cardiovascular disease is that more than eight cups of coffee per day may lead to abnormalities in cardiac rhythm. Being a secretagogue, caffeine has been termed ulcerogenic in susceptible people. Even if this is not the case, it could lead to deterioration in existing peptic ulcers.

The evidence that caffeine is carcinogenic is scant, and at present no reliance can be placed on it. The consensus at the moment is that caffeine in moderation is harmless to almost all coffee-drinkers.

Being a stimulant, caffeine is often used in tablet form by students and long-distance truck drivers as an aid to staying awake. Used sparingly, this probably does little, if any, harm. The use of caffeine as a stimulant in sportspeople is considered illegal in some competitions, such as the Olympic Games (see Chapter 24), although in other competitions, such as Hawaii's Ironman Triathlon, flat cola is one of the acceptable refreshment drinks, along with water and an electrolyte mix.

Caffeine potentiates the action of analgesics, and it is often included in proprietary analgesic, cold and flu, and antimigraine preparations.

OTHER DRUGS OF ABUSE

The drugs mentioned above are freely and legally available and therefore could be classified as recreational drugs. Here, we discuss some drugs that are used by certain sections of the community for recreational purposes but that are illegal, sometimes even for medicinal use. Some of the drugs discussed here are not always illegal but under certain circumstances can be considered to be drugs of abuse, for example glue and petrol. This section does not include drugs of abuse that are normally classed as legitimate drugs, such as the benzodiazepines and the opiates, which are dealt with in Chapters 34 and 39, respectively. Stimulant amphetamines are discussed in Chapter 38.

Drugs of abuse come under several headings depending on their action on the body. Apart from those dealt with in other chapters, there are two classes of drugs commonly abused – the hallucinogens and the stimulants (**cocaine**) – plus miscellaneous substances, which could include glue, as mentioned above. The substances mentioned in this chapter do not usually produce a physical dependence but rather a psychological dependence. A psychological dependence describes a mental reliance on a specific drug or drugs for the pleasure and/or comfort derived from taking it; such dependence can produce intense craving. Alcohol, the barbiturates and the opiates usually produce a physical dependence. This can be defined as a state of cellular adaptation to a drug, which leads to a withdrawal syndrome if the drug is stopped. Both physical and psychological dependencies can and often do occur together.

Hallucinogens

The hallucinogens, psychomimetics or psychedelics are drugs that distort one's perceptions or produce hallucinations. Hallucinations are not always visual; they can be auditory, olfactory, tactile or gustatory – that is, any or all of the senses can be affected. Occasionally, the senses are mixed up, so that one 'sees sounds'. Aldous Huxley, in *The Doors of Perception*, describes how when he was under the influence of **mescaline**, someone knocked at the door; instead of hearing the knocks, he saw coloured clouds emanating from the door and wafting towards him. This may sound like fun, but it is impossible to predict the form a hallucination will take. One of the authors remembers when, as a teenager working in the laboratory of a pharmaceutical firm, one of the laboratory assistants accidentally sucked some **hyoscine** (see Chapter 27) into her mouth when pipetting. That evening, the assistant was terrified when she saw giant white spiders dangling from the ceiling and then bursting into myriad smaller spiders. Other, more serious hallucinations have been known to occur: people thinking they could fly have jumped out of upper-storey windows, and three students, under the influence of **lysergic acid diethylamide** (LSD), thought

the sun was so beautiful that they stared at it for long enough for permanent blindness to ensue.

The discovery of LSD is well known. A biochemist, Dr Alfred Hoffmann, working for a pharmaceutical firm in Switzerland, was experimenting with compounds derived from the ergot fungus, which is the source of the anti-migraine drug **ergotamine** and several other therapeutic substances. One day, when handling the compound, he experienced a strange sensation of unease and dizziness, which forced him to go home. At home, he lay down and experienced a multitude of visual, kaleidoscopic hallucinations, which were, on the whole, quite pleasant – apart from the fact that he found daylight annoyingly bright. He put this experience down to an accidental ingestion of the LSD (it was probably by transdermal absorption). To confirm this, he ingested about 250 μg of the substance and then experienced a trip away from reality much more pronounced than the first experience. This was not surprising, as this dose is about two and a half times the normal dose needed to produce an effect. LSD is one of the most potent of all drugs and occasionally results in flashbacks: These are recurrent episodes of hallucinatory or delusionary states that can occur weeks or months after the initial trip.

The discovery of hallucinogens did not originate with LSD: Such substances have been known since antiquity by peoples throughout the world. Common examples are mescaline, obtained from the peyote cactus, and **psilocybin**, from 'sacred' mushrooms, the use of which dates back to 1000 BC in Guatemala. These substances were used mainly for religious ceremonies in Central American cultures. Numerous other mind-altering drugs are found in many of the world's cultures, but it was the discovery of LSD that promoted a renewed interest in these drugs to see whether they had any potential therapeutic use.

Initially, psychiatrists were very interested in the drugs and whether they could be used to treat various psychological illnesses. To date, little success has been achieved, although there have been a few reported cases of the hallucinogens helping narcotic addicts to overcome their addiction and sexually maladjusted patients to control their problems. The only other condition that may be helped is the intractable pain of terminal cancer, but these drugs will probably not find their way into any pharmacopoeia in the future. The psychologist Timothy Leary, working at Harvard University, promoted the use of LSD among his students. This created much publicity regarding hallucinogenic substances, and the word spread round the world that here was a new group of drugs that could enable one to escape from the 'real world'. These drugs were soon made illegal, which resulted in a thriving black market in hallucinogens that continues today. Since Hoffmann's discovery, many more synthetic hallucinogens have been produced, some of which have become household names.

Phencyclidine (PCP), sometimes called 'angel dust' when mixed with mint, parsley and **marijuana**, was originally developed as an anaesthetic. It rapidly found its way on to the streets as a hallucinogen. PCP is one of the worst of this group of drugs, as its effects are unpredictable. It may produce feelings of peace and tranquility on one occasion but the next time the user may become so violent as to be a danger to themselves and to others. PCP has been known to cause permanent changes, resulting in a chronic toxic psychosis similar to schizophrenia.

Other common hallucinogens are some amphetamine derivatives, of which **3-methoxy-4,5-methylenedioxy-amphetamine** (MDMA) is one of the most widely used. Of the many others in existence, **dimethyltryptamine** (DMT) is relatively well known. It should be noted that these amphetamine derivatives have little or no stimulant activity, unlike the amphetamine dealt with in Chapter 38. MDMA is commonly called 'ecstasy' and has gained a certain notoriety because of a few deaths associated with its use. Although it does not usually produce intense hallucinogenic experiences, it is taken for its euphoric, calming and confidence-enhancing properties. Many other effects have been attributed to this drug, and most of them, in both the short and long term, are not good news. The drug can lead to hyperthermia; if taken, as it often is, in nightclubs, the combination of hyperthermia and excessive physical activity can lead quickly to dehydration. This has been one of the major causes of death from this drug. Paradoxically, another major cause of death is water intoxication: The drug user, being aware of the problem of dehydration, drinks large amounts of water, diluting the blood so much that the resulting hypotonic blood causes swelling of cells, which can lead to enlargement of the brain, eventually crushed it against the skull. There have been several deaths by both of these mechanisms, which have resulted in the drug's notoriety. It must be remembered that tobacco also kills: In the UK, according to Department of Health figures, approximately 106 000 deaths annually are caused by tobacco. This appears to be accepted, probably due to the fact that the development of morbidity and the often resulting mortality related to nicotine take many years to become apparent. Ecstasy is almost certainly habit-forming and may lead to addiction. Long-term use almost certainly leads to hypertension, liver failure and perhaps (although not yet proven in humans, as it has been in rats) brain damage.

Nutmeg, a common household spice, contains hallucinogenic substances. Abuse of nutmeg is not common, as one has to ingest several grams of the powder. This may or may not cause one to hallucinate, but it will definitely produce severe headaches, abdominal cramps and nausea. Interestingly, nutmeg is banned from prison kitchens in the USA. The number of plants containing hallucinogenic substances is large, and reference to the further reading lists in this book will give many more examples.

The mechanism of action of the hallucinogens is not properly understood. LSD is antiserotoninergic as well as being agonistic at other specialised receptors within the CNS.

Marijuana

Marijuana is considered in most countries to be a substance of abuse, as its effects are not considered to be of clinical significance. This drug comes from the plant *Cannabis sativa* and has been used since about 2700 BC as a sedative and analgesic. After the Second World War, marijuana became a common recreational drug and was outlawed as a drug of abuse with no therapeutic use by the World Health Organization. This view now seems to be incorrect, as recent research has shown that the main active substance of marijuana, δ-9-tetrahydrocannabinol (THC), appears to have more potent antiemetic applications than most other antiemetics. A related compound, **nabilone**, is used in some countries, including the UK, as an antiemetic for treating the nausea and vomiting that occurs during chemotherapy and in narcotic-induced emesis in the care of terminal patients.

In its resinous form, marijuana is called hashish, which contains more THC and is thus more active. Marijuana is one of the most used (or abused) of the illicit drugs. It has been estimated that just under 40 per cent of people between 16 and 24 years of age in the UK have tried the drug. Marijuana is unusual in that it can be taken by mouth or smoked. Biscuits and cakes spiked with marijuana are not uncommon at teenagers' parties. Marijuana in the form of a cigarette is commonly called a joint or a reefer. The effect of THC is to produce a dream-like state approaching euphoria. In this state, audio stimuli, such as music, are enhanced. This effect is not unlike that of the hallucinogens, and in high doses THC could be classed as a hallucinogen. In some people, the opposite effect may occur, resulting in paranoia and/or depression. Amnesia is common after THC ingestion. Many people argue that marijuana is less harmful than tobacco. This is a moot point, as THC is a potent vasodilator, which induces a reflex tachycardia; the long-term cardiovascular effects are unknown, but caution is needed. Smoked marijuana almost certainly will produce carcinogenic tars, with their resultant effects. It is argued that people who smoke marijuana do not become physically addicted and tend to smoke the joints only spasmodically; therefore, the incidence of adverse effects would be much lower than that of smoking tobacco. Marijuana is not completely safe, however, and chronic use causes subtle changes in personality that tend to lead to a decrease in motivation in all aspects of the user's life. This is termed amotivational syndrome. There has been noted a significant correlation between marijuana use and the development of both schizophrenia and clinical depression. Like alcohol, marijuana can impair driving performance. THC has been reported to be teratogenic and may result in changes in the morphology of sperm and cause abnormal ova to be produced. Testosterone levels are decreased in men, which may have deleterious effects on male secondary sexual characteristics, especially if marijuana is used during puberty. THC is very lipophilic and is taken up readily by adipose tissue, from where it diffuses slowly back into the bloodstream; its metabolites can be detected in body fluids months after ingestion.

Although legislation of marijuana seems unlikely due to these and many other adverse effects, in the UK cannabis was reclassified from class B to class C in 2004 (see also Chapter 3), which lessened the penalties for its possession but has caused much heated debate.

Cocaine

Britain is now top of the European 'league table' for cocaine abuse, and levels are approaching those seen in the USA. Nearly 12 per cent of adults under the age of 35 years have tried cocaine at least once, and the use of cocaine is spreading from the middle classes to the back streets of inner-city estates. Drug deaths from cocaine have risen from 85 in 2000 to 171 in 2003. These figures are probably an underestimate, as there is underreporting of cocaine-related deaths. Mixing cocaine with alcohol leads to a sharp increase in toxicity.

Cocaine is an alkaloid derived from the coca plant *Erythroxylum coca*, which grows in several South American countries. The leaves of this plant are chewed and are used by natives of the Andes to combat altitude sickness by relieving fatigue and enhancing wellbeing. These native South Americans do not appear to become addicted to the cocaine in the leaves as, when they descend to lower altitudes, their need for the drug wanes. In Western societies, cocaine extracted from the coca leaves has become a favoured but dangerously addictive drug of abuse. Pure cocaine is a very powerful CNS stimulant, creating intense feelings of wellbeing, excitement and alertness. Two types of cocaine are used by drug experimenters: crack and free base. Crack is now the most widely used form of cocaine and is so named because of the crackling sound made when it is burnt. Whichever way it is used, cocaine is highly addictive, perhaps not as a physical but as a strongly psychological addiction.

Cocaine blocks the transporter protein responsible for the reuptake of monoamines such as noradrenaline, serotonin and dopamine. This leads to an increased concentration of these neurotransmitters in the synaptic space, potentiating their effects.

The danger of snorting cocaine is nasal congestion, which can lead to necrosis of the nasal mucosa and septum. Systemic effects are many, with insomnia, impotence, chest pains and headaches being common. In high doses, cocaine can cause tremors and convulsions. Overdose can lead to

cardiac dysrhythmias and death; myocardial infarction, stroke and respiratory arrest can all occur. The action of cocaine in the peripheries is due to increased noradrenaline action, and there is a typical flight-or-fight sympathetic response, with tachycardia, hypertension, dilation of the pupils and peripheral vasoconstriction.

Volatile substances

The volatile substances usually inhaled for recreational purposes are hydrocarbons and halogenated hydrocarbons. Many of these substances are readily available from legitimate sources; because of the widespread uses of many of them, control is impossible. The action of these substances is two-fold: many have anaesthetic properties (see Chapter 41), and they also induce anoxia by displacing oxygen from the inhaled air. This combined effect produces a sense of detachment, leading to a delirious, semiconscious state of altered awareness. The inhalation of only slightly above the dose required to produce a high can cause disorientation, severe confusion and coma; death may result from asphyxiation and/or cardiac dysrhythmias. Prolonged use usually leads to both renal and hepatic damage. These drugs are mainly used by children and adolescents, adults only rarely resorting to their dubious attractions. The popular substances abused are model glue, paint thinners and lacquers, liquid paper, petrol and lighter fluid. Adequate education in susceptible populations may help prevent the many tragedies resulting from this behaviour. Anaesthetists and others in the medical profession have been guilty of abusing inhalant anaesthetics such as **halothane** and **diethyl ether**.

Another category of substances inhaled for pleasure comprises the volatile nitrites, principally **amyl nitrite**. Amyl nitrite is a potent vasodilator and has been used in the past to treat angina pectoris. Being a smooth-muscle relaxant, it has also been used in midwifery to slow down uterine contractions. This action on smooth muscle relaxes the internal anal sphincter, which makes it a favourite drug of abuse by male homosexuals. When acquired immunodeficiency syndrome (AIDS) first appeared, amyl nitrite was suggested as a possible cause. Inhaled during sexual climaxes, amyl nitrite reputedly increases the intensity of an orgasm. Amyl nitrite also causes a sudden drop in blood pressure, with the potential to cause fainting; a throbbing headache may also result.

The abuse of narcotic analgesics is covered in Chapter 39.

SUMMARY

- Recreational use of drugs is considered as drug abuse.
- Some recreational drugs, notably alcohol, can be beneficial when consumed moderately; however, alcohol, if consumed even slightly more than moderately, can be devastating in its direct effect on the user and indirectly on the user's family and associates.
- Alcohol has a very limited use in therapeutics.
- Tobacco, with the constituent nicotine and the thousands of compounds found in cigarette smoke, kills more people than all the other drugs of abuse put together.
- Caffeine found in coffee and tea can, if taken to excess, cause harm to its user.
- Hallucinogens and marijuana can lead to serious mental disorders.
- Volatile substances, such as modellers' glue, have serious toxic effects on the central nervous system.

1. What is the difference between a habit and a dependence?
2. What is meant by the term 'avoidance therapy'?
3. Would one consider nicotine chewing gum as an alternative to smoking for patients with severe cardiovascular disease? Give reasons for your answer.
4. Certain levels of caffeine in the urine of athletes would cause disqualification from the Olympic Games. Why?
5. Referring again to question 4, why would small amounts of caffeine in the urine be ignored?

DRUG ABUSE IN SPORT

24

CHAPTER TWENTY-FOUR

OBJECTIVES

After completing this chapter, the reader should be able to:

- **list the reasons why sportspeople use drugs to enhance performance;**
- **identify major drug groups banned from sporting competitions;**
- **outline the physiological effects and major adverse reactions associated with the abuse of anabolic agents, stimulants, peptide hormones and diuretics.**

KEY TERMS

Drug doping
Drug testing
Ethical behaviour

WE COULD BE EXCUSED FOR THINKING THAT THE USE OF drugs by professional sportspeople for the purpose of enhancing performance is rife. When asked for examples of abuse, most of us can recall at least one notorious incident involving a high-profile sportsperson. These incidents result in rescinded awards, suspensions, ruined careers and, sometimes, death. Indeed, such episodes cast a pall over the integrity of elite sporting contests generally. Official statistics from the UK, however, show that 6500 tests were conducted in the year ending March 2005 but only 1.5 per cent of all tests were positive – well below the worldwide average figure.

Despite these figures, doping in sport is a problem. The reasons often cited as to why sportspeople abuse drugs include gaining competitive edge, dissatisfaction with current performance, developing the ideal body form for a particular sport (e.g. losing or gaining weight in order to qualify for a contest), coping with stress and the intense pressures to win, attempting to acquire the fame and fortune that success brings, and believing that sporting peers have an advantage because they are already using drugs.

Drug use in sport is not a new phenomenon. For reasons similar to those above, substance abuse occurred in ancient Greece during the original Olympic Games. This was anathema to the Olympic ideals, which embraced the purity of the athletic endeavour, sportspersonship and fair play. Cheating was offensive, and wrongdoers suffered public shame and disgrace. The revival of the modern Olympic Games has brought with it the taint of drug abuse for the purpose of enhancing performance. This is still seen to be in opposition to the spirit of the Olympics. Evidence of the use of performance-altering substances, such as mixtures of **alcohol** and strychnine, **heroin**, **caffeine**, **cocaine**, amphetamines and hormones, has been documented. Elite athletes have fallen ill or died under mysterious circumstances, and sportspeople have spoken out about the harm being done to individuals and to sport in general. In 1968, the International Olympic Committee (IOC) developed a list of banned substances and began drug-testing athletes at the Olympics in Mexico that year.

The list of banned substances covers agents that might enhance sporting performance directly, alter body form, or mask the presence of other banned substances in the body. This list is reviewed regularly as novel substances become available. Major drug groups that are banned and their proposed actions are summarised in Table 24.1. Professional sportspeople may be tested in and out of competitions, and individuals contracted to a team can be tested at any time, even during the off-season, for the duration of their contracts.

Detection of some administered substances, such as hormones, can be problematic because they are naturally present in the body. In this case, levels in urine samples that reflect normal physiological conditions are accepted. Some substances are banned in male athletes because they stimulate androgen production but are permitted in female athletes. Another set of substances – those found in recreational beverages and where certain levels are justifiable on medical grounds – are permitted in certain sporting competitions because they are not tested for. These substances and the acceptable levels in urine are listed in Table 24.2.

TABLE 24.1 INTERNATIONAL OLYMPIC COMMITTEE'S LIST OF BANNED SUBSTANCES

Substance grouping	Desired effects	Chapter
Anabolic agents		
Anabolic steroids	Increase muscle strength Promote aggression	
β_2 agonist salbutamol	Increase lean muscle Reduce body fat	26
Diuretics	Dilute drug concentration in urine Reduce weight	47
Narcotics	Raise pain threshold Induce euphoria	39
Peptides		
Gonadotrophins	Induce androgen production in males	56
Corticotrophins (e.g. ACTH)	Induce euphoria	56
Growth hormone, IGF-1, insulin	Promote lean muscle growth and reduce body fat	56, 57
Anti-oestrogens	Reduce anabolic-steroid-induced feminisation	58
Erythropoietin and its derivatives	Increase blood oxygen-carrying capacity	50
Stimulants	Increase concentration Increase competitiveness Reduce fatigue	23, 26

ACTH, adrenocorticotrophic hormone; IGF-1, insulin-like growth factor 1.

TABLE 24.2 INTERNATIONAL OLYMPIC COMMITTEE'S LIST OF RESTRICTED SUBSTANCES

Substance	Permissible effects	Maximum levels permissible in urine	Chapter
Alcohol (ethanol)	Stress relief, relaxation		23
β-Blockers	Treatment of medical conditions		26
Caffeine	Stress relief, relaxation	12 μg/ml	23
Cannabinoids	Stress relief, relaxation	15 ng/ml (carboxy-THC)	23
Ephedrines	Treatment of medical conditions	10 μg/ml 25 μg/ml (pseudoephedrine)	26
Epitestosterone	Physiological androgenic effects	200 ng/ml	
Glucocorticoids (local/topical)	Treatment of medical conditions		58
Local anaesthetics (local/topical)	Treatment of medical conditions		42
Morphine	Treatment of medical conditions		39
19-Norandrosterone	Sex hormone metabolite	2 ng/ml (men), 5 ng/ml (women)	
Salbutamol	Treatment of medical conditions	100 ng/ml (as stimulant)	26
Testosterone : epitestosterone ratio	Physiological androgenic effects	6	

Although the official statistics on drug doping are low, it would be naive to think that no clandestine drug use takes place in sport. Drug cheats can use sophisticated dosing regimens rather than masking agents to avoid or limit the possibility of detection. Strategies such as cyclical dosing rather than continuous doping can be used. This involves taking a drug for a set time interval and then stopping for a period in order to allow its elimination before starting the cycle again. In this way, a sportsperson can reap the benefits of doping but decrease the chances of getting caught.

As you can see from Tables 24.1 and 24.2, a number of drugs can be used to enhance sporting performance. We now examine the effects and health risks associated with some selected doping agents. This discussion focuses on anabolic agents, peptide hormones, beta-blockers, stimulants and diuretics.

ANABOLIC AGENTS

There are two categories of anabolic agent, and these are based on chemistry: steroids (specifically anabolic steroids) and the non-steroidal agent **salbutamol**. Anabolic steroids are synthetic derivatives of androgens, but usually with fewer masculinising effects. As both anabolic steroids and androgens can be used to promote anabolic effects, they are grouped together as anabolic-androgenic steroids (AASs). Sportspeople drawn towards the use of AASs include weightlifters, track and field athletes, footballers and bodybuilders.

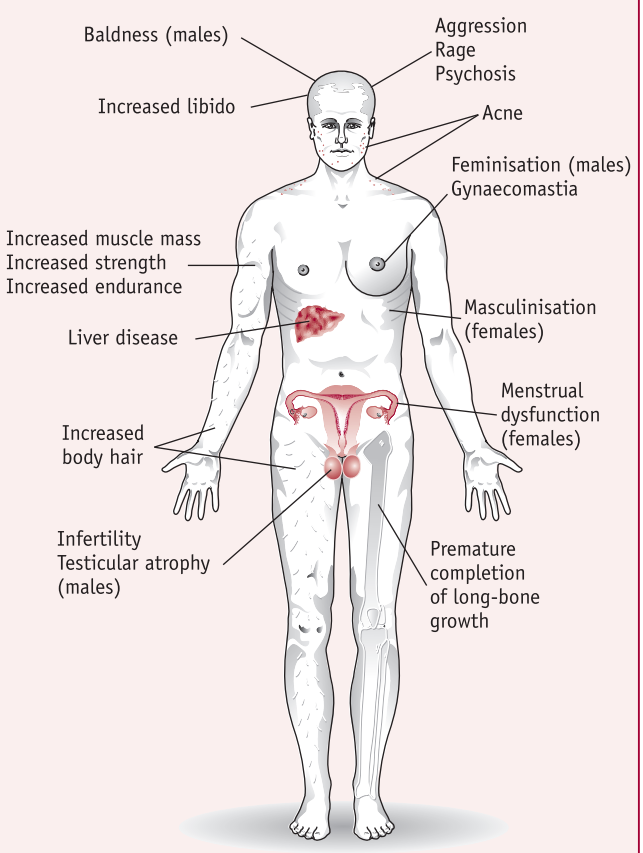
AASs are available in oral, nasal and injectable forms. Examples include **stanozolol** (banned in the UK from 2002), **oxymetholone** and **nandrolone**; the AAS precursors **androstenedione** (illegal in the UK) and **dehydroepiandrosterone** (DHEA) are also available. The latter two substances can be converted into androgens in the body. In many countries, including the UK, the availability of the human clinical AASs is highly restricted, and some people use the more readily accessible veterinary formulations. DHEA is available in some nutritional supplements, and some sportspeople have unknowingly tested positive to an AAS after using these supplements as a part of their training. An important aspect of drug testing is to determine the use of AASs by detecting the ratio of testosterone to one of its major metabolites, epitestosterone. A ratio of less than 6 in a urine sample is considered acceptable; any higher level reflects drug-taking.

The perceived benefits of AASs in a sporting context are to promote increased skeletal muscle mass (producing greater strength or power), to shorten injury recovery time and to increase endurance. In order to produce these effects, sportspeople tend to use significantly higher doses of AASs than would be used for clinically therapeutic purposes. The behavioural effects of the AASs include increased

self-confidence, mood swings, euphoria, depression, paranoia and aggression. High doses of AASs puts users at increased risk regarding the onset of serious adverse drug reactions, which can include liver disease, male infertility, acne, male baldness, testicular atrophy (shrunken testicles), masculinisation of women, altered menstruation, induction of an unhealthy blood lipid profile, stunted long-bone growth, tumour development and feminisation of men. The latter effect arises from conversion of the excess androgen to oestrogens, which can induce gynaecomastia (female breast development). In order to avoid adverse effects such as liver disease, users alter the route of administration (from oral to injectable) or ingest 'protective' herbal preparations. They may also take anti-oestrogens (see Chapter 58), such as **tamoxifen** and the aromatase inhibitors, to curtail the feminising effects. Furthermore, infectious disease is a health risk associated with the injection of these agents when technique, purity and storage are questionable. The effects of AASs are summarised in Figure 24.1.

There is a worrying trend towards the use of AASs by young males – not for gaining a sporting edge, but more for the purpose of altering body image and improving self-esteem. A 1999 US National Institute on Drug Abuse (NIDA) study indicated that 2.7 per cent of 8th to 10th graders (representing more than half a million American children at early secondary-school level) had used an AAS at least once, a significant increase in use compared with that age group in 1991. The use of AASs in young women is also rising. In response, NIDA has co-developed an initiative to alert the community to the health risks associated with these agents.

FIGURE 24.1 PHARMACOLOGICAL EFFECTS OF ANABOLIC STEROIDS



Systemic administration of the β_2 agonist **salbutamol** (see Chapter 26) can also be used as an anabolic agent. It can promote lean muscle growth and reduce body fat levels. Unfortunately, it induces palpitations, tremor, tachycardia, muscle cramps and nausea. Inhaled salbutamol and other β_2 agonists is permitted in competitive sport when it is medically appropriate.

PEPTIDE HORMONES

A number of peptide hormones have been used by sportspeople in order to enhance their performance. These include **growth hormone** (see Chapter 56), **insulin** (see Chapter 57), insulin-like growth factor 1 (IGF-1), **erythropoietin** and its derivatives (see Chapter 50) and the gonadotrophins (see Chapter 56). The detection of such substances poses a real challenge for sporting organisations and scientists alike because these substances are regulatory messengers normally found in the human body. Research into the detection of these peptides is focusing on identifying subtle structural variations to differentiate between the endogenous hormones and the formulations abused by sportspeople.

Growth hormone, insulin and IGF-1 promote anabolic processes that lead to increased lean muscle and reduced body fat. In younger sportspeople, growth hormone and IGF-1 can induce disproportional body growth (leading to distorted features such as enlarged hands and feet and a prominent forehead and jaw), heart disease and diabetes mellitus. The abuse of insulin is worrying, as an inappropriate dose could lead to hypoglycaemic coma and death.

Erythropoietin and its derivatives induce increased erythrocyte production, which in this context increases the oxygen-carrying capacity of the blood. Increased red blood cell levels can lead to a thickening of the blood and clot formation. Gonadotrophin use in men stimulates androgen production, the effects of which are described above.

BETA-BLOCKERS

Beta-adrenergic receptor antagonists (beta-blockers) are subject to restrictions in certain sporting competitions such as the precision sports (e.g. archery, shooting), yachting, soccer and modern pentathlon. The effects of beta-blockers are covered in detail in Chapter 26. As doping agents, beta-blockers act to counteract excessive sympathetic nervous

system activation, which may manifest as anxiety, tremor and tachycardia. This can affect performance, particularly the ability to aim and shoot accurately. The side effects of these drugs include hypotension, bradycardia, headache and gastrointestinal disturbances.

STIMULANTS

Nervous system stimulants such as **cocaine**, amphetamines, **caffeine** (see Chapter 23) and the sympathomimetics (see Chapter 26) are used to gain a competitive advantage. They prolong endurance, delay fatigue, enhance competitiveness and increase self-confidence. The dangers of using stimulants arise from the potential for overstimulation of the nervous system. They can induce cardiovascular problems such as cardiac dysrhythmias, alterations in blood pressure, agitation, aggression, rage and drug-induced psychotic states. They can also lead to drug dependence.

Caffeine is not banned in sport, but its use is somewhat regulated. Permissible levels in the urine are below 12 μg/ml. Drug metabolism and excretion vary greatly between individuals; factors such as genetic makeup, pregnancy, cigarette smoking or other drug use can influence these processes. For some individuals, as little as three cups of brewed coffee over a relatively short period could result in this level in the urine; for others, it may take eight cups.

DIURETIC AGENTS AND URINE TESTING

Some sportspeople, such as wrestlers, boxers and jockeys, use diuretic drugs to accelerate weight loss before contests involving strict weight categories. Diuretics can also be used to mask or decrease the presence of other abused substances, such as AASs, by diluting their concentrations in urine. Adverse effects associated with injudicious use of diuretics include dehydration and imbalances in electrolyte levels.

Drug treatments to manipulate urine samples have also been outlawed. The uricosuric agent **probenecid** (see Chapter 59) has been used to inhibit tubular secretion of some doping agents into the forming urine, thus keeping the urine level of certain listed substances low. The testosterone to epitestosterone ratio may be adjusted by the administration of epitestosterone in order to keep the ratio under a value of 6. This strategy, however, can lead to elevated epitestosterone levels in the urine, which are set to a maximum permissible level of 200 ng/ml (see Table 24.2).

IMPLICATIONS OF DRUG USE AND ABUSE IN SPORT

Drug use in sport is a controversial issue. Frequently, sportspeople returning positive drug tests claim that they are unaware that the dietary supplement, over-the-counter preparation or medicine prescribed by their doctor contains a listed substance. Each case must be dealt with fairly, considering the individual's circumstances. It is becoming harder, however, to plead ignorance as a defence, especially for health professionals involved with sporting clubs and federations.

There is a fine line between drug use and abuse in sport. When does taking drugs to allow an ill or slightly injured sportsperson to demonstrate their natural abilities become an attempt to give that person the competitive edge? As a student of pharmacology, it should be apparent to you that sometimes this line can be crossed by simply choosing a higher dose, a different route of administration or another drug with similar effects.

SUMMARY

- Drugs can be abused by sportspeople to gain an unfair competitive advantage over their opponents.
- Lists of banned and restricted substances have been formulated by the International Olympic Committee and are backed up by a strict regimen of drug testing.
- Anabolic agents are used to increase muscle mass, strength, endurance and competitiveness. Anabolic androgenic steroids, used at high doses, can induce masculinising effects in women and feminising effects in men. They can also cause reproductive dysfunction and liver disease.
- A number of peptide hormones, such as the gonadotrophins, insulin and growth hormone, promote anabolic effects. Erythropoietin derivatives increase the oxygen-carrying capacity of the blood. This group of doping agents poses detection problems because they are found naturally in the body.
- Beta-blockers are prohibited in certain sports. They antagonise the effects of sympathetic activation and reduce anxiety, tremor and tachycardia.
- Stimulants are used to prolong endurance, delay fatigue, enhance competitiveness and increase self-confidence. They can overstimulate the nervous system, leading to cardiovascular problems and aggressive or psychotic states.
- Diuretics are used to lose weight quickly or mask the presence of other doping agents. Adverse effects include dehydration and electrolyte imbalances.

1. State four examples of substances banned from sporting competitions, and indicate the reasons why each is prohibited.
2. State four examples of substances that are permitted in some sporting competitions, and outline the physiological effects of each that may enhance performance.
3. Outline the problems associated with the detection of some banned substances through urine testing of sportspeople.
4. For each of the following substances, indicate whether administration would result in increased androgen production in a male athlete:
   (a) corticotrophin;
   (b) dehydroepiandrosterone;
   (c) growth hormone;
   (d) luteinising hormone;
   (e) salbutamol.
5. At 17 years of age, Marie Duphastin shows promise as a sprinter. She tells you that she has been offered anabolic-androgenic steroids by her coach to increase her strength. Her coach has told her that there are no health risks associated with their use. She asks you whether this is true. What advice can you offer her about the health risks of these agents?
6. Terry Sterculia, 28 years old, is a keen amateur boxer. He broke his leg recently in a work-related accident and has not been able to train during this period. A fight is coming up for which he wants to qualify, but he is a few kilograms overweight. In order to lose weight quickly, he is taking his father's furosemide tablets, diuretics prescribed for his father's heart condition. What kinds of fluid and electrolyte imbalance may result from this drug abuse? State the clinical manifestations of each of these imbalances.

CASE STUDY V.1 A neighbour knocks on your door at home one evening. She is holding her 2-year-old child in her arms and is extremely distressed. She manages to tell you that while she was preparing dinner, the child opened a cupboard and ate a number of paracetamol tablets. She isn't too sure how many tablets the child has ingested, but she estimates that it would be at least two.

The child is conscious, pale and sweating. You invite them into your home and call an ambulance. While you are on the telephone, the child vomits. As you wait for the ambulance, you comfort both mother and child and take some observations of the child's condition.

QUESTIONS

1 *Is this dose of paracetamol harmful to the child? If so, why?*

2 *Name the resources on which you could draw to check whether the amount of paracetamol taken was toxic to this child.*

3 *Would you try to induce emesis before the ambulance arrives? Give your rationale for this decision.*

4 *(a) Outline the treatment that will be followed when the child arrives at the hospital.*
(b) Outline the purpose of each part of the treatment used.

CASE STUDY V.2 HR is 18 years old and is heading to her first rave party in the city. The party is in full swing by the time she and her friends arrive. About 200 people have crowded into a warehouse on the city's edge. It is hot and a little stuffy in the warehouse, but the atmosphere is lively. HR has a couple of vodkas, smokes three cigarettes and takes in the scene before enjoying a number of dances with her friends. As the night progresses, while sitting with her friends she watches them take some white pills out of their bags and swallow them. They tell her it is ecstasy and offer her two tablets. HR takes them and joins her friends on the dance floor.

Within a short period, she is aware of a sense of well-being and calm. Her sense of the music and movement is heightened. She feels less self-conscious about her dancing and dances feverishly. A guy she is dancing with buys her another vodka.

About an hour later, she collapses on the dance floor, unconscious. She is transferred to hospital by ambulance and treated for severe dehydration.

QUESTIONS

1 *What factors have combined to induce severe dehydration in HR?*

2 *Briefly outline the treatment for this condition.*

3 *What is the chemical name for ecstasy? To which class of drugs is it closely related?*

4 *Outline the effects of ecstasy.*

5 *Compare and contrast the effects of ecstasy with those of amphetamines.*

6 *There have been a number of deaths associated with ecstasy administration. In what ways would ecstasy contribute to death?*

7 *One of the men dancing with HR was of similar age and bodyweight. They had both had the same number of vodkas over the same time interval. She claimed that he was more affected by the alcohol. From a physiological perspective, is she likely to be correct? Give your reasons.*

8 *What are the effects of the nicotine absorbed during cigarette smoking?*

9 *What are some of the other known ingredients in cigarettes besides nicotine that are absorbed into our bodies while smoking?*

CASE STUDY V.3 A man in his twenties is found unconscious in a back lane of the centre of the capital city. He is pale and breathing very shallowly. There is a smell of alcohol on his breath. A syringe and empty vial are found nearby. An ambulance is called and arrives within 10 minutes. After completing an assessment, the paramedic administers an intravenous injection of naloxone. There is a rapid improvement in the man's condition; his breathing rate and depth improve, but he remains in a stuporous state. The paramedics take him to the nearest hospital for further treatment.

At the hospital, he is provided with supportive therapy and receives infusions of naloxone over the next 4 hours. Later in the day, he has recovered sufficiently to discharge himself.

QUESTIONS

1 *What situation do you think is represented in this case study?*

2 *Describe the mechanism of action of naloxone.*

3 *Why does this patient require repeat infusions of naloxone in hospital?*

4 *Describe the mechanism of action of alcohol. Is alcohol a central nervous system stimulant or depressant?*

5 *Will alcohol potentiate or diminish the effects of the illicit drug that the patient injected? Why?*

6 *Outline the nature of the supportive therapy that was provided to the man in hospital.*

CASE STUDY V.4 ME is a 22-year-old woman enjoying a summer holiday at a resort in the UK. While paddling in shallow water, she feels a stinging sensation in her foot. Suddenly she experiences

severe and excruciating pain. On returning to her family sitting on the sand, she is screaming with pain. Her family decide to take her to the local accident and emergency department, where they are told this is likely to be the sting of a weever fish.

QUESTIONS

1 *Define the term 'envenomation'.*

2 *What is the appropriate first-aid treatment for this form of envenomation? What is the rationale for this treatment?*

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WEB RESOURCES

Addiction Links www.drugnet.net/metaview.htm

Case Studies in Environmental Medicine www.atsdr.cdc.gov/HEC/CSEM/csem.html

Department of Health www.dh.gov.uk/PolicyAndGuidance

National Poisons Information Service (NPIS) www.toxbase.org

Poisonous plants www.realgardeners.co.uk/goodbadpois/poisonous_plants.htm

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AUTONOMIC PHARMACOLOGY

Men ought to know that from nothing else but the brain come joys, delights, laughter and sports, and sorrows, griefs, despondency and lamentations. And by this, in an especial manner, we acquire wisdom and knowledge, and see and hear, and know what are foul and what are fair, what are bad and what are good, what are sweet and what are unsavoury . . . and by the same organ we become mad and delirious, and fears and terrors assail us . . .

HIPPOCRATES

The autonomic nervous system is involved with the control centre of the function of involuntary body tissues. It also has significant influence over our state of mind – our mood, feelings, and how we respond when frightened or stressed.

It makes sense, then, that a thorough examination of the way in which the autonomic nervous system is organised and operates (see Chapter 25) will facilitate your understanding of the mechanism of action and adverse effects of many clinical agents you work with in practice. Several important drugs used during surgery and in cardiovascular, pulmonary and ophthalmic medicine act by altering autonomic nervous system function (see Chapters 26 and 27).

VI

SECTION VI

GENERAL ASPECTS OF AUTONOMIC PHARMACOLOGY

25

CHAPTER TWENTY-FIVE

KEY TERMS

Autonomic nervous system
Parasympathetic nervous system
Sympathetic nervous system
Acetylcholine
Noradrenaline
Cholinergic nerves/receptors
Adrenergic nerves/receptors
Neuromodulation

OBJECTIVES

After completing this chapter, the reader should be able to:

- **briefly outline the major divisions of the human nervous system and their respective functions;**
- **identify the chemical transmitters involved in autonomic nervous system function;**
- **compare and contrast the anatomical and physiological characteristics of the sympathetic and parasympathetic divisions.**

FOR THE PURPOSES OF CLASSIFICATION, THE HUMAN NERVOUS system is partitioned into central and peripheral divisions. The brain and spinal cord constitute the central nervous system (CNS), while the nerves connecting peripheral tissues with the CNS form the peripheral nervous system (PNS). Functionally, the nervous system can be divided into the afferent division, bringing sensory information back to the CNS for interpretation, and the efferent division, which directs the motor responses of peripheral tissues and organs (otherwise known as effectors). The PNS can be subdivided further into that portion under voluntary or conscious control – the somatic nervous system (SNS) – and that portion serving involuntary effectors – the autonomic nervous system (ANS).

All nervous-system communication to connecting nerves and tissues is achieved via the release of chemical transmitters across a small junction called a synapse rather than by direct contact. These chemical messengers interact with specific surface receptors on either the receiving nerve or the tissue. Activation of these tissue receptors is what underlies the observed effects, such as muscle contraction and glandular secretion.

ORGANISATION OF THE AUTONOMIC NERVOUS SYSTEM

The ANS is the efferent pathway controlling the action of involuntary organs and tissues. Secretion of products from glands, the rate and force of contraction of heart muscle, and the contraction and relaxation of the smooth muscle of the bronchioles, blood vessels and gastrointestinal tract are all controlled by this division of the nervous system. Sensory information concerning the activity of these involuntary structures is relayed back to the control centres of the brain via afferent pathways in order to determine the appropriate response.

Chemical transmitters

The two major chemical transmitters involved in ANS function are acetylcholine (ACh) and noradrenaline. A nerve that releases acetylcholine as its chemical transmitter is said to be cholinergic, while a nerve that releases noradrenaline as its transmitter is adrenergic. In many instances, autonomic tissues bear surface receptors for both transmitters, and the response of that tissue to each chemical is completely different. This is the means by which the tissue carries out the correct intention of the brain to either raise or lower the level of activity.

Other classic chemical messengers involved in ANS function include dopamine and the blood-borne hormone adrenaline. Both of these chemicals stimulate peripheral adrenergic receptors. Some nerves release dopamine (they are dopaminergic) on to specific dopamine receptors located within the brain and peripheral vasculature. Noradrenaline and adrenaline are manufactured from dopamine, which is formed from the amino acid tyrosine. Collectively, the three chemicals are called catecholamines.

Subdivisions of the autonomic nervous system

There are two subdivisions of the ANS: the sympathetic and parasympathetic nervous systems. The physiological effects induced by each division are, for the most part, antagonistic. Broadly speaking, the sympathetic nervous system is activated in an emergency or stressful situation, when the effects are classified as flight-or-fight responses. The parasympathetic division has a restorative function, and the effects are classified as rest-and-repose responses. The processes of digestion and elimination are activated by this division. Table 25.1 shows the effects of sympathetic and parasympathetic stimulation on a variety of effectors.

SYMPATHETIC AND PARASYMPATHETIC DIVISIONS

Similarities

Anatomical studies of ANS pathways have revealed some similarities between the sympathetic and parasympathetic divisions. The pathways consist of two neurons. The first has its cell body located within the CNS and its axon is myelinated. The second has its cell body located in the periphery and its axon is unmyelinated. Between the terminal end of the first neuron and the cell body of the second neuron is a synapse. This region is called an autonomic ganglion, taking its name from the peripheral cell body of the second neuron. The myelinated neuron feeding into the autonomic ganglion is called the preganglionic fibre, while the unmyelinated second neuron feeding out from the ganglion is called the postganglionic fibre. Without exception, the chemical transmitter released from preganglionic fibres is acetylcholine, which interacts with specific surface receptors on postganglionic fibres. This interaction enables the continuation of the message to the tissue (see Figure 25.1). Effectors that are innervated by both divisions of the ANS are said to be dual-innervated (see Table 25.1).

Many effectors receive continual baseline stimulation in order to maintain a constant level of functioning. In other words, these effectors have a resting tone. Examples of such effectors are blood vessels, the iris of the eye, salivary glands and the gastrointestinal tract. A change in function is brought about by a change in the level of stimulation. This is a particularly important way of maintaining control over effectors that are not dual-innervated.

Differences

Sympathetic preganglionic fibres arise from the spinal cord at the level of the first thoracic nerve down to the level of the second lumbar nerve (T1–L2). This gives rise to the alternative name for the sympathetic division: the thoracolumbar outflow. The preganglionic fibres of the parasympathetic division arise from two locations in the CNS: the spinal cord from the second sacral nerve down to the fourth sacral nerve (S2–S4), and the brain as the motor components of the oculomotor (III), facial (VII), glossopharyngeal (IX) and vagus (X) cranial nerves. The alternative name for this division is the craniosacral outflow. The effects of sympathetic stimulation are more widespread than those of parasympathetic stimulation due to greater branching of postganglionic fibres. Furthermore, there is only sympathetic stimulation of glands and the smooth muscle of the body wall. Tissues such as sweat glands, the piloerector muscle of hair follicles and blood vessels to both the skin and skeletal muscle are the beneficiaries of this stimulation.

There are also differences in the chemical transmitter released from postganglionic fibres on to tissue receptors. All parasympathetic postganglionic fibres release acetylcholine as their transmitter; that is, they are cholinergic. On the other hand, most of the sympathetic postganglionic fibres release noradrenaline as their transmitter; that is, they are adrenergic. Interestingly, there is circumstantial evidence to suggest that acetylcholine may act as an intermediary in the

TABLE 25.1 EFFECTS OF THE PARASYMPATHETIC AND SYMPATHETIC NERVOUS SYSTEM DIVISIONS ON VARIOUS ORGANS

Target organ/system	Parasympathetic effects	Sympathetic effects
Eye (iris)	Stimulates constrictor muscles, constricts pupils	Stimulates dilator muscles, dilates pupils
Eye (ciliary muscle)	Stimulates muscles, resulting in bulging of the lens for accommodation and close vision	No effect
Glands (nasal, lacrimal, salivary, gastric, pancreatic)	Stimulates secretory activity	Inhibits secretory activity, causes vasoconstriction of blood vessels supplying the glands
Sweat glands	No effect	Stimulates copious sweating (cholinergic fibres)
Adrenal medulla	No effect	Stimulates medulla cells to secrete adrenaline and noradrenaline
Arrector pili muscles attached to hair follicles	No effect	Stimulates contraction (erects hairs and produces 'goosebumps')
Heart muscle	Decreases rate, slows and steadies heart beat	Increases rate and force of heart beat
Heart: coronary blood vessels	Constricts coronary vessels	Causes vasodilation
Bladder/urethra	Causes contraction of smooth muscle of bladder wall, relaxes urethral sphincter, promotes voiding	Causes relaxation of smooth muscle of bladder wall, constricts urethral sphincter, inhibits voiding
Lungs	Constricts bronchioles	Dilates bronchioles, mildly constricts blood vessels
Digestive tract organs	Increases motility (peristalsis) and amount of secretion by digestive organs, relaxes sphincters to allow movement of foodstuffs along tract	Decreases activity of glands and muscles of digestive system and constricts sphincters (e.g. internal anal sphincter)
Liver	No effect	Adrenaline stimulates liver to release glucose into blood
Gall bladder	Excites (gall bladder contracts to expel bile)	Inhibits (gall bladder is relaxed)
Kidney	No effect	Causes vasoconstriction, decreases urine output, promotes renin formation
Penis	Causes erection (vasodilation)	Causes ejaculation
Vagina/clitoris	Causes erection (vasodilation) of clitoris	Causes reverse peristalsis (contraction) of vagina
Blood vessels	Little or no effect	Constricts most vessels and increases blood pressure; constricts vessels of abdominal viscera and skin to divert blood to muscles, brain and heart when necessary; dilates vessels of the skeletal muscles (via cholinergic fibres and adrenaline) during exercise
Blood coagulation	No effect	Increases coagulation
Cellular metabolism	No effect	Increases metabolic rate
Adipose tissue	No effect	Stimulates lipolysis (fat breakdown)
Mental activity	No effect	Increases alertness

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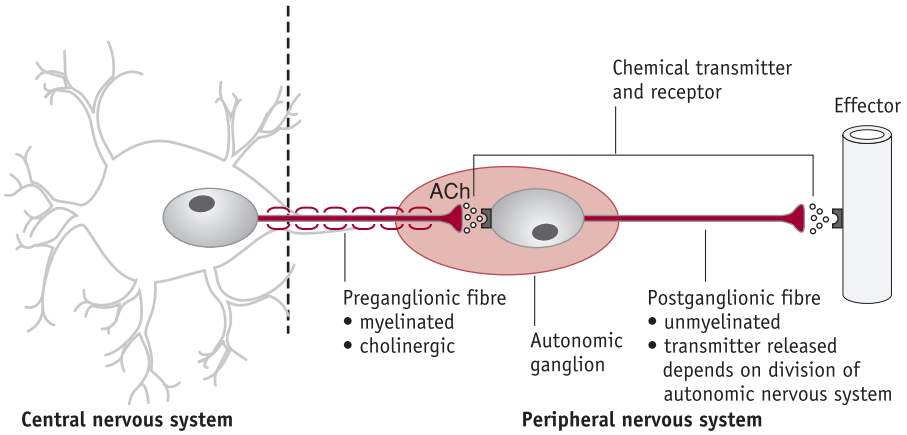
FIGURE 25.1 SCHEMATIC REPRESENTATION OF A TYPICAL AUTONOMIC NERVOUS SYSTEM PATHWAY

A typical autonomic nerve pathway consists of two nerve fibres communicating with an autonomic effector. The cell body of the preganglionic fibre resides within the central nervous system and is a cholinergic myelinated nerve. The cell body of the postganglionic fibre lies within an autonomic ganglion, is unmyelinated and synapses with the effector. The chemical transmitter released from this second fibre depends on the autonomic division to which it belongs.



release of noradrenaline from adrenergic sympathetic nerves. For the purposes of this discussion, however, the terms 'adrenergic' and 'cholinergic' reflect the chemical substance that interacts with receptors on the effector's surface following nerve stimulation.

A number of postganglionic fibres associated with the sympathetic division are cholinergic. Tissues that have been found to be innervated by cholinergic sympathetic postganglionic fibres are sweat glands (these also receive adrenergic stimulation), and peripheral blood vessels associated with skeletal muscle (which also respond to adrenergic stimulation) and the skin of the head and neck (resulting in blushing and flushing). In the sympathetic division, the preganglionic fibre is relatively short and the postganglionic fibre is long. In the parasympathetic division, the converse is true – long preganglionic fibres and short postganglionic fibres. Table 25.2 and Figure 25.2 (a) and (b) summarise the differences between the two divisions.

FIGURE 25.2A CHARACTERISTICS OF A SYMPATHETIC NERVE PATHWAY

(a) Sympathetic pathways consist of a short preganglionic fibre connecting with a relatively long postganglionic fibre. Most sympathetic postganglionic fibres are adrenergic; some are cholinergic.

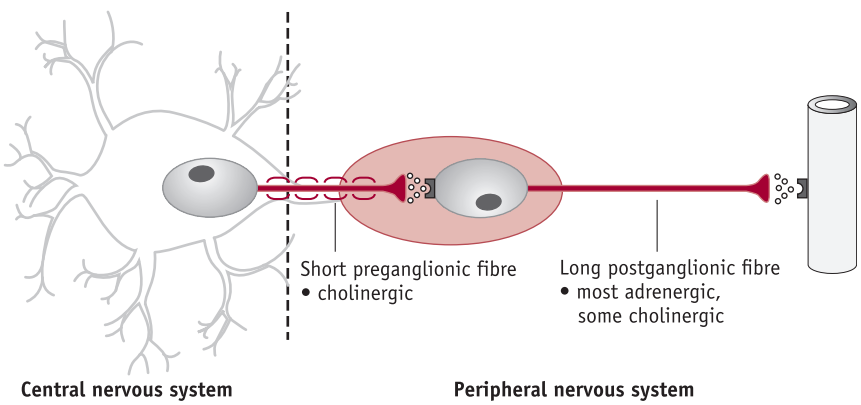


FIGURE 25.2B CHARACTERISTICS OF A PARASYMPATHETIC NERVE PATHWAY

(b) Parasympathetic pathways consist of long preganglionic and short postganglionic fibres. The parasympathetic postganglionic fibre is always cholinergic.

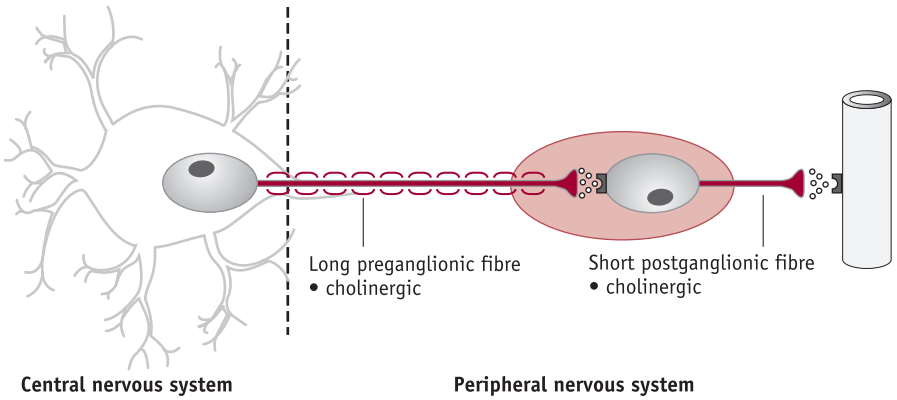


TABLE 25.2 ANATOMICAL AND PHYSIOLOGICAL DIFFERENCES BETWEEN THE PARASYMPATHETIC AND SYMPATHETIC NERVOUS SYSTEM DIVISIONS

Characteristic	Parasympathetic	Sympathetic
Origin	Craniosacral outflow: brain stem nuclei or cranial nerves III, VII, IX and X; spinal cord segments S2–S4	Thoracolumbar outflow: lateral horn of grey matter of spinal cord segments T1–L2
Location of ganglia	Ganglia in (intramural) or close to visceral organ served	Ganglia within a few centimetres of central nervous system: alongside vertebral column (paravertebral ganglia) and anterior to vertebral column (prevertebral ganglia)
Relative length of pre- and postganglionic fibres	Long preganglionic, short postganglionic	Short preganglionic, long postganglionic
Degree of branching of preganglionic fibres	Minimal	Extensive
Functional goal	Maintenance functions, conserves and stores energy	Prepares body to cope with emergencies and intense muscular activity
Neurotransmitters	All fibres release acetylcholine (cholinergic fibres)	All preganglionic fibres release acetylcholine; most postganglionic fibres release noradrenaline (adrenergic fibres); some postganglionic fibres (e.g. those serving sweat glands and blood vessels of skeletal muscles) release acetylcholine; neurotransmitter activity augmented by release of adrenal medullary hormones (noradrenaline and adrenaline)

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NEUROMODULATION OF AUTONOMIC NERVOUS SYSTEM FUNCTION

Neuromodulation is a term describing the phenomenon of altering the responsiveness of nerve fibres and body tissues to nervous stimulation. In some instances responsiveness may be enhanced; in others it is decreased. Such alterations are brought about by the actions of chemical mediators and neurotransmitters. A number of these chemicals can affect ANS function.

Neuromodulation can occur presynaptically (at the point of transmitter release – the nerve terminal) and postsynaptically (on the tissue that responds to the chemical message, which, for example, could be another nerve cell or a muscle cell). In presynaptic modulation, the release of noradrenaline from a sympathetic postganglionic fibre can inhibit the release of acetylcholine from a parasympathetic postganglionic fibre, and vice versa.

There is a self-regulation, or feedback control, of autonomic transmitter function, such that the release of noradrenaline from the nerve terminal may, under some circumstances, inhibit further release of the transmitter or, under other conditions, enhance its release. This kind of feedback control is also evident for selected cholinergic nerves.

The ANS also responds to chemicals other than noradrenaline and acetylcholine, which are therefore described collectively as non-adrenergic non-cholinergic (NANC). Some of these neuromodulators are released with the main neurotransmitter (either noradrenaline or acetylcholine) to enhance the desired tissue effect. Neuromodulators may also act to stimulate the release of the principal neurotransmitter from either cholinergic or adrenergic nerves. Other neuromodulators act to inhibit neurotransmitter release from autonomic nerves. Neuromodulators can be formed and released from cells adjacent to nerves. This type of neuromodulator is exogenous. They may also be made within the autonomic nerve terminal and are then called endogenous neuromodulators. We now recognise that endogenous neuromodulators play a significant role in autonomic transmission. Some examples of ANS neuromodulators are provided in Table 25.3. There is a more detailed discussion of the physiological roles of chemical mediators in Section VII.

TABLE 25.3 EXAMPLES OF NEUROMODULATORS OF THE AUTONOMIC NERVOUS SYSTEM

Substance	Effects
Nitric oxide	Facilitates erection of genitalia, promotes gastric emptying
Serotonin	Inhibits noradrenaline release from sympathetic nerves, enhances peristalsis
Neuropeptide Y	Enhances vasoconstriction
Vasoactive intestinal peptide	Facilitates bronchodilation
Dopamine	Inhibits noradrenaline release from sympathetic nerves, promotes vasodilation in some tissues (e.g. kidneys)

Clearly, the role of neuromodulation in the control and regulation of the autonomic transmission illustrates the functional complexity of this body system. The simplified overview of the ANS presented in this chapter will assist you in your understanding of adrenergic and cholinergic pharmacology (see Chapters 26 and 27), but you should keep in mind that the actual physiology is more complex.

Now, with this foundation in place, we are ready to explore the areas of adrenergic, cholinergic and dopaminergic pharmacology. In so doing, we will gain an understanding of an extraordinary number of commonly prescribed therapeutic agents.

SUMMARY

- The autonomic nervous system (ANS) is an efferent pathway controlling involuntary body structures.
- There are two subdivisions of the ANS: the sympathetic division is activated in emergency or stressful situations and is associated with flight-or-fight responses; the parasympathetic division has a restorative function and is associated with rest-and-repose responses.
- There are two nerve fibres in an autonomic pathway: the preganglionic and postganglionic fibres. The synapse connecting the fibres is the autonomic ganglion. The body structure receiving stimulation is called an effector.
- The two principal transmitters associated with the ANS are acetylcholine and noradrenaline.
- Nerve fibres that release acetylcholine and the receptors that respond to this transmitter are cholinergic, while nerve fibres that release noradrenaline or respond to this transmitter are adrenergic.
- Neuromodulators are chemicals that may alter the responsiveness of nerves and tissues to stimulation of the autonomic nervous system.

1 (a) What are the two divisions of the autonomic nervous system?
(b) Compare and contrast the anatomical organisation of the divisions.

2 For each of the following effectors, deduce the effects (if any) of sympathetic and parasympathetic stimulation:
(a) myocardium;
(b) stomach;
(c) sweat glands;
(d) iris;
(e) salivary glands.

3 For each of the following effects, determine whether it is due to sympathetic or parasympathetic innervation:
(a) increased blood pressure;
(b) pupil constriction;
(c) sweating;
(d) secretion of stomach juices;
(e) micturition (urinary bladder emptying).

4 (a) Define the term 'neuromodulation'.
(b) Give four examples of neuromodulation.

ADRENERGIC PHARMACOLOGY

26

CHAPTER TWENTY-SIX

OBJECTIVES

After completing this chapter, the reader should be able to:

- **identify the types and subtypes of adrenergic receptors;**
- **list the effects observed after stimulation and blockade of peripheral adrenoreceptors;**
- **outline the central nervous system effects of adrenergic stimulation and blockade;**
- **describe the role of dopamine in autonomic nervous system function;**
- **derive the side effects and clinical indications of adrenergic agents from a knowledge of receptor distribution and sympathetic nervous system effects.**

KEY TERMS

Adrenaline
Adrenergic receptors
Catecholamines
Dopamine
G-proteins
Noradrenaline
Second messengers
Sympathetic nervous system

ADRENERGIC PHARMACOLOGY RELATES PRINCIPALLY TO sympathetic nervous system function. In the peripheral nervous system, only sympathetic postganglionic fibres are adrenergic (i.e. a nerve that releases the transmitter noradrenaline), releasing their noradrenaline directly on to adrenergic receptors on the surface of effectors. The hormone adrenaline, released into the circulation from the adrenal gland, also stimulates adrenergic receptors but does not always mimic noradrenaline. The purpose of these interactions is to prepare the body for a flight-or-fight situation. Other names for noradrenaline and adrenaline, and used widely in the literature, are norepinephrine and epinephrine, respectively. In this textbook, noradrenaline and adrenaline are preferred because they can be linked to terms such as ‘adrenergic receptor’ and ‘adrenal gland’.

Administration of adrenergic agonist drugs induces effector responses of a flight-or-fight character. Stimulants such as these are sometimes referred to as sympathomimetics (drugs that mimic sympathetic stimulation), while blocking agents prevent these responses and are termed sympatholytics (drugs that block or inhibit sympathetic stimulation). The rationale for the clinical use of adrenergic stimulants or blockers depends on how illness has altered normal body function. In conditions where the activity of adrenergic effectors is excessive, e.g. a fast heart rate causing the pain of angina pectoris, then the use of an adrenergic blocker is warranted. Adrenergic stimulants are used when the illness state leaves effector activity inadequate, e.g. narrowing of bronchioles in asthma or diminished circulation in neurogenic shock.

MECHANISM OF ADRENERGIC ACTION

When an adrenergic nerve is stimulated, the action potential passes to the terminal, where the transmitter is stored in packets called synaptic vesicles. Depolarisation of the terminal membrane causes the vesicles to fuse with that membrane, rupture and release noradrenaline into the synapse.

The transmitter diffuses across the synaptic gap and interacts reversibly with an adrenergic receptor postsynaptically on the effector's surface. This interaction activates the appropriate cytoplasmic second-messenger system (see later in this chapter). This, in turn, triggers a series of intracellular events, which will manifest as the desired flight-or-fight response.

In order to maintain control of the effector's function, the free transmitter must be removed from the synapse or inactivated by degradative enzymes. Persistence of the transmitter in the synaptic gap can lead to overstimulation of the effector. To facilitate its inactivation, noradrenaline is subject to the processes of synaptic removal and enzymatic breakdown. Noradrenaline and related catecholamines are removed from the synapse by an amine pump located on the surface of the presynaptic terminal. The purpose of this pump is both inactivation and conservation – to remove synaptic noradrenaline and return it to the nerve terminal for later use.

On re-entry to the nerve terminal, the noradrenaline is restored to the synaptic vesicles. When these storage areas are full, any transmitter remaining free in the terminal is broken down by the mitochondrial enzyme monoamine oxidase (MAO). Any noradrenaline escaping reuptake is subject to extraneuronal uptake into the surrounding tissues and degradation by the enzyme catechol-O-methyltransferase (COMT) (see Figure 26.1).

Adrenergic agonists and antagonists are structurally similar to the endogenous catecholamines that bind to adrenergic receptors. Many of these drugs bind reversibly to the adrenoreceptor and are subject to the processes of reuptake by the amine pump and/or enzymatic breakdown by MAO and COMT.

ADRENERGIC RECEPTOR STIMULATION

Two principal types of adrenoreceptor have been identified: alpha (α) and beta (β) receptors. These receptor types have been subdivided further: The main subtypes are α_1, α_2, β_1 and β_2 receptors (β_3 receptors have been found in adipose tissue). The activation of these receptors through the administration of adrenergic agonists will produce effects consistent with sympathetic (flight-or-fight) stimulation. Adrenoreceptors are distributed widely, but not evenly, throughout the body. Figure 26.2 summarises the effects resulting from the stimulation of peripheral adrenergic receptors.

Alpha-1 receptors

Alpha-1 receptors are located on blood vessels and influence both blood pressure and tissue perfusion. Resistance to blood flow is determined by the diameter of these vessels. These receptors are also found on the radial muscle of the iris, the sphincters and smooth muscle of the gastrointestinal tract, liver cells, sweat glands, the arrector pili muscles of the hair follicles, the smooth muscle of the male and female reproductive tracts, and the sphincters and smooth muscle associated with the urinary bladder.

MECHANISM OF ACTION

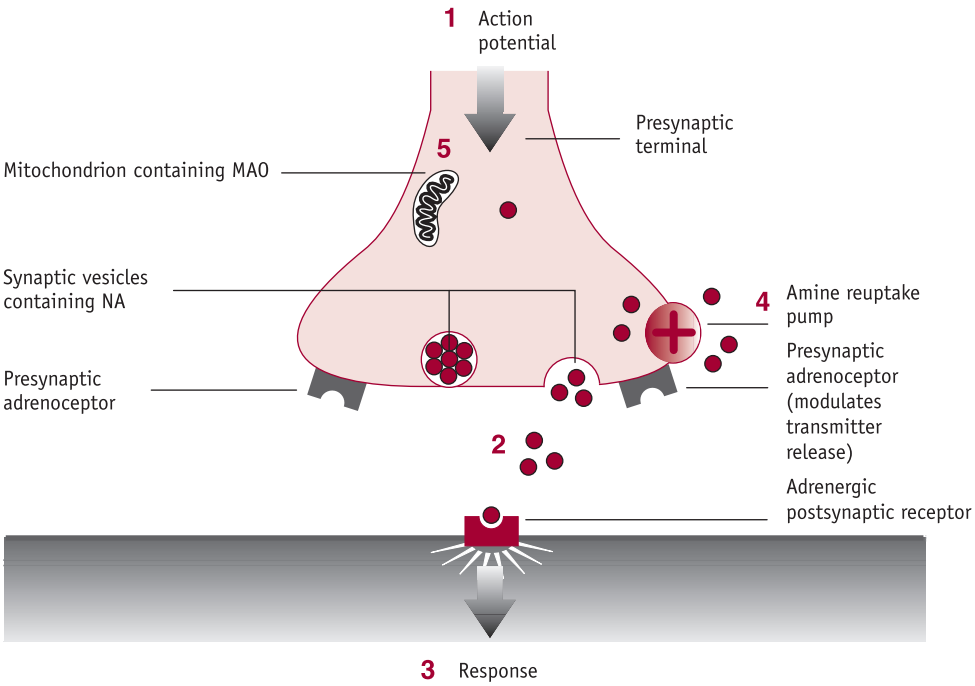
As you can see in Figure 26.2, stimulation of α_1 receptors causes the following effects:

- Vasoconstriction of blood vessels: This effect has a significant influence on tissue perfusion and is used primarily as a means to redirect blood flow from one tissue to another. In addition, in many vessels, this stimulation provides resting vasomotor tone. Vasoconstriction of major systemic blood vessels results in a significant elevation of blood pressure. Vasoconstriction is also an effective means to decongest blocked nasal passages; drugs that do this are called nasal decongestants. Localised vasodilation and increased vascular permeability of nasal capillaries underlies this congestion. In conditions characterised by red eyes, vasoconstriction of scleral blood

FIGURE 26.1 ADRENERGIC NERVE ACTION

A summary of events involved in adrenergic nerve stimulation. The action potential travels along the axon until it reaches the nerve terminal (1). Depolarisation of the terminal causes the release of chemical transmitter, noradrenaline (NA), into the synaptic gap (2). NA diffuses across the gap and interacts with the adrenergic post-synaptic receptors, triggering an effector response (3). The transmitter is removed from the synaptic gap by an amine reuptake pump (4) and is restored to the synaptic vesicles. Any excess transmitter within the terminal not restored to the vesicles is degraded by the mitochondrial enzyme monoamine oxidase (MAO) (5). Any excess transmitter remaining within the synaptic gap is subject to extraneuronal reuptake.

The release of transmitter from the nerve terminal is also subject to modulation by presynaptic adrenoceptors (enhancement of release by one type, inhibition by another).



vessels can greatly diminish this manifestation; drugs that do this are called ophthalmic decongestants.

- Contraction of the radial muscle of the iris, resulting in pupil dilation (mydriasis).
- Contraction of the gastrointestinal sphincters and decreased gastrointestinal motility, resulting in slowed digestion and transport through the gut.
- Contraction of the external sphincter and loss of bladder tone, leading to urinary retention.
- Decreased bile secretion and increased glycogenolysis, the latter leading to raised blood sugar levels.
- Contraction of the smooth muscle of the vas deferens and the non-pregnant uterus to facilitate emission and ejaculation in the former and sperm transport to the fallopian tubes in the latter.
- Stimulation of sweat glands resulting in generalised sweating.
- Contraction of the arrector pili muscles, resulting in 'goosebumps'.

◆ COMMON ADVERSE EFFECTS

The effects of α_1 agonists are shown in Figures 26.3 and 26.4. Common adverse effects include hypertension, blurred vision, constipation and urinary retention.

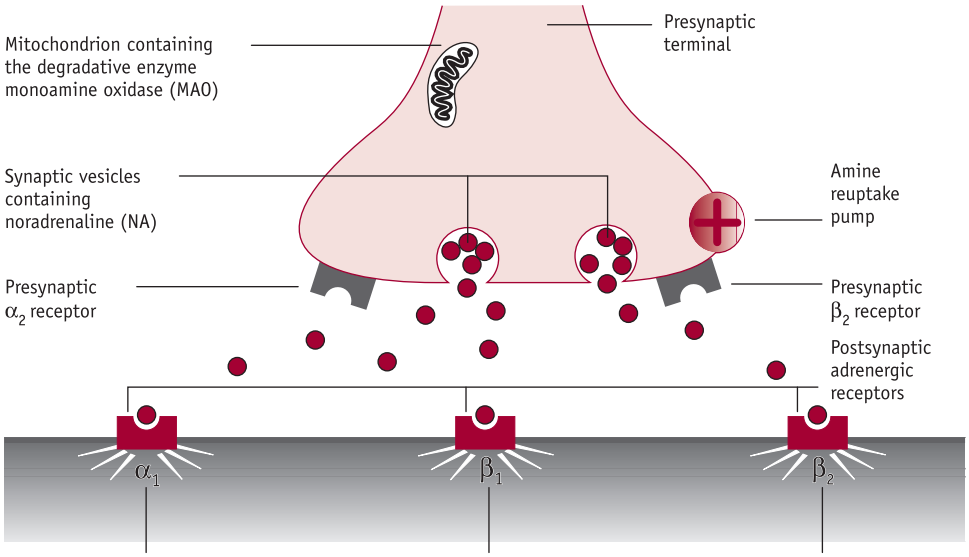
✚ CLINICAL CONSIDERATIONS

Clinical applications for α_1 stimulation include control of hypotension (particularly as an emergency measure for elevating blood pressure), nasal congestion and red eyes. Another application worth noting is the use of these drugs as a vasoconstrictor administered in combination with another drug. This facilitates a slow systemic absorption of the other drug, enhancing its action locally; it also produces a relatively bloodless field for minor surgery. Such a combination is often used in local anaesthesia (see Chapter 42).

Naphazoline, **oxymetazoline**, **phenylephrine** and **xylometazoline** are all direct-acting α_1 agonists. The non-selective sympathomimetic agents, including **noradrenaline**, **pseudoephedrine**, **metaraminol**, **adrenaline**,

FIGURE 26.2 ADRENERGIC AGONIST EFFECTS

A summary of agonist responses following systemic stimulation of each subtype of adrenoceptor. Presynaptic α_2 receptors, when stimulated, inhibit further release of transmitter. Presynaptic β_2 receptors enhance transmitter release.



α_1 *receptors*
- vasoconstriction (increases blood pressure and relieves congestion)
- pupil dilation
- decreased gut motility and secretions
- glycogen breakdown (increases blood glucose levels)
- urinary retention
- contraction of the smooth muscle of the vas deferens (facilitates sperm emission and ejaculation)
- contraction of non-pregnant uterus
- sweating
- 'goosebumps'

β_1 *receptors*
- cardiac acceleration (increases heart rate, stroke volume and cardiac output)
- lipolysis
- decreased gut motility and secretions
- renin release (increases blood pressure)

β_2 *receptors*
- bronchodilation
- fine skeletal muscle tremor
- vasodilation of blood vessels to skeletal muscles
- glycogen breakdown
- relaxation of the pregnant uterus
- mast cell stabilisation

ephedrine and **dopamine**, which induce both α and β effects, may be used clinically for their α_1 effects.

When administering α_1 agonists systemically, such as for local anaesthesia, it is important to scrutinise closely their effects on peripheral perfusion. Decongestant topical preparations are not recommended for prolonged use, as rebound congestion and hyperaemia may occur.

Beta-1 receptors

Beta-1 receptors are located on the myocardium, adipocytes, sphincters and smooth muscle of the gastrointestinal tract, and renal arterioles.

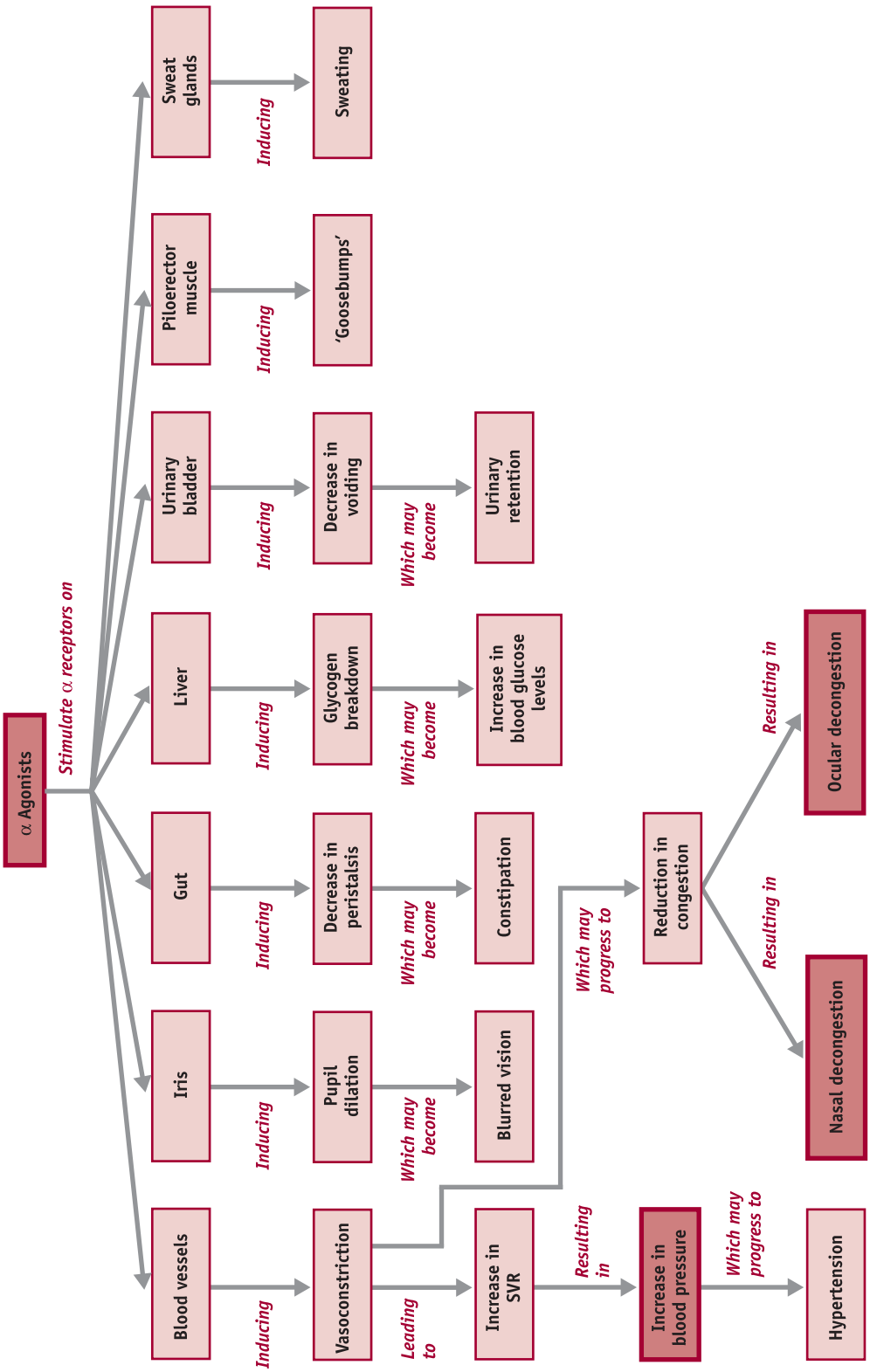
MECHANISM OF ACTION

As you can see in Figure 26.2, stimulation of β_1 receptors results in the following effects:

- Increased rate and force of contraction of the heart: The increased cardiac output that ensues can lead to an elevation in blood pressure. This is a good opportunity to introduce two important terms relating to altered myocardial function. Any change in heart rate is called a chronotropic effect, while any change in contractile force is known as an inotropic effect. An increase in either property is termed positive and a decrease negative. Therefore, β_1 receptors generate positive chronotropic and positive inotropic effects.
- Lipolysis in adipose tissue, leading to a rise in blood lipid levels. Being predominantly free fatty acids, these lipids will be converted into energy (β_3 receptors may also play a role in lipolysis).
- Decreased digestion and gastrointestinal motility.
- Release of renin from the juxtaglomerular apparatus into the renal blood, resulting in the formation of angiotensin II. This substance is a potent vasoconstrictor, which causes an increase in renal blood flow and pressure and, as a result, increased glomerular filtration.

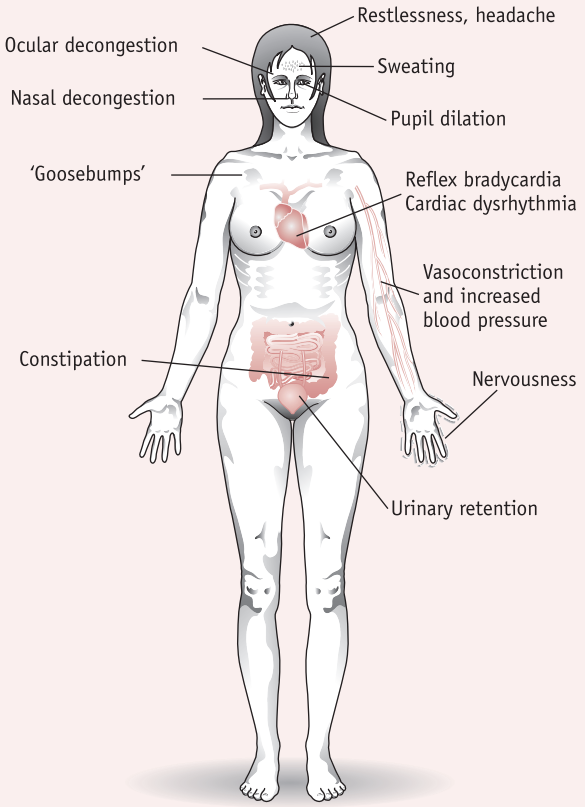
FIGURE 26.3 FLOWCHART SHOWING THE EFFECTS OF α_1 AGONISTS

Therapeutic effects are shown in the darker shaded boxes.



SVR, systemic vascular resistance.

FIGURE 26.4 EFFECTS OF α_1 AGONISTS



◆ COMMON ADVERSE EFFECTS

The effects of β_1 agonists are shown in Figures 26.5 and 26.6. Common adverse effects include hypertension, tachycardia and constipation.

✚ CLINICAL CONSIDERATIONS

Clinical applications for β_1 stimulation are as positive inotropic agents in circulatory shock, hypotension and cardiac arrest.

Dobutamine, a selective β_1 agonist, and **isoprenaline**, a non-selective β_1 agonist, are important representatives of this group. The non-selective sympathomimetic agents may be used therapeutically for their β_1 effects.

As these drugs increase the cardiac workload and output, the patient must be monitored closely within the confines of a specialty unit, such as intensive care. The patient's blood pressure, heart rate and rhythm, oxygenation, urinary output and conscious state should be scrutinised regularly and strictly.

Beta-2 receptors

These adrenoreceptors are distributed on the smooth muscle of the bronchioles, skeletal muscle, blood vessels supplying the brain, heart, kidneys and skeletal muscle, mast cells, the uterus and liver cells.

■ MECHANISM OF ACTION

As you can see in Figure 26.2, stimulation of β_2 receptors results in the following effects:

- bronchodilation;
- increased skeletal muscle excitability, resulting in fine muscle tremors;
- vasodilation of blood vessels to the brain, heart, kidneys and skeletal muscle, leading to increased blood flow through those tissues;
- relaxation of the pregnant uterus, and rhythmic contraction of the non-pregnant uterus during sexual intercourse to promote sperm transport towards the fallopian tubes;
- decreased bile secretion and increased glycogenolysis;
- stabilisation of the membrane of the mast cell, preventing the release of inflammatory mediators.

Beta-2 receptors are also located on the presynaptic terminal of adrenergic nerves and act to enhance the release of stored noradrenaline. This is a form of positive feedback control.

◆ COMMON ADVERSE EFFECTS

The effects of β_2 agonists are shown in Figures 26.7 and 26.8. Common adverse effects include fine muscle tremor (especially involving the hands) and, in some patients, increased muscle tension and feelings of warmth (the latter due to increased blood flow through skeletal muscles). Although this drug group is relatively selective for β_2 receptors, some residual β_1 stimulation may result in tachycardia.

Rises in blood glucose and insulin levels are metabolic effects associated with parenteral or nebuliser therapy, the latter leading to a fall in serum potassium levels. When β_2 agonists are administered by these routes, the patient should be monitored closely for hypokalaemia.

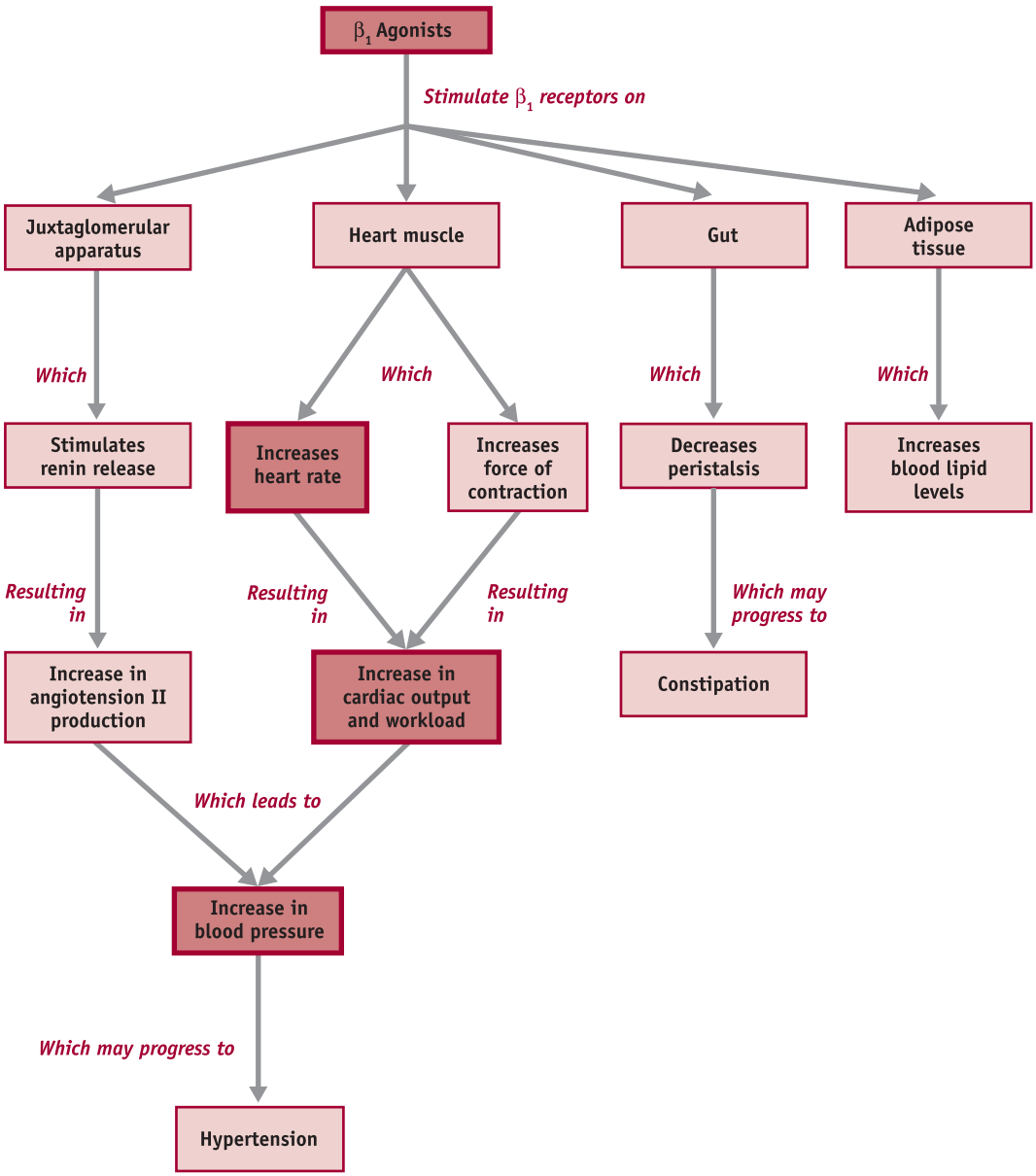
✚ CLINICAL CONSIDERATIONS

Clinical applications for β_2 stimulation include chronic obstructive airways disease, circulatory shock, premature labour and peripheral vascular disease.

Fenoterol, **formoterol**, **salbutamol**, **salmeterol** and **terbutaline** are relatively selective β_2 agonists. A β_2 agonist called **bambuterol** is a prodrug of terbutaline. Salmeterol is notable in that, unlike the other drugs in this group, its

FIGURE 26.5 FLOWCHART SHOWING THE EFFECTS OF β_1 AGONISTS

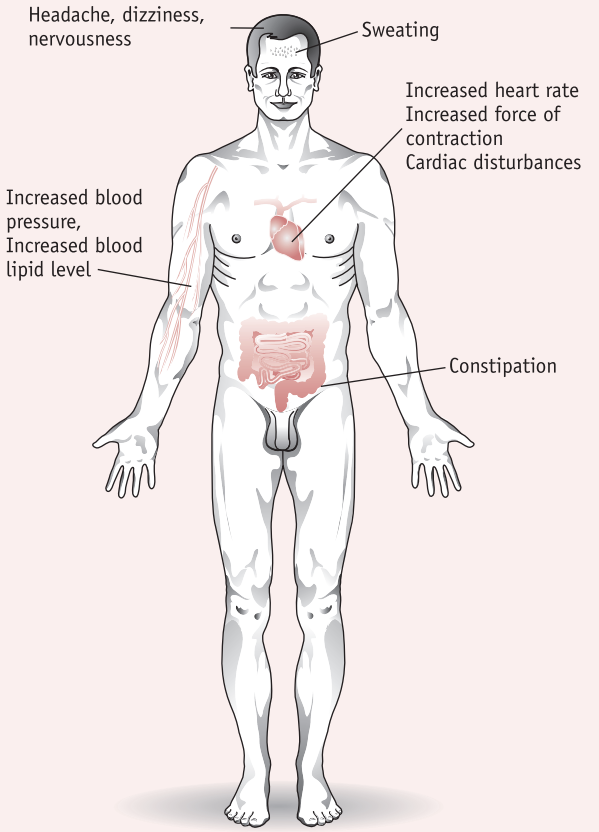
Therapeutic effects are shown in the darker shaded boxes.



effect on mast-cell membranes lasts long enough to be clinically significant.

The short-acting β_2 agonists such as salbutamol have a quick onset of action (5–15 minutes) and therefore are recommended to relieve acute symptoms of asthma. On the other hand, long-acting β_2 agonists such as salmeterol should be used as maintenance treatment for asthma. Corticosteroid anti-inflammatory use should also be considered if a short-acting β_2 agonist is required for more than three or four times each week. Nebulisers should be used mainly in the hospital setting and reserved for severe asthma. High doses of β_2 agonists are normally delivered by nebuliser, which can increase the incidence of hypokalaemia.

FIGURE 26.6 EFFECTS OF β_1 AGONISTS



Alpha-2 receptors

■ MECHANISM OF ACTION

The α_2 receptor is located presynaptically and is found on all adrenergic nerve terminals. Its purpose is one of negative feedback control at the local level. When adrenergic nerve stimulation is excessive and leads to a build-up of transmitter in the synapse, activation of the α_2 receptor results in inhibition of transmitter release from the terminal, even though the stimulation persists. This prevents overstimulation of the effector. It is also located postsynaptically on the surface of some effectors, such as the pancreas.

◆ CLINICAL CONSIDERATIONS

Clonidine, **apraclonidine** and **brimonidine** are selective α_2 agonists. Clonidine is used mainly in the treatment of hypertension, while the other two are used as an adjunct in controlling glaucoma. In effect, they act by blocking sympathetic nerve transmission associated with vasomotor tone. Clonidine acts centrally at the level of the medulla, while apraclonidine and brimonidine, applied topically, affect the rate of production of aqueous humour.

A rebound phenomenon may occur with clonidine, whereby a rapid rise in blood pressure occurs approximately 18–72 hours following the last dose. To avoid this phenomenon, clonidine should be withdrawn gradually over a period of several weeks. The use of apraclonidine in the treatment of glaucoma is limited because of its tendency to cause local allergic reactions and its loss of effect after 3 months of treatment. Brimonidine is tolerated better and is more effective when used for long-term treatment. Clonidine is discussed in Chapter 44. Apraclonidine and brimonidine are described further in Chapter 79.

SECOND-MESSENGER SYSTEMS

The activation of a receptor on a cell's surface is only the first step in an elaborate intracellular signalling system that results in the desired cell response. In this section, aspects of this system are described.

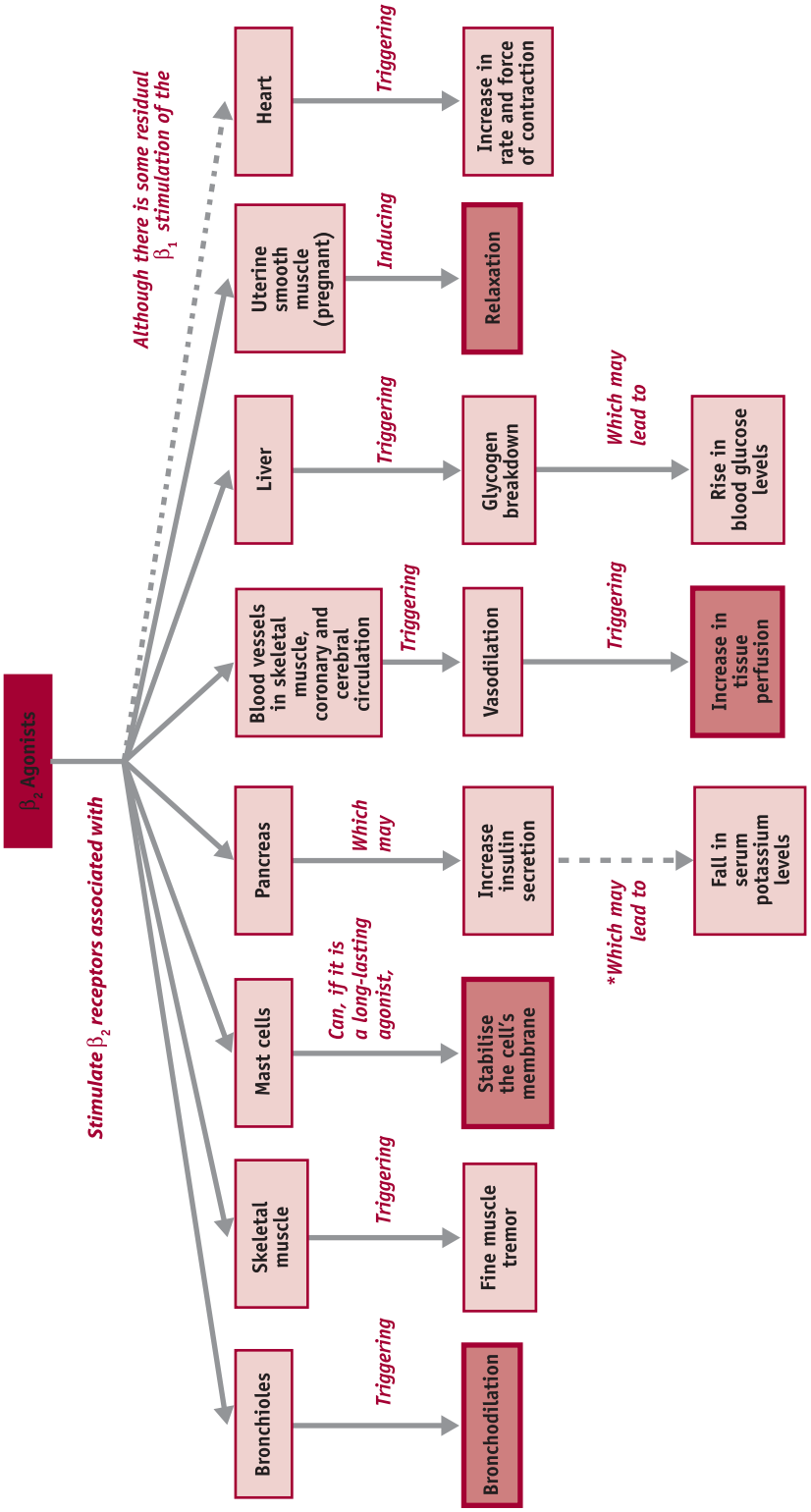
In general, the chemical that makes contact with the effector cell is regarded as the first messenger. This could be a neurotransmitter, a hormone, an agonist drug or a chemical mediator. A progression of intracellular events then commences (see Figure 26.9). The first step is to alter the activity of a membrane-bound enzyme. This enzyme is responsible for the synthesis of the second messenger in the cytoplasm. Examples of second messengers are cyclic adenosine monophosphate (cAMP), cyclic guanosine monophosphate (cGMP), calcium ion, diacylglycerol (DAG) and inositol trisphosphate (IP_3). Table 26.1 provides examples of important second messengers, the membrane-bound enzymes that catalyse their formation and some tissues where they can be found. The second messenger usually activates a cascade of enzymes, particularly the protein kinases, or opens an ion channel in the membrane, which more directly induces the appropriate cellular response.

The interaction of one first-messenger chemical with the cell leads to the synthesis of a number of second-messenger molecules, which in turn produce numerous enzymic cascades. In effect, this amplifies the original cellular message. Cellular responses can include the activation of particular genes, an alteration in the cell's permeability, the relaxation or contraction of a muscle cell, increased or decreased nerve cell firing, and the synthesis and release of a certain cell product.

Interestingly, some lipid-soluble chemical mediators can bypass the extracellular receptor and directly activate the membrane-bound enzyme to produce the cell's second messenger (see Figure 26.9). An example of this is nitric oxide (see Chapter 31). It still requires the second messenger to produce the desired cellular response, however.

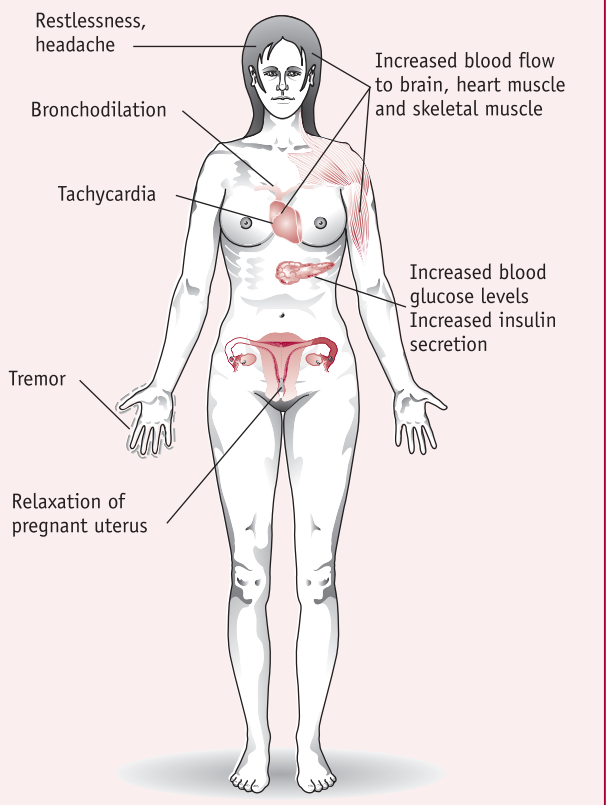
FIGURE 26.7 FLOWCHART SHOWING THE EFFECTS OF β_2 AGONISTS

Therapeutic effects are shown in the darker shaded boxes.



* More likely when systemic absorption is greater, e.g. after intravenous injection or frequent nebuliser use

FIGURE 26.8 EFFECTS OF β_2 AGONISTS



Second-messenger systems are finely controlled. Once the second messenger is produced, it needs to be broken down. Phosphodiesterases are important in the breakdown of some second messengers. Moreover, activation of one receptor may stimulate the production of the second messenger, while activation of another receptor on that cell may inhibit the production of this second messenger. This is achieved by inclusion of an intermediary substance (a go-between, if you like) between the receptor and the membrane-bound enzyme responsible for the synthesis of the second messenger. The intermediary is called a G-protein. One type of G-protein stimulates the membrane-bound enzyme and is called a G_s-protein; the other type inhibits the membrane-bound enzyme and is called a G_i-protein (see Figure 26.9). Some tissues that receive innervation by both parasympathetic and sympathetic divisions are mediated by G-proteins; one division activates a G_s-protein, while the other activates a G_i-protein on the same second messenger.

The two most well-established second messengers associated with adrenergic receptors are cAMP and IP_3 (see Figure 26.10). The intracellular levels of these messengers determine whether the flight-or-fight response will occur.

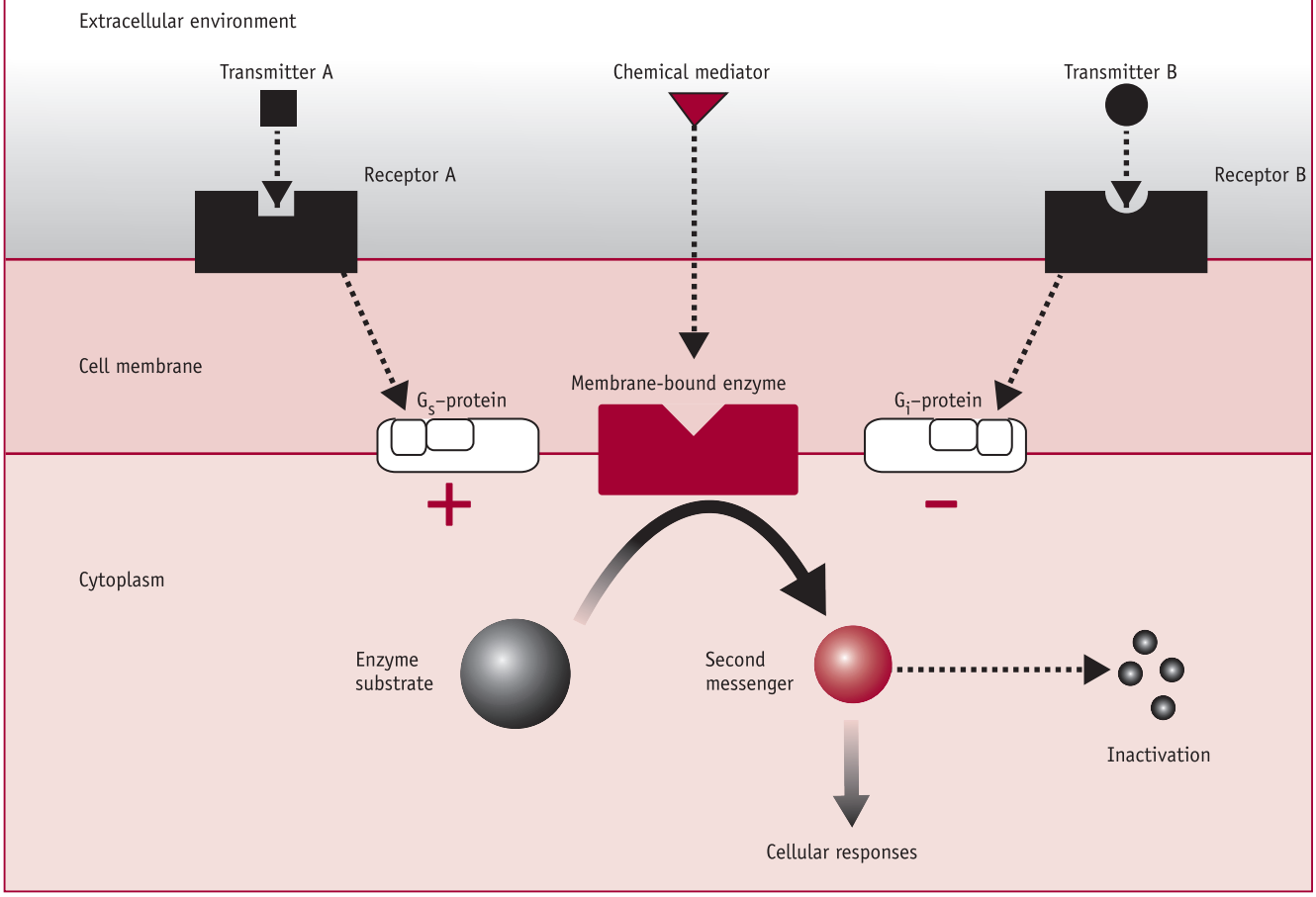
Beta-1 and beta-2 receptor activation is associated with elevated intracellular levels of cAMP. The membrane-bound enzyme adenylate cyclase is responsible for the conversion of cytoplasmic ATP into cAMP. Then, depending on the cell type, a sequence of events takes place that culminates in the desired response. The effect is terminated by the degradation of cAMP by phosphodiesterase. The methylxanthines **theophylline** and **caffeine** produce their stimulatory effects on the body (see Chapters 23, 51 and 52) through the inhibition of cAMP degradation by phosphodiesterase, which leads to elevated cAMP levels.

IP_3 is associated with α_1 receptor activation and is produced from a phospholipid component of the cell membrane by phospholipase C (PLC). Another second messenger, called diacylglycerol (DAG), is also produced in this reaction. When the cytoplasmic levels of IP_3 rise, calcium ions are released from intracellular stores, which

TABLE 26.1 EXAMPLES OF AUTONOMIC SECOND-MESSENGER SYSTEMS

Second messenger	Catalytic enzyme	Linked receptor	Example of tissue response
Inositol trisphosphate (IP_3) Diacylglycerol (DAG)	Phospholipase C (PLC)	Adrenergic α_1 (activates PLC via G-protein)	Vasoconstriction
		Cholinergic M_1 and M_3 (activates PLC via G-protein)	Smooth-muscle contraction
Cyclic adenosine monophosphate (cAMP)	Adenylate cyclase (AC)	Adrenergic β (activates AC via G_s-protein)	Increased heart rate
		Adrenergic α_2 (inhibits AC via G_i-protein)	Membrane hyperpolarisation
		Cholinergic M_2, M_3 and M_5 (inhibits AC via G_i-protein)	Decreased heart rate

FIGURE 26.9 INTRACELLULAR EVENTS TRIGGERED BY THE ACTION OF A FIRST MESSENGER



catalyse a cascade of calcium-dependent enzymic reactions to produce the biological effect. DAG activates a cascade of cytoplasmic reactions, which also contribute to the effect. IP_3 is deactivated by dephosphorylation (the removal of a phosphate group), and calcium is subsequently returned to its cytoplasmic storage sites. DAG is deactivated by phosphorylation (the addition of a phosphate group).

DIRECT- AND INDIRECT-ACTING SYMPATHOMIMETICS

Sympathomimetic agents can be either direct-acting or indirect-acting. The two mechanisms are represented in Figure 26.11. Direct-acting agents are agonists that bind to and interact with adrenergic receptors, causing a change in the effector's activity. Agonists can also possess the property of receptor selectivity. An agonist can show selectivity for either α or β receptors, or even selectivity for one subpopulation of α or β receptors (e.g. β_1-specific). Selectivity is desirable in a clinical agent because effects associated with stimulation of adrenergic receptors that do not contribute to the desired outcome are then diminished.

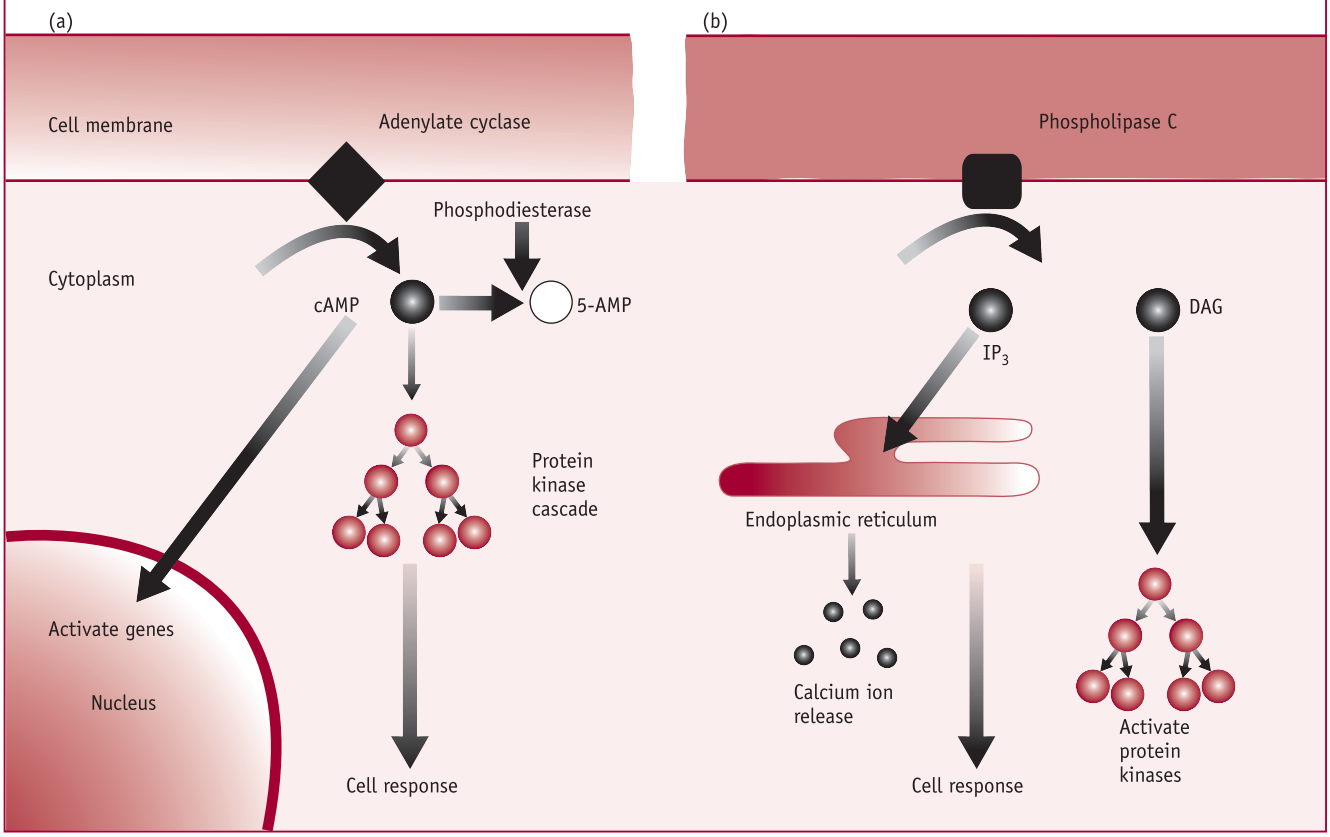
Indirect-acting agents cause the release of a stored transmitter from within the adrenergic nerve terminal. The transmitter noradrenaline then stimulates adrenergic receptors on the effector. Some sympathomimetic agents (e.g. ephedrine, metaraminol, pseudoephedrine) possess a mixed action or release of transmitter plus direct agonist activity. Another drug, **dipivefrine**, is an adrenaline prodrug principally used in the treatment of glaucoma. Once absorbed, it is converted rapidly into adrenaline, which produces the desired therapeutic effect.

Noradrenaline and adrenaline are the least specific of adrenergic agonists and can stimulate both α and β receptors. There are differences in potency, however. Subtle differences in chemical structure cause the effects of noradrenaline at α receptors to be more pronounced than at β receptors, whereas the converse is true of adrenaline.

FIGURE 26.10 SECOND MESSENGERS INVOLVED IN ADRENERGIC FUNCTION

(a) The receptor–chemical interaction on the surface of an effector triggers the activation of the membrane-bound enzyme adenylate cyclase. This enzyme facilitates the conversion of cytoplasmic reactions, which manifest as altered cell activity. The enzyme phosphodiesterase is responsible for the inactivation of cyclic adenosine monophosphate (cAMP) into 5-adenosine monophosphate (5-AMP).

(b) Receptor stimulation results in the activation of a membrane-bound enzyme called phospholipase C (PLC). The enzyme facilitates the production of inositol triphosphate (IP_3) and diacylglycerol (DAG) from lipids contained within the cell membrane. IP_3 stimulates the release of calcium from intracellular storage sites. DAG activates a cascade of cytoplasmic reactions. These responses result in altered cellular activity.



ADRENERGIC ACTION IN THE CENTRAL NERVOUS SYSTEM

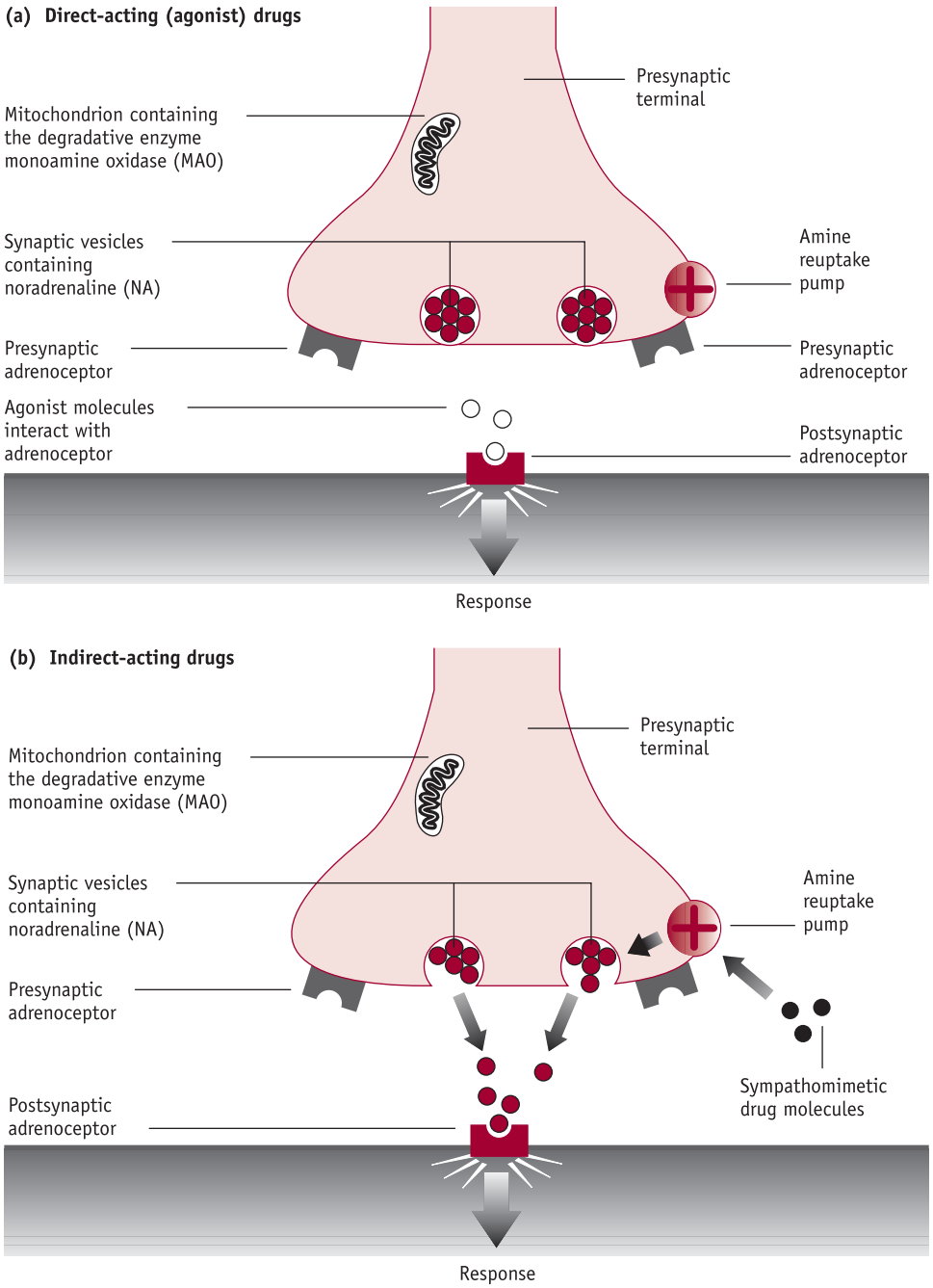
The catecholamines have a prominent role in central nervous system function. Noradrenaline, dopamine and adrenaline are brain transmitters. These neurotransmitters have been implicated in arousal and wakefulness, mood, emotional behaviour, hormone release, libido, motor control and coordination – important effects in flight-or-fight situations.

Therefore, it is not surprising that adrenergic drugs capable of crossing the blood–brain barrier can induce alterations in the above. Generally, the kinds of effect observed when sympathomimetics with central activity are administered relate to stimulation of these functions. As a result, an excessive level of arousal is observed. Manifestations such as restlessness, insomnia, anxiety, nervousness, euphoria, sense of wellbeing, irritability, talkativeness and aggression may be seen.

FIGURE 26.11 DIRECT- AND INDIRECT-ACTING SYMPATHOMIMETICS

(a) The action of agonist drugs does not primarily involve the presynaptic terminal. The agonist triggers an effector response once it binds to a postsynaptic receptor.

(b) Indirect-acting drugs are taken up into the presynaptic terminal by the amine reuptake pump and trigger the release of chemical transmitter from synaptic vesicles into the synapse. The transmitter substance interacts with the postsynaptic receptor, causing an effector response. Some indirect-acting sympathomimetics have agonist activity as well.



ADRENERGIC SIDE EFFECTS

In the main, the side effects of adrenergic agents derive from the widespread distribution of these receptors around the body. If an adrenergic drug has affinity for β receptors, then effects will be observed in all effectors bearing these receptors around the body, including the heart, bronchioles, adipose tissue, renal arterioles, brain and blood vessels to the brain, heart and skeletal muscle (see Figure 26.2). The only desirable effect, however, might be that produced in the heart (e.g. cardiac acceleration in the β_1 action column of Figure 26.2). If this is the case, then all other β effects not related to that therapeutic goal, both peripheral and central, are side effects.

An effective approach to raise your awareness of adrenergic side effects is to learn the distribution of various subtypes of adrenoreceptor in the body. If you know the effects of sympathetic stimulation on particular effectors (see Chapter 25), then you will be able to recognise clinical applications and side effects of sympathomimetic agents. As a general rule, the effects of antagonists are either opposite to that of the agonist or not clinically manifested. Examples of this approach are included in the study questions at the end of this chapter.

SYMPATHOLYTICS

Like sympathomimetic agents, sympatholytics can act either directly or indirectly. Direct-acting sympatholytics are antagonists that have affinity for a receptor but block the normal response. Like adrenergic agonists, antagonists can show specificity for one receptor or subtype. Indirect-acting agents block adrenergic nerve transmission, usually by inhibiting the release of neurotransmitter or depleting the stores of transmitter. **Tetrabenazine** acts by depleting the stores of transmitter centrally. It is useful in treating some forms of dystonia and dyskinesia (see Chapter 36). Another drug, **guanethidine**, blocks adrenergic nerve transmission. The principal clinical use of both of these adrenergic nerve blockers is to control hypertension, but because of their side effects they are used infrequently (most of the information pertaining to these agents is detailed in Chapter 44).

The results of either blocking adrenoreceptors on the surface of an effector or preventing transmission by an adrenergic nerve are the same: the normal effector response cannot take place. As many effectors receive dual innervation from both divisions of the autonomic nervous system, the observed drug effect is often opposite to that of stimulation. The effects of adrenoreceptor blockade are summarised in Figure 26.12. Sympatholytic agents that have central activity trigger diminished levels of function: lethargy, depression of mood, reduced anxiety and a loss of libido are examples. It is worth mentioning that there are no natural antagonists or adrenergic nerve blockers present in the body. Antagonism of adrenergic effects is achieved either by parasympathetic innervation of the effector or by decreasing the degree of sympathetic stimulation.

A discussion of specific antagonists now follows.

Alpha antagonist action

■ MECHANISM OF ACTION

Phenoxybenzamine, **phentolamine**, **prazosin**, **doxazosin**, **tamsulosin** and **terazosin** are α-adrenergic antagonists. All but phenoxybenzamine and phentolamine are relatively selective to α_1 receptors. As stated earlier, presynaptic α_2 receptors, when activated, suppress overstimulation of postsynaptic adrenoreceptors. A consequence of phenoxybenzamine and phentolamine blocking peripheral α_2 receptors is tachycardia – an unwanted effect in the context of the clinical indications.

◆ COMMON ADVERSE EFFECTS

The effects of α antagonists are shown in Figures 26.13 and 26.14. Common adverse reactions include nasal congestion, postural hypotension, inhibition of ejaculation and a lack of energy. A contraindication for use is known hypersensitivity to any of these drugs.

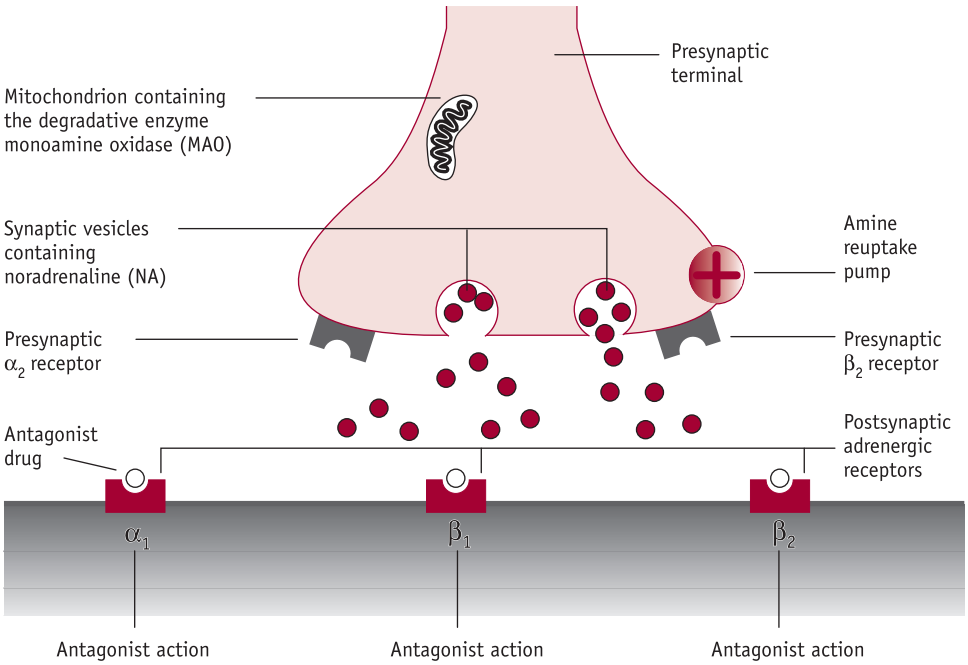
✚ CLINICAL CONSIDERATIONS

Applications for α antagonists include the control of hypertension, peripheral vascular disease, adrenal medulla tumour (phaeochromocytoma) and urinary retention. In the first three conditions, the desired effect is peripheral vasodilation.

The α_1 antagonists may cause a rapid fall in blood pressure after the first dose. The patient should be advised to take the first dose at bedtime in order to reduce the consequences of this effect. This hypotensive effect is likely to be more severe in older people and in people taking diuretics. It is recommended that diuretics are withheld for a few days before commencing an α antagonist. Postural hypotension and dizziness may occur, and the patient is advised to get up gradually from a lying or sitting position.

FIGURE 26.12 ADRENERGIC ANTAGONISTIC EFFECTS

A summary of antagonistic responses following systemic blockade of each subtype of adrenergic receptor. Blocking presynaptic α_2 receptors leads to enhanced transmitter release, while blocking presynaptic β_2 receptors inhibits transmitter release.



α_1 receptors
- vasodilation (decreases blood pressure)
- pupil constriction
- increased gut motility and secretions
- glycogen synthesis (decreases blood glucose levels)
- promotes micturition
- impotence

β_1 receptors
- cardiac deceleration (decreases heart rate, stroke volume and cardiac output)
- increased gut motility and secretions
- inhibition of renin release (decreases blood pressure)

β_2 receptors
- bronchoconstriction
- glycogen synthesis

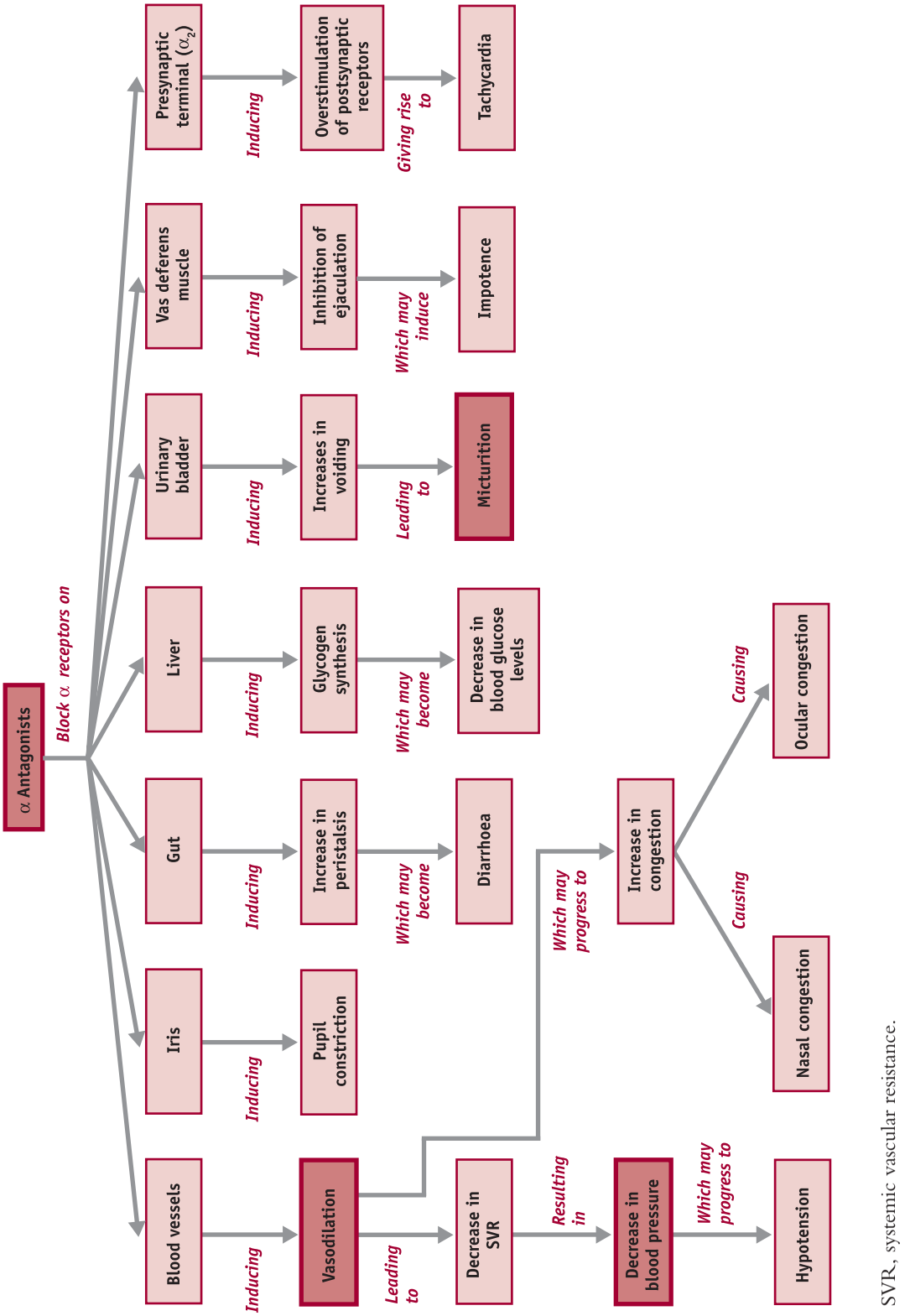
Beta antagonist action

MECHANISM OF ACTION

Acebutolol, **carvedilol**, **nadolol**, **oxprenolol**, **pindolol**, **propranolol**, **sotalol** and **timolol** are non-selective β antagonists, or beta-blockers. **Atenolol**, **bisoprolol**, **celiprolol**, **esmolol**, **metoprolol** and **nebivolol** are relatively β_1-selective (cardioselective) antagonists. Cardioselective beta-blockers were developed to reduce potentially life-threatening reactions, such as bronchospasm, resulting from β_2 receptor blockade. Oxprenolol, pindolol, celiprolol and acebutolol are partial agonists and induce sympathomimetic effects when there is low sympathetic tone. These agents are therefore said to have intrinsic sympathomimetic activity.

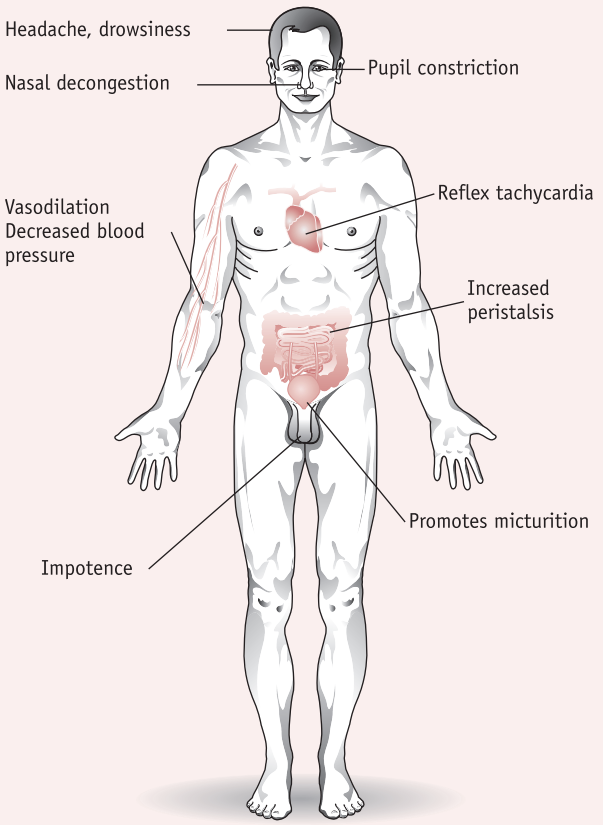
FIGURE 26.13 FLOWCHART SHOWING THE EFFECTS OF α ANTAGONISTS

Therapeutic effects are shown in the darker shaded boxes.



SVR, systemic vascular resistance.

FIGURE 26.14 EFFECTS OF α ANTAGONISTS



◆ COMMON ADVERSE EFFECTS

The effects of beta-blockers are shown in Figures 26.15 and 26.16. Common adverse effects include dizziness, lethargy, insomnia and diarrhoea. Contraindications include known hypersensitivity, heart block, severe heart failure, cardiogenic shock and other severe circulatory disorders. Beta-blockers should be avoided in patients with a history of asthma or chronic obstructive airways disease unless no alternative is available.

✚ CLINICAL CONSIDERATIONS

Applications for β_1 antagonists are to be found in the control of cardiac disease, hypertension, migraine prophylaxis, situational anxiety and thyrotoxicosis. There are no clinical applications for β_2 antagonists.

Abrupt withdrawal of β antagonists may accentuate angina or produce rebound hypertension, myocardial infarction or ventricular dysrhythmias. It is important, therefore, that β antagonists are reduced slowly when treatment is to cease. Cardioselective β antagonists may be preferred in conditions such as peripheral vascular disease, Raynaud's syndrome and diabetes mellitus because of their decreased effect on altering glucose metabolism and causing peripheral vasoconstriction.

Non-selective adrenergic blocking agents

■ MECHANISM OF ACTION

Labetalol blocks both α and β adrenoreceptors in the periphery, although it is more active against the latter.

◆ COMMON ADVERSE EFFECTS

The adverse effects one expects to observe when using adrenergic blocking agents derive from the antagonist columns in Figure 26.12. These agents are not tolerated very well. Specifically, we expect adverse effects such as postural hypotension, bradycardia, lethargy, blurred vision, bronchospasm, urinary retention, swollen ankles, nasal congestion and failure to ejaculate.

✚ CLINICAL CONSIDERATIONS

These drugs are used as antihypertensive agents and, by virtue of their effects on both the heart and vasculature, can be used to treat all grades of hypertension.

FIGURE 26.15 FLOWCHART SHOWING THE EFFECTS OF β ANTAGONISTS

Therapeutic effects are shown in the darker shaded boxes.

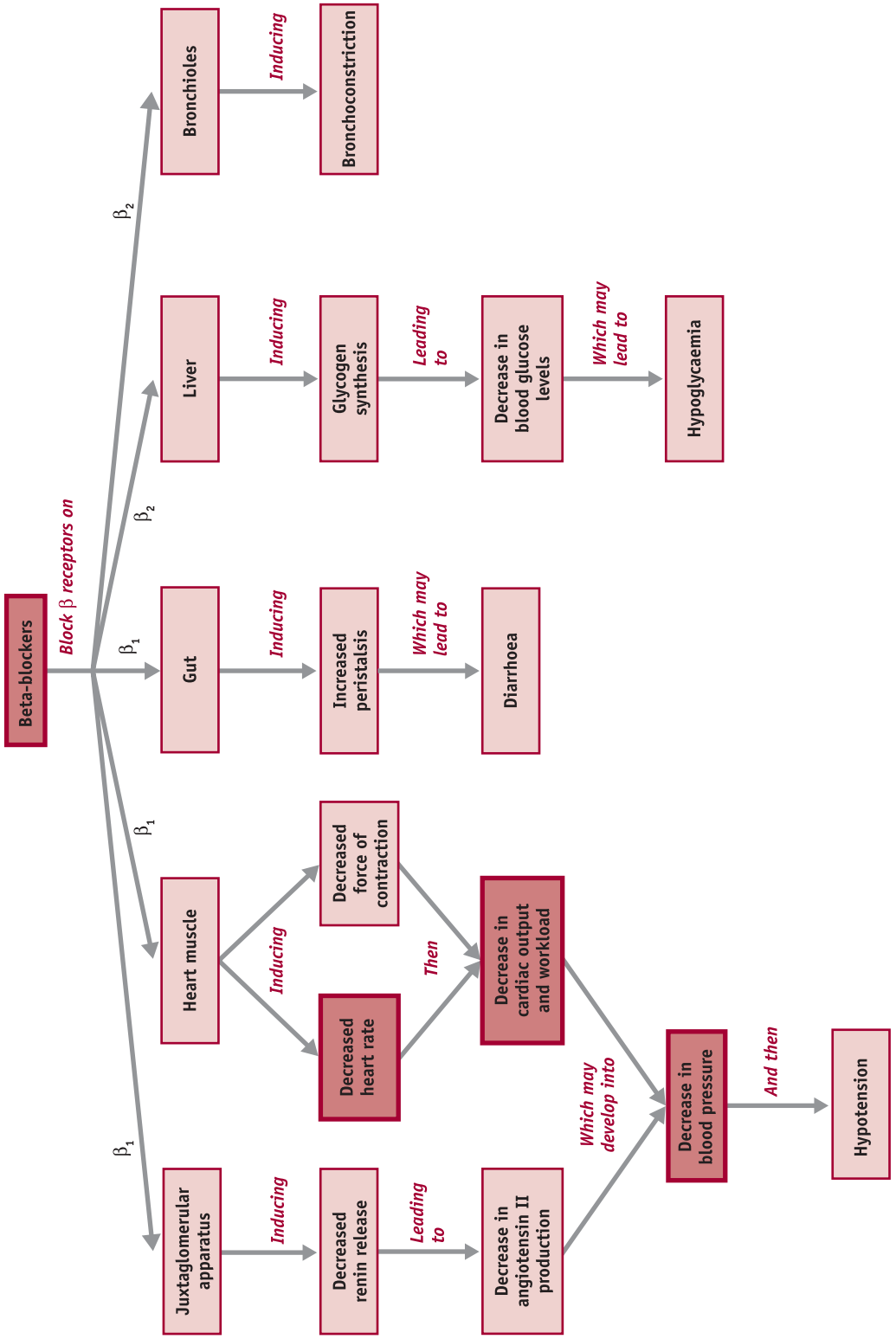
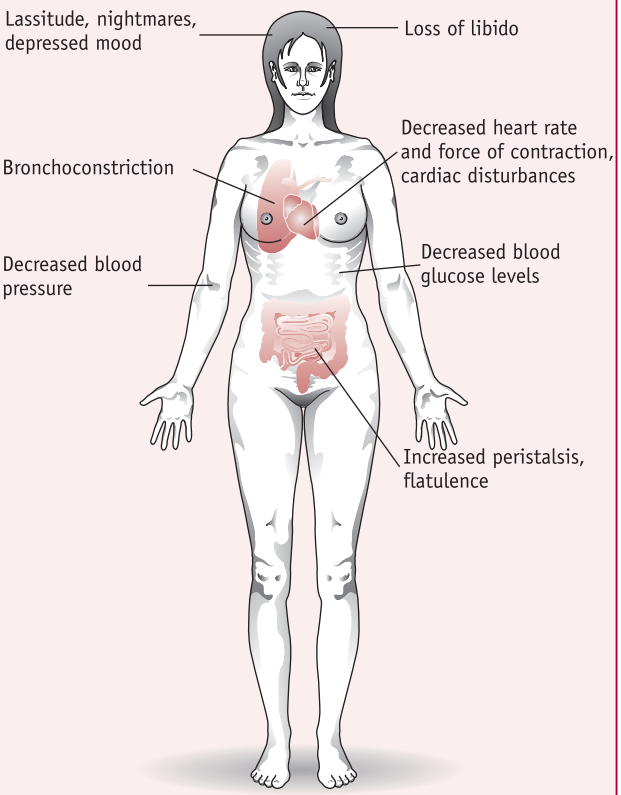


FIGURE 26.16 EFFECTS OF β ANTAGONISTS



PERIPHERAL ACTIONS OF DOPAMINE

■ MECHANISM OF ACTION

Dopamine has a role in sympathetic nervous system function. It can stimulate β_1 receptors on heart muscle and, at high doses, α receptors associated with systemic blood vessels. It does this indirectly through the release of noradrenaline from the nerve terminal, rather than by direct receptor stimulation itself.

Specific dopamine receptors are associated with the vasculature of a number of vital tissues (kidneys, heart, brain, mesentery) and mediate vasodilation. The effects of dopamine are particularly important during stress. Dopamine indirectly stimulates the heart's pumping action and directly enhances blood flow through vital tissues.

◆ COMMON ADVERSE EFFECTS

The effects of dopamine agonists are shown in Figure 26.17. Common adverse effects include effects on cardiac function (e.g. anginal pain, tachycardia, dysrhythmias), vascular function (e.g. hypotension, vasocontriction) and gastrointestinal function (nausea, vomiting). The latter disturbances occur because dopamine stimulates the vomiting centre in the medulla.

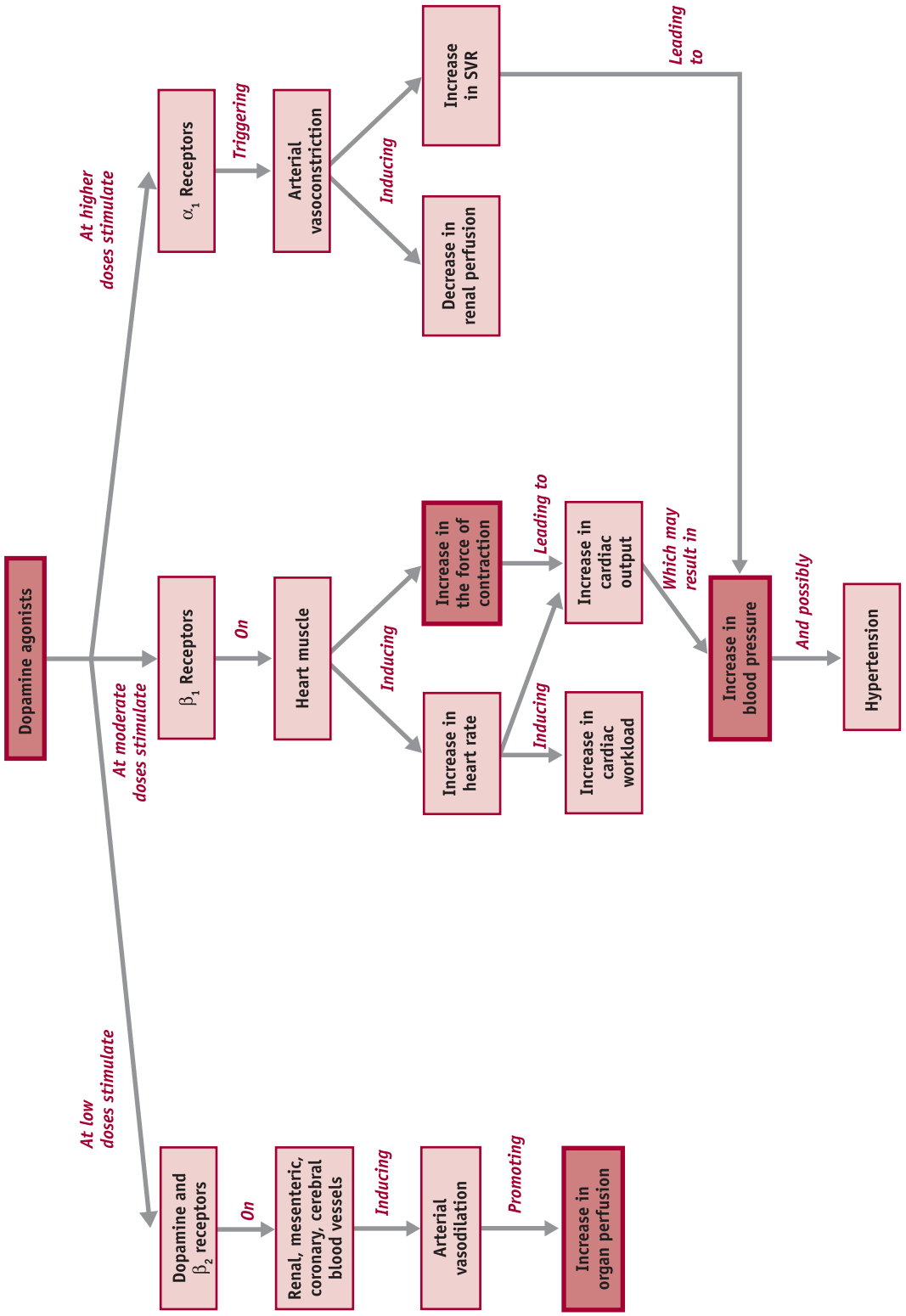
✚ CLINICAL CONSIDERATIONS

These effects have clinical application in circulatory shock, which is characterised by a deterioration of blood pressure and flow. Dopamine and its derivative dobutamine are used in this context to produce positive inotropic effects on the heart, reduce the heart's workload and maintain renal blood flow through the stimulation of both dopamine and adrenergic receptors. The advantage of dobutamine is that it is a direct-acting β_1 agonist; unlike drugs such as isoprenaline, dobutamine produces its inotropic effects without making the heart work harder by increasing its rate (positive chronotropy) as well.

Both dopamine and dobutamine are administered in special units that have facilities for the monitoring of blood pressure, cardiac rhythm and rate, central venous pressure, pulmonary wedge pressure, cardiac output and oxygenation. Dopamine should be administered in a large vein to prevent tissue necrosis.

FIGURE 26.17 FLOWCHART SHOWING THE EFFECTS OF DOPAMINE AGONISTS

Therapeutic effects are shown in the darker shaded boxes.



SVR, systemic vascular resistance.

CLINICAL MANAGEMENT

Sympathomimetics

Assessment

- Obtain baseline vital signs for the patient. Report any abnormal findings. These include blood pressure and rate, and rhythm of pulse. Assess colour and temperature of the patient's extremities (for drugs with α_1 effects). Conscious state is assessed to determine cerebral perfusion (this is an important consideration if the drug is administered intravenously for the purpose of maintaining blood pressure). Determine rate, rhythm and depth of respiration. Perform pre- and post-peak flow meter readings if the drug is used for asthma. Listen to the heart with a stethoscope for dysrhythmias and palpitations (for drugs with α_1 or β_1 effects). Compare the patient's apical beat with the radial rate. A difference indicates irregularity in rhythm. Determine urinary output and assess for bladder distension (for drugs with α_1 effects).
- Assess whether the patient has a history of the following:
  - glaucoma or prostatic hypertrophy (for drugs with α_1 effects);
  - cardiovascular, cerebrovascular or circulatory disease, hyperthyroidism (for drugs with α_1 or β_1 effects);
  - diabetes mellitus (for drugs with α_1 or β_2 effects). The sympathomimetic agent may intensify the condition. The situation would require further clarification with the prescriber.
- Determine whether the patient is taking monoamine oxidase inhibitors, beta-blockers or digoxin, as their effects can be either nullified or intensified by the administration of sympathomimetics.

Planning

- The patient's vital signs will remain within an acceptable range for the patient.
- The patient will experience minimal or no adverse effects from the sympathomimetic.

Implementation

- Carefully and regularly monitor the patient's vital signs, conscious state and urinary output.
- Sympathomimetics administered intravenously can produce profound effects on vital organs at small dosages. Their haemodynamic effects should, therefore, be monitored carefully and recorded. Dosages are then titrated according to the patient's response. A large central vein should be used for the administration of intravenous sympathomimetics to prevent peripheral necrosis. The use of intravenous sympathomimetics is restricted generally to clinical settings in which close monitoring of venous and arterial pressures, electrocardiogram (ECG) and urinary output can be performed.
- Report and record adverse effects of the sympathomimetic, including palpitations, tachycardia (pulse greater than 100 beats/min), tremors or increased glucose levels.
- Regularly monitor the patient's urinary output (for drugs with α_1 effects).
- Prolonged use of a sympathomimetic may lead to a diminished clinical effect, which is caused by a regulatory decrease in receptor numbers.

Patient teaching

- Drugs with β_2 effects are usually given by inhalation or nebuliser. Check the methods for inhalation and nebulisation (refer to Tables 7.17 and 7.18 in Chapter 7 for a description of methods).
- Instruct the patient on the method of administering cold or flu preparations by nasal spray and drops (refer to Tables 7.7 and 7.8 in Chapter 7 for description of methods).
- Instruct the patient that nasal sprays used in excess could lead to a rebound nasal congestion. Directions for dosage should be followed carefully.
- Excessive use of bronchodilator inhalers could lead to adverse effects such as tachycardia and skeletal muscle tremor. If asthma symptoms appear to be getting worse, the doctor should be consulted.
- Instruct the patient to read all labels of over-the-counter preparations. Many of these preparations contain sympathomimetics and should not be taken if the patient has a history of cardiac disease, diabetes, hypertension or cardiac dysrhythmias.

Evaluation

- Examine the patient's response to the sympathomimetic for expected and adverse effects. Continue to monitor vital signs and other aspects of assessment, depending on the drug used.
- Evaluate the effectiveness of the drug according to its expected action. The expected therapeutic effect may be to treat allergic reactions, anaphylactic shock, asthma or cardiac arrest.
- Examine the patient's use of preparations for self-administration. The use of these preparations may need to be reviewed to ensure safety and effectiveness.

Sympatholytics

Assessment

- Assess the patient's vital signs and conscious state. If the purpose of the sympatholytic is to lower the blood pressure, then assess the difference between lying and standing blood pressure, and dizziness on standing. This gives an indication of postural hypotension. If the drug is for chest pain, assess its effects on location, intensity and duration.
- Assess whether the patient has a history of the following:
  - Asthma: patients with asthma should take only β_1 cardioselective blockers (such as atenolol or metoprolol) and avoid non-selective beta-blockers (such as propranolol or oxprenolol) in order to prevent bronchoconstriction.
  - Congestive cardiac failure, bradycardia, heart block and cardiogenic shock (for drugs that block β_1 receptors): these drugs have the effect of slowing the heart, leading to pooling of blood in the peripheries and decreased force of contraction. The effects of such drugs will aggravate these disease states.
- Beta-blockers with a β_1-selective effect, such as atenolol and metoprolol, tend to produce less bronchospasm, less peripheral vasoconstriction and fewer alterations to glucose and lipid metabolism than other beta-blockers. They may be preferred in patients with peripheral vascular disease, Raynaud's syndrome, asthma and diabetes.
- Beta-blockers with an intrinsic sympathomimetic activity, such as oxprenolol and pindolol, may cause less bradycardia and less coldness of the extremities and fewer alterations to lipid profiles than other beta-blockers. They may, therefore, be preferred in patients with peripheral vascular disease; however, they could be less effective in treating angina and tachydysrhythmias.

Planning

- The patient's vital signs will remain within an acceptable range for the patient.
- The patient will experience minimal or no adverse effects from the sympatholytic.

Implementation

- Monitor the patient's vital signs. Report and document changes such as falls in blood pressure and pulse rate (for drugs that block β_1 receptors) or wheezing and dyspnoea (for drugs that block β_2 receptors).
- Report and document any manifestations of dizziness due to vasodilation by α_1-blockers. The dosage may need adjustment.
- Check the patient's lungs for oedema (indicated by crackles) and peripheries for oedema (indicated by a pitting mark when skin is pressed). Oedema is caused by vasodilation (an α_1-blocking effect) and decreased force and rate of contraction (a β_1-blocking effect).
- If the patient has diabetes and is receiving a drug that has α_1- or β_2-blocking properties, the dose of insulin or oral hypoglycaemic drug may need adjustment.

Patient teaching

- If the patient is taking a sympatholytic drug for hypertension, teach the patient and family how to take blood pressure and pulse so that these vital signs can be monitored at home.
- Teach the patient how to avoid dizziness and postural hypotension (see Tables 11.3 and 11.6 in Chapter 11).
- Advise male patients that alpha-blockers, such as prazosin and terazosin, can cause impotence, which may warrant a change in medication.
- The patient should be strongly advised not to stop taking the medication abruptly. This can lead to rebound hypertension, angina attacks and rebound tachycardia.
- Patients with diabetes should be encouraged to check their blood glucose levels regularly, as beta-blocking drugs can mask the manifestations of hypoglycaemia, including tachycardia and anxiety.
- Inform the patient and family that beta-blocking drugs can cause mood changes, such as vivid dreams and depression. If these adverse effects occur, the dosage or drug may need to be altered.

Evaluation

- Examine the patient's response to the sympatholytic for expected and adverse effects. Continue to monitor vital signs and other aspects of assessment depending on the drug used.
- Evaluate the effectiveness of the drug according to its expected action. The expected therapeutic effect may include the alleviation of hypertension, dysrhythmias, angina and the complications of acute myocardial infarction.

SUMMARY

- Adrenergic receptors are associated predominately with sympathetic effectors. There are four main subtypes of adrenergic receptors: α_1, α_2, β_1 and β_2.
- The catecholamines are important messengers in adrenergic function and comprise noradrenaline, adrenaline and dopamine.
- Adrenergic pharmacology is concerned with the following drug groups: α agonists and antagonists and β agonists and antagonists. In some instances, relatively selective drug groups have been developed to stimulate or block the subtypes of α and β receptors; this reduces the side effects of drug therapy.
- Agonists may also be called sympathomimetics; antagonists can be called sympatholytics.
- After the activation of an extracellular receptor, a membrane-bound enzyme catalyses the formation of a second-messenger chemical. The second messenger can activate a number of cellular processes that produce the desired cell response.
- Second-messenger systems may also include an intermediary between the receptor and the membrane-bound enzyme. This intermediary is called a G-protein. G-proteins can activate or inhibit the membrane-bound enzyme.
- Sympathomimetics can be used in the management of hypotension, asthma, nasal and ocular congestion, shock and cardiac arrest. Sympatholytics can be used in the treatment of hypertension, glaucoma, cardiac disease and thyroid disease.

1 Outline the process of adrenergic nerve stimulation and transmitter inactivation.

2 Name the chemical messengers involved in adrenergic stimulation of sympathetic effectors.

3 What are the types of adrenergic receptor present in the human body?

4 Indicate whether the following effects are related to an action at α_1, α_2, β_1 or β_2 receptors and whether the action is that of an agonist or antagonist:
(a) elevated blood pressure;
(b) decreased heart rate;
(c) pupil dilation;
(d) bronchodilation;
(e) glycogenolysis.

5 State three adverse reactions associated with each of the following adrenergic drug groups:
(a) α_1 agonists;
(b) β_1 antagonists;
(c) β_2 agonists;
(d) non-selective α and β antagonists.

6 Outline the processes involved in a second-messenger system.

7 Mario Molitario, who suffers from asthma, visits the community health centre to have his condition and medication reviewed. He comments to the community nurse that a local general practitioner has put him on propranolol (a non-selective beta-blocker) for high blood pressure. What would the community health nurse query about this medication? Why?

8 What are the major adverse effects of sympathomimetics? What are the implications for patient teaching?

9 Dopamine produces sympathetic effects in the periphery. Does it induce these effects by stimulating dopamine or adrenergic receptors? For what conditions could dopamine administration be therapeutically beneficial?

10 What are the major adverse effects of sympatholytics? What are the implications for patient teaching?

11 What potential problem is associated with administering short-term beta-blocker treatment to a patient suffering from congestive cardiac failure? Explain your answer with reference to the mechanism of action of beta-blockers.

12 β_2 agonists produce bronchodilation as a therapeutic effect and tachycardia and skeletal muscle tremor as adverse effects. Explain these effects with reference to the mechanism of action of this group.

13 Cecilia Wong is diagnosed with glaucoma. Her drug therapy for this condition comprises the beta-blocker timolol and the α_2 agonist apraclonidine. These medicines are administered as eye drops. What are the advantages of this route of administration?

14 Bill Caries is 28 years of age and is suffering from depression. He is being treated for this with a monoamine oxidase (MAO) inhibitor. What is the role of MAO in adrenergic nerve function? What would you expect this medicine to do to the synaptic levels of the neurotransmitter noradrenaline?

26 DRUG SUMMARY TABLE: ADRENERGIC PHARAMACOLOGY

FAMILY NAME	GENERIC NAME	TRADE NAME(S)
Non-selective sympathomimetics	Adrenaline/epinephrine	EpiPen preparations
	Dipivefrine	Propine
	Dopamine	
	Ephedrine	
	Metaraminol	
	Noradrenaline/norepinephrine	
	Pseudoephedrine	Galpseud
		Sudafed preparations
Alpha agonists	Oxymetazoline	
	Phenylephrine	
	Xylometazoline	Otrivine
		Otraspray
Alpha-2 agonists	Apraclonidine	Iopidine
	Brimonidine	Combigan
	Clonidine	Catapres
		Dixarit
Beta agonists (non-selective)	Isoprenaline	
Beta-1 agonists (cardioselective)	Dobutamine	
Beta-2 agonists	Bambuterol	Bambec
	Formoterol	Atimos Modulite
		Foradil
		Oxis
	Orciprenaline	Alupent
	Salbutamol	Airomir
		Asmasal
		Salamol
		Ventmax
		Ventolin
		Volmax
	Salmeterol	Serevent
	Terbutaline	Bricanyl

FAMILY NAME	GENERIC NAME	TRADE NAME(S)
Alpha antagonists (non-selective)	Phenoxybenzamine	Dibenyline
	Phentolamine	Rogitine
Alpha-1 antagonists	Doxazosin	Cardura
	Prazosin	Hypovase
	Tamsulosin	Flomaxtra
	Terazosin	Hytrin
Beta-blockers (non-selective)	Acebutolol	Sectral
	Carvedilol	Eucardic
	Levobunolol	Betagan
	Nadolol	Corgard
	Oxprenolol	Trasicor
	Pindolol	Visken
	Propranolol	Inderal
	Sotalol	Beta-Cardone
		Sotacor
	Timolol	Betim
Beta-blockers (cardioselective)	Atenolol	Tenormin
	Betaxolol	Betoptic
	Bisoprolol	Cardicor
		Emcor
	Esmolol	Brevibloc
	Metoprolol	Betaloc
		Lopresor
Beta and alpha receptor blockers	Celiprolol	Celectol
	Labetalol	Trandate
Centrally acting sympathetic depressant	Methyldopa	Aldomet
Adrenergic nerve blockers	Guanethidine	Ismelin
	Tetrabenazine	Xenazine

CHOLINERGIC PHARMACOLOGY

27

CHAPTER TWENTY-SEVEN

OBJECTIVES

After completing this chapter, the reader should be able to:

- **outline the mechanism of cholinergic nerve stimulation, transmitter release and deactivation;**
- **identify the subtypes and distribution of cholinergic receptors in the body;**
- **list the effects of cholinergic receptor stimulation and, from this, derive the effects of cholinergic receptor blockade;**
- **derive the side effects and clinical applications of cholinergic agents from a knowledge of cholinergic receptor distribution and autonomic nervous system effects;**
- **compare aspects of cholinergic and adrenergic pharmacology in terms of similarities and differences.**

KEY TERMS

Autonomic nervous system
Cholinergic nerves
Cholinergic receptors
Muscarinic receptors
Nicotinic receptors
Parasympathetic nervous system
Sympathetic nervous system

ALL PARASYMPATHETIC EFFECTORS, SOME SYMPATHETIC effectors, all autonomic ganglia and voluntary muscles bear cholinergic receptors. As a consequence, cholinergic drugs may affect the function of both divisions of the autonomic nervous system (sympathetic and parasympathetic) and the somatic nervous system.

MECHANISMS OF CHOLINERGIC ACTION

When a cholinergic nerve is stimulated, the action potential travels to the presynaptic terminal (see Figure 27.1). The action potential triggers the release of the chemical transmitter acetylcholine (ACh) from the synaptic vesicles into the synaptic gap. This transmitter diffuses across the gap, eventually interacting with postsynaptic cholinergic receptors located on the surface of either the effector or the postganglionic cell body. This triggers either an effector response or a continuation of the nerve impulse along the postganglionic fibre, respectively.

Inactivation of the transmitter is achieved mostly through rapid enzymatic degradation within the synaptic gap, although at autonomic ganglia simple diffusion away from the postsynaptic receptors may be important. The enzyme responsible for the degradation is called acetylcholinesterase. Acetylcholinesterase is highly specific to acetylcholine and is localised to nervous and skeletal muscle tissue. It breaks down acetylcholine into choline and acetate molecules. Chemical conservation comes into play here; nothing is wasted. The choline fragment of the acetylcholine molecule is taken back up into the presynaptic terminal, where it may be reformed as acetylcholine and returned to the synaptic vesicles for reuse. The acetate is used in energy production. Compared with the inactivation of noradrenaline, the neuronal and extraneuronal breakdown of acetylcholine is swift. As a result, the action of acetylcholine is relatively short-lasting.

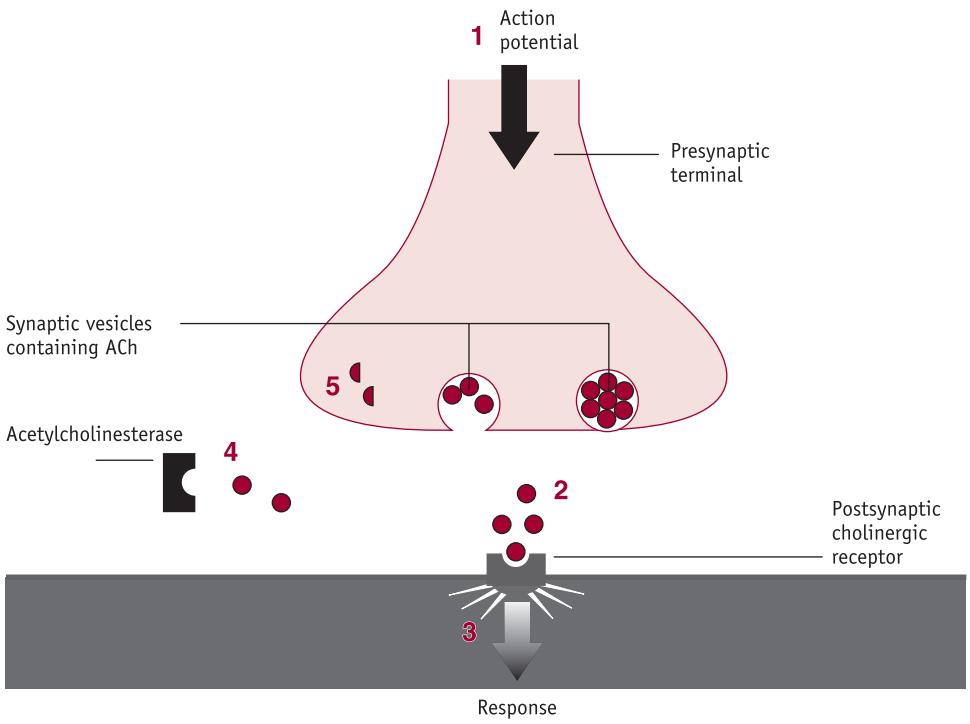
There are other relatively non-specific cholinesterases present in blood and other tissues whose roles are not fully elucidated but that appear to be the local modulation of the response to acetylcholine. These are called pseudocholinesterases.

CHOLINERGIC RECEPTOR STIMULATION

Like adrenergic receptors, two main subtypes of cholinergic receptor have been identified. One group of receptors responds to stimulation by **nicotine**; these are

FIGURE 27.1 CHOLINERGIC NERVE STIMULATION

A summary of events involved in cholinergic nerve stimulation. The action potential travels along the axon until it reaches the nerve terminal (1). Depolarisation of the terminal causes the release of the chemical transmitter acetylcholine (ACh) into the synaptic gap (2). ACh diffuses across the gap and interacts with cholinergic postsynaptic receptors, triggering an effector response (3). The transmitter is removed from the synaptic gap by an enzyme called acetylcholinesterase (4). Choline is taken back up into the presynaptic terminal to contribute to the synthesis of new transmitter (5).



termed nicotinic receptors. The other group responds to a chemical, muscarine, extracted from the toadstool *Amanita muscaria*; these are termed muscarinic receptors. Both subtypes can be activated by acetylcholine but bear subtle structural differences that have enabled the pharmacologist to develop cholinergic agents specific to one subtype of receptor.

Nicotinic receptors

Nicotinic receptors are located centrally, in autonomic ganglia and in the neuromuscular junction of skeletal muscles.

■ MECHANISM OF ACTION

The effects of stimulating these receptors are as follows:

- behavioural changes, including feelings of relaxation and wellbeing;
- an increase in autonomic tone above the resting state of activity of both parasympathetic and sympathetic effectors;
- release of adrenaline and noradrenaline from the adrenal medulla. This occurs because the adrenal medulla is a modified autonomic ganglion;
- an increase in skeletal muscle tone.

◆ COMMON ADVERSE EFFECTS

The wanted and unwanted effects of stimulating nicotinic receptors are shown in Figure 27.2 (opposite) and Figure 27.3 (on p. 242). Essentially, at the doses absorbed during smoking, nicotine is a stimulant in which many of the peripheral effects (particularly cardiovascular) are brought about via an increase in autonomic tone. Nicotine treatment for people trying to quit cigarette smoking mimics these effects. Adverse effects include cardiovascular stimulation, headache, nausea and insomnia. Nicotine patches can cause skin reactions such as itching, burning and redness.

Nicotine therapy is contraindicated in pregnancy and lactation, in patients with known hypersensitivity and in patients with serious cardiovascular conditions, e.g. acute myocardial infarction, unstable angina, recent cerebrovascular accident or dysrhythmia.

✚ CLINICAL CONSIDERATIONS

Clinical applications of nicotinic receptor stimulation include overcoming skeletal muscle weakness (which characterises motor neuron disease and muscle-wasting disorders) and controlling nicotine dependence associated with cigarette smoking. There are no direct-acting nicotinic agonists used in the treatment of conditions affecting skeletal muscle function. These conditions are best treated using anticholinesterases (see later in this chapter).

People who want to give up smoking may be treated with preparations containing nicotine in the form of transdermal patches, lozenges, chewing gum, a nasal spray or an oral inhalant (see Chapter 23). Therapy is centred around a behavioural-modification programme, while the drug treatment decreases the symptoms of nicotine withdrawal. Treatment should be continued for at least 12 weeks, which includes a tapering period. Individuals who have made multiple attempts at stopping smoking may also benefit from combining patch and gum formulations. It is important to remember that nicotine is a poison, which needs to be kept away from children and pets. Smoking while taking nicotine preparations can lead to toxicity, resulting in vomiting, palpitations, nausea and chest pain.

Muscarinic receptors

Muscarinic receptors are located both centrally and peripherally. Peripheral muscarinic receptors are found on the surfaces of effectors stimulated by cholinergic nerves – that is, all parasympathetic and some sympathetic effectors. More specifically, these receptors are found on the following peripheral tissues: iris, sweat glands, lacrimal glands, digestive glands, myocardium, bronchioles, gastrointestinal tract, urinary tract, liver and sex organs, and blood vessels of the skin, genitalia and skeletal muscle.

■ MECHANISM OF ACTION

Five distinct functional subtypes of muscarinic receptors have been identified, known as M_1, M_2, M_3, M_4 and M_5 receptors. The physiological roles of M_4 and M_5 receptors remain unclear. M_1 muscarinic receptors are associated predominantly with the brain and mediate higher cerebral function; reduction in receptor numbers within the cerebral cortex has been linked to dementias such as Alzheimer's disease (see Chapter 36). Interestingly, all five subtypes have been found in the brain. M_1 receptors are also found peripherally on the parietal cells of the stomach and stimulate increased acid secretion and on postganglionic neurons at autonomic ganglia. M_2 receptors are located on the myocardium and when stimulated trigger a decrease in the rate and force of contraction of the heart (negative inotropic and chronotropic effects; see Chapter 26).

M_3 muscarinic receptors are associated with visceral smooth muscle and exocrine glands. Stimulation of these receptors causes the following parasympathetic-like effects:

- pupil constriction (miosis) and increased rate of drainage of aqueous humour from the anterior cavity of the eye;
- relaxation of gastrointestinal sphincters, increased gastrointestinal motility and increased secretion of digestive juices (saliva, pancreatic juice, bile);
- promotion of micturition and defecation;
- promotion of glycogenesis and gluconeogenesis – increases insulin secretion;
- promotion of lacrimal secretion (tears);
- bronchoconstriction and increased bronchial mucus secretion.

FIGURE 27.2 FLOWCHART SHOWING THE EFFECTS OF NICOTINIC RECEPTOR AGONISTS

Therapeutic effects are shown in the darker shaded boxes.

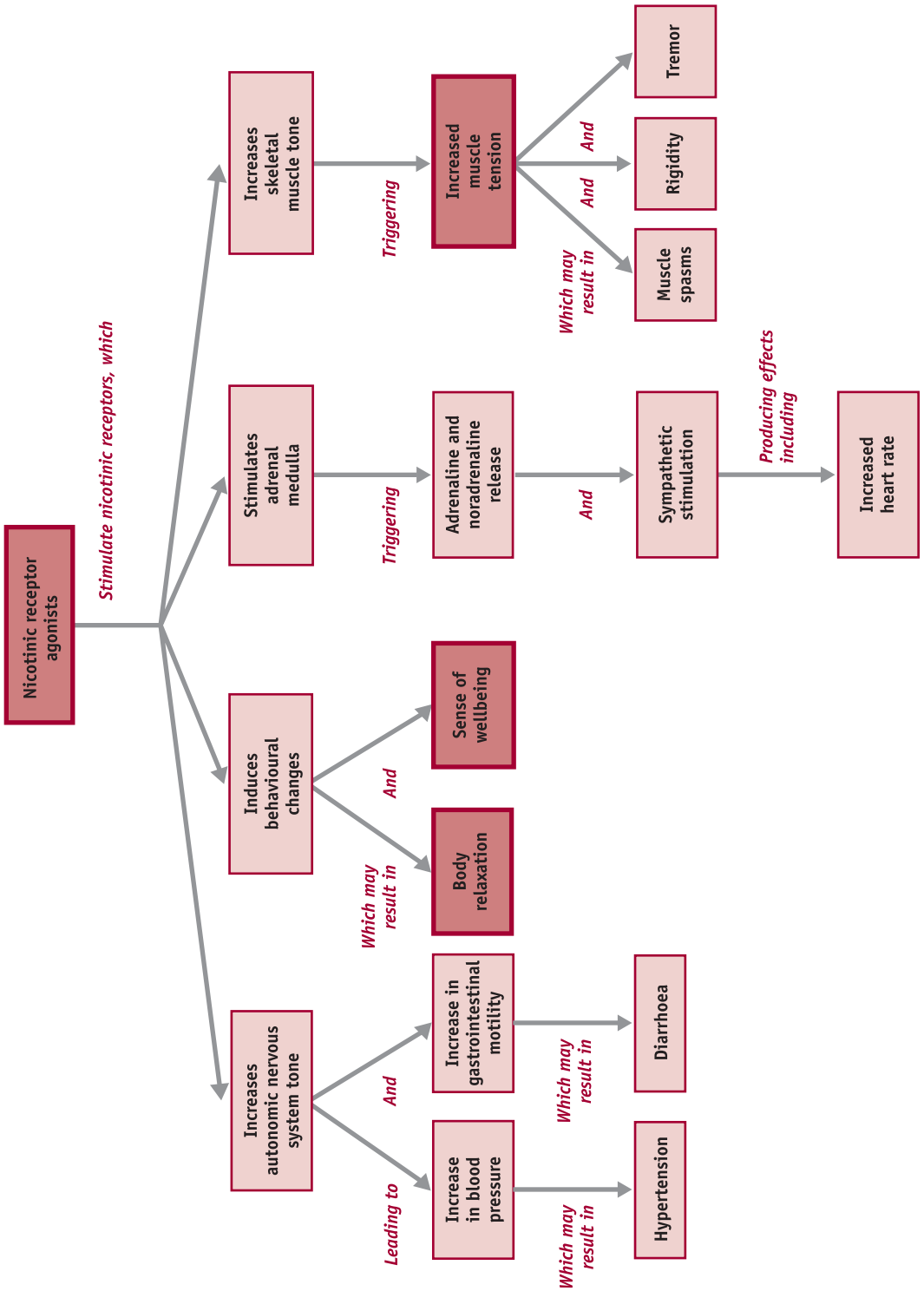
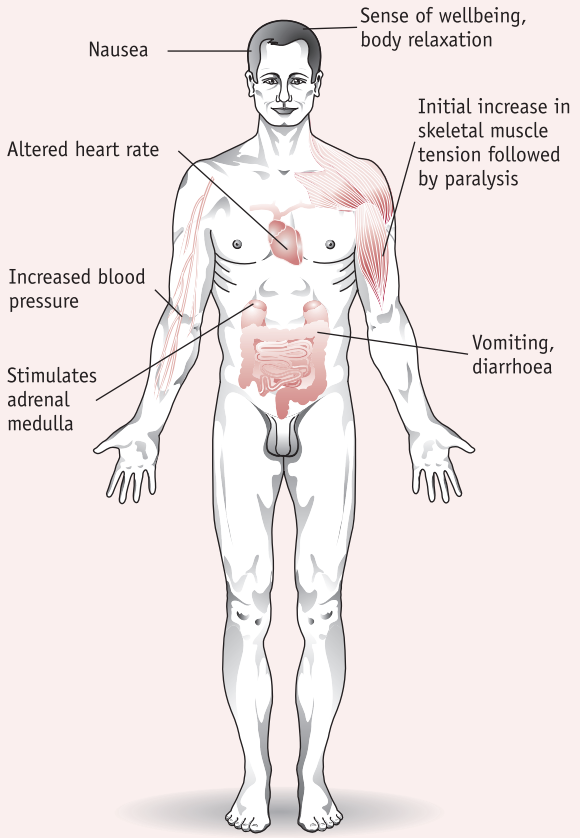


FIGURE 27.3 EFFECTS OF NICOTINIC RECEPTOR AGONISTS



Stimulation of these receptors induces the following sympathetic responses:

- vasoconstriction of blood vessels associated with the skin and external genitalia;
- vasodilation of blood vessels to skeletal muscle;
- generalised sweating.

◆ COMMON ADVERSE EFFECTS

Figures 27.4 (a and b) and 27.5 show the therapeutic and adverse effects of muscarinic receptor stimulation. Figure 27.6 summarises the agonist effects associated with the stimulation of all types of peripheral cholinergic receptor. Common adverse effects depend on the desired clinical effect but can include bradycardia, hypotension, pupil constriction, sweating, bronchoconstriction, drooling and diarrhoea. Contraindications include intestinal and urinary obstruction.

CLINICAL CONSIDERATIONS

Acetylcholine, **bethanechol**, **carbachol** and **pilocarpine** are direct-acting muscarinic agonists. **Cisapride** is an indirect-acting cholinergic agent that stimulates the release of acetylcholine from the myenteric plexus. The release of endogenous transmitter from this plexus stimulates gastrointestinal motility.

Clinical applications for these agents include the treatment of mydriasis, glaucoma, constipation and other gastrointestinal conditions characterised by diminished motility, urinary retention and tachycardia.

FIGURE 27.4A FLOWCHART SHOWING THE EFFECTS OF MUSCARINIC RECEPTOR (M_1 AND M_2) AGONISTS

Therapeutic effects are shown in the darker shaded boxes.

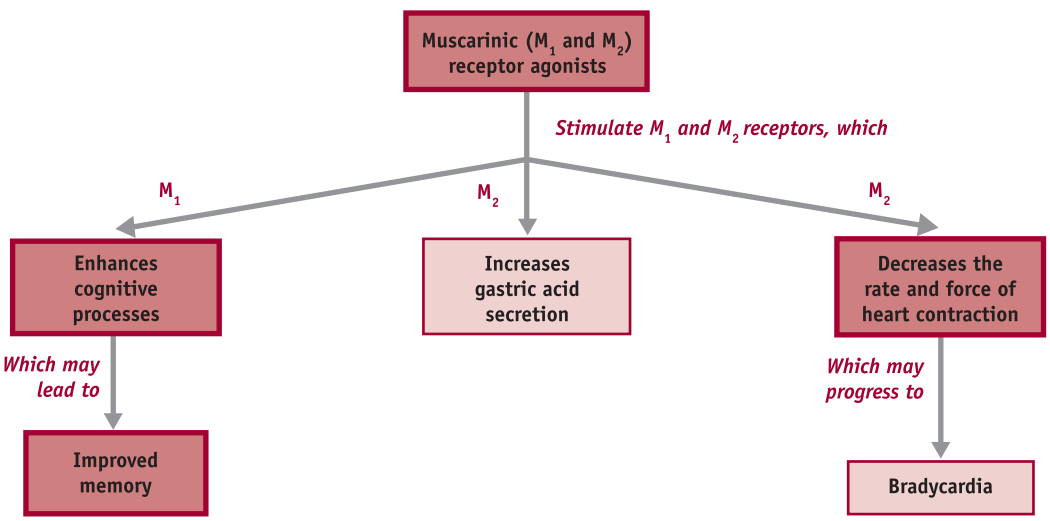


FIGURE 27.4B FLOWCHART SHOWING THE EFFECTS OF MUSCARINIC RECEPTOR (M_3) AGONISTS

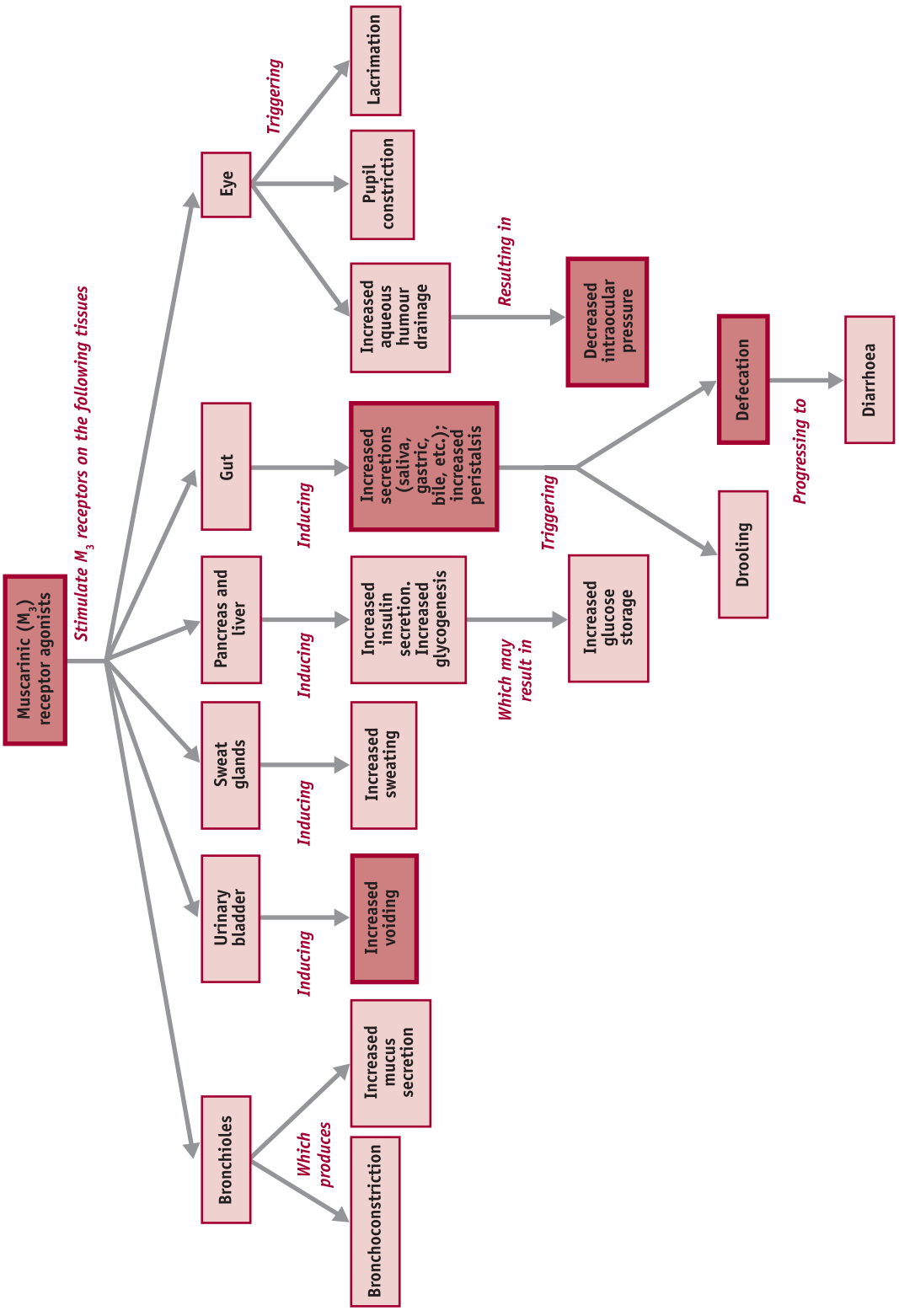
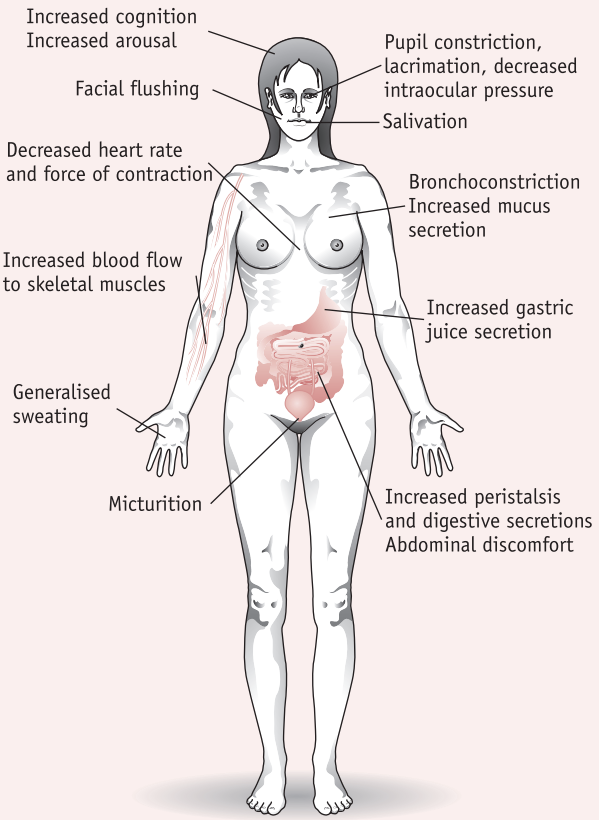


FIGURE 27.5 EFFECTS OF MUSCARINIC RECEPTOR AGONISTS



When using these agents for the treatment of glaucoma, it is important to start with a low dose and then increase slowly in order to minimise the incidence of adverse effects. Miosis may become a permanent effect following long-term use, which can constrict the visual field and impair vision in dim light.

When using drugs such as bethanechol and carbachol to stimulate bladder emptying, it is advisable to exclude the possibility of bladder-neck obstruction before treatment.

ANTICHOLINESTERASES

■ MECHANISM OF ACTION

Muscarinic agonist drugs specifically stimulate muscarinic receptors and therefore mimic the effects of acetylcholine at these receptors, but there is another important group of cholinergic stimulants that are yet to be discussed. These agents reversibly inactivate the cholinesterase enzymes responsible for the degradation of acetylcholine. Remember from the mechanism of cholinergic action earlier that the predominant form of cholinesterase in nervous and muscle tissue is acetylcholinesterase, whereas pseudocholinesterases are found in blood and other tissues. As a result, the action of acetylcholine in the synapse and in other tissues is prolonged. These indirect-acting drugs are called the anticholinesterases (not to be confused with the anticholinergic (antimuscarinic) agents, which are antagonists) and will enhance the action of endogenous acetylcholine at both nicotinic and muscarinic receptors. Therefore, the observed effects (both desired and adverse) will be represented by the agonist columns of both nicotinic and muscarinic receptors in Figure 27.6.

◆ COMMON ADVERSE EFFECTS

The desirable and undesirable effects of the anticholinesterases are shown in Figures 27.2 and 27.4. Common adverse effects include pupil constriction, hypotension, bradycardia, diarrhoea, muscle twitching, bronchoconstriction, increased lacrimation and sweating.

✚ CLINICAL CONSIDERATIONS

The principal uses of the anticholinesterases are in the treatment of postoperative urinary retention, Alzheimer's disease (see Chapter 36) and conditions of the neuromuscular junction, such as myasthenia gravis and motor neuron disease. They are also used in cases of overdose with either the muscarinic antagonist atropine or muscle relaxants (nicotinic antagonists). Anticholinesterases include **donepezil**, **galantamine**, **pyridostigmine**, **neostigmine** and **physostigmine**. **Edrophonium** is a very short-acting anticholinesterase with a duration of action of about 10 minutes.

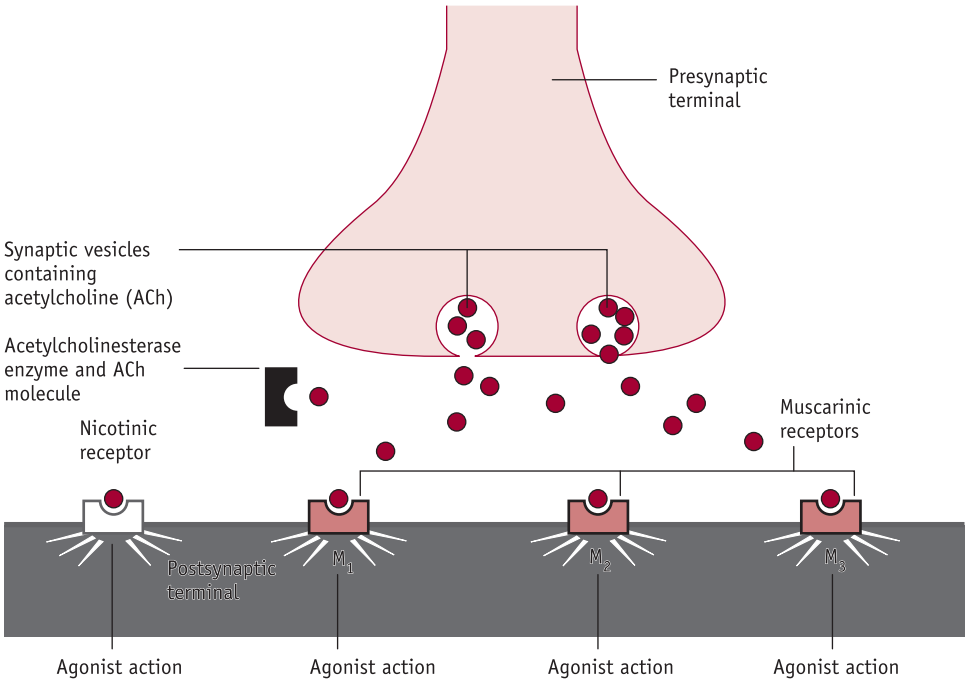
When giving anticholinesterases to reverse the effects of neuromuscular blocking agents, atropine or propantheline is also necessary in order to minimise the muscarinic adverse effects.

When using an anticholinesterase to treat myasthenia gravis, it is important to know how to distinguish between drug-induced weakness and weakness caused by the disease itself. Medications used for myasthenia gravis should be taken early in the day because it is during this time that muscle weakness and fatigue are most severe.

Overdose with an anticholinesterase may lead to a cholinergic crisis, as demonstrated by excessive sweating, defecation, urination, miosis, salivation, bradycardia and muscle weakness. As it may be difficult to determine the difference between a cholinergic crisis (excessive dose) and a myasthenic crisis (insufficient dose), an edrophonium test can be used as a diagnostic tool. If the weakness improves, then it is due to the myasthenia disease and more anticholinesterase is warranted. There is a risk, however, that in cholinergic crises the overstimulation of nicotinic receptors at the neuromuscular junction will prevent repolarisation of the end plate and induce paralysis. Resuscitation equipment should be on hand during the procedure. It may be more prudent in this situation to cease therapy and reassess the patient.

FIGURE 27.6 CHOLINERGIC AGONIST EFFECTS

This shows a summary of the effects of systemic stimulation of each subtype of muscarinic receptor and nicotinic receptors located within autonomic ganglia and the neuromuscular junction.



Autonomic ganglia
- increased autonomic tone

Neuromuscular junction
- increased skeletal muscle tone

M_1 receptors
- enhanced cognition
- increased gastric acid secretion

M_2 receptors
- decreased rate and force of cardiac contraction

M_3 receptors
- pupil constriction and increased aqueous humour drainage
- increased gastrointestinal motility
- increased digestive juice secretion
- promotion of micturition
- defecation
- increased insulin secretion
- promotes glycogenesis and gluconeogenesis
- lacrimal gland secretion
- generalised sweating
- increased blood flow to skeletal muscles
- bronchoconstriction and increased bronchial mucus secretion

CHOLINERGIC SECOND-MESSENGER SYSTEMS

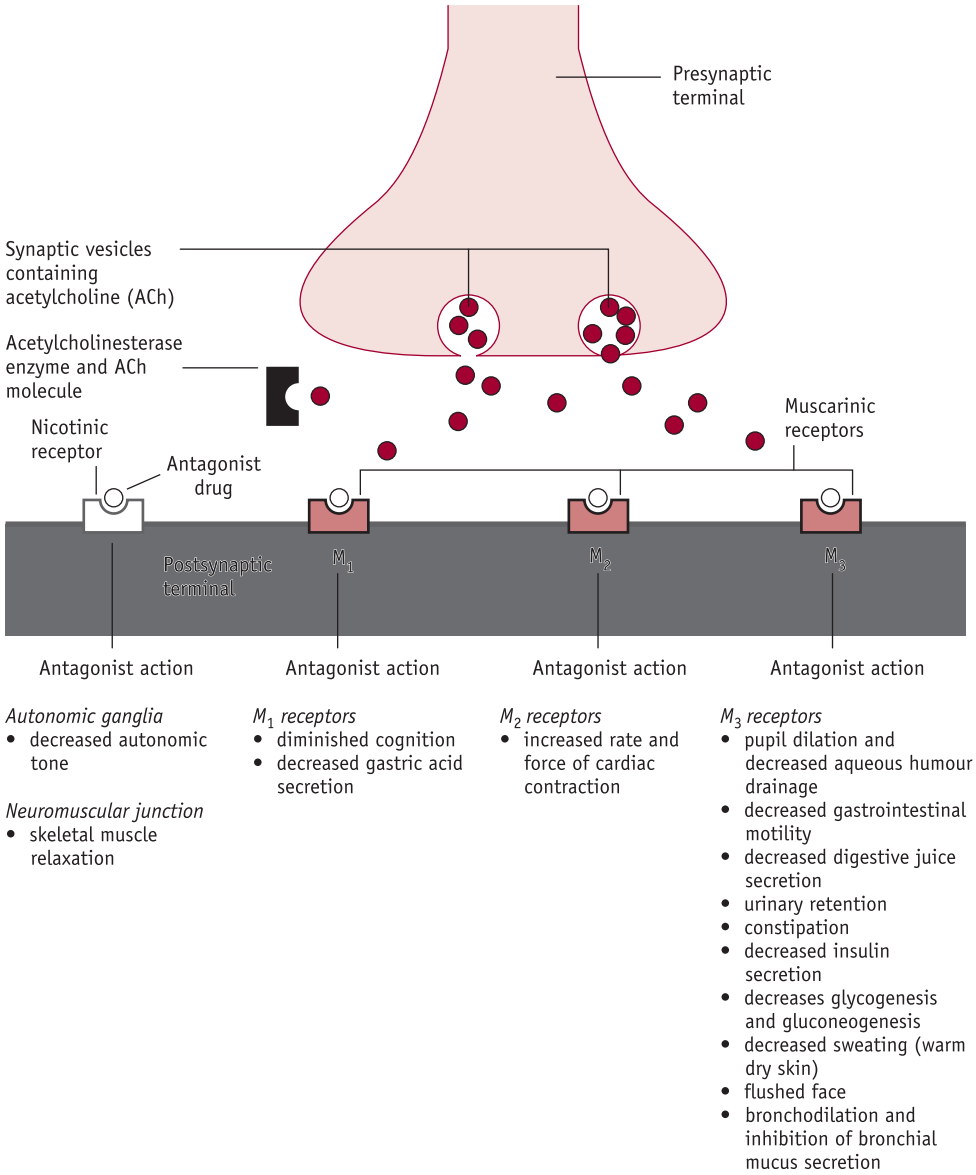
While nicotinic receptor activation leads to the opening of ion channels, muscarinic receptor activation involves second-messenger systems. Stimulation of M_2 and M_4 receptors results in a decrease in intracellular cyclic adenosine monophosphate (cAMP) via an inhibition of adenylate cyclase (see Chapter 26). Not surprisingly, the myocardial responses observed following muscarinic receptor stimulation are the opposite of those seen after β adrenoreceptor activation. Stimulation of other muscarinic receptor subtypes leads to inositol triphosphate (IP_3) and diacylglycerol (DAG) production (see Chapter 26), which act as second messengers.

CHOLINERGIC RECEPTOR BLOCKADE

Like adrenergic receptor blockade, cholinergic antagonism prevents the normal effector response from occurring. As a result, the usual observed effects of antagonist agents are often the opposite of those of stimulation. The effects of cholinergic receptor blockade are represented in Figure 27.7.

FIGURE 27.7 CHOLINERGIC ANTAGONISTIC EFFECTS

Effects of systemic blockade of nicotinic receptors and each subtype of muscarinic receptor.



Nicotinic antagonists

✚ CLINICAL CONSIDERATIONS

Clinically, antagonists at nicotinic receptors have been used for two purposes: (i) as ganglionic blockers, to diminish transmission through autonomic ganglia as a means of inducing vasodilation of systemic blood vessels which control blood pressure; and (ii) as neuromuscular blocking agents given before surgery (e.g. in order to intubate a patient) and in the treatment of painful skeletal muscle spasms caused by trauma and disease.

Ganglion blockers

■ MECHANISM OF ACTION

Today, ganglion blockers have largely been replaced by safer adrenergic antagonists (see Chapter 26). **Propantheline** has some ganglion blocking activity, but its predominant action is as a muscarinic receptor antagonist (described later in this chapter).

◆ COMMON ADVERSE EFFECTS

Common adverse reactions occur as a result of decreased autonomic tone and include diminished gastrointestinal

motility, urinary retention and impaired accommodation. Propantheline is contraindicated in patients with serious cardiovascular disease or pyloric stenosis. The desirable and undesirable effects of the nicotinic receptor antagonists are shown in Figures 27.8 and 27.9.

Neuromuscular blocking agents

Neuromuscular blocking agents that act at the neuromuscular junction, as opposed to the true muscle relaxants discussed in Chapter 37, are classified as either depolarising or non-depolarising.

DEPOLARISING NEUROMUSCULAR BLOCKING AGENTS

■ MECHANISM OF ACTION

Suxamethonium, or succinylcholine, is the only clinical representative of a depolarising nicotinic agonist. Suxamethonium is similar to acetylcholine and acts as an acetylcholine agonist on nicotinic receptors. Unlike acetylcholine, however, suxamethonium is not destroyed by acetylcholinesterase; therefore, when suxamethonium acts on the nicotinic receptors, its action is sustained. This prevents repolarisation of the end plate, and paralysis ensues. The action of suxamethonium as an agonist can be seen immediately after it is injected: the muscles of the patient's body, from toe to the scalp, go into spasm. The spasms are very noticeable and are known as muscle fasciculations. This lasts only a second or so and then the patient goes flaccid.

◆ COMMON ADVERSE EFFECTS

Suxamethonium may cause muscular pain during induction and when the patient returns to consciousness; this effect may be due to the muscle fasciculations. Suxamethonium can also cause hyperkalaemia, which can result in cardiac arrest and increased intraocular pressure.

Another problem seen occasionally with suxamethonium is malignant hyperthermia, which results in severe muscle rigidity and body temperatures of over 41 °C. The apparent cause of this condition is the release of large numbers of calcium ions into the sarcoplasm. This increases the metabolic activity of all the body's skeletal muscle, resulting in muscle rigidity and hyperthermia. This is a life-threatening condition and requires prompt treatment to reduce the body temperature and to reverse the muscle spasm. Body temperature can be lowered by conventional methods and the muscle spasm can be treated by the use of intravenous **dantrolene** (see Chapter 37). Malignant hyperthermia does not necessarily occur during surgery but can happen postoperatively in the ward, hence the need for close surveillance of patients after anaesthetic procedures. Patients known to be at risk can be given dantrolene prophylactically.

Suxamethonium is contraindicated in narrow-angle glaucoma, in penetrating eye injuries and in burns patients. Evidence of pharmacogenetic variation in pseudocholinesterase levels (see Chapter 18) is also a contraindication, as is a known drug hypersensitivity.

✚ CLINICAL CONSIDERATIONS

The action of suxamethonium is terminated by the enzyme pseudocholinesterase after about 4–5 minutes, and so if sustained paralysis is required the drug must be administered by a drip set. Other, longer-acting neuromuscular blocking agents are normally used for prolonged paralysis. As suxamethonium acts rapidly, it is useful for abolishing the gag reflex, enabling speedy intubation of the patient. It is also the preferred neuromuscular blocking agent for electroconvulsive therapy (ECT). It does not require a reversal drug because its duration of action is very short.

When the effects of neuromuscular blockade are reversed, the return of normal neuromuscular function should be assessed. If these agents are administered long term to a critically ill patient, they must be accompanied by a suitable sedative, such as a benzodiazepine.

NON-DEPOLARISING NEUROMUSCULAR BLOCKING AGENTS

■ MECHANISM OF ACTION

Non-depolarising blockers are antagonistic towards acetylcholine and completely block the receptors. This results in non-depolarisation of the motor end plate, and complete paralysis sets in without any fasciculations occurring. Non-depolarising agents include **atracurium**, **cisatracurium**, **mivacurium**, **pancuronium**, **rocuronium** and **vecuronium**. Cisatracurium is a single isomer of atracurium. The prototype agent in this class is tubocurarine. Its clinical use has been superseded by these newer, safer agents. Tubocurarine remains of historical interest and is outlined in Chapter 1.

The non-depolarising agents have an advantage over suxamethonium in that their action can be reversed. As they compete with acetylcholine for the receptors, their reversal can be obtained by increasing the amount of acetylcholine at the neuromuscular junction. This is done by giving an acetylcholinesterase inhibitor, such as neostigmine.

◆ COMMON ADVERSE EFFECTS

Some of the non-depolarising neuromuscular blocking agents, including mivacurium, rocuronium and atracurium, can induce histamine release, which can lead to a drop in blood pressure and bronchospasm. Atracurium is unusual in that it is metabolised by a chemical process (i.e. enzymes are not involved); therefore, it can be given with comparative safety to patients with circulatory, hepatic and renal problems.

Neither cistracurium nor pancuronium causes histamine release, but pancuronium may produce tachycardia.

FIGURE 27.8 FLOWCHART SHOWING THE EFFECTS OF NICOTINIC RECEPTOR ANTAGONISTS

Therapeutic effects are shown in the darker shaded boxes.

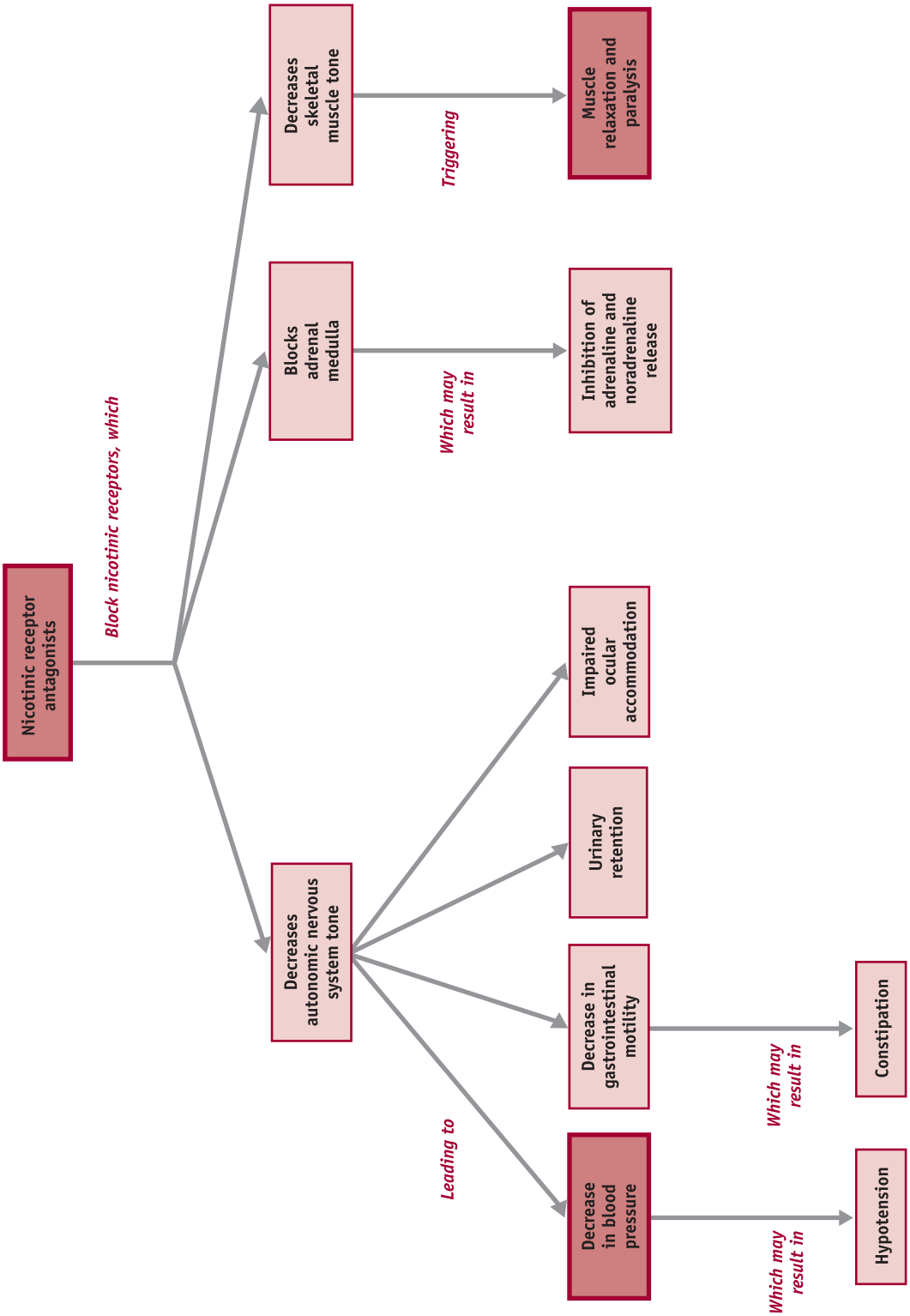
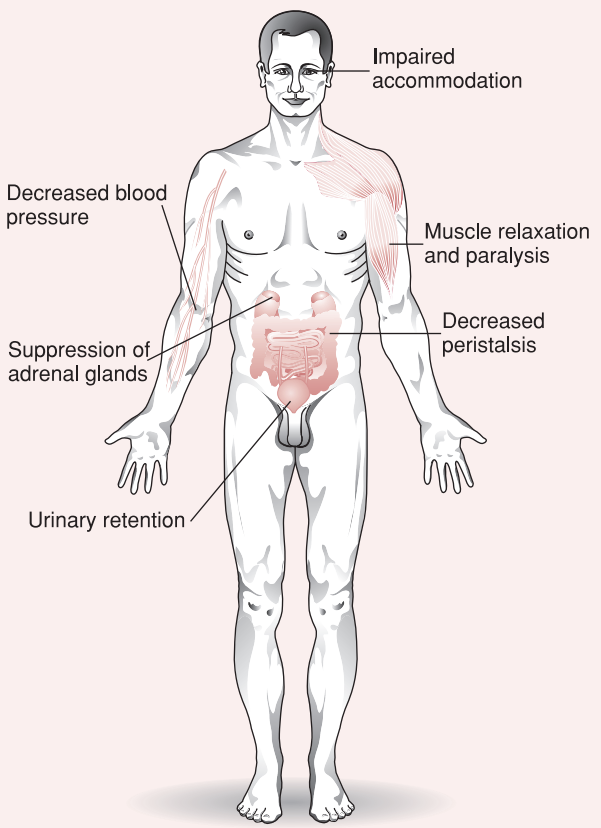


TABLE 27.1 PHARMACOKINETIC PROFILES OF SOME NON-DEPOLARISING NEUROMUSCULAR BLOCKING AGENTS

Drug	Elimination half-life (min)	Time taken to onset of muscle relaxation	Duration of effect (min)
Atracurium	20	2 min	35–40
Mivacurium	2	2–2.5 min	15–20
Pancuronium	120	45–90 s	25
Rocuronium	73	60 s	30–40
Vecuronium	60–80	90–120 s	20–30

FIGURE 27.9 EFFECTS OF NICOTINIC RECEPTOR ANTAGONISTS



Vecuronium does not produce tachycardia or induce histamine release; it is commonly used during and following open-heart surgery. These agents are contraindicated where there is known evidence of hypersensitivity.

✚ CLINICAL CONSIDERATIONS

The non-depolarising agents vary somewhat in their onset and duration of action. The pharmacokinetic profile of each drug determines which is chosen in a particular clinical situation (see Table 27.1 for examples).

When the effects of neuromuscular blockade are reversed, the return of normal neuromuscular function should be assessed. If these agents are administered long term to a critically ill patient, they must be accompanied by a suitable sedative, such as a benzodiazepine. Non-depolarising agents, for example atracurium and cisatracurium, require a reversal drug in the form of an anticholinesterase, such as neostigmine. As anticholinesterases can produce profound muscarinic effects (e.g. hypotension, bradycardia, increased gastric motility), atropine is often also administered. Emergency cardiac and respiratory equipment and medications must be available in case respiratory depression or circulatory collapse occurs.

Muscarinic antagonists

■ MECHANISM OF ACTION

Muscarinic antagonists block muscarinic receptors. At this time, no selective antagonists of individual muscarinic receptor subtypes are available in the UK. Muscarinic antagonists are generally known as anticholinergic drugs but are more correctly called antimuscarinic drugs. The group consists of the following agents: **atropine**, **hyoscine** and **hyoscyamine** (the belladonna alkaloids), **glycopyrronium**, **ipratropium**, **homatropine**, **dicycloverine** (dicyclomine), **mebeverine**, **tropicamide**, **tiotropium**, **tolterodine**, **cyclopentolate** and **propantheline**.

◆ COMMON ADVERSE EFFECTS

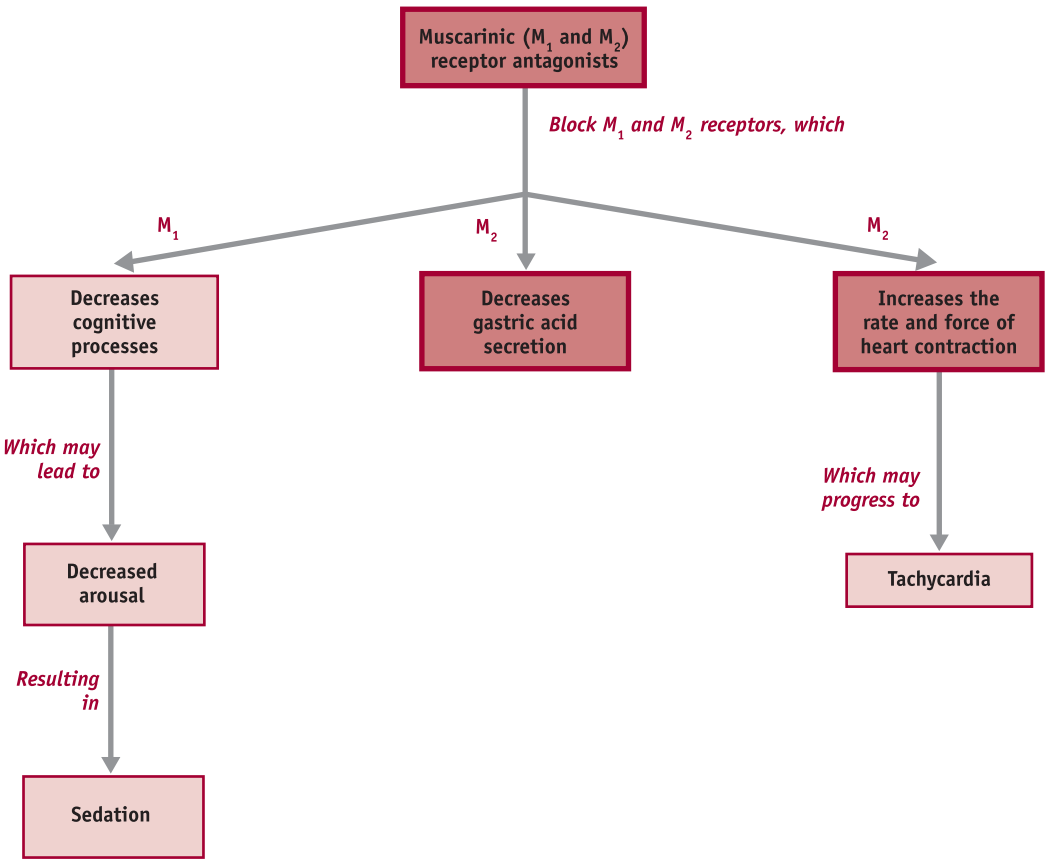
The effects of the muscarinic antagonists are shown in Figures 27.10 and 27.11. Common adverse reactions can be derived from Figure 27.7 and include drowsiness, tachycardia, constipation, blurred vision, dry mouth and facial flushing. Muscarinic antagonists are contraindicated in obstructive diseases of the gastrointestinal tract and bladder and cardiospasm.

✚ CLINICAL CONSIDERATIONS

These drugs have widespread clinical applications, including the following:

FIGURE 27.10A FLOWCHART SHOWING THE EFFECTS OF MUSCARINIC (M_1 AND M_2) ANTAGONISTS

Therapeutic effects are shown in the darker shaded boxes.



- as antispasmodics, to counteract gastrointestinal muscle spasm;
- as antiulcerants, because they suppress gastric acid secretion;
- as antidysrhythmics, to counteract bradycardia;
- as antiemetics, in motion sickness because of their central action;
- as mydriatics/cycloplegics for ophthalmic procedures (see Chapter 79);
- as premedication agents, given before anaesthesia;
- as antiasthma agents, because they enhance bronchodilation and (theoretically) suppress respiratory mucus production;
- as treatment for urinary frequency, enuresis and incontinence.

It is important to ensure that patients with glaucoma, urinary retention and gastrointestinal obstruction avoid taking muscarinic antagonists. As drowsiness is a common adverse effect with these drugs, patients should be advised to avoid driving and operating machinery following administration. They may also need assistance with normal daily activities. It is advisable for patients who develop mydriasis (pupil dilation), which occurs mainly from the use of eye drops, to wear sunglasses in bright light to prevent the light sensitivity associated with photophobia. Vital signs, bowel sounds and movements, and urine output should be monitored regularly.

CHOLINERGIC ACTION IN THE CENTRAL NERVOUS SYSTEM

Acetylcholine is a prominent neurotransmitter in the brain. Cholinergic nerves form a part of motor and sensory pathways and have a role in the control of wakefulness, cognitive and intellectual functioning, and behaviour.

Generally speaking, the dose of the cholinergic agent will greatly affect the kind of effects observed. At standard therapeutic doses, antimuscarinic drugs decrease the levels of arousal, resulting in sedation. If the dose is increased, however, excitement may be observed. **Benzatropine**, **trihexyphenidyl**, **orphenadrine** and **procyclidine** are centrally acting antimuscarinic drugs used to control the

FIGURE 27.10B FLOWCHART SHOWING THE EFFECTS OF MUSCARINIC (M_3) ANTAGONISTS

Therapeutic effects are shown in the darker shaded boxes.

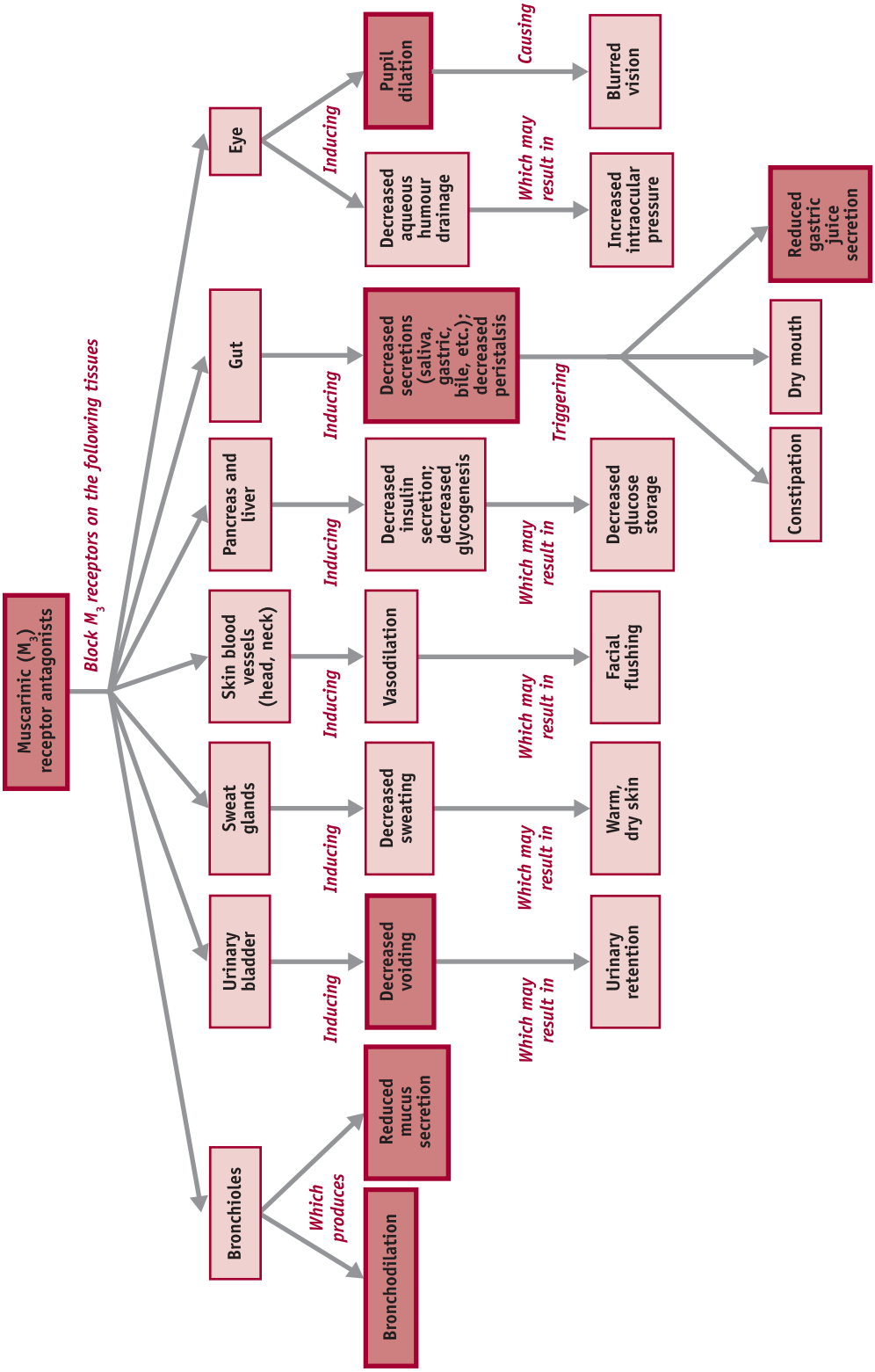
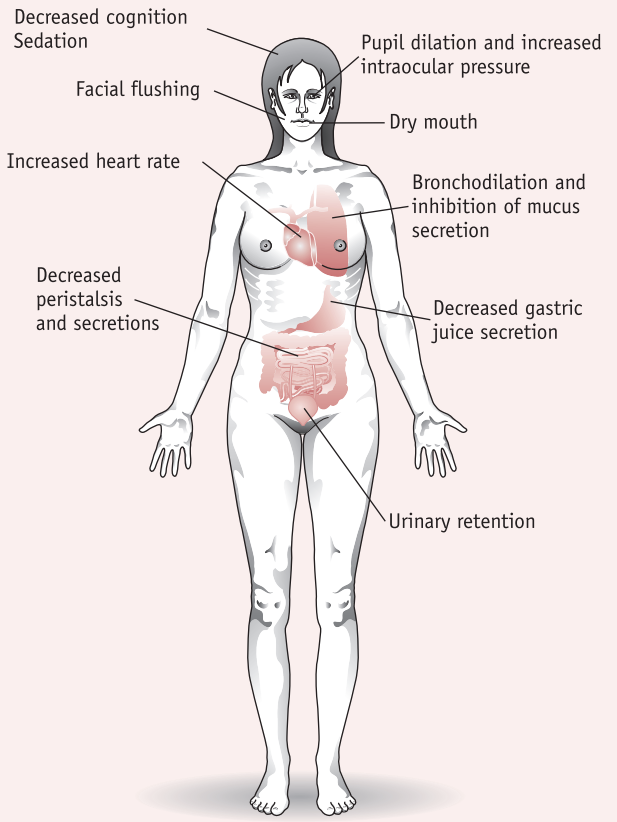


FIGURE 27.11 EFFECTS OF MUSCARINIC ANTAGONISTS



motor disturbances associated with parkinsonism (see Chapter 36) and antipsychotic drug therapy (see Chapter 33).

Lightheadedness and dizziness have been reported when using cholinergic agonists. Moreover, agonists can induce motor disturbances such as tremor and rigidity.

CHOLINERGIC SIDE EFFECTS

As in adrenergic pharmacology, the side effects of cholinergic agents derive from the distribution of cholinergic receptors around the body. Cholinergic agents are selected clinically depending on the desired action; all the other observed effects are the side effects. Learning the effects related to agonist action at a particular cholinergic receptor subtype will enable you to recognise both clinical effects and side effects of the whole drug class. As a general rule, the effects of antagonists will be the opposite of those of the agonists. You will have an opportunity to practise this approach in the study questions at the end of this chapter.

The identification of muscarinic receptor subtypes will lead eventually to the development of agonists and antagonists with specificity for particular subtypes. The clinical consequence of this should be a reduction in undesirable drug effects. Side effects may be reduced dramatically by administering cholinergic drugs directly to the required site of action rather than systemically. An example of this is inhaling an antimuscarinic drug, such as ipratropium, into the lungs as part of the therapy for asthma.

CLINICAL MANAGEMENT

Anticholinesterases

Assessment

- The patient should be reviewed for a history of the following conditions: peptic ulcer, hypotension, coronary artery disease, asthma, epilepsy and parkinsonism. Anticholinesterases are contraindicated in these conditions.
- Assess the patient for the presence of gastrointestinal conditions, such as intestinal obstruction, acute inflammatory bowel disease, peritonitis, and surgery involving the bladder and gastrointestinal tract. Extreme caution should be used in these conditions, as anticholinesterases can intensify the symptoms.
- Obtain a set of baseline observations for vital signs. Subsequent observations are compared with the baseline values.

Planning

- Depending on the therapeutic use of the anticholinesterase:
  - for myasthenia gravis, the patient will have increased neuromuscular strength;
  - to stimulate gastric motility or for urinary retention, the patient will have increased bladder and gastrointestinal tone;
  - to reverse paralysis postsurgery, the patient will regain normal neuromuscular strength.

Implementation

- Following intravenous administration of these drugs, the patient should have vital signs and level of consciousness checked every 15 minutes. Atropine (0.6 mg intravenously) is kept on hand to reverse any decrease in pulse.
- Be prepared for any decrease in pulse, blood pressure or respiration, or any progressive change in the depth and rhythm of respiration. In this instance, the drug should be withheld and the prescriber notified.
- Be aware of the possibility of cholinergic crisis (overdose). Symptoms include muscle weakness, abdominal cramps, ocular pain, bronchoconstriction, increased salivation and diarrhoea. These effects can be reversed by the administration of atropine or propantheline; however, atropine and propantheline should not be given routinely at the beginning of anticholinesterase treatment because they may mask the signs of overdosage.
- Monitor for the presence of unwanted effects, such as excessive salivation, involuntary defecation, urinary urgency, abdominal cramping, wheezing and vomiting.

Patient teaching

- Instruct the patient with myasthenia gravis to take the drug at the specified times in order to avoid muscle weakness.
- Advise the patient on how to determine changes in muscle strength.
- The patient should be able to determine the difference between the effects of underdose and overdose of the drug. An explanation of the symptoms of a cholinergic crisis should help the patient to determine the difference. To avoid tripping over, unnecessary obstacles should be removed from the patient's living areas and the home should be well lit. The patient should be instructed not to drive at night due to poor visual perception.

Evaluation

- Depending on the therapeutic use of the anticholinesterase:
  - for myasthenia gravis, the patient will have improved neuromuscular strength;
  - for lack of gastric motility or urinary retention, the patient will have increased bladder and gastrointestinal tone;
  - to reverse muscle relaxation postsurgery, the patient will regain normal neuromuscular strength.
- Evaluate the stability of the patient's vital signs and conscious state following administration of the drug.
- Observe, document and report the presence of adverse effects.

Muscarinic agonists

Assessment

- Refer to information contained in the clinical management of anticholinesterases.

Planning

- Anticipate the effect of the drug to improve the condition for which it is intended. This effect may involve the stimulation of gastric motility, improvement in bladder tone, or the reduction of intraocular pressure.
- Ensure that atropine is close at hand in case the patient has a cholinergic crisis. Adult dose is 0.6–1.2 mg intravenously.

Implementation

- Monitor the patient's vital signs for decreases in pulse rate and blood pressure.
- When using these drugs for gastric atony, listen for bowel sounds with a stethoscope. Report and document the level of peristaltic movement.
- Auscultate breath sounds for crackles (fluid secretions in lungs) and wheezing (narrowed airway passages). Report and document adverse findings.
- Give oral muscarinic drugs 1 hour before and 2 hours after meals to reduce the incidence of nausea and vomiting.
- When using these drugs to treat urinary retention, monitor fluid balance for level of urinary output.
- These drugs have a rapid onset of action when administered parenterally. As a desire to urinate may develop quickly, ensure that a bedpan is next to the bed or that the patient is close to the bathroom.
- Patients receiving these drugs are prone to diaphoresis (excessive sweating), so the bed linen may need to be changed regularly.

Patient teaching

- Instruct the patient to report adverse effects such as dizziness and slowing of pulse rate (teach the patient how to take their own pulse if they are going home with these drugs).
- Teach the patient various methods to avoid problems associated with dizziness and postural hypotension. One strategy involves moving slowly from a lying to a standing position. (Refer to Tables 11.3 and 11.20 in Chapter 11 for other strategies.)
- When these drugs are used as eye preparations, the patient should be instructed on the correct method of instillation (see Table 7.3 in Chapter 7 for further information). As these eye preparations can cause blurred vision, the patient should be instructed not to drive or work with dangerous tools immediately following instillation.

Evaluation

- Following systemic administration, the patient should be observed for a sudden drop in blood pressure, decreased pulse rate, changes in rate, rhythm and depth of respiration and abdominal cramps. These symptoms may indicate a cholinergic crisis, requiring the administration of atropine.
- To evaluate the presence of residual urine following the use of these drugs for urinary retention, a urinary catheter may be inserted after voiding.
- Following topical ophthalmic use of muscarinic drugs, the doctor will check the intraocular pressure with a tonometer in order to evaluate their effectiveness in glaucoma.

Muscarinic antagonists

Assessment

- Before administration, the patient's history should be checked for documentation of glaucoma, hypertension, coronary artery disease, urinary obstruction, renal disease, respiratory conditions and gastrointestinal obstruction. Muscarinic antagonists increase the heart rate, leading to aggravation of conditions affecting the heart. Secretions of the respiratory tract glands are depressed, which can affect respiratory conditions. The mydriasis produced by these drugs can block drainage of aqueous humour, leading to increased intraocular pressure. They also decrease gastrointestinal motility and secretions and urinary bladder tone, thus aggravating gastrointestinal obstruction and renal conditions.
- The patient's baseline observations are obtained and compared with those obtained following administration.
- Assess bowel sounds and urinary output before administration.

Planning

- Anticipate the effect of the drug to improve the condition for which it is intended. This effect may involve a decrease in the patient's secretions preoperatively, decrease in gastrointestinal spasms, bradycardia, treatment of asthma or alleviation of motion sickness.

Implementation

- Regularly monitor the patient's vital signs. Tachycardia is a common adverse effect.
- Regularly monitor bowel sounds if the drug is used to modify gastrointestinal function. An absence of bowel sounds signifies decreased gastrointestinal motility (paralytic ileus).
- Check for constipation due to decreased gastrointestinal motility. Advise the patient to eat foods that are high in fibre, to drink adequate fluids and to exercise (if able). (Refer to Table 11.4 in Chapter 11 for further information about action to take for constipation.)
- Monitor the patient's fluid balance. Report any decrease in urine output.
- If these drugs are given as part of preoperative medication, the patient should remain in bed and the side rails should be raised to prevent falls.
- When instilling these drugs into the eye, the patient should be allowed to rest comfortably until the effects of mydriasis and cycloplegia wear off. These effects prevent the patient from accommodating for near vision, and therefore increase the patient's risk of injury.
- Do not administer less than 0.25 mg atropine intravenously in adults, as a paradoxical slowing of the heart may occur with a low dosage.

Patient teaching

- Instruct the patient with glaucoma, urinary retention or gastrointestinal obstruction to avoid taking antimuscarinic drugs. The patients should alert their pharmacist about their condition so that any over-the-counter preparations sought out are checked thoroughly beforehand.
- Have food items such as boiled sweets, drinks, ice chips or chewing gum available if the mouth becomes dry. (See Table 11.9 in Chapter 11 for other measures that can be used for a dry mouth.)
- If the patient is using ipratropium inhalation as asthma therapy, ensure that the patient is familiar with the technique of administration. (Refer to Table 7.17 in Chapter 7 for further information.) Caution the patient to comply with the recommended number of inhalations per day to prevent adverse effects of therapy.
- Instruct the patient not to drive or operate machinery following administration of these drugs as drowsiness is a common adverse effect.
- Advise the patient with mydriasis (pupil dilation) to wear sunglasses in bright light due to photophobia. (See Table 11.13 in Chapter 11 for other measures that may be used with photophobia.)
- Encourage the patient to use artificial tears for dry eyes. Contact lenses will be fairly uncomfortable to wear during this time.
- Encourage the patient to avoid hot environments and strenuous exercise in these conditions, as inhibition of sweat gland activity can lead to raised body temperature.

Evaluation

- Evaluate the patient's response to the antimuscarinic drug, depending on the purpose of administration.
- Determine whether adverse effects such as constipation, increased pulse rate and urinary retention remain a problem.
- For patients using an ipratropium inhaler, evaluate the therapeutic response by listening to the patient's chest and the use of peak-flow meters. Also evaluate the patient's long-term tolerance for the preparation.

Nicotinic antagonists (neuromuscular blocking agents)

Assessment

- Assess baseline vital signs and compare with subsequent observations.
- The presence of renal, liver, cardiac or respiratory disease is reported and documented because of the possibility of adverse effects associated with these systems.
- Note that suxamethonium is contraindicated in severe burns, severe trauma and neurological lesions, as these conditions cause the release of potassium from damaged muscle and nerve cells, leading to a massive rise in serum potassium levels (around 10–15 mmol/l), which may cause cardiac dysrhythmias and cardiac arrest.

Planning

- The patient's vital signs will remain within acceptable limits.
- Full neuromuscular blockade is achieved for the duration of the procedure or intended therapy.
- There is no indication of adverse effects following the use of these drugs.

Implementation

- Monitor vital signs carefully and regularly. These drugs can produce tachycardia. Hypotension is also a possibility through the release of histamine.
- Body temperature must be regularly monitored, as these agents can cause malignant hyperthermia.
- It is vitally important to assess for return of neuromuscular function when the effects of blockade are reversed. Recovery occurs in longer muscle groups first, followed by recovery in short muscle groups. For example, the intercostal muscles, larynx, diaphragm, neck, shoulder and abdominal muscles recover first; these groups will then be followed by recovery of the tongue, pharynx limbs, and finally the oculomotor muscles, eyelids, mouth, facial muscles and fingers.
- Monitor the patient's urinary output. Except for atracurium and vecuronium, most of these drugs are excreted by the kidneys. Ensure that the patient maintains an adequate output.
- Monitor electrolyte levels. Electrolyte imbalances can lead to cardiac arrest because of circulatory collapse.

- Patients usually have an endotracheal breathing tube inserted following administration of these drugs. These breathing tubes are subsequently attached to some form of ventilation, such as an oxygen re-breathing bag or a mechanical ventilator. Nevertheless, it is still important to auscultate for breath sounds to ensure equal air entry in both lungs. Listen for a wheeze, which is indicative of bronchospasm.
- If the patient is receiving these drugs on a long-term basis for muscle paralysis, adequate sedation should also be used. Benzodiazepines are commonly employed. Ensure that the patient is adequately sedated by examining the vital signs. Inadequate sedation is shown by tachycardia and hypertension.
- These drugs are usually administered only by an anaesthetist because the patient is intubated.
- An anticholinesterase is administered following non-depolarising competitive agents to reverse their effects. Usually, neostigmine is used because of its long duration of action. Atropine (an antimuscarinic drug) is administered either before or in conjunction with neostigmine to minimise the muscarinic effects (bradycardia, hypotension, bronchoconstriction). The patient should be connected to a cardiac monitor during the reversal process, as neostigmine may cause dysrhythmias.
- If bradycardia develops from the neostigmine/atropine combination, glycopyrronium, a long-acting antimuscarinic drug, can be administered to reverse the bradycardia. Bradycardia is due to the long duration of action of neostigmine compared with that of atropine.
- If profound hypotension occurs following the administration of neuromuscular blocking agents, a sympathomimetic may need to be administered (e.g. adrenaline).

Evaluation

- It is important to regularly evaluate the patient's recovery from neuromuscular blockade. General evaluation parameters include the ability to open eyes wide, sustained protrusion of tongue, sustained hand-grip, sustained head-lift for at least 5 seconds and the ability to cough effectively. Respiratory parameters include a vital capacity of at least 15–20 ml/kg using a peak-flow meter. A peripheral nerve stimulator can be attached at the wrist to stimulate the ulnar nerve.
- If symptoms of neuromuscular blockade persist, the reversal agent neostigmine must be used until symptoms disappear.
- Vital signs should continue to be monitored and evaluated against the baseline levels.

SUMMARY

- Cholinergic nerves are associated with the activation of all parasympathetic effectors, some sympathetic effectors, skeletal muscles and all autonomic ganglia.
- Cholinergic action at these synapses tends to be short-lived. Most of the deactivation of acetylcholine (ACh) occurs in the synaptic gap through the action of cholinesterases, although at autonomic ganglia diffusion away from the receptor site is also important.
- There are two subtypes of cholinergic receptors: nicotinic and muscarinic. Most nicotinic receptors are associated with the neuromuscular junction and the autonomic ganglia; the remainder are predominately muscarinic.
- Drug groups associated with cholinergic action consist of nicotinic agonists and antagonists, muscarinic agonists and antagonists, and the anticholinesterases (drugs that inhibit the action of the degradative enzyme, thus prolonging the action of acetylcholine in the synapse).
- Muscarinic antagonists are sometimes called anticholinergic drugs, but they are more correctly known as antimuscarinic agents. Depending on their site of action, nicotinic antagonists are known as ganglionic blockers and neuromuscular blocking agents.
- Acetylcholine plays a key role in central nervous system function. Muscarinic antagonists tend to decrease the levels of arousal, leading to drowsiness and sedation. Muscarinic agonists tend to induce lightheadedness and motor disturbances.
- Cholinergic agonists can be used in the treatment of cigarette-smoking dependence, muscle weakness, glaucoma, gastrointestinal disorders characterised by diminished motility, and urinary retention. Cholinergic antagonists can be used in the management of asthma, cardiac disease and gastrointestinal disorders and as premedication before surgery.

1. Explain how the physiological effects of acetylcholine are terminated in terms of your understanding of cholinergic nerve action.
2. Indicate whether the following effects are related to an action at nicotinic or muscarinic receptors and whether the action is that of an agonist or antagonist:
   (a) skeletal muscle spasm;
   (b) decreased heart rate;
   (c) pupil dilation;
   (d) dry mouth;
   (e) decreased intraocular pressure.
3. Identify the three types of muscarinic receptor and their distribution around the body.
4. State the major adverse effects of muscarinic and antimuscarinic drugs. What are the implications for patient teaching with these classes of drugs?
5. State three conditions that are contraindications for antimuscarinic therapy. State two conditions that are contraindications for muscarinic agonist therapy. For each condition, explain the basis of the contraindication.
6. Why is muscle pain an after effect of suxamethonium use in some patients?
7. Why is suxamethonium used in electroconvulsive therapy (ECT) in preference to other neuromuscular blocking agents?
8. Why is a depolarising agent usually chosen for administration before a non-depolarising agent?
9. Ralph Salaman, who is about to undergo surgery, is given suxamethonium as part of the anaesthetic course of treatment. You are the nurse working in the operating theatre; what are the adverse effects of suxamethonium of which you should be aware?
10. Soo Wong, a 65-year-old smoker, has been ordered nicotine patches as part of her quit-smoking programme. As Ms Wong's clinical health educator, what would you tell her about the possible adverse effects of nicotine patches?
11. What is the advantage of administering ipratropium inhalation for asthma, as opposed to using it systemically?
12. Boris Lebia is receiving bethanechol for urinary retention. He develops severe diarrhoea a couple of days after commencement of administration. With reference to bethanechol's mechanism of action, explain how diarrhoea occurs.
13. As the theatre nurse, you are responsible for Christianne Van Dyke's care during her rhinoplasty procedure. What observations would lead you to suspect that insufficient neostigmine was used to reverse the effects of atracurium, the non-depolarising neuromuscular blocking agent given for muscle relaxation?

27 DRUG SUMMARY TABLE: CHOLINERGIC PHARMACOLOGY

FAMILY NAME	GENERIC NAME	TRADE NAME
Nicotinic agonists	Nicotine	Nicorette (chewing gum, inhaler, nasal spray, transdermal patches) Nicotinell (chewing gum, lozenge, transdermal patches) NiQuitin CQ (lozenges, transdermal patches)
	Botulinum toxin type A	Botox Dysport
Muscarinic agonists	Acetylcholine	Miochol-E
	Bethanechol	Myotonine
	Carbachol	
	Pilocarpine	Isopto Carpine Minims Pilocarpine
	Long-acting	Pilogel
Anticholinesterases	Donepezil	Aricept
	Galantamine	Reminyl XL
	Neostigmine	
	Physostigmine	
	Pyridostigmine	Mestinon
	Rivastigmine	Exelon
Antimuscarinic agents	Atropine	
	+ diphenoxylate (co-phenotrope)	Lomotil
	Trihexyphenidyl (benzhexol)	Broflex
	Benzatropine (benztropine)	Cogentin
	Cyclopentolate	Minims Cyclopentolate
	Dicycloverine (dicyclomine)	Merbentyl
	Glycopyrronium (glycopyrrolate)	Robinul Injection
	Homatropine	
	Hyoscine	Buscopan IBS relief
	Ipratropium	Atrovent preparations Respontin
	+ salbutamol	Combivent
	Mebeverine	Colofac
	Orphenadrine	Biorphen Disipal
	Oxybutynin	Cystrin Ditropan
	Procyclidine	Arpicolin Kemadrin
	Tiotropium	Spiriva
	Tolterodine	Detrusitol
	Tropicamide	Minims Tropicamide
Antimuscarinic/ganglionic blocker	Propantheline	Pro-Banthine
Nicotinic agonist (depolarising)	Suxamethonium	Anectine
Nicotinic antagonists (non-depolarising)	Atracurium	Tracrium
	Cisatracurium	Nimbex
	Mivacurium	Mivacron
	Pancuronium	
	Rocuronium	Esmeron
	Vecuronium	Norcuron

CASE STUDY VI.1

Ms J is a 62-year-old woman who has had rheumatoid arthritis in her hands, hips and knees for about 8 years. She is receiving weekly assistance from her local district nursing service because of impaired mobility. For the arthritis, she takes the non-steroidal anti-inflammatory drug ibuprofen daily and receives intermittent hydrocortisone therapy when the condition worsens.

Ms J tells the nurse that her eyes have 'not been the best of late', and she is finding it hard to see things out of the corners of her eyes. She is referred to her family doctor. He, in turn, refers her to the local eye clinic, where a diagnosis of open-angle glaucoma is made. Ms J is prescribed eye drops containing a miotic agent. This agent causes pupil constriction and facilitates the drainage of aqueous humour through the canal of Schlemm.

QUESTIONS

1 *(a) Applying your knowledge of adrenergic and cholinergic pharmacology, which drug groups are well suited as miotics?*
(b) On what receptor types are they acting, and how are they affecting the function of these receptors?

2 *(a) State three common side effects associated with each of these drug groups.*
(b) Would you expect to observe systemic side effects associated with this therapy? Why?

3 *Referring to Chapter 18, explain why Ms J may be predisposed to glaucoma.*

CASE STUDY VI.2

Mr FT is a 22-year-old man who has been taken to your hospital accident and emergency department. He has been working as a labourer at a nearby market garden that specialises in growing flowers. He was spraying the crops with the organophosphate insecticide malathion when he collapsed. He was not wearing the appropriate protective clothing. You observe that he is conscious and complains of gastrointestinal cramps and nausea. He vomited a couple times in the ambulance as he was transported to hospital. You note the manifestations: profuse sweating, drooling, lacrimation, bradycardia, agitation, muscle twitching and constricted pupils.

Supportive treatment is implemented, which involves respiratory support and the administration of antidotes. His progress is monitored carefully during this critical period. His recovery is without complications. He is discharged from hospital several days later.

QUESTIONS

1 *Underlying this patient's condition is a change in the level of activity of a division of the autonomic nervous system. Which division is affected, and what is the nature of the change?*

2 *Which type or types of tissue receptor is or are involved in this condition?*

3 *Explain the mechanism by which the organophosphate insecticides induce this state.*

4 *Which clinical drug group do the organophosphate insecticides closely resemble in terms of their action? Why?*

5 *Which drug group can be used as an antidote to oppose the effects of the insecticide? Why?*

CASE STUDY VI.3

Mr JJ, aged 68 years, visits the outpatient clinic for a check-up relating to his asthma. He has occasional bouts of acute asthma, which is controlled adequately using a salbutamol inhaler. Mr JJ indicates to the outpatient nurse that he has just been diagnosed with open-angle glaucoma, which is being treated with timolol 0.25% eye drops. He inserts one drop in each eye twice daily. The outpatient nurse ascertains that he has used the eye drops for 2 days.

QUESTIONS

1 To which drug group does salbutamol belong, and how does it act to relieve asthma? You may wish to refer to Chapter 26.

2 To which drug group does timolol belong, and how does it act to lower intraocular pressure? You may wish to refer to Chapters 26 and 79.

3 What is the potential problem for this patient using salbutamol and timolol?

CASE STUDY VI.4

Ms RW is a 50-year-old woman who is suffering from sinus bradycardia (slow heart rate). Recently, she has had some problems maintaining a normal blood pressure. She is given a drug that acts on the autonomic innervation of the heart and returns her heart rate to normal.

QUESTIONS

1 *State the divisions involved, the transmitters released, the receptors concerned and the effects associated with autonomic nervous system innervation of the heart.*

2 *Name the possible cholinergic and/or adrenergic drug groups that could be used to reverse Ms RW's bradycardia.*

3 *From your knowledge of the mechanisms of action of cholinergic and adrenergic drug groups, what would be the common side effects of each of these treatments?*

4 *Which of these drug groups would have less effect on blood pressure?*

5 *Which one of the possible drug groups would you select to use in Ms RW's case? Why?*

FURTHER READING

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WEB RESOURCES

Adrenergic pharmacology http://home.mira.net/~reynella/chime/adr_tuta.htm

CHEMICAL MEDIATORS

It will have blood, they say;
blood will have blood

WILLIAM SHAKESPEARE – *MACBETH*

Many substances in the body act on blood vessels. We have already met some neurotransmitters that act on blood vessels and help to control the circulatory system – noradrenaline and its related hormone adrenaline. Other substances are produced in the body that also have effects on blood vessels, but their actions differ considerably from those of noradrenaline and adrenaline. These differences are due to the fact that some chemicals produced locally in different parts of the body can control the microcirculation in a specific area or organ. These compounds may be neurotransmitters, but most are produced from cells outside the nervous system, mainly from mast cells and other immunocompetent cells.

Nitric oxide (Chapter 31) is produced locally by smooth-muscle cells, nervous tissues and immune cells on which its action occurs. The other main compounds that are vasoactive are histamine (Chapter 29), prostaglandins and serotonin (Chapter 30), and endothelins (Chapter 31). These substances are very often involved in disease states and, as such, are given special consideration in the next four chapters. Their action is not always confined to blood vessels, and further reference will be made to these compounds in many sections of this book.

VII

SECTION VII

INTRODUCTION TO CHEMICAL MEDIATORS

28

CHAPTER TWENTY-EIGHT

OBJECTIVES

After completing this chapter, the reader should be able to:

- **provide examples of the functions with which chemical mediators are involved;**
- **compare and contrast neurocrine, endocrine, paracrine and autocrine communication;**
- **define the role of a chemical modulator;**
- **provide examples of peptide mediators;**
- **state the limitations of peptides as drugs.**

KEY TERMS

Autacoid
Endocrine mediator
Neurocrine mediator
Neuromodulation
Paracrine mediator
Peptide mediator

CHEMICAL MESSENGER SYSTEMS ARE AN INTEGRAL PART OF body regulation and coordination, allowing effective cell-to-cell communication throughout the body. Broadly speaking, the substances involved in cell-to-cell signalling are known as *chemical mediators*. Substances as diverse as neurotransmitters, hormones, growth factors, peptides and derivatives of cell membranes are examples of chemical mediators involved in cell communication. The means by which these communicate with cells varies greatly, resulting in very different cellular responses. Chemical mediators are involved in diverse functions, such as cognition, motor control, mood, inflammation, control of blood pressure and tissue perfusion, gastrointestinal secretion and motility, stress responses, cell proliferation and specialisation, and pain transmission. Chemical mediators also play significant roles in pathophysiological processes.

The medicines we use to treat illness produce their effects by altering cell-to-cell communication. In this section, we discuss drugs used in the treatment of motion sickness, inflammation and allergy, migraine, problematic pregnancies, myocardial ischaemia and hypertension. We introduce a number of key groupings of chemical mediators, describe their physiological roles and explain their pharmacological manipulation. In this chapter, we concentrate on the classification of chemical mediators.

CLASSIFICATION OF CHEMICAL MEDIATORS

Neuroendocrine communication is a good place to start our discussion of chemical mediators. In Section VI, the pharmacology of the peripheral nervous system is explained. The focus of that discussion is on the phenomenon of neurotransmission and the way we use drugs to alter this process. In Section XII, endocrine pharmacology is covered. Here, the focus is on altering hormone action.

Traditionally, the way in which the nervous and endocrine systems function is well contrasted. The chemical mediators associated with the endocrine system are called hormones, and those linked to the nervous system are neurotransmitters. Hormones are made in and released from endocrine glands directly into the bloodstream in order to communicate with distant target tissues, whereas neurotransmitters are released from nerves and interact with short-range targets. Hormones are thought to produce their responses relatively slowly and for a prolonged period compared with neurotransmitters. This classification system has presented endocrine and neurocrine communication in a dichotomous, or non-overlapping, way.

It has become apparent, however, that although this classification system is useful in many respects, it is an oversimplification. Non-nervous cells can produce chemical mediators that act at short range and produce effects relatively rapidly; these mediators are known as paracrine secretions, or local hormones. Examples of local hormones are histamine and prostaglandins, which both play key roles in inflammation. The pharmacology of histamine and prostaglandins is covered in Chapters 29 and 30, respectively. Another important local hormone is serotonin, or 5-hydroxytryptamine (5-HT). You may already be aware that serotonin is a neurotransmitter with a key role in the control of mood and behaviour (see Chapter 35). It is also produced by non-nervous cells in the periphery, where it is regarded as a paracrine secretion (see Chapter 30). Indeed, the other mediators examined in this section – nitric oxide and the endothelins (see Chapter 31) – can also be synthesised by both nerve cells and non-nervous peripheral cells. Thus, the classification of a chemical mediator as a paracrine or neurocrine secretion is determined by its context rather than by an inflexible, rigid categorisation.

A cell may also secrete a chemical mediator that acts within the confines of a localised region, such as a lesion, or even on itself. These mediators induce their effects without entering the circulation and are referred to as autocrine secretions, or autacoids. Many of the cytokines produced by immune cells (e.g. interferons, interleukins, lymphokines) to regulate immune processes are regarded as autacoids. Immunomodulating chemical mediators such as these are covered in Chapter 75.

Generally speaking, it is better to regard the classification of chemical mediators in a less rigid way than what was once proposed. Try to keep in mind that there may be significant overlap in the roles of chemical mediators and in the types of cell that release them. In some contexts, a chemical mediator may act as a neurocrine secretion and in others may be regarded as a paracrine secretion or autacoid. The classification of chemical mediators is summarised in Table 28.1.

Another important concept related to chemical mediator function is that of modulation. A chemical modulator is not primarily responsible for initiating a particular physiological response, but it can modify it (i.e. decrease or increase the physiological response). An example of this is nerve-impulse transmission. Imagine a sensory nerve being stimulated by tissue injury. A train of impulses is transmitted towards the brain along the sensory pathway, triggered by neurotransmitter release at the synapse. Neighbouring cells release chemical mediators, such as prostaglandins, which increase the frequency of nerve impulse transmission, making the perception of the sensation stronger. In this instance, the prostaglandins are chemical modulators that have affected

TABLE 28.1 CLASSIFICATION OF CHEMICAL MEDIATORS

Classification	Mediator type	Characteristics	Example
Neurone secretion	Neurotransmitter	Stored in and released from axon terminal, acts over short range, relatively rapid action	Acetylcholine
Endocrine secretion	Classic hormone	Released from endocrine gland into blood, acts on distant target, relatively prolonged action	Growth hormone
Paracrine secretion	Local hormone	Released from tissue, enters circulation, acts on neighbouring cells, relatively rapid action	Cholecystokinin (CCK)
Autocrine secretion	Autacoid	Released from tissue, confined to tissue, acts locally (may act on secreting cell)	Cytokines

nervous system function. This is called *neuromodulation*. Neuromodulation plays a significant role in control of the human nervous system. Important neuromodulators are discussed in Chapters 25 and 32.

PEPTIDE AND PROTEIN MEDIATORS

Peptides play important physiological roles as chemical mediators. Throughout this book, you will encounter these mediators and the diverse roles they play in physiological and pathophysiological processes. Peptides are implicated in cardiovascular function, pain transmission, inflammation, neurotransmission, gastrointestinal regulation and endocrine communication. Indeed, they can function as neurocrine, endocrine, paracrine and autocrine mediators. They range in size from around 3 to 200 amino acids. Examples of peptide mediators are provided in Table 28.2.

From a pharmacological perspective, peptide mediators attract a lot of attention. Analogues and antagonists of these peptides have been, and are being, investigated as therapeutic agents. Advances in molecular biology, and especially recombinant DNA technology (see Chapter 57), have facilitated this development. In peptide pharmacology, the physiological properties of the peptide can be altered by a slight manipulation of the peptide structure. As an example, changing one or two amino acids in human **insulin** creates an insulin analogue, which acts faster than regular insulin (see Chapter 57). It is also possible to substitute amino acids within a sequence in order to turn a peptide mediator into an antagonist.

It must be mentioned, however, that peptide drugs may be of only limited use in clinical practice. As with therapeutic insulin, peptides generally cannot be given orally because they are broken down in the gut or absorbed poorly. They also tend to have short half-lives, as peptide enzyme systems are well established in the blood and tissues.

Nevertheless, there are many situations where peptide mediators are targeted in the treatment of common diseases. You will discover that peptide mediators are important in pain control (see Section IX), cardiovascular and respiratory pharmacology (see Section X), the regulation of gastrointestinal function (see Section XI), endocrine pharmacology (see Section XII), as immunomodulating drugs (see Chapter 75) and as cytotoxic drugs (see Chapter 76).

TABLE 28.2 EXAMPLES OF PEPTIDE AND PROTEIN MEDIATORS

Mediator	Size*	Physiological role	Chapter
Angiotensin II	8	Vasoconstriction	44
Substance P	11	Pain transmission	39
Endothelin	21	Vasoconstriction	31
Endorphin	31	Analgesia	39
Neuropeptide Y	40	Vasoconstriction	25
Insulin	51	Glucose metabolism	57
Most cytokines	120–220	Inflammation	75

* Approximate number of amino acids.

SUMMARY

- Chemical mediators are involved in cell-to-cell communication. Mediators may be classified as neurocrine, paracrine, endocrine or autocrine secretions.
- Chemical modulators modify cell-to-cell communication without activating the actual cell response.
- Peptide mediators are involved in a diverse range of physiological and pathophysiological processes. Advances in peptide pharmacology are being made, but their use as drugs may be limited.

1 Compare and contrast the characteristics of neurocrine, endocrine, paracrine and autocrine mediators.

2 Define the term ‘chemical modulation’ and provide an example.

3 State four examples of peptide mediators and indicate their physiological roles.

4 State the limitations of peptides as drugs.

HISTAMINE AND ANTIHISTAMINES

29

CHAPTER TWENTY-NINE

OBJECTIVES

After completing this chapter, the reader should be able to:

- **describe the role of histamine as a chemical modulator of certain physiological functions;**
- **describe the mechanism of action and pharmacological effects of antihistamines;**
- **describe the problems associated with antihistamine therapy;**
- **identify the various therapeutic uses of antihistamines.**

KEY TERMS

Inflammation
Allergy
Anaphylaxis

HISTAMINE IS APTLY NAMED: THE NAME LITERALLY MEANS tissue amine and it is almost ubiquitous in mammalian tissues. Histamine occurs in plentiful amounts in lung, skin and the gastrointestinal mucosa. Mast cells, basophils and platelets contain histamine in an inactive bound form. Histamine is derived from the amino acid histidine by decarboxylation. In spite of its widespread occurrence, however, the precise physiological necessity for histamine is still not completely clear. Two probable functions are the control of the microcirculation and the secretion of hydrochloric acid from the stomach's parietal cells. Histamine causes vasodilation and an increase in permeability of arteries, arterioles and capillaries. This may be important in the immune response, where an increase in capillary permeability helps to mobilise the immunocompetent cells and other immunological mediators to the site of tissue injury.

Unfortunately, in many people, this response occurs in the presence of innocuous antigens, causing a local anaphylactic reaction. In severe cases, a systemic reaction can, without treatment, lead to death within minutes. The local release of histamines in the nasal epithelia due to, for example, pollen grains leads in susceptible people to hayfever or allergic rhinitis. Release

in the skin as a result of an insect bite (e.g. from a horsefly) can lead to swelling and itching called urticaria. Destruction of cells by many causes can also initiate histamine release. Histamine will cause bronchoconstriction due to its smooth-muscle-contracting effect on the bronchioles.

Histamine reacts with receptors to cause a response. There are at least two different receptors found in tissues: H_1 and H_2 receptors. H_1 receptors are found in smooth muscle and exocrine glands of the respiratory tract. H_2 receptors are found mainly in the parietal cells of the stomach. Both types of receptor are found in the central nervous system (CNS) and in cardiac muscle. In the heart, stimulation of H_2 receptors is only positively chronotropic, whereas stimulation of H_1 receptors is both positively chronotropic and positively inotropic. This differentiation has been made possible by using specific agonists to both receptors. Histamine functions as a neurotransmitter in the CNS, but its exact role in neurotransmission is unclear.

ALLERGY AND ANAPHYLAXIS

Histamine plays an important part in allergy and anaphylaxis. Localised allergy is usually treated with drugs known as antihistamines (see below).

Anaphylaxis is a medical emergency. It is not uncommon, but it responds to treatment if administered quickly enough. It is important that health-care professionals involved with immunisations are competent in the treatment of anaphylaxis, as prompt action in the case of a systemic allergy may be life-saving.

Anaphylaxis is due to the systemic release of not only histamine but also other mediators such as 5-hydroxytryptamine (5-HT; serotonin) and leukotrienes (previously termed the slow-reacting substance of anaphylaxis [SRS-A]), which are of importance in asthma (see Chapter 51). Because of this, it was once thought inappropriate to treat asthma attacks with antihistamines; however, recent experience with antihistamines in some asthmatics has shown these drugs to be beneficial. Antihistamines can also be used as an adjunct to adrenaline in the treatment of anaphylactic shock (see later).

These substances can all lead to massive vasodilation, with resultant hypotension, causing shock and sometimes death. At the same time, bronchoconstriction can lead to laboured breathing and, if allowed to continue unabated, asphyxiation. The use of antihistamines alone in the treatment of this condition would not be satisfactory. Blockade of H_1 receptors would help to stop the development of only the more severe sequelae and would not reverse vasodilation and bronchoconstriction. The goal is, therefore, to reverse these conditions as quickly as possible; **adrenaline** (epinephrine) does both (see Chapter 26). **Noradrenaline** is not an effective bronchodilator and is not indicated. The route of administration of adrenaline in an emergency depends on the severity of the anaphylaxis. If adrenaline is administered intravenously, it can cause ventricular fibrillation; if given subcutaneously, it can cause a local vasoconstriction, which will delay its absorption. Intramuscular injection seems to be the best route, but even this can lead to ventricular fibrillation. Only experience in the clinical situation can be used to determine which route to use, depending on the severity of the reaction. Many people who are allergic to bee or wasp stings or similar carry adrenaline for self-administered subcutaneous injection in case of emergency. Adrenaline itself can prevent further histamine release.

Injection of the antihistamines chlorphenamine (chlorpheniramine) or promethazine is used as an adjunct to adrenaline to stop further histaminic action. Corticosteroids are often given to stabilise the immunologic cells causing the problem (see Chapter 58). Corticosteroids take at least 30 minutes to produce an effect and several hours to reach maximum activity and so are given last and help to prevent delayed reactions.

ANTIHISTAMINES

There are numerous drugs available for both topical and systemic use that have antihistaminic activity. Apart from treating allergies, antihistamines are useful in the treatment of nausea, especially travel and motion sickness (see Chapter 55). Some other uses are mentioned below. Many antihistamines have complicated names, which makes the use of proprietary names common.

■ MECHANISM OF ACTION

The term 'antihistamine' is usually reserved for describing the H_1-receptor blockers or antagonists. When one talks about drugs that antagonise the H_2 receptors, they are termed H_2 blockers or antagonists (these are discussed in Chapter 53). Apart from blocking histamine receptors, antihistamines may have a secondary effect in blocking the release of histamine from mast cells.

The original antihistamines were able to cross the blood–brain barrier and therefore had effects on the CNS. There have been several developments with antihistamines in recent years, with the synthesis of drugs that are less lipophilic and hence cross the blood–brain barrier in only relatively small amounts.

◆ ADVERSE EFFECTS

There is often little difference between the available antihistamines, the main side effects of most of them being drowsiness and dry mouth, as most have antimuscarinic activity. Finding an antihistamine that does not adversely

affect a patient may be by trial and error. Because they cross the blood–brain barrier, the older antihistamines cause sedation. **Alimemazine** (trimeprazine) and **promethazine** may be more sedating, whereas **chlorphenamine** and **cyclizine** may be less so. This sedating activity is sometimes used to manage the pruritus associated with some allergies.

The newer antihistamines, such as **acrivastine**, **cetirizine**, **desloratadine** (an active metabolite of loratadine), **fexofenadine** (an active metabolite of terfenadine), **levocetirizine** (an isomer of cetirizine), **loratadine**, **mizolastine** and **terfenadine**, cause less sedation and psychomotor impairment than the older antihistamines because they are less likely to cross the blood–brain barrier.

Antihistamines differ in their duration of action. Many of the older antihistamines are relatively short-acting, but some (e.g. promethazine) act for up to 12 hours. The newer antihistamines are longer-acting. Loratadine acts quicker than fexofenadine and has a long half-life, which, in theory, makes it the best alternative. Cetirizine has the added advantage of inhibiting eosinophil migration to inflammatory sites, thus minimising the inflammatory response by another mechanism. Even though cetirizine is relatively lipophobic, it crosses the blood–brain barrier in about 15 per cent of patients and thus is more likely to induce drowsiness than some of the other drugs mentioned above. An important, dangerous drug interaction sometimes occurs when terfenadine is taken with the antibiotic **erythromycin** (and other macrolide antibiotics and some antifungal drugs). This interaction can result in a potentially fatal abnormality in cardiac rhythm called *torsades des pointes*. This interaction is due to the liver-enzyme-inhibiting properties of these antimicrobial drugs, which can lead to toxic blood levels of the antihistamine. Terfenadine must also be avoided if there is hepatic impairment, electrolyte imbalance or existing disturbances of cardiac rhythm. Due to the problems associated with terfenadine, it has been withdrawn in some countries. The manufacturer of terfenadine has developed fexofenadine, an active metabolite of terfenadine, which has antihistaminic properties but is relatively safe when used with other drugs. Loratadine is much less likely to cause the major problems seen with terfenadine. The active metabolite of loratadine, **desloratadine**, is also available.

When providing antihistamines, what really matters is the patient's response and preference. Some antihistamines, such as **alimemazine** and **promethazine**, are so good at promoting drowsiness in many patients that they are commonly used as sedatives, especially in children. Promethazine is one of the few drugs available considered to be safe in the sedation of children.

The antihistamine **doxylamine** is used in combination with analgesics and may give a beneficial effect in the treatment of pain when drowsiness and sedation pose no problems. As such, doxylamine is sometimes termed a calmative. Doxylamine was previously used to treat the nausea of pregnancy, but it is no longer recommended for this purpose. The preparation known as Debendox™ containing doxylamine became infamous in the 1970s after being accused of being teratogenic; these accusations were later found to be fraudulent.

Patients taking any antihistamine should be warned of concurrent drowsiness and told, if so affected, not to drive or operate hazardous machinery.

Apart from drowsiness, antihistamines tend to be well-tolerated drugs. The other common side effects are dizziness and lassitude; some antihistamines also have antimuscarinic effects. As antihistamines are a very diverse group of drugs insofar as their chemical structure is concerned, they have differing side effects, and a drug handbook should be consulted for details of these. In high doses, convulsions and cardiac depression can occur.

When used topically, antihistamines can be allergenic. This makes the use of antihistamine creams relatively unsatisfactory for the topical treatment of skin allergies and pruritus. Histamine receptors in the skin consist of both H_1 and H_2 receptors. The H_1 receptors predominate, but this explains why antihistamines are not 100 per cent effective in the treatment of allergic skin reactions. Combinations of H_1 and H_2 antihistamines may eventually be used for conditions such as allergic itch.

Sedating antihistamines can interact with other CNS depressants, and they should not be taken together because of a potentiated CNS depressant effect. Fexofenadine, cetirizine, loratadine and desloratadine may be precluded from this, as they tend not to produce sedation.

✚ CLINICAL CONSIDERATIONS

Uses of antihistamines for conditions other than allergies is varied. **Cyproheptadine** is sometimes beneficial in the prophylaxis of migraine. Cyproheptadine also has appetite-stimulatory effects, which can be useful in convalescence.

Histamine is not involved in the production of respiratory secretions in the common cold, and so the use of antihistamines in cold preparations is not particularly beneficial. Loratadine has been combined with a decongestant (see Chapter 52) in an attempt to improve the efficacy of the antihistamine; the sedation and/or antitussive effect may be helpful at night in the promotion of sleep. If nasal stuffiness is due to an allergy, then an antihistamine nasal spray and/or corticosteroid preparation may be of benefit.

Levocabastine is an antihistamine available only for topical application to the nasal mucosa in allergic rhinitis and to the eyes in allergic conjunctivitis. The systemic absorption of this drug is minimal, thus avoiding CNS effects. The drug has a relatively long half-life when used via these routes, and only two applications daily are required for the relief of symptoms. Irritation to the mucosal surfaces has been reported with use of this drug.

There are many other antihistamines present in some proprietary preparations used for the relief of the symptoms of the common cold and influenza (see Chapter 52).

Oral antihistamine preparations should be given with milk or food to decrease the likelihood of gastrointestinal symptoms. Topical antihistamine preparations should be given about half an hour before meals so that the nasal passages are clear to facilitate eating or drinking. Sufficient amounts of fluids should be consumed, as antihistamines can dry up mucous membranes and thicken bronchial secretions.

The problem associated with the less sedating antihistamines involves the tendency to cause life-threatening ventricular dysrhythmias and serious drug interactions because of their hepatic metabolism. The most likely antihistamines to produce these effects – terfenadine and **astemizole** – have been withdrawn in some countries. Response to antihistamines may vary widely, and the patient is advised to try different preparations to determine the one that is best tolerated and most effective. Antihistamines that have been used in infants to improve sleep should be avoided because epidemiological research has demonstrated a link between the use of these preparations and an increased incidence of sudden infant death syndrome (SIDS).

In summary, antihistamine drugs have varied uses in therapeutics, and deciding which one to use can be difficult. It is often a matter of trial and error to see which one is of help to a patient and produces the fewest adverse effects.

CLINICAL MANAGEMENT

Antihistamines

Assessment

- Assess for a history of convulsions, as paradoxical effects of antihistamines include irritability, insomnia and an increased tendency to convulsions.
- Avoid use in elderly people and young children in view of the sedative properties of these drugs.
- When used for allergy, determine with the patient any obvious deviations from usual habits (e.g. diet, environment, stress) that may have caused the allergic reaction.

Planning

- Depending on the therapeutic use of the drug, the following symptoms will be alleviated:
  - symptoms of allergy, including nasal congestion, bronchoconstriction, sneezing, rhinorrhoea, and pruritus of the nose, eyes and throat;
  - symptoms of motion or travel sickness – ensure that the medication is taken about 30 minutes before travel;
  - symptoms of the common cold and influenza, including nasal congestion, sneezing and rhinorrhoea.

Implementation

- Observe the colour of bronchial secretions. A yellow or green mucus indicates a bronchial infection, and an antibiotic may be required.
- Give the drug with milk or food to decrease the gastrointestinal effects.
- In cough and cold preparations containing antihistamines, determine the nature of the other drugs present. Sympathomimetic decongestants can lead to an elevation in blood pressure. Preparations containing codeine can cause tolerance. Generally, antihistamines contained in cough and cold preparations are not particularly useful because histamine is not involved in the production of respiratory secretions.
- Antihistamines should not be used for the symptomatic treatment of respiratory infections in young children because of the self-limiting nature of the infection and the lack of benefit associated with these preparations.

Patient teaching

- The patient should be warned that antihistamines can cause drowsiness. The patient should avoid driving and using machinery. Note that the newer antihistamines are supposedly non-sedating but can induce drowsiness in susceptible people.
- The central nervous system depressant effects of these drugs can be accentuated by alcohol and by other drugs such as sedatives, hypnotics and anxiolytics.
- The patient should be advised to take plenty of fluids, as antihistamines can thicken bronchial secretions and dry mucous membranes.
- Instruct the patient on the proper use of nasal sprays (refer to Table 7.8 in Chapter 7 for further information). Inform the patient that rebound congestion can occur with overuse.

- Advise the patient to read the labels on over-the-counter preparations. The patient's pharmacist and doctor should be consulted to ensure that other ingredients would not affect the patient's health status, such as with hypertension or hyperthyroidism.
- Topical antihistamine preparations should be administered about half an hour before meals so that the nasal passages are clear to facilitate eating or drinking.

Evaluation

- Evaluate the effectiveness of antihistamine therapy, depending on the reason for use.
- Evaluate for adverse effects, including sedation, dizziness, diplopia, loss of appetite, nausea and vomiting.
- Observe closely for any additive effects if used with other drugs that depress the central nervous system.

SUMMARY

- The drugs termed 'antihistamines' are usually compounds that antagonise H_1 receptors.
- Histamine is one of the causes of rhinitis and pruritus in allergies.
- There are two types of antihistamine: sedating and non-sedating.
- Antihistamines are used to treat allergic reactions.
- Some antihistamines are strongly sedating and are used as sedatives/hypnotics.
- Some of the newer antihistamines do not cross the blood–brain barrier efficiently and are termed 'non-sedating antihistamines'.
- Some antihistamines have diversified uses, for example in the treatment of migraine and eating disorders.

1 Why are antihistamine nasal sprays of little use in nasal stuffiness due to the common cold?

2 Name as many indications for antihistamines as you can. (There are at least ten.)

3 Antihistamines can lead to a rare condition known as tardive dyskinesia. Why?

4 What are some other serious consequences of antihistamine use?

5 Alfred Adams is taking an antihistamine preparation for allergy-induced sinusitis. What patient education would you offer Mr Adams?

6 Explain why the following conditions cannot be treated with antihistamines:
(a) common cold;
(b) skin allergies and pruritus.

7 Cristina Vicario, a 70-year-old widow, has been prescribed doxylamine for insomnia and diazepam for anxiety following the death of her husband. What is the problem involved with this combination of drugs?

8 Joe Guthrey, a 40-year-old lorry driver, suffers from severe allergic rhinitis. What antihistamine preparation would you recommend for him?

9 A 35-year-old mother with severe sinusitis often experiences difficulty sleeping at night because of her condition. What antihistamine preparation would you recommend for her to take at night?

29 DRUG SUMMARY TABLE: HISTAMINE AND ANTIHISTAMINES

FAMILY NAME	GENERIC NAME	TRADE NAME(S)
H_1 antagonists (antihistamines)	Acrivistine	Benadryl
	Alimemazine	Vallergan
	Azelastine	Optilast
	Cetirizine	
	Chlorphenamine (chlorpheniramine)	Piriton
	Cyproheptadine	Periactin
	Desloratadine	Neoclarityn
	Dexchlorpheniramine	Polaramine
	Diphenhydramine	Found in Benadryl preparations
	Doxylamine	In compound preparations on sale to the public
	Loratadine	Clarityn
	Promethazine	Phenergan

PROSTAGLANDINS AND SEROTONIN

30

CHAPTER THIRTY

OBJECTIVES

After completing this chapter, the reader should be able to:

- **list the main functions of prostaglandins in the body;**
- **identify the use of prostaglandins in reproductive processes;**
- **describe the main functions of serotonin in the body;**
- **explain the aetiology of migraine;**
- **identify the drugs used in the prophylaxis and treatment of migraine.**

KEY TERMS

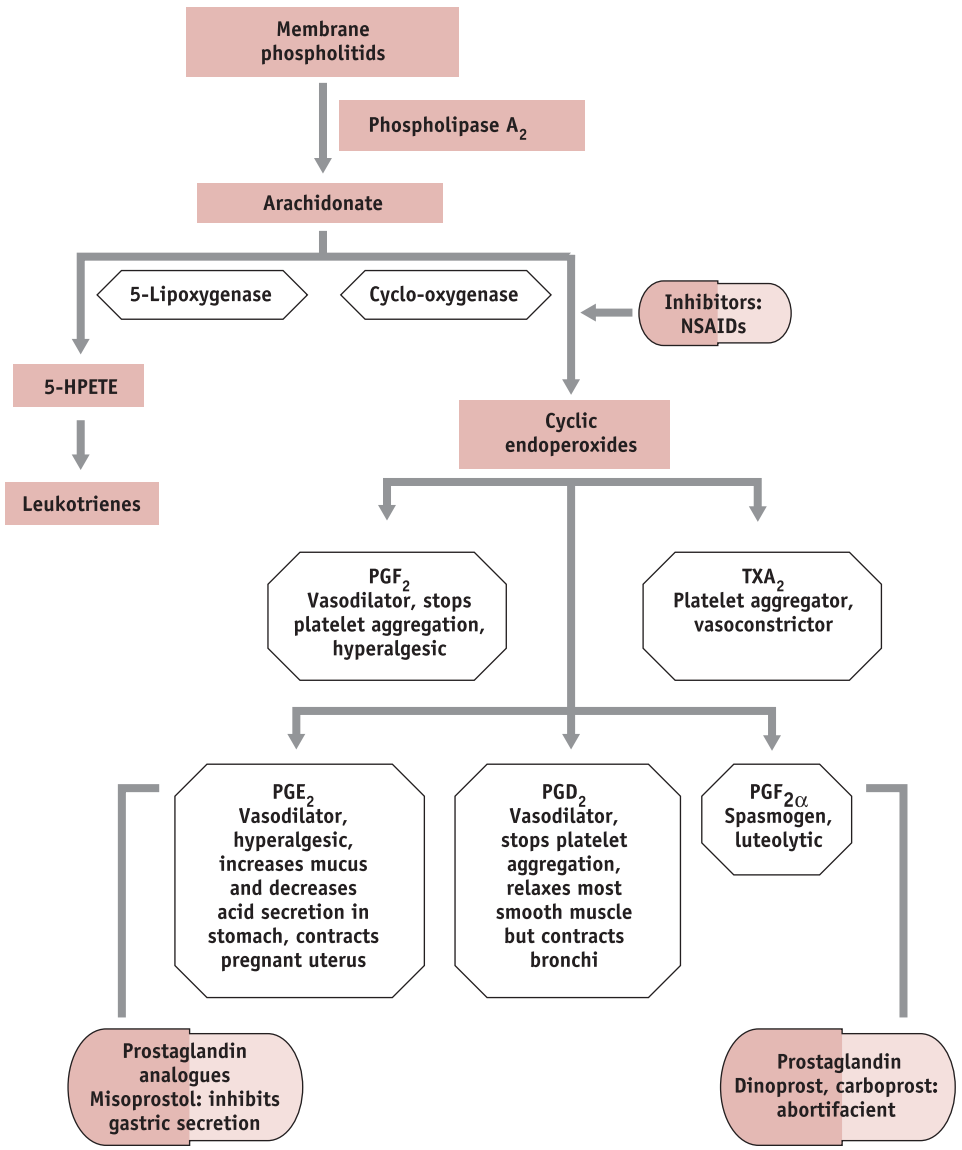
Prostaglandins
Serotonin
Migraine

THIS CHAPTER DEALS WITH THE PROSTAGLANDINS (PROVIDING information about their derivation, properties and functions), serotonin and the antiserotonins, and the prevention and treatment of migraine.

PROSTAGLANDINS

Prostaglandins are so named because they were first isolated from semen and were assumed to come from the prostate gland. Since their discovery in the early 1930s, numerous prostaglandins have been found throughout the body, such that they can be considered ubiquitous. The function of these compounds depends on two factors: their chemical nature and their location. Because prostaglandins have a very short half-life, their action is confined mainly to the tissues in which they are produced. Any prostaglandin that escapes into the general circulation is destroyed before it can act elsewhere. As prostaglandins act where they are produced, they are termed 'local hormones'. All prostaglandins are derived from the 20-carbon fatty acid arachidonic acid (see Figure 30.1); as some of the derivatives that have been isolated today do not conform to the original definition of a prostaglandin, the term 'eicosanoid' (from the Greek word for 20) is often used to describe them. The nomenclature of prostaglandins is complicated, but they are usually designated by a letter, often followed by a subscript number and sometimes a Greek letter. This naming is based on differences in chemical structure. Prostaglandin is often abbreviated to PG. Other common eicosanoids are the

FIGURE 30.1 PATHWAY FOR PROSTAGLANDIN SYNTHESIS, WITH RELEVANT INHIBITORS



HPETE, hydroxyperoxyeicosatetrienoic acid; PGD_2, prostaglandin D2; PGE_2, prostaglandin E2; PGF_2, prostaglandin F2; $PGF_{2\alpha}$, prostaglandin F2α; TXA_2, thromboxane 2.

TABLE 30.1 GENERAL ACTIONS OF PROSTAGLANDINS

Inhibit gastric secretion (see Chapter 53)
Stimulate pancreatic and small-intestine secretions
Induce water and electrolyte flow into the intestinal lumen
Sensitise nerve endings, causing pain (see Chapter 40)
Stimulate release of anterior pituitary hormones
Maintain renal blood flow

thromboxanes (TX), the leukotrienes (LT) and the hydroperoxyeicosatrienoic acids (HPETE). Some general actions of prostaglandins are listed in Table 30.1. Table 30.2 details some of the body's eicosanoids and their more specific functions.

As the prostaglandins have so many diverse functions, it is not surprising that drugs that inhibit the synthesis of these local hormones have an important place in therapy. A number of prostaglandin agonists have been produced, and it might be expected that the number of such drugs will increase in the future. Prostaglandins given by intra-amniotic infusion or as pessaries have been used for many years to induce abortion and labour. Prostaglandins are very unstable and usually must be kept frozen. After thawing, any excess should be discarded; they must not be refrozen. The prostaglandins commonly used in obstetrics, gynaecology and other reproductive health care are dealt with below. Other drugs that act on the eicosanoids or as eicosanoids are dealt with in the appropriate chapters, as indicated in Table 30.1.

From Tables 30.1 and 30.2, it can be seen that prostaglandins have many functions in the body. Some drugs that affect prostaglandins and their synthesis are discussed in Chapters 40, 45 and 46.

Termination of pregnancy and induction of labour

The most commonly used method of termination of pregnancy in the first trimester in most countries is vacuum aspiration of the uterine contents. This procedure is made easier if the cervix is both softened and dilated. This can be achieved by the use of prostaglandins, namely prostaglandin E_2 (**dinoprostone**) and prostaglandin $F_{2\alpha}$ (**dinoprost**, **carboprost**). As these prostaglandins can also

TABLE 30.2 SPECIFIC FUNCTIONS OF SOME EICOSANOIDS

Eicosanoid	Function
Prostaglandins	
PGE_1	Contracts myometrium Causes vasodilation
PGE_2	Contracts myometrium Relaxes bronchial smooth muscle Stimulates renin release Induces fever
$PGF_{2\alpha}$	Contracts myometrium Causes regression of corpus luteum in many mammals but not in humans
PGI_2 (prostacyclin)	Opposes platelet aggregation Reverses platelet aggregation Inhibits formation of thrombi Causes vasodilation
Thromboxanes	
TXA_2	General vasoconstrictor Causes platelet aggregation
Leukotrienes	
LTC_4	Increases tracheal mucus production Increases vascular wall permeability Increases bronchoconstriction
LTB_4	Induces accumulation of granulocytes in diseases such as gout
HPETEs	
12-HPETE	May stimulate insulin production

cause uterine contractions if given in large doses, the need for surgical procedures can sometimes be avoided. The progesterone antagonist **mifepristone** (RU496) given orally greatly enhances the actions of these prostaglandins on the myometrium. **Gemeprost**, a synthetic analogue of prostaglandin E_1, has similar actions and is administered as a pessary. Dinoprost is usually administered by the intra-amniotic route for terminations. Dinoprostone is given intravaginally as a gel for the induction of labour. The prostaglandins have short half-lives and, therefore, minimal systemic adverse effects; nausea, vomiting and diarrhoea are usually observed, however. As the prostaglandins have bronchoconstrictor properties, they must be used with extreme caution in patients with obstructive airways disease. In the induction of labour, care must be taken not to produce excessive uterine contractions, as this can lead to uterine rupture and fetal distress.

Treatment of impotence

An estimated 10 per cent of men over the age of 21 years suffer from erectile dysfunction or impotence. The treatment of this condition has, until recently, not been successful and has involved the use of penile implants of various kinds. The implants help to stiffen the penis sufficiently to enable penetration and intercourse. Prostaglandins have been known for some time to be associated with erections. Prostaglandin E_1 (**alprostadil**) is now available for the treatment of impotence (see Chapter 45).

Maintenance of patent ductus arteriosus

In utero, the fetus does not use its lungs and the pulmonary circulation is bypassed by the ductus arteriosus, a vessel connecting the pulmonary artery with the descending aorta. This vessel normally closes at birth due to a fall in prostaglandin levels. Occasionally, closure does not occur, a condition termed patent ductus arteriosus. Sometimes this condition can be treated using a prostaglandin inhibitor such as **indometacin** (see Chapter 40), but surgery is often needed to close off the offending vessel. If surgery is necessary, it may not be possible to carry out the procedure immediately, and patency of the ductus arteriosus may be advantageous in some neonates with other cardiovascular defects in order to maintain sufficient oxygenation of the blood. If this is the case, prostaglandin E_1 (alprostadil) can be utilised to maintain patency until surgery is convenient and feasible. Unfortunately, this drug has many adverse effects, including apnoea, fever, bone defects and intravascular coagulation. This necessitates extreme watchfulness on the part of the carers.

SEROTONIN

Serotonin is a derivative of the amino acid tryptophan and is often known by its chemical name 5-hydroxytryptamine (5-HT). There has been an upsurge of interest in the role of 5-HT in the body. Most of the body's serotonin is found in the enterochromaffin cells of the gastrointestinal tract, where its function remains obscure but where it probably acts as an autacoid in the control of gastrointestinal motility. In carcinoid tumours of these cells, serotonin causes many of the pathophysiological symptoms associated with this condition. It promotes tachycardia and release of both acetylcholine and noradrenaline at efferent nerve endings. Platelets also contain serotonin.

The principal interest in serotonin is in its role in the central nervous system (CNS) as a neurotransmitter. It acts as an inhibitory neurotransmitter, being principally involved in the regulation of sleep, mood and hunger (see Section VIII).

Many drugs are active as either agonists or antagonists at serotonin receptors. There are at least four different types, and probably more, of serotonin receptor. Table 30.3 shows some of the actions of serotonin at the different receptor sites and some drugs that act at these sites. Apart from those agents used to treat migraine, these drugs are discussed in more detail in Chapters 35 and 55. It is highly likely that many more selective serotonin agonists and antagonists will appear on the market for clinical use in the future for the treatment of many centrally and peripherally related conditions. In a period of less than 12 months in the early 1990s, four very different and novel drugs were released that had actions related to serotonin: **fluoxetine** for the treatment of depression (see Chapter 35), **ondansetron** for the treatment of severe nausea (see Chapter 55), **cisapride** for the treatment of gastric reflux (see Chapter 53) and **sumatriptan** for the treatment of migraine. Ondansetron has been reported to help control memory loss in elderly people. A study of Table 30.3 will show you the tremendous possibilities that exist in this area of pharmacology.

MIGRAINE

Migraine results from a vasodilation of cerebral blood vessels, leading to a build-up of intracranial pressure. This results in a severe headache, which can have multiple symptomatology and can last for several days. The symptoms are often incapacitating to the patient and commonly include visual disturbances and nausea. The aetiology of migraine is obscure, but the following explanation is accepted widely. Initially, the intracranial blood vessels constrict, which causes the prodromal symptoms, usually of a visual nature. The vasoconstriction results in a reflex vasodilation; this is probably a protective reflex, resulting in an increase in blood flow to the brain to protect it from ischaemia. This vasodilation is an overreaction and causes a rise in intracranial pressure, which leads to a severe headache. This headache can be either unilateral or bilateral and is often associated

TABLE 30.3 ACTIONS OF SEROTONIN AT DIFFERENT RECEPTOR SITES

Receptor	Principal actions	Agonists	Antagonists
5-HT_1	**Neuroinhibition**: CNS tryptoaminergic terminals (autoreceptors), raphe cell bodies, peripheral adrenergic terminals, intestinal cholinergic terminals **Neuroexcitation**: spinal motor neurons, centrally mediated hypotension, smooth-muscle contraction in some vascular and gastrointestinal tissues, smooth-muscle relaxation, endothelium-derived relaxing factor release	Buspirone (partial), lysergic acid diethylamide (LSD), sumatriptan	LSD (peripheral), propranolol
5-HT_2	**Neuroexcitation**: cortical cell bodies, neuroendocrine functions, smooth-muscle contractions in many vascular and other smooth-muscle tissues, platelet aggregation, increased capillary permeability	LSD, α-methyl-5-HT, methysergide (partial)	Cyproheptadine, methysergide, mianserin, pizotifen, nefazodone
5-HT_3	**Afferent neuroexcitation**: vagal afferents, chemoreceptors, gastrointestinal sensory afferents, pain afferents (and axon reflex-mediated neurogenic inflammation) **Efferent neuroexcitation**: superior cervical ganglion, some cardiac adrenergic terminals, bladder parasympathetic ganglion, intestinal substance P-containing neurons, intestinal neurons mediating fluid secretion, modulation of gastric emptying, nausea and vomiting	2-Methyl-5-HT	Cocaine, metoclopramide, ondansetron
5-HT_4	**Efferent neuroexcitation** in gastrointestinal tissues, cardiac stimulation	Cisapride, metoclopramide	

with nausea. It is certain that at least some of these problems are associated with fluctuating levels of serotonin.

Migraine attacks can occur often, and in many cases prevention is necessary. Management is aimed at preventing the prodromal stage and may be achieved by the avoidance of factors that can precipitate attacks. These factors are often related to diet and include cheese, chocolate and alcohol. Drugs are justified as prophylactics only if frequent attacks are incapacitating.

Migraine prophylaxis

Some of the drugs used in migraine prophylaxis are used more for other conditions and only a brief mention of them will be made here. Migraine prophylaxis is usually suitable only for patients who experience more than two migraine attacks per month.

Beta-blockers such as **propranolol**, **nadolol**, **timolol** and **atenolol** (see Chapter 26) are sometimes effective in preventing attacks. Their mechanism of action is probably by blocking β receptors on cerebral blood vessels, resulting in a reduced vasodilation in the secondary phase of the attack. Calcium-channel blockers such as **nifedipine** and **verapamil** (see Chapters 44 and 45) have also been used with some success. This explanation of mechanism of action is fraught with difficulties, as the prodromal stage would be exacerbated if this were the only mode of action.

Antidepressants such as **amitriptyline** (see Chapter 35), taken at night, are often helpful. Their mechanism of action may be due to the fact that these drugs have some antiserotonin activity and block the 5-HT receptors on the cerebral blood vessels. This action may prevent the initial vasoconstrictive phase.

Up to 600 mg **aspirin** daily may be effective in controlling frequent attacks; more than this can exacerbate attacks. Other non-steroidal anti-inflammatory drugs (NSAIDs) are also effective. (See Chapter 40 for a fuller discussion of these drugs.)

PIZOTIFEN

■ MECHANISM OF ACTION

Pizotifen (and **cyproheptadine**; see Chapter 29) is an antihistamine with antiserotonin properties that has been found to be effective in the prophylaxis of migraine.

◆ COMMON ADVERSE EFFECTS

In some patients, pizotifen has a potent sedative action, which may be desirable. Like most antihistamines, pizotifen has antimuscarinic properties and appetite-stimulating properties. It may affect concentration in the initial days of therapy.

METHYSERGIDE

■ MECHANISM OF ACTION

Methysergide, which is a derivative of ergot (see below), has 5-HT antagonistic properties that make it useful in preventing migraine attacks if no other therapeutic agent is effective.

◆ COMMON ADVERSE EFFECTS

The adverse-effects profile of methysergide is not favourable due to the incidence of an inflammatory fibrosis, which, although rare, can be life-threatening. This fibrosis can be retroperitoneal, leading to ureteric obstruction. Pulmonary fibrosis and fibrosis of the heart valves can also occur. Regression of this condition is usual after withdrawal of the drug. Due to these side effects, patients are not usually given this drug for any more than 6 months at a time, and 'drug holidays' of 1–2 months are used if treatment needs to be continued.

CLINICAL CONSIDERATIONS OF MIGRAINE PROPHYLAXIS

When using beta-blockers for migraine prophylaxis, it is important to commence with a low dose and gradually titrate higher to achieve the required response. Treatment is usually maintained for about 6 months. Contraindications for the use of beta-blockers include asthma, chronic obstructive airways disease, atrioventricular block and peripheral vascular disease. Pizotifen is tolerated well and does not produce any major problems that detract from its usefulness. When testing the effectiveness of different prophylactic preparations, it is important to try one agent at a time, increasing the dose gradually and attempting treatment for about 3–6 months. Responses to treatment should be documented.

Treatment of acute attacks of migraine

If prodromal symptoms are evident, then appropriate therapy should be initiated as soon as possible. This is of great importance, as nausea and vomiting make oral preventive measures difficult. Simple analgesics such as aspirin and paracetamol are often effective in dealing with the headache; other NSAIDs are not as effective as aspirin. The addition of an antiemetic to this regimen may be of help. The antiemetic **metoclopramide** (see Chapter 55) enhances the absorption of both **aspirin** and **paracetamol**, making their onset of action faster. If nausea and vomiting are a problem, then rectal antiemetics are indicated.

Some authorities propose that sleep induction with benzodiazepines can be useful in warding off an attack, and sublingual administration of **flunitrazepam** has been used with some success.

Two main drugs are used in the treatment of severe migraine attacks and they are fairly specific in their action. These are **ergotamine** and the triptans group.

ERGOTAMINE

■ MECHANISM OF ACTION

Ergotamine is prepared from ergot, a fungal product obtained from *Claviceps purpurea*, a contaminant of cereal grains, especially rye. Many ancient civilisations were aware that ingestion of rye occasionally led to severe disorders of the body, the most dramatic effect being gangrene of the extremities, with subsequent mummification of the limbs. This phenomenon initially produced a burning sensation of the limbs and was called St Anthony's fire. If contaminated rye was ingested during pregnancy, abortion usually ensued.

The ultimate cause of the gangrene was due to the vasoconstrictive effect of products from the contaminant fungus, principally ergotamine. Ergotamine is a partial α-adrenoceptor agonist and a 5-HT antagonist. The action on the α receptors leads to vasoconstriction and, thus, gangrene. It seems likely that the action of ergotamine on the cerebral arteries causes vasoconstriction, leading to cessation of the headache, and this has long been thought to be its mechanism of action. Due to the characterisation of different 5-HT receptors, it appears likely that the ergotamine action is actually much more complicated than this; as yet it is not wholly understood.

◆ COMMON ADVERSE EFFECTS

An unfortunate property of ergotamine is its ability to stimulate the chemoreceptor trigger zone (CTZ), an area of the brain that can initiate vomiting (see Chapter 55); as migraine is often accompanied by nausea, the problem may be compounded. This can be avoided by the concomitant administration of an antiemetic, preferably given rectally. Ergotamine is available as an inhalant for pulmonary absorption; this may be useful in nauseous patients in whom rectal administration is undesirable.

Most of the peripheral adverse reactions of ergotamine are due to its vasoconstrictor effect on arterioles; overdosing

can lead to gangrene. Even though ergotamine has a short half-life of about 2 hours, it can bind to arterioles and its effect can last for more than 24 hours. This precludes frequent dosing, and it is recommended that no more than five doses be given in any one week.

✚ CLINICAL CONSIDERATIONS

As too much ergotamine can lead to a headache, care must be taken not to increase the dose, as this will lead to a worsening of the condition, with the resultant adverse consequences of the excess ergotamine.

Caffeine enhances the absorption of ergotamine and is often included in antimigraine preparations to speed up the onset of action. Caffeine also potentiates the action of analgesics that may have been given concurrently.

As ergotamine is an oxytocic, it could be disastrous if used in pregnancy (see Chapter 56).

SUMATRIPTAN

■ MECHANISM OF ACTION

It has been noted that serotonin injections quickly alleviate an attack of migraine, but the multitude of side effects is not acceptable. **Sumatriptan** is a 5-HT agonist with a high specificity for receptors on the cranial blood vessels. In view of sumatriptan's high specificity for the cranial blood vessels, side effects are thus less of a problem. Potentially, the most serious effect is due to coronary artery constriction, which leads to angina in susceptible patients and consequently should not be used in patients with coronary artery disease. This is most common with intravenous administration of the drug and seldom occurs with oral administration.

◆ COMMON ADVERSE EFFECTS

Sumatriptan should not be given with ergotamine, as the potential for excessive vasoconstriction exists. Sumatriptan is an expensive drug, but its freedom from adverse effects in most instances and its effectiveness make it a valuable addition to the pharmacopoeia of migraine treatments. Sumatriptan given subcutaneously is useful in the treatment of the agonising pain of cluster headaches. As the triptans may cause coronary vasoconstriction, they are contraindicated in coronary heart disease.

✚ CLINICAL CONSIDERATIONS

Sumatriptan is absorbed speedily after oral administration but is subject to a high hepatic first pass; therefore, a comparatively large dose must be given orally. If given by subcutaneous injection, its onset of action is fast, and this may be the preferred route of administration for many patients. It is available for self-administration in prefilled syringes with an automatic injection device. Injection of sumatriptan can be accompanied by pain at the injection site and by transient flushing in various parts of the body. A nasal spray is available for patients who cannot handle self-injection, but this formulation must not be used in asthmatics, as bronchoconstriction may occur.

Other triptans are also on the market, including almotriptan, eletriptan, frovatriptan, rizatriptan, naratriptan and zolmitriptan. Rizatriptan can be given as a lingual wafer to be dissolved on the tongue; the other drugs are taken orally. Rizatriptan wafers contain aspartame and thus are precluded from use in phenylketonuria. Studies have shown that rizatriptan 10 mg can begin working within 30 minutes, with about 70 per cent of patients reporting a lessening of pain within 2 hours.

CLINICAL CONSIDERATIONS OF MIGRAINE TREATMENT

Non-pharmacological measures should be considered first, including rest, sleep and relaxation techniques. First-line therapy for an acute attack includes paracetamol, aspirin and other NSAIDs, such as **naproxen** and **diclofenac**. Gastrointestinal irritation and possible renal problems need to be considered and observed when using NSAIDs. Contraindications to ergot alkaloids, which include various types of vascular disease, should be observed closely. Treatment with ergotamine should be for no more than 1 week at a time in order to prevent a severe withdrawal syndrome. Triptans are generally effective in more than half of individuals suffering from an acute migraine attack. Neither ergot alkaloids nor triptans are recommended for use in children under 12 years of age because a benefit has not been established.

CLINICAL MANAGEMENT

Migraine prophylaxis and treatment

- For clinical management of serotonergic drugs, see Chapters 35 and 55.

Assessment

- Confirm the diagnosis of a migraine, especially if a neurological examination indicates other abnormalities.
- Assess the patient for contraindications of ergotamine-type drugs and methysergide, including hepatic and renal disorders, as these drugs are metabolised in the liver and also eliminated by the kidneys.
- Ergotamine-type drugs and methysergide should not be used in patients with vascular disease such as hypertension, atherosclerosis, Raynaud's phenomenon and Buerger's disease. The vasoconstriction produced could lead to tissue ischaemia.
- These drugs should not be given to pregnant patients or women contemplating pregnancy because of possible harm to the fetus.
- Assess the patient for valvular heart disease, pulmonary, urinary tract and collagen disease when placed on methysergide. Methysergide can cause a rare fibrosis of the pulmonary tissue, retroperitoneal area and cardiac valves.

Planning

- The symptoms of the migraine attack will lessen.
- The patient will not experience adverse effects associated with drug therapy.

Implementation

- Monitor and document aspects of the migraine attack, including severity, duration, location, frequency, aggravating factors and alleviating factors. Monitor additional characteristics, such as the presence of an aura, nausea, vomiting, visual changes, slowness of thought, drowsiness, vertigo and mood changes.
- Preventive therapies should be used one at a time over a period of about 3–6 months to determine adequately the effectiveness of a particular medication. The medication should be withdrawn slowly in order to prevent any rebound migraines before another medication is commenced.
- Give medications for prophylaxis on a regular basis.
- Remember that ergotamine-type preparations are not absorbed well, despite the route of administration. Doses will, therefore, need to be titrated individually.
- Ergotamine-type preparations are administered about 2 hours before an attack or immediately at the onset.
- Antiemetics, such as prochlorperazine, can be used to control nausea and vomiting.
- Bed rest in a darkened room with uninterrupted sleep often lessens the symptoms.

Clinical teaching

- Patients on prophylactic therapy should be advised to move slowly from a lying position to prevent effects of postural hypotension.
- Patients on methysergide should not be on this drug for more than 6 months at a time and should have drug holidays lasting 1–2 months.
- Patients on ergotamine-type drugs should report coldness, numbness and tingling of the extremities.
- Encourage the patient to avoid foods containing tyramine and food additives.
- Administer the drug with meals to alleviate symptoms of nausea and vomiting.
- Encourage the patient to follow a regular exercise and rest programme.
- Reinforce stress-reducing activities, such as relaxation and massage.
- Encourage the patient to maintain a diary to record the medications used, doses, responses to treatment, adverse effects, and any event that may have caused or aggravated a migraine attack.

Evaluation

- Evaluate the effectiveness of the drug to alleviate the symptoms of migraine. The dose may need to be titrated further to obtain more effective control of symptoms.
- Evaluate the presence of adverse effects of the drug.

Migraine prophylaxis: clinical issues

- Beta-blockers used for migraine prophylaxis include propranolol, atenolol and metoprolol. A trial for 6 months is considered to determine the possible effectiveness of treatment.
- Pizotifen may be an effective prophylactic measure. The patient should be advised not to operate machinery or to drive if feeling drowsy.
- The potent ergot alkaloid methysergide is associated with serious risks and therefore should be reserved for preventing migraine headaches that are not responding to other preparations.

Migraine treatment: clinical issues

- Within the ergot alkaloid group, ergotamine causes more vasoconstriction than other drugs and has a higher incidence of nausea, vomiting, peripheral vasoconstriction and ischaemia.
- Ergotamine should not be used for more than 2 days per week because of the possibility of dependence and rebound headaches.
- Sumatriptan and other triptans should not be administered with ergotamine because of an increased predisposition to coronary vascular disease.

SUMMARY

- Prostaglandins and related compounds affect every organ system in the body.
- Prostaglandins are used in the treatment of impotence, initiation of labour and to close a patent ductus arteriosus.
- Serotonin is involved in the aetiology of migraine.
- Migraine is a vascular disorder of the cerebral blood vessels.
- Frequent migraine attacks are usually treated with prophylactics.
- Acute migraine attacks are treated with cerebral vasoconstrictors.

1. Why is cyclizine, an antihistamine, included in some antimigraine preparations?
2. What is an advantage of rectal administration of antimigraine preparations?
3. What two functions may the addition of caffeine serve in antimigraine preparations?
4. Why should ‘drug holidays’ be given during methysergide therapy?
5. The oral dose for sumatriptan is 100 mg and yet the subcutaneous dose is only 6 mg. Why?
6. Mohamed Allaraz, a 65-year-old patient with angina, also suffers from severe migraine attacks. Why is sumatriptan an unsuitable form of treatment for his migraine condition?
7. Explain how amitriptyline assists in preventing a migraine attack.
8. What education can you offer a patient who wants to decrease the frequency of migraine attacks without resorting to drug therapy?
9. With reference to its adverse effects, explain why methysergide is not commonly prescribed for migraine prophylaxis.
10. Explain how metoclopramide assists in the treatment of an acute migraine attack.

30 DRUG SUMMARY TABLE: PROSTAGLANDINS AND SEROTONIN

FAMILY NAME	GENERIC NAME	TRADE NAME(S)
Ergot alkaloids and derivatives	Ergotamine, caffeine	Cafergot Migril
	Methysergide	Deseril
Prostaglandins	Dinoprostone	Prostin E_2 vaginal tablets
E_2	Dinoprost	Prostin F_2 alpha
$F_{2\alpha}$		Propess (pessaries)
E_1	Carboprost	Hemabate
	Alprostadil	Caverject Muse Viridal Duo
Prostaglandin analogues	Gemeprost	
	Misoprostol	Cytotec
Miscellaneous	Pizotifen	Sanomigran
Serotonin agonists	Almotriptan	Almogran
	Eletriptan	Relpax
	Frovatriptan	Migard
	Naratriptan	Naramig
	Rizatriptan	Maxalt
	Sumatriptan	Imigran
	Zolmitriptan	Zomig

NITRIC OXIDE AND THE ENDOTHELINS

31

CHAPTER THIRTY-ONE

OBJECTIVES

KEY TERMS

Endothelins
Non-noradrenaline, non-cholinergic (NANC) transmission
Neuromodulation
Nitric oxide
Nitric oxide synthase (NOS)

After completing this chapter, the reader should be able to:

- **briefly describe the physiological effects of nitric oxide and the endothelins;**
- **identify the pathophysiological conditions to which nitric oxide and the endothelins contribute;**
- **outline the therapeutic applications of these mediators that derive from a knowledge of their pathophysiological roles.**

NITRIC OXIDE (NO) AND THE ENDOTHELINS ARE IMPORTANT signalling molecules that appear to play significant regulatory roles in health and disease. They affect physiological processes as diverse as vascular responsiveness, neurotransmission, cell differentiation, airway tone, cardiac contractility and inflammation. There is some interplay between the two mediators. In some tissues, nitric oxide produces similar effects to the endothelins, while in others they counteract each other. Broadly speaking, in low concentrations nitric oxide and the endothelins tend to be beneficial to health, while at high concentrations they tend to produce detrimental effects. There is persuasive evidence to suggest that these substances participate in the development of some human diseases.

As mediators of physiological and pathophysiological processes, nitric oxide and the endothelins have attracted a lot of attention. A greater understanding of the properties of these substances and their roles has led to the development of therapeutic agents that alter either the tissue levels of these molecules or their effects. Our knowledge of their functions is far

from complete, but further research will probably yield new drugs derived from these substances for use in the treatment of debilitating chronic diseases.

The purpose of this chapter is to provide an overview of the functions of nitric oxide and the endothelins and to discuss the current and potential therapeutic applications of these molecules in disease.

NITRIC OXIDE

Nitric oxide, also known as nitrogen monoxide, is a highly reactive gas formed endogenously from the amino acid arginine. The reaction that forms nitric oxide is catalysed by the enzyme nitric oxide synthase (NOS). During its relatively brief existence (less than 1 second in the blood and several minutes in tissue), nitric oxide exerts its physiological effects and then is converted rapidly into various other metabolites, including nitrogen dioxide, nitrite, nitrate and, under some conditions, peroxynitrite ion.

When it was first identified, nitric oxide was shown to induce vasodilation following release by vascular endothelial cells. Its role here is considered constitutive, exerting a homeostatic regulatory effect on tissue blood flow. The nitrates (e.g. **glyceryl trinitrate**) and related substances are used in angina (see Chapter 45) and hypertensive emergencies (see Chapter 44). These act as nitric-oxide donors, providing an exogenous supply of nitric oxide to the endothelium for this purpose. Nitric oxide also reduces haemoglobin to methaemoglobin, converting the iron in haem from the ferrous ion (Fe^{2+}) to the ferric ion (Fe^{3+}). In the presence of nitric oxide, cyanide is drawn off the cytochromes and on to methaemoglobin, reactivating cellular energy production. For this reason, the nitric oxide donors **amyl nitrite** and **sodium nitrite** are used as antidotes in cyanide poisoning (see Chapter 21).

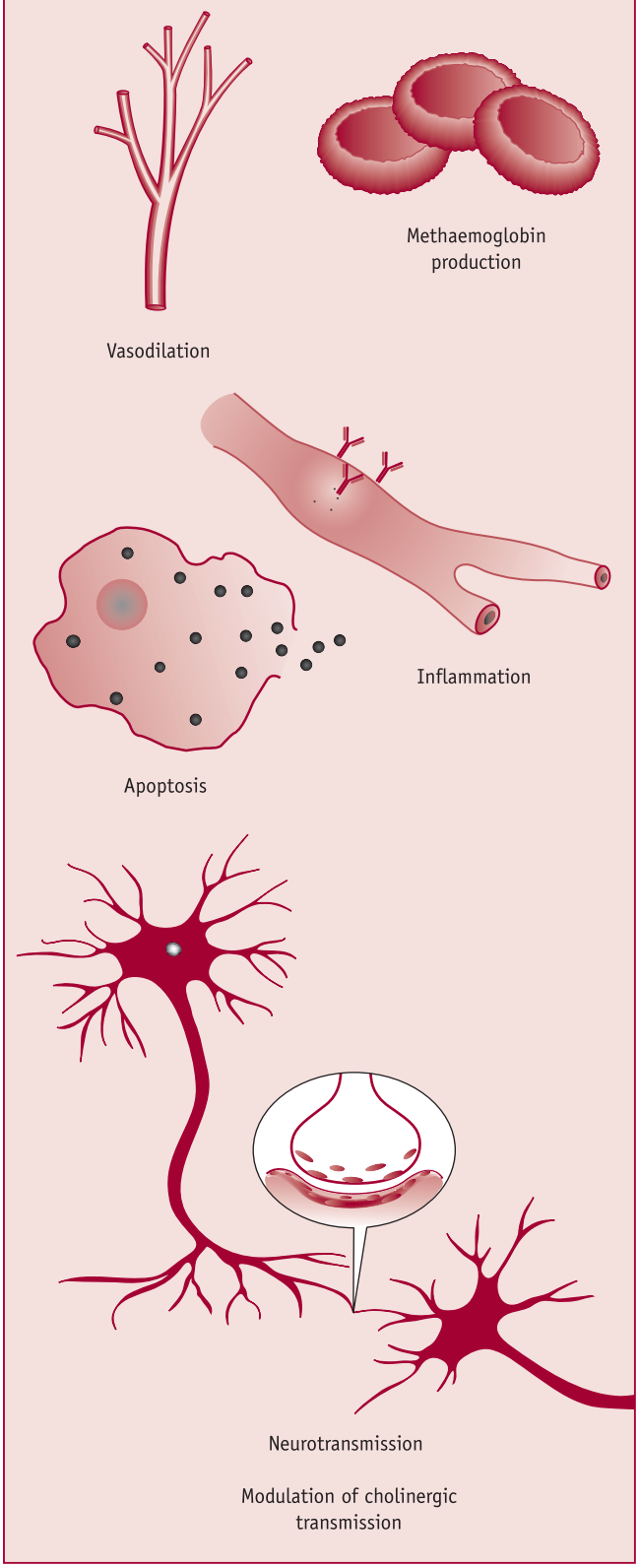
Our understanding of the possible physiological roles of nitric oxide has expanded greatly (see Figure 31.1). Nitric oxide plays a significant role in nervous-system function. There is evidence that nitric oxide acts as a neurotransmitter in some neural pathways and is involved in autonomic nervous system pathways (see Chapter 25). Indeed, this illustrates that noradrenaline and acetylcholine are not the only neurotransmitters operating in this system. Neurotransmission involving chemical messengers such as nitric oxide can also contribute to autonomic function, falling under the category non-noradrenergic, non-cholinergic (NANC) transmission. The role of nitric oxide and other novel chemical transmitters has forced us to reconsider the nature of neurotransmission and paracrine communication. Unlike classic neurotransmitters, nitric oxide is not stored in the axon terminal in vesicles and released to produce a rapid, short-lived response. Instead, it is synthesised when required and produces a relatively slow response. As an autonomic nervous system transmitter, nitric oxide has been implicated in human physiology in the respiratory passages (it induces bronchodilation) and in the stomach (it stimulates gastric emptying). Nitric oxide is also considered a modulator of neural transmission. This means that it can influence the release of neurotransmitter from the axon terminal and has been shown to enhance the release of acetylcholine from autonomic postganglionic fibres (see Section VI). Moreover, nitric oxide has a role in early nervous system development. This is achieved through its involvement in the regulation of apoptosis (programmed cell death). Its role is complex, as it appears to promote apoptosis in some cells but to protect others from this fate. Nitric oxide is believed to contribute to the formation of appropriate synaptic connections in the developing nervous system.

The role of nitric oxide in inflammation is primarily to enhance this response. As a vasodilator, it contributes to the vascular phase of inflammation. It also increases the permeability of the blood vessels and induces prostaglandin synthesis. Nitric oxide plays a part in the non-specific host defence against a range of microbes and cancerous cells. It also inhibits the aggregation of a number of formed elements in the blood, particularly platelets and neutrophils, and the tendency for them to adhere to the blood-vessel wall.

Three forms of the synthesising enzyme nitric oxide synthase (NOS) have been identified. One form is associated with neuronal tissues and is called nNOS or NOS1. The second form, isolated from macrophages, is associated with immune/inflammatory functions and is called mNOS, iNOS or NOS2. The 'i' stands for inducible, because all body cells have the potential to express this form in response to cellular signals such as bacterial products, cytokines and lipid mediators (e.g. leukotriene B_4). The third form is allied with endothelial cells and is called eNOS or NOS3. The nitric oxide induced in response to stimulation in nervous and endothelial cells (via the activation of nNOS and eNOS) is produced relatively rapidly at very low concentrations and is short-lived. This pattern of production is associated with homeostasis. Its cellular effects are associated with the activation of a calcium-dependent second-messenger system involving cyclic guanosine monophosphate (cGMP) (see Chapter 26). In contrast, the nitric oxide induced in response to immune and inflammatory signals (derived via iNOS) is produced slowly and at higher concentrations and can be sustained for a prolonged period.

Alterations in the normal production of nitric oxide have been implicated in some human disease states. There is evidence that inadequate nitric oxide production may contribute to the pathophysiology of diabetes mellitus, atherosclerotic

FIGURE 31.1 PHYSIOLOGICAL EFFECTS OF NITRIC OXIDE



diseases, impaired wound healing and hypercholesterolaemia. Excessive or chronic nitric oxide production has been proposed as a factor in neurodegenerative disorders such as Parkinson's disease, septic shock, pain, cancer and chronic inflammation.

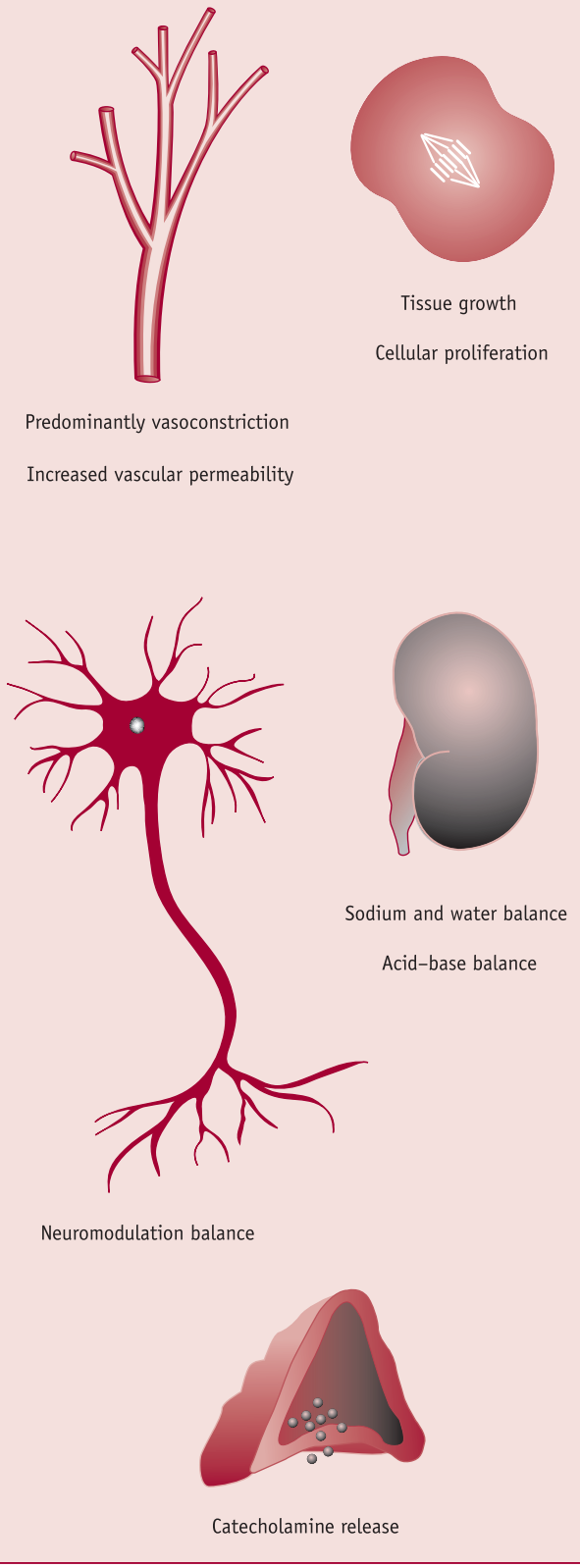
There is a lot of interest related to the development of therapeutic agents that act by altering nitric oxide levels in the body. For diseases characterised by excessive nitric oxide production, research is continuing on arginine analogues that compete with arginine for NOS binding sites (for more on enzyme competition, see Chapter 16) and result in lower nitric oxide production. NOS inhibitors may provide a useful strategy, particularly if they show selectivity for the different forms of NOS. For diseases associated with deficiencies in nitric oxide levels, the nitric-oxide-donating nitrovasodilators (e.g. glyceryl trinitrate, **sodium nitroprusside**) have been used for decades. Gene therapy (see Chapter 77) may also provide a means to treat such conditions by introducing the gene for NOS into diseased tissues.

THE ENDOTHELINS

The endothelins are a group of three related endogenous peptides – endothelin-1 (ET-1), endothelin-2 (ET-2) and endothelin-3 (ET-3) – produced by endothelial cells. The focus of this discussion is on endothelin-1, as more of its functions have been described. Endothelin-1 produces contraction of smooth-muscle cells (a spasmogenic action), induces increased vascular permeability, acts as a tissue growth factor and stimulates cellular proliferation (a mitogenic action). At this stage, two endothelin receptor subtypes have been identified, ET_A and ET_B, which are coupled to a G-protein and second-messenger system. The second messenger in this case is inositol trisphosphate (see Chapter 26). The ET_A receptor is relatively selective for endothelin-1 and endothelin-2, while the ET_B receptor shows no particular selectivity for one or other of the endothelins.

The role of endothelin-1 in each of the body systems has been described, at least to some degree (see Figure 31.2). In the cardiovascular system, it acts as a potent vasoconstrictor at ET_A receptors. It has been suggested that this effect may be due to the release of renin, aldosterone, angiotensin II, vasopressin and the catecholamines and the modulation of nitric oxide and atrial natiuretic hormone release. The role of endothelins in blood-pressure control is complex, as stimulation of ET_B receptors stimulates vasodilation; this is due to the release of nitric oxide and prostacyclin (see Chapter 30) from endothelial cells. The seemingly paradoxical effects can be explained by the finding that the distribution of these receptor subtypes varies across types of blood vessel, which results in different net effects on blood pressure and perfusion in various parts of the circulation. Endothelin-1 is also believed to have

FIGURE 31.2 PHYSIOLOGICAL EFFECTS OF THE ENDOTHELINS



positive inotropic effects on the heart and may even have negative chronotropic effects. Endothelins are thought to play a part in the pathophysiology of cardiovascular-related diseases such as hypertension (systemic and pulmonary forms), ischaemic heart disease, myocardial infarction, congestive cardiac failure and cerebral vasospasm. This is due to the vasoconstricting action and also the mitogenic action (which leads to fibrosis, hypertrophy and hyperplasia) in the vasculature and heart.

In the lungs, endothelin-1 can induce bronchoconstriction, increase mucus secretion and activate inflammatory cells. It has been implicated in the development of allergic rhinitis. In the central nervous system, the endothelins appear to modulate endocrine function, cardiorespiratory function and, possibly, behaviour. In the adrenal gland, endothelin-1 increases the release of catecholamines into the circulation from the adrenal medulla. In the endometrium, there is evidence that endothelin-1 stimulates a vasoconstrictive response to reduce menstrual bleeding and may stimulate endometrial regeneration after menstruation. In the kidney, the endothelins play a role in sodium and water excretion and in acid–base balance. Research has shown that these substances are implicated in renal failure.

The endothelins have been shown to play a role in embryonic tissue development and differentiation as a growth factor. Animal studies have indicated that these peptides contribute to the normal development of facial and throat structures, the middle ear, the aorta and adjacent arteries and intestines.

Drugs that are emerging from a better understanding of the role of endothelins in health and disease are the endothelin receptor antagonists. This group of therapeutic agents shows some promise in treating cardiovascular disease.

BOSENTAN

An endothelin receptor antagonist, **bosentan**, has been approved in a number of developed countries, including the UK, for use in the treatment of pulmonary arterial hypertension.

■ MECHANISM OF ACTION

Bosentan binds to ET_A and ET_B receptors and blocks access to endothelin-1. This triggers arterial vasodilation and decreases inflammation and tissue remodelling.

◆ COMMON ADVERSE EFFECTS

Common adverse effects of bosentan include raised serum liver enzyme levels, headache, flushing and leg oedema. A dose-related decrease in haemoglobin levels is associated with treatment.

✚ CLINICAL CONSIDERATIONS

Liver function needs to be monitored during therapy for evidence of hepatotoxicity. Patients with moderate to severe liver impairment should not receive treatment with bosentan. Haemoglobin levels should also be monitored.

Bosentan is contraindicated in pregnancy, and female patients should use a barrier method of contraception to prevent pregnancy during treatment. Concurrent therapy with the immunosuppressant **ciclosporin** or the sulphonylurea **glibenclamide** is also contraindicated. The former will increase plasma bosentan levels and the latter induces elevations in serum liver enzyme levels.

SUMMARY

- Nitric oxide and the endothelins are important signalling molecules.
- They play a role in normal homeostasis and in the development of disease.
- A number of drugs are being developed to alter the levels of, or the responses to, these mediators in order to treat selected diseases. An endothelin-1 antagonist called bosentan is now available in the UK for the treatment of pulmonary arterial hypertension.

1 For each of the following processes, indicate whether nitric oxide and/or the endothelins have a role and briefly outline that role:
(a) inflammation;
(b) airway responsiveness;
(c) vascular responsiveness;
(d) embryonic tissue development;
(e) neurotransmission.

2 For each of the following diseases, indicate whether nitric oxide and/or the endothelins have a role to play:
(a) hypertension;
(b) chronic inflammation;
(c) diabetes mellitus;
(d) renal failure.

3 Outline the rationale for the development of drugs that affect nitric oxide levels.

4 Outline the rationale for the development of drugs that affect the responses to the endothelins.

CASE STUDY VII.1

Mr HJ frequently suffered from migraine attacks, which often coincided with attacks of hayfever. In spring, when the pollen count was high, his hayfever was usually at its height, resulting in severe rhinitis, with copious, thin mucus production. At other times, various stimuli would result in nasal congestion rather than a runny nose. These stimuli included red wine, cigarette smoke and strange beds.

Mr HJ regularly visited his general practitioner and was prescribed many medications for both his allergies and his migraine. Many years ago, he was prescribed chlorphenamine tablets and a chlorphenamine nasal spray. These were helpful in relieving his rhinitis but caused a dry mouth as well as considerable drowsiness, especially at commencement of treatment. These preparations were of no use in the treatment of his nasal congestion. To relieve his congestion, he was originally prescribed xylometazoline drops and pseudoephedrine tablets. During treatment with these, he suffered from insomnia; the pseudoephedrine tablets were stopped, which improved his sleeping problem. He then had to increase the number of sprays to each nostril. He had been told not to overuse these drops, but he found that, after several weeks' use, he had to increase the number of sprays dramatically. He also found that if he tried to decrease the amount of spraying, his nasal congestion returned very quickly and was even worse than it had been at the start of the treatment. He reported this to his doctor, who then prescribed a budesonide nasal spray, which, after several weeks, improved his nasal congestion.

Mr HJ's migraine was treated with ergotamine, caffeine and paracetamol. This combination usually proved effective, but sometimes he would suffer from several attacks per week. He had been told not to take more than five ergotamine tablets in a week.

Recently, he has been given sumatriptan tablets, which have worked wonders but have proven to be too expensive to use because of the frequency of his attacks.

QUESTIONS

1. *Why would Mr HJ suffer from a dry mouth with chlorphenamine tablets?*
2. *What antihistamine could Mr HJ have been prescribed to avoid the drowsiness?*
3. *Why would strange beds trigger an allergic attack?*
4. *Why are antihistamines of little value in the treatment of nasal congestion?*
5. *What is the main problem with the overuse of xylometazoline?*
6. *Why did the budesonide take time to show an improvement? What might be an advantage with budesonide when compared with betamethasone?*
7. *What is the problem with taking too much ergotamine?*
8. *How does sumatriptan exert its effect?*
9. *What alternative therapy would be useful to help Mr HJ in migraine prophylaxis?*
10. *If Mr HJ proved unresponsive to the answer in question 9, what alternative therapy could be used?*

FURTHER READING

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WEB RESOURCES

Migraine Awareness Group www.migraines.org/treatment/

New developments in Allergy http://allergies.about.com/cs/food/a/blacaai110703.htm

Nitric Oxide Research www.nitricoxideresearch.com/

Nitric oxide and vascular health www.healthandage.com

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MODULATION OF BEHAVIOUR, COGNITION AND MOTOR ACTIVITY

Canst thou not minister to a mind diseas'd
Pluck from the memory a rooted sorrow,
Raze out the written troubles of the brain,
And with some sweet oblivious antidote
Cleanse the stuff'd bosom of that perilous stuff
Which weighs upon the heart.

WILLIAM SHAKESPEARE – *MACBETH*

Throughout the ages, human beings have attempted to use substances obtained from natural sources to alter the functioning of the mind. This has led indirectly to the development of drugs used to treat various disorders of the central nervous system (CNS). This section deals with the drugs that affect the CNS in cases of malfunction, such as can occur in schizophrenia (Chapter 33), anxiety and insomnia (Chapter 34) and depression (Chapter 35). These disorders are often due to defects in neurotransmission. Considerable emphasis will be put on the neurotransmitters involved (Chapter 32), their role in psychiatric states and the effects of drugs on neurotransmission.

Abnormal neural function in the CNS can also give rise to disturbed body movements and cognition. An upset in their function can lead to conditions such as Parkinson's disease, epilepsy, Alzheimer's disease, attention disorders and narcolepsy. Chapters 36, 37 and 38 deal with the drugs that can be used to treat or ameliorate these conditions.

VIII

GENERAL CONCEPTS OF CENTRAL NERVOUS SYSTEM PHARMACOLOGY

32

CHAPTER THIRTY-TWO

OBJECTIVES

After completing this chapter, the reader should be able to:

- **identify the major brain regions and their functions;**
- **indicate how discrete brain regions interplay to control some functions;**
- **identify the principal chemical transmitters involved in brain function, and the functions they influence;**
- **identify some examples of illnesses that are based on alterations in neurotransmission in the brain.**

KEY TERMS

Brain functions
Drug specificity
Neuromodulation
Neurotransmitters

THE HUMAN BRAIN IS AN EXTREMELY COMPLEX ORGAN, OUR present understanding of which can at best be described as rudimentary. The brain is responsible for all affective (emotional) and cognitive (thinking) processes, and it is as capable of coordinating corporeal functions (e.g. eating, sleeping, walking, talking) as it is of pursuing abstract thought. Sometimes imbalances in mental functioning occur that can result in one of a number of brain disturbances – disorders such as schizophrenia, depression, anxiety and parkinsonism. (The pathophysiology of these conditions is discussed in subsequent chapters in this section.) The onset of such conditions can make normal functioning within society extremely difficult. The use of pharmacotherapy may be a necessary part of the reintegration of affected individuals in the community.

The drugs used to treat behavioural abnormalities are known as psychotropic agents. The mechanism of action of many of these drugs is not understood well. This is not surprising, as our understanding of how the brain works is far from complete. Essentially, psychotropic drugs act on chemical transmitter–receptor systems within the brain. Depending on the nature of the brain disturbance, it may be desirable to either mimic or block endogenous transmitters in order to produce favourable mental effects.

To gain an understanding of how these drugs work, it is necessary first to look at the functions of the principal brain regions and then the nature of the chemical transmitter–receptor systems found within these regions.

DIVISIONS OF THE BRAIN

Moving in a rostrocaudal direction through the brain, the first anatomical region is the cerebrum, comprising the left and right cerebral hemispheres, cortex and associated subcortical nuclei (hippocampus, basal ganglia and amygdala). The next region is the diencephalon, encompassing the thalamus and the hypothalamus. Then, most inferiorly, come the brain stem and cerebellum. The brain stem consists of the midbrain, pons and medulla oblongata. The cerebellum is positioned posteriorly between the pons and medulla. These anatomical regions are represented in Figure 32.1.

Functionally, some processes are the exclusive domain of one particular brain region. It is apparent, however, that many brain regions are interconnected so that the control of certain cerebral functions can be achieved in an integrated and cooperative way. A brief summary of the main functions of these regions follows.

Cerebrum

The cerebrum is responsible for the precise perception and interpretation of sensation, the initiation of skeletal muscle movement, and communication. It is also the seat of the intellect and of abstract thought.

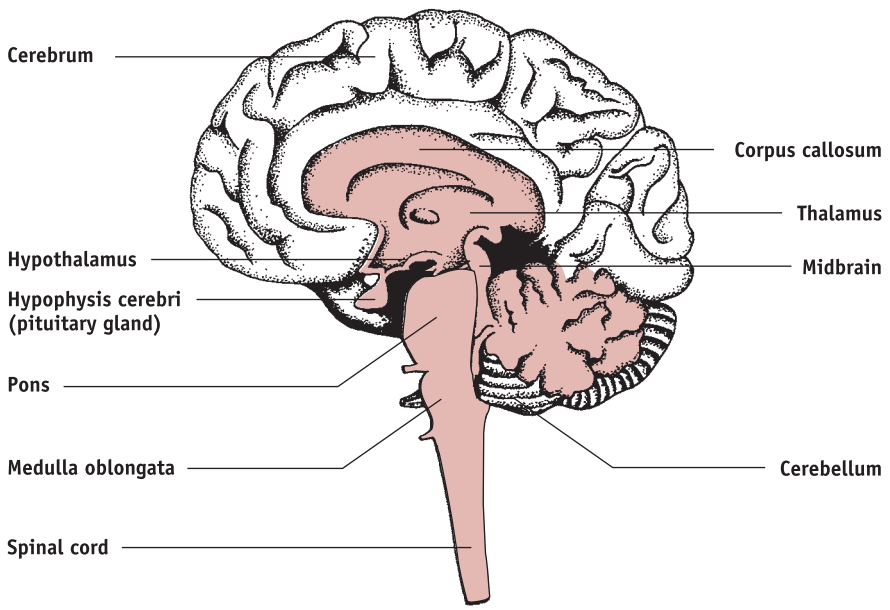
Diencephalon

The thalamus acts as a relay for incoming sensory information by sorting out one type of sensation from another and sending it to the most appropriate region of the cortex for processing. It also relays motor impulses from the cortex to lower motor centres.

The hypothalamus is the principal integration centre of visceral function. It regulates appetite, body temperature, fluid levels, hormone production and secretion, and biological rhythms.

FIGURE 32.1 PRINCIPAL PARTS OF THE HUMAN BRAIN

Sagittal cross-section indicating the principal parts located within the right side of the human brain.



Cerebrum–diencephalon interactions

The cerebrum and diencephalon cooperate in memory formation and in the control of emotions and behaviour. The network involved with these functions is called the limbic system, which includes areas of the cortex, hippocampus, amygdala, fornix, thalamus and hypothalamus.

Brain stem

The brain stem acts as a conduction pathway between higher and lower brain centres for both sensory and motor information. The medulla oblongata contains control centres for important visceral functions, such as heart rate (cardiac centre), blood pressure (vasomotor centre), respiratory rate (respiratory centres), coughing (cough centre) and vomiting.

Brain stem–diencephalon–cerebrum interactions

The brain stem, thalamus and cerebral cortex cooperate to control the level of consciousness via an integrated network called the reticular activating system.

Cerebellum

The cerebellum is involved in the maintenance of equilibrium and posture. It monitors and modifies motor impulses from higher centres to provide smooth and coordinated skeletal muscle movements. It may also be involved in the control of behaviour.

Motor pathways

The motor pathways from cerebrum to spinal cord that control skeletal muscles incorporate two discrete systems: the pyramidal and extrapyramidal pathways. The pyramidal pathways are responsible for the activation of skeletal muscles, whereas the extrapyramidal pathways dampen and adjust voluntary muscle movements. The extrapyramidal pathways are involved in the maintenance of muscle tone and balance and are concerned with the coordinated movement of the head and eyes towards visual stimuli.

CHEMICAL TRANSMITTERS

Chemical transmitters known to be involved in mental processes include noradrenaline, adrenaline, dopamine, serotonin, acetylcholine, glutamate and gamma-aminobutyric acid (GABA). The number of putative neurotransmitters thought to be involved in brain function is ever increasing; the list includes glycine and histamine. In addition to their classical role in synaptic transmission, some neurotransmitters may act as neuromodulators in certain nerve pathways. Before describing the characteristics of each of the major transmitters, it is useful to define the term 'neuromodulation'.

Neuromodulation

Classically, neurotransmitters are released from one neuron to activate or inhibit another. The activation involves triggering an action potential in the receiving cell. Neuromodulators bias a nerve cell's response to its neurotransmitter. They alter the response of a nerve cell or a nerve circuit to its neurotransmitter(s) to either enhance or suppress impulse transmission. Importantly, neuromodulators may produce little effect on the nerve membrane potential of the target neuron in the pathway.

As we examine each of the following neurotransmitters, we should note that in some pathways the chemical may act to modulate activity and in others it may primarily activate nerve cells.

Acetylcholine

Acetylcholine is thought to play a major role in cognitive function, memory formation and motor control. Cholinergic nerves are associated with the pyramidal pathway, thalamocortical sensory pathways (particularly those involved in hearing and sight), the hippocampus (involved in memory), and the reticular activating system controlling arousal and consciousness. The motor pathways are essentially nicotinic, whereas in cognitive function, memory and consciousness, M_1 muscarinic receptors predominate (see Chapter 27).

Dopamine

Dopamine is involved in behaviour, hormone release, motor control and emesis. Areas of the brain that are found to contain dopaminergic nerves are the limbic system, the extrapyramidal pathway (where dopamine modulates the cholinergic activation of skeletal muscles), the chemoreceptor trigger zone within the medulla (which can stimulate the vomiting centre), and the pathways connecting the hypothalamus with the pituitary gland (involved in the release of prolactin and other hormones). At least four subtypes of central dopamine receptor have been identified – D_1, D_2, D_3 and D_4. Central dopamine receptor activation has been linked to the development of drug addiction. The distribution of dopamine receptor subtypes is yet to be elucidated fully.

Noradrenaline and serotonin

Both of these transmitters seem to be involved in similar functions within the brain: arousal, sleep, mood, appetite, temperature control and hormone release. Noradrenaline can stimulate α- and β-adrenergic receptor subtypes (see Chapter 26). Serotonin (also known as 5-hydroxytryptamine, 5-HT) may also have a role in pain perception and behaviour. At least two subtypes of central serotonin receptor have been identified – 5-HT_1 and 5-HT_2. The effects of serotonin receptor activation are described in Chapter 30.

Consistent with this, these neurotransmitters are distributed throughout similar areas of the brain, predominantly

TABLE 32.1 BRAIN REGIONS AND CHEMICAL TRANSMITTERS

Transmitter	Brain region	Functions	Related condition
Acetylcholine	Cerebral cortex, thalamocortical tracts, pyramidal pathway, reticular activating system	Cognition, skeletal muscle movement, memory, consciousness	Parkinson's disease, dementia
Dopamine	Extrapyramidal pathway, limbic system, chemoreceptor trigger zone, hypothalamus	Skeletal muscle movement, behaviour, emesis, hormone release	Parkinson's disease, inhibition of hormone release, aberrant behaviour
Noradrenaline	Hypothalamus, reticular activating system	Arousal, sleep, mood, appetite, hormone release, body temperature	Eating disorders, depression, insomnia
Serotonin	As for noradrenaline	As for noradrenaline, plus behaviour and pain transmission	As for noradrenaline
Glutamate	All regions, but abundant in cortex and basal ganglia	Learning and memory	Epilepsy, excitotoxicity, neurodegenerative disease
GABA	All regions	Motor control, memory, consciousness	Aberrant behaviour, insomnia, anxiety

GABA, gamma-aminobutyric acid.

in lower brain centres: the hypothalamus and brain stem (important parts of the reticular activating system). The raphe nuclei of the midbrain are rich in serotonin-containing neurones.

GABA

GABA is distributed throughout the brain and spinal cord. It is now considered to be the major inhibitory neurotransmitter in the central nervous system (CNS), and it acts to modulate the activity of excitatory pathways. It is formed from the excitatory transmitter glutamate (see below). There are two subtypes of GABA receptor: $GABA_A$ and $GABA_B$. Motor control, consciousness, level of arousal and memory formation are all inhibited by GABA.

Glutamate

Like GABA, glutamate is distributed throughout the CNS. It is considered the major excitatory CNS neurotransmitter. It can stimulate a number of receptor types in the brain and spinal cord, the most important being *N*-methyl-D-aspartate (NMDA), α-amino-3-hydroxy-5-methyl-isoxazole propionic acid (AMPA) and kainate receptors. When stimulated, NMDA receptors promote calcium movement into cells, and this underlies the excitation. The psychotropic agents **ketamine** and **phencyclidine** (see Chapters 41 and 23) are selective NMDA receptor antagonists.

Glutamate appears to perform a modulatory influence on CNS circuitry. Glutamate is involved in the facilitation of learning and memory. The brain is very vulnerable to glutamate-mediated overexcitation; this results in excitotoxicity. In this state, calcium influx into the nerve cell is enhanced. Raised intracellular calcium levels lead to the activation of enzymes and free radicals. Ultimately, cell integrity is disrupted and the nerve cell dies. Excitotoxicity has been demonstrated in stroke and some neurodegenerative diseases. Glutamate has also been implicated in the development of epilepsy.

A summary of the functions controlled by particular brain regions, the transmitters involved and the conditions with which they are associated can be found in Table 32.1.

DRUG SPECIFICITY

One of the problems associated with psychotropic agents is specificity. For example, the particular brain function we want to alter may be mediated by dopamine receptors. Dopamine receptors, however, are known to be involved in a number of brain functions. These other functions will be affected by the drug therapy because we have no way of restricting the site of action to one region once the drug enters the brain. This accounts for many of the profound side effects associated with psychotropic therapy. The only way to overcome these side effects is to identify subtypes of receptors that may lead to the development of more specific clinical agents. As you will see in the following chapters, to some extent this approach has proven successful.

SUMMARY

- The major parts of the human brain are the cerebrum, diencephalon, brain stem and cerebellum.
- The cerebrum is involved in motor and sensory function and is the seat of the intellect. The diencephalon comprises the thalamus, which acts as an information-sorting area, and the hypothalamus, which is an integration area for visceral functioning. The brain stem contains control centres for heart rate, respiratory rate and blood pressure. The cerebellum controls muscle tone and posture and facilitates smooth, coordinated muscle movements.
- Neuromodulators act to modify neurotransmission but do not actually activate nerve transmission along a pathway.
- Acetylcholine, dopamine, noradrenaline and serotonin are key neurotransmitters in the brain. Glutamate and gamma-aminobutyric acid (GABA) can act as neuromodulators in the central nervous system.

1 State the function(s) of the following brain regions:
(a) thalamus;
(b) cerebellum;
(c) cerebrum;
(d) medulla.

2 Identify the brain regions that participate in the control of the following functions:
(a) consciousness;
(b) motor control.

3 Which neurotransmitter(s) is/are involved in the control of the following functions?
(a) mood;
(b) behaviour;
(c) skeletal muscle movement;
(d) arousal;
(e) emesis.

4 Which brain functions are thought to be associated with the following neurotransmitters?
(a) GABA;
(b) dopamine;
(c) noradrenaline;
(d) serotonin;
(e) glutamate.

5 State which neurotransmitter(s) is/are involved in the following conditions:
(a) parkinsonism;
(b) depression;
(c) aberrant behaviour;
(d) stroke.

6 Identify the receptor subtypes associated with the following transmitters:
(a) dopamine;
(b) glutamate;
(c) GABA.

ANTIPSYCHOTIC DRUGS

33

CHAPTER THIRTY-THREE

KEY TERMS

Psychoses
Schizophrenia
Neuroleptic malignant syndrome
Extrapyramidal effects
Oculogyric crisis

OBJECTIVES

After completing this chapter, the reader should be able to:

- **explain what is meant by the psychoses;**
- **recognise the principle types of antipsychotic drug;**
- **discuss the use, mechanism of action and adverse effects of antipsychotic drugs.**

PSYCHOSES ARE MENTAL HEALTH DISORDERS CHARACTERISED by aberrant behaviour and disturbed emotional states. They include conditions such as schizophrenia, severe agitation, certain types of depression and some forms of dementia. The defects in the psychoses are not yet known in detail, but they appear to reflect disturbances in catecholamines in the central nervous system (CNS). Schizophrenia, for example, traditionally has been linked to an abnormal function in dopamine pathways, particularly the mesolimbic pathway. The two major pieces of supporting evidence are that many antipsychotics block dopamine receptors, particularly the D_2 subtype, and drugs that boost dopamine activity, such as amphetamine, trigger amphetamine psychosis (which is like schizophrenia) in some people.

Nevertheless, no matter how attractive such theories are, they may vastly oversimplify the situation. While antipsychotic drugs immediately block dopamine receptors, they usually take a week or two to reduce the symptoms of psychosis. Furthermore, some of the newer antipsychotics are atypical and less effective at blocking dopamine receptors and have effects on a range of other transmitters, such as serotonin, which may be relevant.

SCHIZOPHRENIA AND DOPAMINE RECEPTORS

Schizophrenia is a relatively common psychosis with multiple symptoms. Symptoms are described as negative or positive. Positive symptoms include delusions of thought, distorted perceptions and emotions, and the belief that one is under the control of an external agency. The 2002 Oscar-winning film *A Beautiful Mind* showed very well how the main character thought he was under the control of the Central Intelligence Agency (CIA). Negative symptoms include terseness in speech, social withdrawal, anhedonia and apathy.

The causes of schizophrenia are still a mystery but can be genetically determined or induced by drugs that increase dophminergic activity in the brain. There are a number of distinct G protein coupled dopamine receptors. Positron emission tomography (PET) has demonstrated an increase in D_2 receptors in the nucleus accumbens area of the brain (a region associated with reward and addictive behaviour) and, as stated above, the D_2 receptors may be important in psychotic illnesses. D_3 and D_4 receptors are probably also involved, as are the neurotransmitters serotonin, gamma-aminobutyric acid (GABA) and glutamate. Different sub-types of the D_2 receptor have been found on the post synaptic and presynaptic membranes the latter being termed an autoreceptor that modulates transmitter release. Thus anti-psychotics that act as D_2 antagonists may inhibit post synaptic transmission but through the blocking of autoreceptors increase transmitter release. Antipsychotic drugs are classified as either typical or atypical agents. Typical antipsychotics are much more active on the D_2 receptors than the atypical ones. The therapeutic effect is presumed to be a result of this effect in the limbic system and cerebral cortex. Unfortunately, it is also the D_2 types that predominate in the basal ganglia, hence the symtpoms of parkinsonism are associated with these drugs. The atypical ones, having less affinity for the D_2 receptors, are usually devoid of parkinsonian effects. These drugs readily bind with D_3 and D_4 receptors sub-types that do not predominate in the basal ganglia. Most antipsychotics also have inhibitory effects on other monoamine receptors, and this may explain the variation in response to these drugs.

ANTIPSYCHOTIC DRUGS

Typical antipsychotics

■ MECHANISM OF ACTION

The antipsychotic drugs, sometimes referred to as neuro-leptics or major tranquillisers, are normally classified accord-ing to their chemical nature. The term 'neuroleptic' is derived from neurolepsy, which has been used to define a state of apathy and mental detachment (Greek *neuron* nerve, *lepsis* seizure). Reference to major tranquillisers should be avoided as the term is misleading. There are at least five basic types of antipsychotic agent, based on their chemistry. The three typical, or classic, antipsychotic drug groups are the phenothiazines, butyrophenones and the thioxanthenes (see Table 33.1 for a list of specific agents). These three groups of drugs probably have similar mechanisms of action on the CNS, although their exact mode of action remains to be elucidated fully. As mentioned previously, their main action is to antagonise dopamine, but they also have antimuscarinic, antihistaminic (H_1) and antiserotoninergic action and act as α_1-blockers. Due to their broad spectrum of activity, many adverse effects are associated with these drugs. Their *large* number of *actions* led to the choice of the trade name Largactil™, for chlorpromazine, the first antipsychotic.

Some of the antipsychotics are available in a depot injectable form, which enables long-term action from one injection; this type of drug is useful where non-compliance is a problem. **Haloperidol**, **flupenthixol**, **pipothiazine** and **fluphenazine** are available in this form as their decano-ate or other long-chain-fatty-acid derivatives. Long-chain fatty acids, combined with a basic drug increase the lipo-philicity of the drug. The resulting ester dissociates slowly into the free base, which is then absorbed slowly into the muscle blood vessels. People with schizophrenia may have problems with medication compliance; therefore, an injection may make their treatment more effective.

◆ COMMON ADVERSE EFFECTS

Extrapyramidal effects are often seen with the antipsychotics. The extrapyramidal symptoms produced by the anti-psychotics can be classified into four types. Drug-induced parkinsonian symptoms, including tremor, rigidity and poverty of movement, are the most common. These effects are particularly common with the depot injections, and an antimuscarinic drug (see Chapter 27) such as **benzhexol** is often given with these drugs. It is advisable to administer these antimuscarinic drugs with the oral preparations if they are to be given for prolonged periods, and especially with high doses. Note that other antiparkinsonian drugs are ineffective in treating the extrapyramidal symptoms induced by antipsychotics.

The second type of extrapyramidal symptom is the dys-tonic reactions, which include facial grimacing, torticollis (wry neck) and spasticity of the limbs. A severe type of dys-tonia is termed an oculogyric crisis. This can occur after only one dose of an antipsychotic and is particularly common in children. The orbital muscles of the eye go into spasm and the pupils may disappear, usually upwards into the eye socket. This is distressing to both the patient and observers. More seriously, the tongue muscles are affected, and choking may result. Prompt parenteral treatment with an antimuscarinic drug is life-saving in such crises. Oculogyric crises can occur with other phenothiazine-like compounds such as **metoclopramide** (see Chapter 55), a common antiemetic. A rare but extremely disturbing effect is opisthotonos, in which the muscles of the head, neck and back cause the body to arch, in extreme cases causing the spine to snap.

TABLE 33.1 TENDENCY OF ANTIPSYCHOTICS TO CAUSE ADVERSE EFFECTS

	Symptoms			
Antipsychotic	**Extrapyramidal**	**Sedation**	**Hypotension**	**Antimuscarinic activity**
Phenothiazines				
Chlorpromazine	**	***	**	**
Fluphenazine	***	*	*	*
Levomepromazine	**	***	***	**
Pericyazine	*	***	**	***
Pipotiazine	***	*	***	*
Thioridazine	*	**	**	***
Trifluoperazine	***	*	*	*
Butyrophenones				
Droperidol	***	*	*	*
Haloperidol	***	*	*	*
Pimozide	*	*	*	*
Thioxanthenes				
Flupentixol	**	*	**	***
Thiothixene	***	*	**	***
Zuclopenthixol	**	*	**	***
Dibenzoxazepine				
Loxapine	**	*	*	**
Dibenzodiazepine				
Clozapine	*	***	***	***
Miscellaneous				
Fluspirilene	**	*	*	*

Key: * = minor effect; ** = intermediate effect; *** = major effect.

The third type of extrapyramidal symptom is akathisia, with restlessness being the most predominant symptom. The patient fidget, smack their lips, tap their feet and pace about the room. Antimuscarinic drugs may alleviate this condition, but a reduction in dose of the antipsychotic is often necessary.

The fourth type of extrapyramidal effect is tardive dyskinesia, which affects muscular coordination. This effect tends to occur only after prolonged treatment, especially in elderly patients. It is characterised by stereotyped involuntary movements, commonly seen in feature films depicting mental institutions. The patient commonly smack their lips, the tongue darts in and out like a snake's, the jaws move continually and they slaver. Purposeless movements of the limbs may also occur. This condition is not responsive to antimuscarinic drugs and tends to be permanent. The prospect of tardive dyskinesia makes long-term use of antipsychotics problematic.

The sedation accompanying some of the antipsychotics may be useful or troublesome, depending on the circumstances of their use.

The α_1-blocking effect can cause hypotension and fainting in many patients, especially in the first few days of treatment. Patients should be warned of this.

Table 33.1 details the antipsychotics and their tendency to cause the common adverse effects of parkinsonism, sedation, antimuscarinic effects and hypotension.

A rare but potentially serious result of administration of antipsychotics is neuroleptic malignant syndrome (NMS). This can occur early on in treatment and is similar to severe parkinsonism with autonomic dysfunction and concurrent hyperthermia. Treatment is urgent and involves administration of **dantrolene** (see Chapter 37) and a dopamine agonist such as **bromocriptine** (see Chapter 36). NMS can also result from use of antidepressants.

The antipsychotics may induce a range of other adverse effects. Cholestatic jaundice is much more likely to occur with **chlorpromazine** than the other phenothiazines. The butyrophenones rarely cause this condition. Cholestatic jaundice, which tends to occur after several weeks of therapy, can be identified by the appearance of bile pigments in the urine and resembles obstructive jaundice. Cessation of the

drug usually reverses the condition, but permanent liver damage has been known to result. The incidence of this condition can be as high as 4 per cent. The incidence is even higher in past or present alcoholics. Close observation of patients on chlorpromazine is therefore necessary. The cause of cholestatic jaundice is unknown, but it may be a type of hypersensitivity reaction. Hypersensitivity reactions may sometimes result in blood dyscrasias, but these are not common.

Antipsychotic drugs, as dopamine antagonists, sometimes inhibit the action of prolactin inhibitory factor (PIF). PIF is dopamine. It acts on the anterior pituitary gland to continuously inhibit prolactin, except during lactation. Inhibition of PIF can lead to milk production; when milk production is not postpartum, this is called galactorrhoea. Gynaecomastia (breast development in males) sometimes accompanied by loss of libido, can also result from antipsychotic drug use. In women, this can be accompanied by amenorrhoea. The α-blocking effect of these drugs can lead to suppression of the ejaculatory response.

The phenothiazines may accumulate in the skin, resulting in abnormal pigmentation, rash or urticaria. As the sun can exacerbate these effects, this condition is called photosensitivity. Handling the drug can have adverse effects on the skin, so care should be taken with these preparations. Deposits of the drugs can also accumulate in the eye, leading to opacities in the lens, with resulting vision defects.

The effects of antipsychotic drugs are summarised in Figure 33.1.

✚ CLINICAL CONSIDERATIONS

Antipsychotic drugs are used to treat a wide variety of mental disorders, including schizophrenia, delirium and dementia. It is not recommended that these drugs are used to treat minor anxiety problems, although some authorities recommend the use of a phenothiazine, such as low-dose **thioridazine**, with its low adverse-effects profile, to treat short-term severe anxiety. The rationale for this is that antipsychotics are generally not addictive. Antipsychotics are potent antiemetics, particularly **prochlorperazine**, which is often used as an antiemetic and only rarely used as an antipsychotic. This antiemetic property can occasionally prove to be disadvantageous in that nausea induced by toxicity of other drugs or organic disorders may be masked, leading to incorrect diagnoses. A novel use of antipsychotics is to suppress severe, intractable hiccups (singultus); the mechanism of action is unknown. Antipsychotics can induce a lowering of body temperature, and this property has been utilised during surgery where a lower body temperature is desired.

There is much similarity between the antipsychotics, and the decision about which drug to use is often based on clinical intuition. The ideal drug is that which will cause a remission of symptoms at the lowest dose – a criterion not easy to achieve when so many drugs are available. Because the onset of the drug's antipsychotic effect is often delayed for several weeks from the commencement of drug therapy, an additional problem may be determining the appropriate dosage. In severe mental illness, therapy may have to be continued indefinitely.

Many of the antipsychotics are available in syrup form, as patients often retain the tablets in their mouths for ejection once the nurse has departed. This is not so easy to do with a syrup.

The thioxanthenes such as **flupentixol** and **zuclopenthixol** are parenteral agents. These two drugs may have mood-elevating properties, which can be of benefit in depressed or flat patients. Zuclopenthixol has the added advantage of being effective in cases of mania and exacerbated psychotic symptoms. Both of these thioxanthenes are formulated in coconut oil for use as depot injections for sustained action; the action of flupentixol lasts 2–4 weeks, but the action of similarly formulated zuclopenthixol lasts only several days. Nevertheless, both of these drugs have a speedy onset of action, particularly zuclopenthixol, which is beneficial when a rapid onset of antipsychotic or antimanic activity is requisite. Zuclopenthixol is one of the most powerful antipsychotics; not unexpectedly, it also has more adverse effects. Treatment with zuclopenthixol is not recommended for more than 2 weeks. Both the oral and parenteral thioxanthenes have similar adverse-effects profiles to those of the phenothiazines and butyrophenones, except that the antimuscarinic profile of the thioxanthenes is weak.

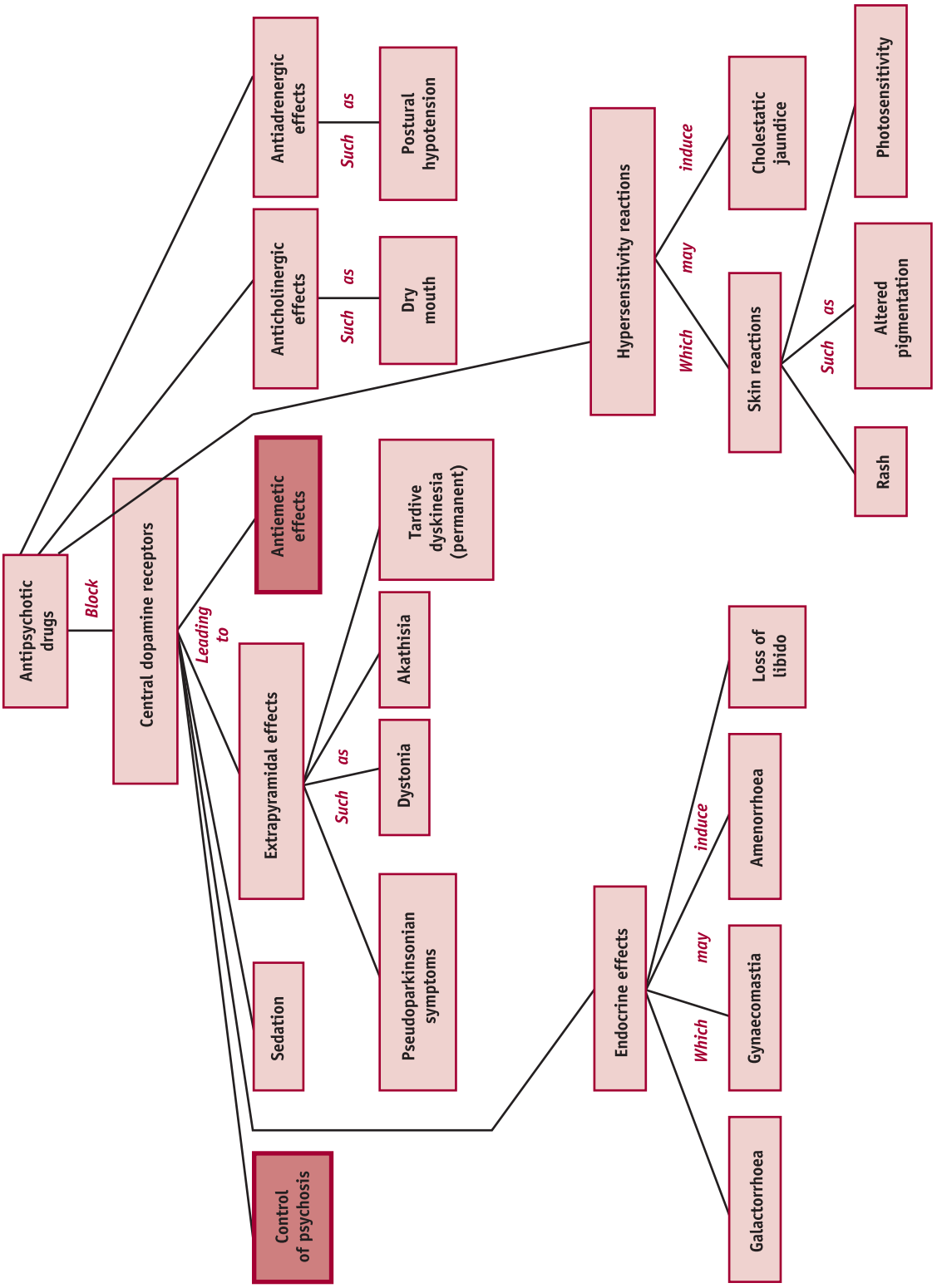
The only oral thioxanthene available is **thiothixene**. Like the other thioxanthenes, thiothixene is very powerful and is usually reserved for the treatment of schizophrenia and other psychoses when other antipsychotics have not produced a good response. An example of the effectiveness of thiothixene is in the case of a socially withdrawn and apathetic person with schizophrenia who becomes cooperative, socially competent and more interested in their surroundings and in their personal appearance after taking the drug, sometimes having been refractory to treatment with other drugs. Thiothixene, more so than the other thioxanthenes, has particularly beneficial antidepressant properties, which are useful in many psychotic states.

Levomepromazine is sometimes used to augment the analgesic action of narcotic drugs and to help allay severe anxiety states.

Overall, it is important to warn patients about the symptoms of extrapyramidal reactions with the use of antipsychotics, as the effects may be quite distressing. Patients should also be advised about the need to avoid concurrently taking illicit substances, such as cannabis and amphetamines, because these substances can severely diminish the effectiveness of antipsychotic agents. Ensuring compliance helps to prevent relapse of psychotic symptoms and suicide. Individuals

FIGURE 33.1 FLOWCHART SHOWNG THE EFFECTS OF ANTIPSYCHOTICS

The therapeutic effects are shown in shaded boxes.



should, therefore, be counselled about taking their medication regularly in order to prevent symptoms. Patients experiencing agitation respond better to the more sedating agents such as chlorpromazine and thioridazine. Concurrent use of more than one antipsychotic agent is not recommended, except when required to accentuate an intramuscular depot treatment or when replacing one antipsychotic agent with another. If decreasing the dose of antipsychotic agent, this should be done gradually to avoid relapse.

Atypical antipsychotics

Many of the more recently introduced antipsychotics have been described as 'atypical'. The basis of this description is that their pharmacological profile differs from that of conventional antipsychotic drugs and they are much less likely to cause extrapyramidal side effects. Differences in the affinity of atypical antipsychotics for various central receptors may explain the reduced incidence of these side effects. Chemical groups include the benzamides (sulpiride), benzisoxazoles (risperidone), diphenylbutylpiperidines (pimozide) and the dibenzodiazepines (clozapine, olanzapine, quetiapine).

BENZAMIDES

The sole benzamide antipsychotic used in the UK is **amisulpiride**. Amisulpiride has a lower incidence of adverse effects when compared with other antipsychotics, both typical and atypical. As with all antipsychotics, NMS is a problem with amisulpiride. Amisulpiride can interact with many drugs, and these interactions should be referred to before prescribing. The drug should be avoided in patients with a history of seizures and in Parkinson's disease.

BENZISOXAZOLES

■ MECHANISM OF ACTION

The one benzisoxazole in clinical use is **risperidone**, a selective antagonist with a high affinity for 5-HT_2 (see Chapter 30) and D_2 receptors. It has no affinity for muscarinic receptors. This affinity for 5-HT receptors may be responsible for the reduction in extrapyramidal effects seen with risperidone when compared with other D_2 antagonists.

◆ COMMON ADVERSE EFFECTS

5-HT antagonism combined with the antihistaminic effect of risperidone often causes weight gain, which may not be desirable. Risperidone also has α_2 antagonistic properties, which can cause orthostatic hypotension and swelling of the nasal mucosa, particularly in the initial stages of therapy. NMS has been reported with risperidone, as have most of the other antipsychotic adverse effects; however, risperidone has a markedly lower incidence of parkinsonism and galactorrhoea. It is likely that the incidence of tardive dyskinesia is decreased with risperidone, but adequate studies have not been carried out to show this conclusively.

DIPHENYLBUTYLPIPERIDINES

Pimozide is similar in action to the phenothiazines but has a prolonged half-life, enabling once-per-day dosage.

DIBENZODIAZEPINES

■ MECHANISM OF ACTION

The mechanism of action of **clozapine** is as a dopamine antagonist. It acts on D_1 and D_4 receptors, but not on the D_2 receptors that cause the major side effects of the other dopamine antagonists. Clozapine also has potent sympatholytic, antimuscarinic, antiserotonergic, antihistaminic and arousal-inhibiting effects. All these actions may contribute to the pharmacological action of clozapine.

◆ COMMON ADVERSE EFFECTS

Clozapine (which is related to the benzodiazepines but must not be thought to be similar in action to them) has been used for several years, but it was abandoned as an antipsychotic after it caused the death of several patients due to the development of irreversible neutropenia, a type of agranulocytosis. Clozapine has been reintroduced recently as an antipsychotic for use in patients who do not respond to or are intolerant of other drugs. Clozapine is effective in over 30 per cent of patients unresponsive to other drugs, but because of its potential for toxicity it has a limited use and can be prescribed only by suitably experienced psychiatrists, who are obliged to register patients with the clozapine-monitoring service offered by the manufacturer holding the marketing authorisation holder. Frequent full blood examinations are required during therapy, as early detection of blood abnormalities is critical. Immediate cessation of the drug in abnormal cases may reverse the abnormalities detected. On the positive side is an almost complete lack of extrapyramidal effects and no development of tardive dyskinesia with clozapine. Clozapine is also devoid of endocrine effects. Compared with the other antipsychotics, the adverse effects of clozapine are minimal, apart from the potentially fatal neutropenia. The common adverse effects are sedation and mild epileptic attacks (absence seizures), in addition to the expected effects from the list of actions given above. NMS has been known to occur.

Olanzapine is related closely to clozapine. Originally it was not thought to affect leukopoiesis, but towards the end of 1999 reports appeared of neutropenia developing in some patients taking olanzapine. It is not known how serious this will turn out to be, and routine blood cell counts are currently not mandatory in patients taking olanzapine. Weight gain and somnolescence may occur with olanzapine. Unlike clozapine, olanzapine does not appear to trigger epileptiform seizures.

Quetiapine has a similar profile to that of chlorpromazine, but with a significantly lower incidence of adverse effects. It is also more efficacious in treating symptoms such as flat affect and lack of motivation, compared with its ability to treat symptoms such as hallucinations, thought disorders and delusions.

✚ CLINICAL CONSIDERATIONS

Risperidone may have advantages over the more conventional antipsychotics and is now considered to be the first-line treatment for most cases of psychotic illnesses. Risperidone is being trialled to help in the management of cocaine and alcohol addiction.

Olanzapine is available as neutral-tasting wafers, which are dissolved in the mouth, followed by a drink for patients who have difficulty in swallowing tablets.

Clozapine may be beneficial for patients whose symptoms are resistant to other treatments. Atypical antipsychotic agents have a tendency to cause weight gain. If a patient gains a large amount of weight while taking an atypical agent, the patient may be at risk of developing type 2 diabetes. Both clozapine and olanzapine can produce blood dyscrasias and, as a result, all patients must have normal blood counts before treatment. Quetiapine is the most sedating of the atypical antipsychotics and may, therefore, be beneficial in the treatment of symptoms associated with agitation.

ARIPIPRAZOLE

A novel antipsychotic agent called **aripiprazole** has been introduced into the UK for the treatment of schizophrenia.

■ MECHANISM OF ACTION

Aripiprazole acts as a partial agonist at D_2 receptors and a subtype of 5-HT_1 receptors, while acting as an antagonist at a subpopulation of 5-HT_2 receptors.

Clinical trials have shown comparable efficacy to haloperidol against a number of criteria.

◆ COMMON ADVERSE EFFECTS

Aripiprazole appears to be tolerated well. The most common adverse effects reported are somnolence and weight gain.

✚ CLINICAL CONSIDERATIONS

As with other antipsychotic agents, it is important to monitor the patient for signs of suicidal intention, NMS, changes in blood pressure and altered body temperature. Aripiprazole should be used with caution in patients with a history of seizures.

The list of adverse effects of the antipsychotic drugs appears abnormally long and debilitating. It must be remembered, however, that these drugs have revolutionised the treatment of many severe mental disorders and have led to less institutionalisation of individuals. Before the introduction of these drugs, many mentally disturbed individuals were given a life sentence in a psychiatric institution. These drugs have resulted in many people with psychosis being able to lead comparatively normal lives.

Other uses of antipsychotics

Apart from the treatment of nausea, vertigo and singultus that have been mentioned above, there are some other uses of antipsychotic medications. Haloperidol can be useful in the rare condition Tourette's syndrome, in which the patient repeats things said to them (echolalia) or uses obscene words in inappropriate situations (coprolalia). Haloperidol is also occasionally of use in ballismus, which involves the flailing of the arms and legs. The butyrophenones are used in neuroleptoanalgesia (see Chapter 39). Pimozide alleviates the pain of trigeminal neuralgia.

CLINICAL MANAGEMENT

Antipsychotic drugs

Assessment

- Assess patient for liver disease, coronary heart disease, parkinsonism, hypotension, hypertension and blood dyscrasias. These are contraindications to antipsychotic therapy.
- Use these drugs with caution in patients with glaucoma, diabetes, epilepsy, ulcers, cardiovascular disease, renal disease, prostatic hypertrophy and chronic respiratory disease and in elderly patients.
- Determine concurrent use of other central nervous system (CNS) depressants, such as alcohol and anxiolytics. Drugs with antimuscarinic activity can also potentiate the action of antipsychotic agents.
- Obtain baseline observations of vital signs, including lying and standing blood pressure. Compare with subsequent observations.
- Determine body weight before initial therapy.

Planning

- The patient's psychotic activity will be controlled by the antipsychotic agent and psychotherapy.
- The patient will experience minimal adverse effects.

Implementation

- Regularly monitor observations during administration. Check lying, sitting and standing blood pressure.
- Remain with the patient while the medication is taken, and make certain it is swallowed. Some patients hide their tablets to use in later suicide attempts.
- Fluid input and output need regular monitoring due to the ability of these drugs to block muscarinic receptors, therefore inhibiting parasympathetic function and causing urinary retention.
- Observe for adverse effects, including:
  - parkinsonian effects, such as slowing of voluntary movements, associated with a masked face, tremor at rest, and decreased arm movements when walking;
  - dystonic effects such as facial grimacing and uncoordinated spastic movements of body and limbs;
  - akathisia (the patient fidgets and paces constantly) and tardive dyskinesia (the patient makes lateral jaw movements, fly-catching movements with the tongue, and quick jerky movements with the extremities);
  - antimuscarinic effects, such as dry mouth, urinary retention, constipation, blurred vision and decreased tear production.
- When administering antipsychotics intramuscularly, discomfort can be reduced by mixing with saline.
- For patients taking clozapine, regular full blood examinations are required during treatment.
- For intravenous antipsychotic therapy, administer at the required rate to minimise hypotension.
- Care must be taken when administering antipsychotics to elderly patients, who are at greater risk of suffering from adverse effects. Common adverse effects in elderly people include confusion, dizziness, parkinsonian-type symptoms and hypothermia. Treatment should be initiated at a lower dose than normal and increased gradually.
- Antipsychotics should be withdrawn slowly in order to avoid a rapid relapse and to avoid withdrawal symptoms.

Patient teaching

- Suggest sucking boiled sweets, lozenges or ice chips to help ease a dry mouth (see Table 11.9 in Chapter 11 for further information).
- Inform patient not to drive or operate machinery until a maintenance dose has been established.
- Instruct patient to continue taking the medication. If problems occur, medical advice should be sought to determine whether a change in dose or medication will help. Antipsychotics do not cure psychotic illnesses but alleviate psychotic symptoms. The medication should never be discontinued abruptly.
- Oral candidiasis, a common effect of dry mouth, can be avoided by taking frequent sips of water and ensuring good oral hygiene (see Table 11.7 in Chapter 11 for further information).
- Instruct the patient taking phenothiazines such as chlorpromazine that the urine may turn pink or red-brown. This discoloration is not harmful.
- Constipation, a common effect of these drugs, can be minimised by consuming a high-fibre diet, adequate fluids and taking sufficient exercise (see Table 11.4 in Chapter 11 for further information).
- Instruct the patient not to consume alcohol, as this intensifies the sedative effect of the antipsychotic drug.
- The patient should take precautions in direct sunlight because of photosensitivity. Instruct the patient to wear protective clothing and to use a sunblock. The sun should be avoided during its hottest period between 10 a.m. and 2 p.m. (see Table 11.19 in Chapter 11 for further information).
- As several over-the-counter medications interact with antipsychotic drugs, the patient should consult the doctor and pharmacist before taking over-the-counter drugs.
- Effects of postural hypotension can be reduced by the patient arising slowly from a lying to sitting or standing position (see Table 11.20 in Chapter 11 for further information).
- Inform the patient that sexual changes may occur. Menstruation may become irregular or stop temporarily (amenorrhoea). Males may experience gynaecomastia (enlarged breast tissue) or loss of libido. Changing the antipsychotic drug group may assist in alleviating these effects.

Evaluation

- Determine whether the patient is able to cope with everyday activities.
- Establish the incidence of adverse effects and whether a change in medication or dose is warranted.

SUMMARY

- Antipsychotics are used in the treatment of psychoses such as schizophrenia, dementia and severe agitation.
- All antipsychotics exert their effect on dopamine receptors and antagonise dopaminergic activity in the central nervous system.
- There are two principal groups of antipsychotics: typical and atypical antipsychotics.
- Typical antipsychotics act on D_2 receptors and can cause extrapyramidal adverse effects.
- Atypical antipsychotics act principally on D_4 receptors and tend not to cause extrapyramidal effects.
- Antipsychotics have a diverse and potentially debilitating adverse-effects profile.

1. Explain why amantadine would not be considered in the treatment of thiopropazate-induced parkinsonism.
2. Explain the galactorrhoea that can occur during droperidol therapy.
3. Flupenthixol may be administered intramuscularly to patients with schizophrenia. Why?
4. The drug chlorpromazine can cause extrapyramidal symptoms. What would one use to correct these symptoms? Why?
5. Promazine can cause an oculogyric crisis. Explain.
6. What conditions, other than antipsychotic drug use, can cause opisthotonos?
7. Joe Smith, a 35-year-old newly diagnosed schizophrenic, has been put on chlorpromazine to treat his condition. As his psychiatric nurse, what patient education would you give Mr Smith?
8. During his visit to the psychiatric clinic, John Brown indicated his frustration in forgetting to take his oral promazine medication. What alternative formulation can you offer Mr Brown?
9. Barbara Lowe, who is newly diagnosed with schizophrenia, asks you about the possibility of taking alcohol with her antipsychotic medication. What would you say to Ms Lowe? Why?
10. A patient complains to you about severe tremor and rigidity following ingestion of fluphenazine tablets. What alternative medication is less likely to elicit these symptoms?
11. Cindy Nash is taking antipsychotic therapy and enjoys spending time in the sun. What instructions would you provide for Ms Nash when she goes outdoors?

33 DRUG SUMMARY TABLE: ANTIPSYCHOTIC DRUGS

FAMILY NAME	GENERIC NAME	TRADE NAME(S)
Phenothiazines	Chlorpromazine	Largactil
	Fluphenazine	Moditen
		Modecate
	Levomeprazine (methotrimeprazine)	Nozinan
	Pericyazine	Neulactil
	Pipotiazine	Piportil Depot
	Prochlorperazine	Buccastem
		Stemetil
	Trifluoperazine	Stelazine
Butyrophenones	Haloperidol	Haldol
		Serenace
Thioxanthenes	Flupentixol	Depixol
	Zuclopenthixol	Clopixol
Diphenylbutylpiperidines	Pimozide	Orap
Miscellaneous	Amisulpiride	Solian
	Aripiprazole	Abilify
	Clozapine	Denzapine
		Zaponex
		Clozaril
	Olanzapine	Zyprexa
	Quetiapine	Seroquel
	Risperidone	Risperdal
	Sertindole	Serdolect
	Zotepine	Zoleptil

ANXIOLYTICS AND HYPNOTICS

34

CHAPTER THIRTY-FOUR

OBJECTIVES

KEY TERMS

Anxiety
Insomnia
Sleep
Rapid eye movement (REM)
Gamma-aminobutyric acid (GABA)

After completing this chapter, the reader should be able to:

- **describe the difference between a sedative or anxiolytic and a hypnotic;**
- **list the uses of anxiolytics and hypnotics;**
- **outline the problems associated with anxiolytics and hypnotics;**
- **recognise the various types of anxiolytic and hypnotic.**

THE GENERAL DEFINITION OF A SEDATIVE IS A SUBSTANCE that diminishes the activity of an organ or tissue, but today the meaning of this word is confined to this action on the central nervous system (CNS). In many circumstances, this effect on the CNS can relieve anxiety and, hence, sedatives are often termed anxiolytics. In older terminology, the expression 'minor tranquillisers' was also applied to sedatives. 'Hypnotic' is the term used to describe a substance that induces sleep. In most cases, it is difficult to distinguish between a sedative and a hypnotic, as sleep (hypnosis) could be considered to be an extension of sedation. Therefore, it is not surprising that the majority of the drugs that can be used to promote sleep can also be used in lesser dosages as sedatives. The converse is also true, with only a few exceptions.

Many of the drugs in these categories are addictive if taken regularly for even short periods. In some cases, addiction has been known to occur in about 10 days. Thus, the use of these drugs is controversial; if prescribed, they should be taken for only limited periods (no more than 7 days under normal circumstances).

Anxiety is a very common disorder, and considerable pressure is exerted on the medical profession to provide relief. In many cases, the anxiety is self-limiting and recourse to drugs is not necessary. Occasionally, however, anxiety is so stressful and mentally painful that drug therapy is required. Anxiety and stress are parts of everyday life, and it is important that education programmes include life skills that help patients develop coping mechanisms. Furthermore, anxiety may be accompanied by mild reactive or even endogenous depression; as anxiolytics can exacerbate depression, they are best avoided in such situations. The medical practitioner's role in the handling of patients demanding prescriptions for such drugs is difficult.

Sleep and its necessity to normal life is a process that is little understood. Sleep disturbances are extremely common; if continuous, they have the potential to seriously disrupt normal day-to-day living. Many people with a sleep disorder want to use drugs to solve their problem. The use of drugs in many of these situations is undesirable for several reasons: A non-pharmacological approach and an evaluation of the causes of the sleeplessness is usually all that is required to alleviate the condition. Appropriate textbooks should be consulted for further information on this.

The use of hypnotics in the treatment of short-term insomnia is often beneficial in cases where the insomnia can be predicted. Indications for such treatment are to help people overcome the disruption to circadian rhythms that occurs when crossing several time zones, resulting in jet lag; some airlines use such drugs to help pilots and flight attendants overcome the many time changes to which their occupation subjects them. Likewise, hypnotics can be of benefit to people who carry out shift work to help them adjust to changes in their shifts. Other indications are to give patients a good night's rest before operative procedures and in cases of bereavement. There is some evidence that the use of anxiolytics and/or hypnotics in bereaved people is less than beneficial, as the grieving process may be a condition through which people have to go in order to accept rationally what has happened. Prolonged use of hypnotics tends to lead to a certain amount of tolerance, such that sleep is no longer induced without increasing the dosage. Tolerance can develop in about 2 weeks with many of the commonly used hypnotics. Another problem experienced with many of the hypnotics is rebound insomnia: After hypnotic withdrawal, several nights of disturbed sleep may ensue.

Sleep research has shown that there are at least two stages of sleep: rapid-eye-movement (REM) sleep, which is the dreaming stage, and a non-REM stage. Many hypnotics upset the REM stage of sleep, sometimes abolishing it altogether. This can lead to psychological disturbances, which can be difficult to treat and may necessitate psychiatric intervention. This was particularly true for the older types of hypnotic, but it is less common with the newer hypnotic drugs. The barbiturates were particularly prone to interfering with REM sleep. Withdrawal of barbiturates used routinely in the treatment of insomnia often resulted in vivid dreams and nightmares, as if the brain was trying to make up for the loss of its usual REM sleep. It is important to remember that no hypnotic in current use induces what could be termed 'natural' sleep.

In this chapter, the drugs will be dealt with according to their chemical classification rather than their therapeutic classification as either anxiolytics or hypnotics.

BARBITURATES

Until the 1960s, the barbiturates were the favoured hypnotic – especially as little else was available. Their use as hypnotics is now no longer advised, and they are gradually being phased out from this use. Their availability today is mainly because some are still used in the treatment of epilepsy (see **phenobarbitone**, Chapter 37) and as anaesthetics (see Chapter 41). Barbiturates are only rarely prescribed as hypnotics; when they are prescribed, it is mainly to elderly patients who are addicted to them and where withdrawal may be dangerous (see below). It is expected that drugs such as **amylobarbitone** will disappear from most pharmacopoeias in the near future. Some reasons for their demise are their low therapeutic index (~10), their potency as hepatic enzyme inducers and the problem of their hangover effect. Addiction to barbiturates is a serious problem, as sudden withdrawal ('cold turkey') can result in convulsions, occasionally ending in death.

BENZODIAZEPINES

Most of the benzodiazepines have the suffix '-azepam' and so are readily identifiable. But beware – there are a few exceptions.

MECHANISM OF ACTION

The benzodiazepines act on receptors in the CNS to potentiate the inhibitory action of gamma-aminobutyric acid (GABA), a natural neurotransmitter. It appears that there are several receptor subtypes associated with the GABA receptor, and selective stimulation of these subtypes leads to differing physiological responses. Stimulation of one subtype may decrease anxiety and stimulation of another leads to the induction of sleep.

The GABA receptor complex is indeed very complex and not understood completely. Stimulation of the receptor complex by GABA increases chloride ion conductance in the neurons, rendering them refractory to excitatory depolarisation – hence, the negative effect. Associated with the GABA receptor complex are at least two benzodiazepine receptors – BZ_1 and BZ_2 – and when stimulated these further enhance the inhibition by GABA. These so-called benzodiazepine receptors will have a naturally occurring neurotransmitter in the CNS, but as yet this has not been identified. BZ_1 receptors are found mainly in the cerebellum and are related to anxiety and sedation. BZ_2 receptors are found mainly in the basal ganglia and hippocampus and are associated with muscle relaxation, memory and learning. This helps explain the differences between some of the benzodiazepines and their actions. For example, midazolam acts strongly on the BZ_2 receptors, thus causing amnesia. Barbiturates and some of the newer non-benzodiazepine hypnotics, namely zopiclone and zolpidem, are mediated through similar receptors but at a slightly different, as yet unknown, site.

Other receptors in this complex are associated with seizure activity. This explains the use of some of the benzodiazepines and barbiturates in epilepsy and other convulsive conditions. This may help to explain the differing actions of many of the benzodiazepines and why some are superior as anxiolytics and some as hypnotics.

◆ COMMON ADVERSE EFFECTS

Some of the effects of the benzodiazepines may be adverse in some situations but not others. Clonazepam used as an antiseizure drug would have sedation as an adverse effect, but not if it was used as a sedative. Midazolam used as a hypnotic in minor medical and surgical procedures has amnesia as an effect, which is useful in these situations but would be considered to be an adverse effect when used as a night-time hypnotic.

There are many other adverse effects of benzodiazepines. Some of note are diplopia and blurred vision, slurring of speech, paradoxical rage, paradoxical insomnia, depression and dizziness. More details regarding adverse effects are given under the headings of some selected benzodiazepines detailed below.

The benzodiazepines are among the safest of all CNS drugs as far as toxicity is concerned; however, they are addictive. This was one of the factors instrumental in the general demise of barbiturates. It has been suggested that even *following intake of* large amounts of benzodiazepines, the subject is easily aroused. Unfortunately, deaths have occurred when benzodiazepines are taken in excess with alcohol, a common combination. A specific antagonist to the benzodiazepines is available, which is useful in the treatment of life-threatening situations, such as can occur with alcohol–benzodiazepine combinations. This antagonist is **flumazenil** and is discussed in Chapter 22.

✚ CLINICAL CONSIDERATIONS

The development of long-term memory may be dependent on the increased activity in the higher parts of the brain, and increased GABA activity may cause defects in long-term memory. This accounts for the development of amnesia after the use of some benzodiazepines – a property sometimes useful in, for example, endoscopic procedures. As endoscopies often require the cooperation of the patient but are unpleasant, the use of a benzodiazepine such as **midazolam** is efficient at producing anterograde amnesia; this drug is, therefore, often used as an adjunct in such procedures.

Some benzodiazepines, such as **clonazepam** and **diazepam**, are effective muscle relaxants. Their action is thought to be due to potentiating the action of GABA on the brain stem and the spinal cord. This makes these drugs useful as antiseizure drugs in epilepsy and in muscle spasticity therapy (see Chapter 37). Other benzodiazepines can also be used as antiseizure drugs but have unacceptable side effects, especially drowsiness.

A pharmacokinetic property of the benzodiazepines that often determines their clinical use is their half-life ($t_{1/2}$). Short-half-life benzodiazepines, such as **triazolam** ($t_{1/2}$ = 2–3 hours), are useful for the initiation of sleep if the patient has difficulty getting to sleep. Drugs with such a short half-life are not much use as anxiolytics, as frequent dosing would be required. If the problem is early-morning awakening, then a benzodiazepine with a longer half-life would be desirable. **Temazepam**, which has a half-life of approximately 8 hours, is ideal for such problems. Benzodiazepines with longer half-lives tend to produce undesirable subsequent drowsiness. Those with longer half-lives tend to be better used for their anxiolytic effects, but in some cases of sleep induction it may be preferable to use benzodiazepines with a longer half-life. This is particularly the case when long-term therapy is envisaged. Benzodiazepines with short half-lives are cleared from the bloodstream fairly quickly and may induce withdrawal effects, such as rebound excitement and insomnia. For instance, short-acting benzodiazepines such as triazolam may cause confusion and delirium. Benzodiazepines with longer half-lives are cleared less quickly, resulting in a decrease in withdrawal effects. For example, as **nitrazepam** may take several days to be cleared from the bloodstream, the resulting slow drop in blood levels allows the body to adjust to the lack of drug more effectively. For similar reasons, addiction to benzodiazepines is easier to treat when the offending drug has a long half-life.

This use of half-lives to determine the choice of benzodiazepines is not always followed in health care, and there often appears to be no reason why one benzodiazepine

TABLE 34.1 BENZODIAZEPINES: HALF-LIVES AND THERAPEUTIC USES

Generic name	Biological half-life (h)	Therapeutic use
Alprazolam	16–20	Anxiolytic, antidepressant
Chlordiazepoxide	20–24	Anxiolytic
Clobazam	35–42	Anxiolytic
Diazepam	50–100	Anxiolytic
Loprazolam	7	Hypnotic
Lorazepam	12–15	Anxiolytic
Lormetazepam	9	Hypnotic
Midazolam	2–3	Hypnotic
Nitrazepam	26–30	Hypnotic
Oxazepam	4–13	Anxiolytic
Temazepam	8–10	Hypnotic

is used as an anxiolytic and another as a hypnotic. Differing chemical structures of the benzodiazepines may affect receptor subtypes differently, and receptors for promoting sleep are different from those that promote peace and calm. There is little doubt that nitrazepam, even in large doses, would never attain the hypnotic effect of **flunitrazepam** or midazolam; for example, in at least one overdose case with nitrazepam, involving about 50 tablets, the individual did not even fall asleep. Table 34.1 lists the benzodiazepines available, with their respective half-lives and their usual therapeutic use. Some of the half-lives given are not only for the parent compound but also for the active metabolites.

There is a great deal of similarity between many of the benzodiazepines. Therefore, only those with unusual properties and uses are discussed individually in this book. In general, the benzodiazepines are a well-tolerated group of drugs with only infrequent adverse effects, apart from drowsiness. The following effects and precautions are applicable to all of the benzodiazepines: As benzodiazepines cause sedation, the patient should be advised to avoid operating machinery, driving, and using other centrally active agents, including alcohol. More than 2–4 weeks of continuous use may result in dependence and tolerance. Consequently, benzodiazepines should be considered only as a short-term regimen and as part of a more extensive treatment plan. It needs to be acknowledged that a sudden decrease in dose of benzodiazepines may lead to withdrawal symptoms; a gradual drop in dose can avoid withdrawal symptoms.

Specific benzodiazepines

ALPRAZOLAM

Alprazolam is unique among the benzodiazepines, as it possesses antidepressant activity and so can be useful in the treatment of depression associated with anxiety. Like other drugs used in the treatment of depression, its onset of antidepressant action takes up to 2 weeks to appear. A potential problem with alprazolam when compared with the other antidepressants (see Chapter 35) is addiction.

CLONAZEPAM

Clonazepam is one of the most potent benzodiazepines and has strong muscle-relaxant properties, which make it a drug usually employed in the treatment of epilepsy rather than anxiety or insomnia (see Chapter 37). This drug is useful in the treatment of restless leg syndrome and some other parasomnias. Drowsiness and the potential for addiction are the major problems, although the drowsiness usually dissipates with time.

LORAZEPAM

Lorazepam is less lipid-soluble than most of the other benzodiazepines and thus enters and leaves the CNS at a slow, controlled rate. This causes fewer problems with the onset and cessation of action. Lorazepam is one of the most addictive of the benzodiazepines. It is commonly associated with the production of retrograde amnesia and diplopia.

DIAZEPAM

Diazepam is one of the few benzodiazepines that is regularly given both parenterally and by mouth. In the UK, diazepam is also available as a rectal solution in a rectal tube; as such, it is used to control seizures, especially in prehospital care. When given parenterally, diazepam is useful as a premedication and as a tranquilliser for minor surgical procedures. Given intravenously, it is commonly used in the treatment of status epilepticus.

FLUNITRAZEPAM

Flunitrazepam is one of the most potent and effective hypnotics of the benzodiazepines. When taken orally, it induces a deep sleep – almost unconsciousness – in about 10–20 minutes. It is completely tasteless, a factor that has made it a drug of abuse. Flunitrazepam is sometimes called a 'date-rape drug': There have been reports of individuals spiking women's drinks with the drug; before long, the victim falls into a deep sleep for several hours. Since 1998, the manufacturer has added a dye to flunitrazepam that turns spiked drinks bright blue in order to aid detection. Some reports document that cases of flunitrazepam being used as a sedative and amnesic in date rape are still in evidence. Flunitrazepam has been withdrawn from use in the NHS.

MIDAZOLAM

Midazolam is often used more as an anaesthetic than as a hypnotic. It is used for sedation with amnesia as needed in endoscopies and in intensive care for sedation. Like flunitrazepam, midazolam has been used as a date-rape drug.

MISCELLANEOUS ANXIOLYTICS AND HYPNOTICS

ZOLPIDEM

Although chemically unrelated to the benzodiazepines, **zolpidem** acts selectively on the GABA receptors in the brain. It is much more specific in its action, however, as it acts as an agonist only on the omega-1 receptor (a subunit of the $GABA_A$ receptor complex) and thus has no muscle-relaxing or antiseizure activity. There are many similarities between zolpidem and the other benzodiazepines, including the risk of addiction, tolerance and rebound insomnia. It is recommended that zolpidem be used for a maximum of 4 weeks. Memory impairment appears not to be a problem with zolpidem, and retrograde amnesia occurs only with high doses. Flumazenil can reverse the action of zolpidem (see Chapter 22).

ZOPICLONE

Zopiclone belongs to a class of compounds known as cyclopyrralones, which are structurally unrelated to the benzodiazepines but similar in action. Zopiclone is used as a hypnotic and has a similar adverse-effects profile to the benzodiazepines, except for one common effect – leaving a bitter taste in the mouth. Zopiclone is reported not to cause rebound insomnia and is said to be less addictive than the benzodiazepines. This was said about the benzodiazepines when they were first introduced, however, and so it would be prudent not to use zopiclone for sustained periods.

BUSPIRONE

Buspirone is a fairly new and unique drug in the armamentarium against anxiety. Its mechanism of action is completely different from that of other anxiolytics, as it is a partial agonist at both dopaminergic and serotonergic receptors in certain parts of the brain. The action is mainly in the limbic system and, unlike the antipsychotics, it does not appear to affect the dopamine receptors in the basal ganglia; therefore, it is devoid of parkinsonian effects. The main advantage of buspirone over the benzodiazepines is that little or no sedation is apparent with this drug; therefore, it is a pure anxiolytic. Unfortunately, the effects of buspirone may not be shown for a couple of weeks. Buspirone has no antiseizure or muscle-relaxing properties.

CHLORMETHIAZOLE

■ MECHANISM OF ACTION

Chlormethiazole is similar to the benzodiazepines in that it potentiates the action of GABA. There, the similarity ends, as it does not bind to either the GABA receptor or the benzodiazepine receptor, and its exact mechanism of action remains to be elucidated. The hypnotic and anticonvulsant properties of chlormethiazole were found quite by chance. It was developed in the process of preparing thiamine (vitamin B_1) analogues. It is structurally closely related to thiamine.

◆ COMMON ADVERSE EFFECTS

In elderly patients, chlormethiazole can cause confusion, which can be mistaken for senile dementia. An odd but common problem with chlormethiazole is intense nasal discomfort and bouts of sneezing.

✚ CLINICAL CONSIDERATIONS

Chlormethiazole is commonly used as a sedative/hypnotic to tide a patient with alcohol problems over the initial stages of withdrawal. Intravenous preparations can be used in status epilepticus. Its routine use as a hypnotic is not advised, as habituation can occur. Its use both in alcoholism and as a hypnotic is gradually being taken over by an appropriate benzodiazepine.

CHLORAL HYDRATE

Chloral hydrate is a prodrug and is converted in the liver to its active metabolite, trichlorethanol. Its rapid onset of action demonstrates how quickly metabolism can take place in the liver. Its exact mechanism of action is unknown.

■ COMMON ADVERSE EFFECTS

Chloral hydrate is very irritant to the stomach and so should be taken with milk at bedtime. It has been known to induce a hangover effect, resulting in a headache on awakening. The drug is addictive, and tolerance to its hypnotic action develops quickly.

✚ CLINICAL CONSIDERATIONS

Chloral hydrate is a powerful hypnotic often mentioned in detective fiction and as a drug of ill-repute. It is often thought of as a sleeping draught to initiate sleep in unsuspecting victims. It has an uncommonly rapid onset of action when taken orally (it is a liquid), sometimes inducing sleep in a matter of minutes. Chloral hydrate was sometimes administered in drinks to unsuspecting people in the bars of port cities, quickly inducing sleep, whereupon the victims were kidnapped. When chloral hydrate is mixed with alcohol, is known as a Mickey Finn, a fairly potent and much-abused soporific. Chloral hydrate is metabolised by

the same enzyme as alcohol, which explains the potentiating effect one has over the other. It is hard to believe that chloral hydrate could be administered without some suspicion being entertained by the drinker, as it usually takes about 2 g to be certain of inducing sleep and it has a distinctive taste, which would be very difficult to disguise.

Chloral hydrate has a half-life of about 6 hours. This makes it a useful hypnotic, as daytime drowsiness is not likely to occur.

DEXMEDETOMIDINE

Dexmedetomidine is a novel addition to this chapter as far as its drug category is concerned. It is an α_2-adrenoceptor agonist that is currently not licensed in the UK. It is used in the USA and Australia. Adrenergic receptors were dealt with in Chapter 26; you may recall that α_2 receptors are presynaptic and, when stimulated, inhibit adrenergic impulses. Adrenergic firing is associated with arousal in the CNS (see Chapter 38); dampening these receptors in the CNS will cause sedation. Not surprisingly, the body's response to dexmedetomidine includes other adrenergic inhibitory effects, such as hypotension. This drug is administered only intravenously and is used for short-term sedation of patients who are admitted to intensive care after surgery. Dexmedetomidine also has the added advantage of analgesic properties.

PARALDEHYDE

Paraldehyde is an unpleasant-smelling liquid, the odour of which is apparent on the breath of the patient to whom it is administered. In the UK, it is available only in injectable form, which can be given rectally, intravenously or intramuscularly. For rectal use, it is given as an enema diluted with physiological saline. When given by injection, it induces sleep rapidly. Its main use today is in the treatment of status epilepticus. Intramuscular injection is painful and has been known to cause muscle necrosis. It must be remembered (as mentioned in Chapter 15) that as paraldehyde dissolves plastic, glass syringes must always be used. Ampoules that contain any discoloration, usually a brown colour, should be discarded.

ANTIHISTAMINES

In recent years, some of the more sedating antihistamines have been made available as over-the-counter sedative/hypnotic drugs. These all tend to have long half-lives, which may cause drowsiness the next day. They do not work in everyone. The other adverse effects of antihistamines are considered in Chapter 29. In children, paradoxical stimulation is common. Sedating antihistamines should be used only in the short term, as rebound insomnia and tolerance can occur.

CLINICAL MANAGEMENT

Anxiolytics and hypnotics

Assessment

- If the agent is used for sleep, a description of sleep patterns is needed.
- Determine vital signs, such as lying and standing blood pressure, pulse and respirations, as objective parameters for anxiety. Compare with subsequent observations.
- Talk to the patient about lifestyle, work and support networks to determine subjective parameters for anxiety.
- For benzodiazepines, the patient should be assessed for previous hypersensitivity reactions, allergies and asthma.
- Attempt to establish possible causes or precipitating factors for anxiety or difficulty in sleeping.
- Before barbiturate use, determine whether the patient has encountered a hypersensivity reaction to barbiturates, chronic respiratory disease or liver disease. Clarify the prescription with the doctor if these conditions are present.

Planning

- The patient's anxiety will be reduced by anxiolytic drugs and non-pharmacological therapy, such as relaxation and psychotherapy.
- The patient's sleep patterns will be improved by hypnotic drugs and non-pharmacological therapy, such as relaxation and psychotherapy.
- The patient will encounter minimal adverse effects.

Implementation

- Determine the patient's sleep or anxiety patterns during therapy.
- Recognise that drug tolerance and physical and psychological dependence can occur with these agents. They should, therefore, be administered according to institutional policies and procedures and legal regulations. Due to the potential for tolerance or dependence, these agents should not be used for more than 14–28 days at a time.
- Be aware that dosage for elderly patients and patients with debilitating disease should be lower than for younger, healthier adults.
- Sudden discontinuation of treatment in dependent patients may lead to withdrawal symptoms. Symptoms include anxiety, irritability, insomnia, sweating, hallucinations and tremors. A gradual reduction of dose can prevent the incidence of withdrawal symptoms.

Patient teaching

- The patient should be alerted to the problems associated with driving and operating machinery, as dizziness or drowsiness can lead to serious injury or death.
- Instruct the patient about methods to decrease anxiety, such as relaxation and aromatherapy.
- Instruct the patient about methods to assist with sleep, such as curling up with a good novel and avoiding coffee, heavy meals and excessive stimuli close to bedtime.
- Advise the patient not to stop the medication abruptly after prolonged use, as withdrawal symptoms may occur.
- Advise the patient not to take alcohol or other central nervous system depressants while on hypnotics or anxiolytics. These drug combinations can compound the central depressant effects.
- Responsible family members and the patient should be counselled about the problems of drug dependency, the symptoms of adverse effects and symptoms of abrupt drug withdrawal.

Evaluation

- Determine the effectiveness of the drug in allaying anxiety or promoting sleep. A patient's request for stronger medication, increased dose or reduced effectiveness should be interpreted as evidence of drug dependence or tolerance. Refer the patient to the doctor immediately.
- Evaluate the presence of adverse effects, such as confusion, ataxia, and a drowsy hangover effect. The dosage or medication may need adjustment.

Clinical issues

- Benzodiazepines should be considered for short-term use only.
- Long-term use may result in dependence and tolerance.
- Sudden withdrawal of benzodiazepines may lead to withdrawal symptoms. A gradual reduction in dose can avoid withdrawal symptoms.
- Avoid alcohol and operating machinery while taking benzodiazepines.
- Avoid other sedating drugs while taking benzodiazepines.

SUMMARY

- There are several different groups of hypnotics and sedatives, of which the benzodiazepines are the most common.
- Benzodiazepines act on the gamma-aminobutyric (GABA) receptor complex.
- Benzodiazepines are relatively non-toxic but can have several undesirable adverse effects.
- Benzodiazepines can be addictive.
- With most anxiolytics, the antianxiety effect is related to their sedative effect.
- Hypnotic drugs should be used for short-term therapy only.

1 Differentiate between an anxiolytic and a hypnotic.

2 Why are short-acting benzodiazepines more of a problem with addiction than long-acting benzodiazepines?

3 What are the advantages of benzodiazepines over barbiturates?

4 Why has triazolam been withdrawn from clinical use in some countries?

5 What are the major problems associated with the use of paraldehyde?

6 Differentiate between rapid-eye-movement (REM) and non-REM sleep.

7 What is a problem with abolishing REM sleep?

8 Why are anxiolytics useful in the treatment of individuals with alcohol problems?

9 Why should hypnotics be used for only a limited period of time to assist with sleep?

10 Explain why clonazepam and diazepam are useful in epilepsy.

11 Explain the benefit of using temazepam over nitrazepam to assist with sleep.

12 What non-drug measures would you recommend for Natalie Milakoviska, a 60-year-old widow whose husband has died recently and who has been experiencing difficulty getting to sleep?

13 Benzodiazepines are highly protein-bound drugs. Would the drug dosage for patients with liver or renal disease be increased, decreased or remain unchanged? Why?

34 DRUG SUMMARY TABLE: ANXIOLYTICS AND HYPNOTICS

FAMILY NAME	GENERIC NAME	TRADE NAME(S)
Benzodiazepines	Alprazolam	Xanax
	Chlordiazepoxide	
	Clobazam	
	Clonazepam	Rivotril
	Diazepam	Diazemuls, Stesolid Rectal Tube
	Flunitrazepam	
	Lorazepam	Ativan
	Lormetazepam	
	Midazolam	Hypnovel
	Nitrazepam	Remnos, Mogadon
	Oxazepam	
	Temazepam	
Miscellaneous	Amobarbitol (amylobarbitone)	Amytal
	Buspirone	Buspar
	Zolpidem	Stilnoct
	Zopiclone	Zimovane
Antihistamines	Diphenhydramine	
	Doxylamine	
	Hydroxyzine	Atarax, Ucerax
	Promethazine	Phenergan

ANTIDEPRESSANTS AND MOOD STABILISERS

35

CHAPTER THIRTY-FIVE

KEY TERMS

Bipolar affective disorder
Depression
Drug interactions
Mania
Mood
Noradrenaline
Panic disorder
Obsessive–compulsive disorder
Serotonin
Tyramine

OBJECTIVES

After completing this chapter, the reader should be able to:

- **define depression and identify the types of affective condition that respond to drug therapy;**
- **describe the mechanisms of action, common adverse reactions and clinical considerations of the major antidepressant groups;**
- **state the mechanisms of action of the mood stabilisers;**
- **state the adverse reactions and clinical considerations of lithium carbonate.**

DEPRESSION IS A STATE OF PROFOUND SADNESS OR melancholy. It is a condition that affects the patient's frame of mind, mood and attitudes. Common manifestations of this state include lethargy, apathy, loss of appetite, insomnia, feelings of unworthiness, personal neglect and suicidal tendencies.

TYPES OF DEPRESSION

Essentially, there are three types of depressive state. The most common form is reactive depression, which occurs either in response to a life crisis or as an adverse reaction to treatment with certain drugs, e.g. some antihypertensive agents. Less prevalent is endogenous depression, which manifests without any apparent trigger. It is this form that is usually treated using standard antidepressant therapy. The least common form of depression is bipolar affective disorder, otherwise known as a manic-depressive state. As the name suggests, there are two extreme emotional states – mania and depression – between which the individual alternates.

PHYSIOLOGY OF DEPRESSION

Like other affective states, our mood manifests as a result of a complex interplay between brain regions. Unfortunately, we know little of the detail of the workings of this interplay. To date, the synaptic hypothesis (monoamine theory) of depression has guided the development of many of the useful therapeutic agents. Essentially, it is proposed that there is a link between the levels of two brain neurotransmitters noradrenaline (NA) and serotonin (5-hydroxytryptamine, 5-HT) and the depressed state. There is evidence of a depletion in the synaptic levels of these two transmitters in people with depression. The action of antidepressants is simply directed towards increasing the synaptic levels of one or both of these transmitters.

Comprehension of the actions of antidepressant drugs draws on an understanding of the mechanism of synaptic transmission for adrenergic nerves (discussed in Chapter 26). This mechanism is relevant to all amine transmitters: noradrenaline, dopamine and serotonin. The following is a brief revision of the main points in synaptic transmission involving amine transmitters. On reaching the nerve terminal, the action potential causes the release of transmitter from synaptic vesicles. The transmitter diffuses across the synaptic gap to interact with postsynaptic receptors. The transmitter is then pumped back into the presynaptic terminal by an amine-reuptake pump and incorporated back into the synaptic vesicles. In the brain, these amine transmitters may diffuse further and modulate neuronal activity at more distant sites. Any excess transmitter within the terminal is degraded by a mitochondrial enzyme, monoamine oxidase (MAO) (see Figure 35.1). Moreover, positioned on the surface of the presynaptic terminal are α_2 receptors, which, when stimulated, act to inhibit the release of transmitter from the nerve terminal during excessive impulse transmission. The purpose of these presynaptic receptors is to prevent the overstimulation of postsynaptic receptors.

ANTIDEPRESSANT DRUG GROUPS

The scene is now set to discuss the action of antidepressant drugs in the context of nerve physiology within the brain. The main drug groups are the tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), monoamine oxidase inhibitors (MAOIs), reversible inhibitors of monoamine oxidase (RIMAs), tetracyclic antidepressants, noradrenaline–serotonin reuptake inhibitors (NSRIs), selective serotonin receptor ($5\text{-}HT_2$) blockers and selective noradrenaline reuptake inhibitors (SNRIs).

Tricyclic antidepressants

Historically, drugs from this group have been the first choice in the treatment of depression. They include **imipramine**, **amitriptyline**, **doxepin** and related drugs. The term 'tricyclic' derives from the common three-ringed structure of the drug molecule itself.

■ MECHANISM OF ACTION

These drugs act primarily by blocking the amine reuptake pump on the presynaptic terminal (see Figure 35.2). As a consequence, the synaptic levels of the transmitters rise. They are not considered central nervous system (CNS) stimulants because they do not induce stimulatory effects in individuals who are not depressed.

◆ COMMON ADVERSE EFFECTS

Adverse effects derive from the fact that the TCAs have secondary actions: antimuscarinic, antihistaminic and antiadrenergic activity. Their antimuscarinic action accounts for dry mouth, blurred vision, constipation, urinary retention and tachycardia. Mental confusion and sedation arise from a central antihistamine action, and postural hypotension can occur as a result of an antiadrenergic effect. The wanted and unwanted effects of the TCAs are shown in the flowchart in Figure 35.3.

✚ CLINICAL CONSIDERATIONS

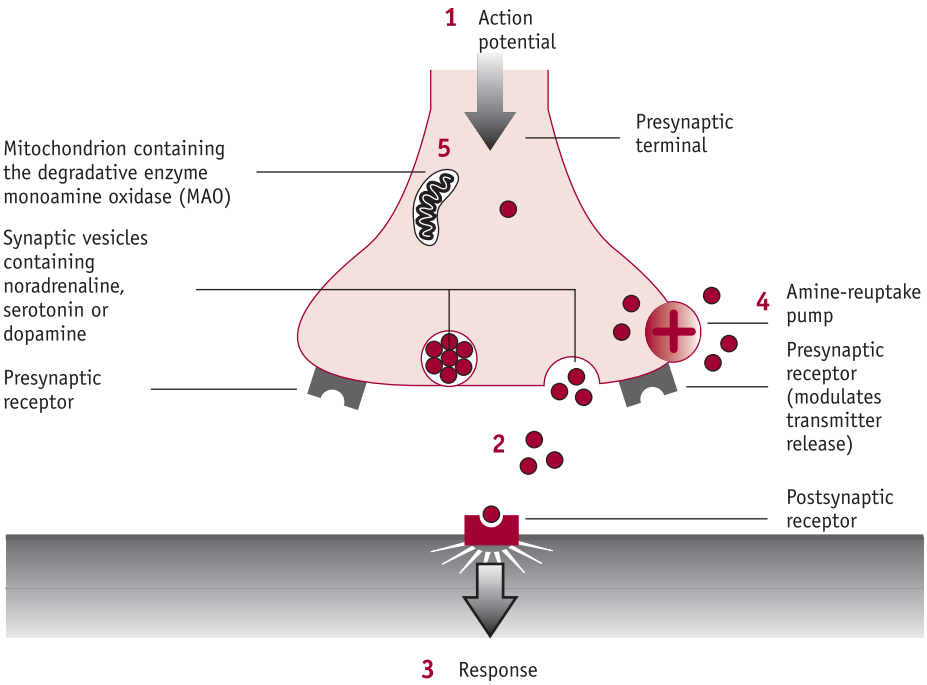
Poisoning is a major concern associated with the use of certain antidepressant drugs. Patients suffering erratic moods and suicidal tendencies are at great risk of poisoning themselves with TCAs. The potential for lethal dysrhythmias during therapy is significant with the TCAs and is a focus of concern in overdose. If this occurs, the patient requires hospitalisation for management of the overdose. TCAs are contraindicated in patients who have recently suffered a myocardial infarction.

Postural hypotension is a major problem with the TCAs. Lying and standing blood pressure should be checked at the start of therapy and following each change in dose. To assist with compliance, it is helpful to administer a single dose at bedtime. TCAs are no longer considered first-line therapy for depression, and they should be particularly

FIGURE 35.1 MONOAMINE NERVE FUNCTION

A summary of events involved in monoamine nerve stimulation. The nerve may make and release noradrenaline, serotonin or dopamine as its neurotransmitter. (1) The action potential travels along the axon until it reaches the nerve terminal. (2) Depolarisation of the terminal causes the release of chemical transmitter into the synaptic gap. (3) The transmitter diffuses across the gap and interacts with its postsynaptic receptors, triggering an effector response. (4) The transmitter is removed from the synaptic gap by an amine reuptake pump and is restored to the synaptic vesicles. (5) Any excess transmitter within the terminal not restored to the vesicles is degraded by the mitochondrial enzyme monoamine oxidase (MAO). Any excess transmitter remaining within the synaptic gap is subject to extraneuronal reuptake.

The release of transmitter from the nerve terminal is also subject to modulation by presynaptic receptors (enhancement of release by one type, inhibition by another).



avoided in children, adolescents and older people. As several TCAs cause sedation, patients taking these drugs should avoid driving and operating machinery, especially during the initial phase of therapy.

The sedation observed when therapy with these drugs is commenced is put to beneficial use in the treatment of depression. Insomnia is a common characteristic of depression. These drugs are often administered at bedtime in order to promote a normal sleeping pattern.

The problems with TCA therapy are two-fold. First, with the exception of sleeping behaviour, the changes in the depressed person take 2–4 weeks to manifest; however, adverse drug effects are observed as treatment commences. Clearly, this may greatly influence patient compliance. Second, depressed patients may express suicidal thoughts but lack the energy to proceed with suicide. Once they begin to show improvement, they may also find the willpower to act on their suicidal inclination. Use of TCAs still has an important part to play in antidepressant therapy, however.

Selective serotonin reuptake inhibitors

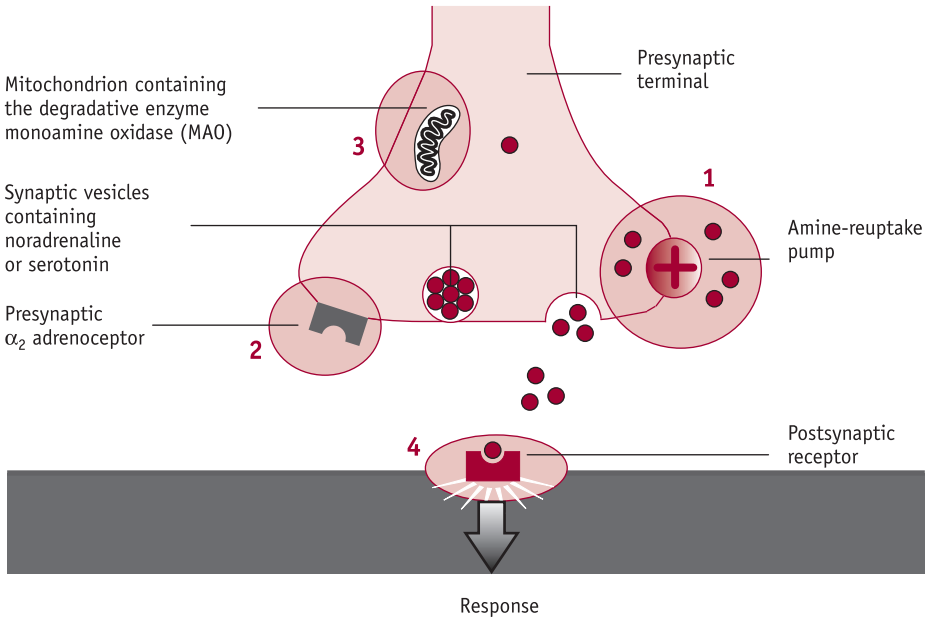
Fluoxetine, **paroxetine**, **sertraline**, **fluvoxamine**, **escitalopram** and **citalopram** are SSRIs. Since their arrival on the market, these new antidepressants have had a tremendous impact on prescribing patterns. They are now considered the first-line drugs in the treatment of major depression.

MECHANISM OF ACTION

SSRIs block the presynaptic amine reuptake pump, as do the TCAs; however, SSRIs primarily affect serotonin reuptake (see Figure 35.2). The half-lives of paroxetine, fluvoxamine and sertraline are around 24 hours. The half-life of citalopram is about 36 hours. Fluoxetine has a longer half-life (up to 9 days) due to the presence of an active metabolite.

FIGURE 35.2 PROPOSED SYNAPTIC SITES OF ACTION OF THE ANTIDEPRESSANT DRUGS

In this diagram, the major synaptic sites affected by antidepressant drugs are depicted. (1) Inhibition of the presynaptic monoamine pump will prolong the duration of the transmitter in the synaptic gap. (2) Blockade of presynaptic α_2 receptors removes the inhibition of transmitter release from the nerve terminal. As a result, levels of the transmitter in the synaptic gap are increased. (3) Inhibition of the degradative enzyme monoamine oxidase (MAO) enables release of more transmitter when the terminal is stimulated. (4) A change in the sensitivity of the postsynaptic receptor to its transmitter will alter the magnitude of the responses to stimulation.



Clinical studies have found that generally the SSRIs have comparable efficacy to the TCAs. The TCAs, however, have been found to be more effective in the treatment of melancholic and severe depression.

◆ COMMON ADVERSE EFFECTS

Importantly, the SSRIs have little affinity for muscarinic, adrenergic and histamine receptors. As a consequence, the profile of adverse reactions associated with the SSRIs is quite different from, and less troublesome than, that of the TCAs. The SSRIs do not cause CNS stimulation and, unlike the TCAs, are non-sedating. Generally, the adverse effects of SSRIs are relatively mild, of short duration and cease as treatment continues. Cardiac toxicity and the risk of death after overdose is less likely than with the TCAs. Common adverse effects include headache, nausea, vomiting, tremor, insomnia, dizziness and diarrhoea. There have been some reports of motor disturbances, such as dyskinesia and akathisia, associated with SSRI therapy. Combined SSRI and TCA therapy is contraindicated, as lethal toxicity could develop.

✚ CLINICAL CONSIDERATIONS

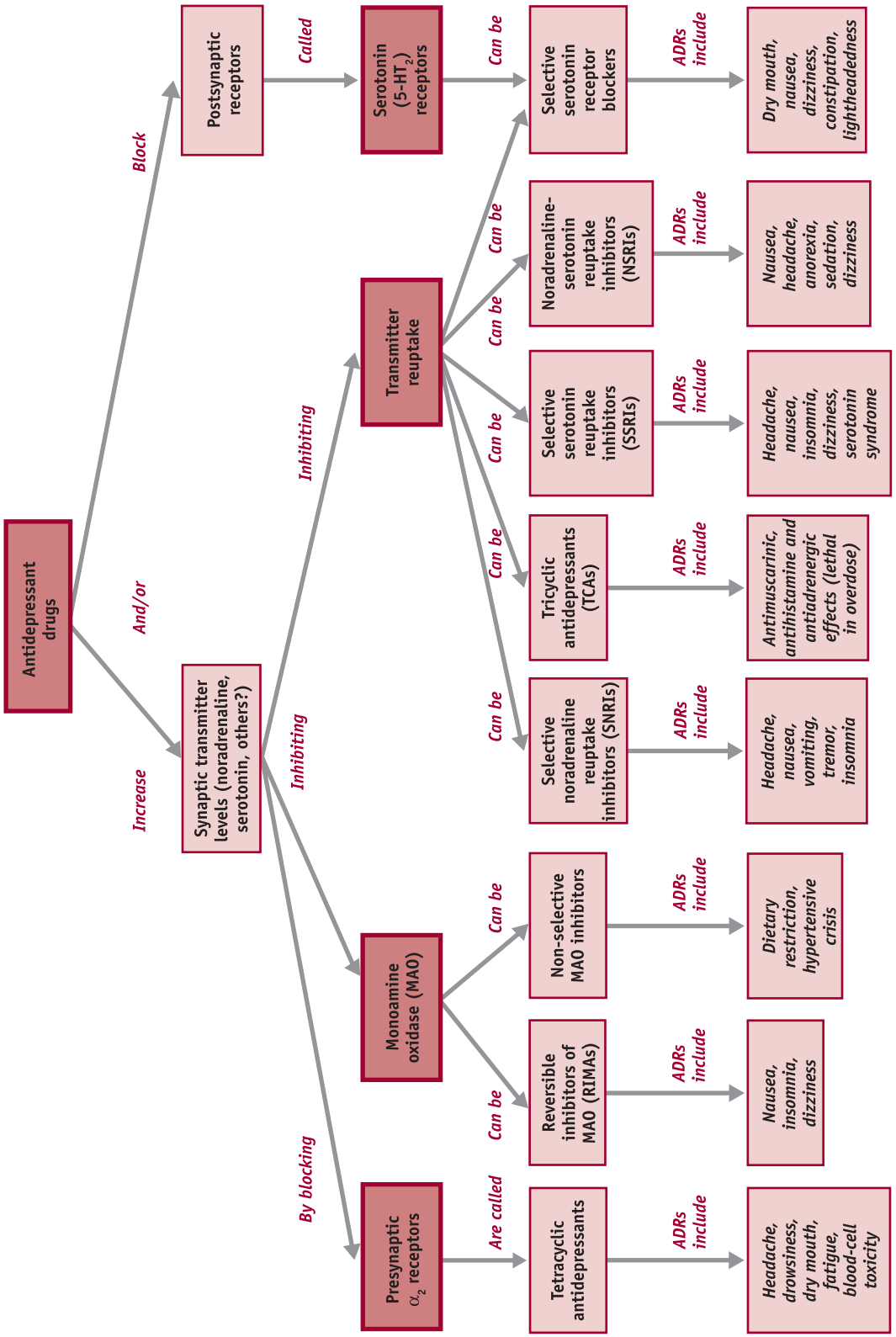
The increased use of SSRIs in the management of depression is widely thought to underlie a rise in the observed rates of a relatively uncommon, toxic, potentially fatal condition called serotonin syndrome. This syndrome is associated with a hyperserotonergic state characterised by euphoria, drowsiness, abnormal muscle movements, sweating, intoxication, hyperthermia, diarrhoea, loss of consciousness and, sometimes, death. It is usually brought on by combination therapy for depression, where one medication is often a selective serotonergic agent. The other could be a monoamine oxidase inhibitor (MAOI), lithium carbonate or a TCA. Treatment involves stopping drug therapy and providing supportive measures until the symptoms resolve. Serotonin syndrome is indistinguishable from the neuroleptic malignant syndrome (NMS) often associated with antipsychotic therapy (see Chapter 33).

The effects of the SSRIs are shown in Figure 35.3.

To avoid the serotonin syndrome in the use of SSRIs, it is beneficial to prevent the co-administration of antidepressant agents, to have an adequate washout period when

FIGURE 35.3 MECHANISM OF ACTION AND ADVERSE EFFECTS OF THE ANTIDEPRESSANT DRUGS

The proposed mechanisms of action of the major antidepressant drug groups (with the specific synaptic sites affected shown in darker shaded boxes) and their common adverse drug reaction (ADR) profiles.



switching drugs, and to avoid administering a high dose of a single drug. Even if the dose is progressively increased, SSRIs do not generally lead to better control of depression. All SSRIs are relatively safe in an overdose; however, toxicity is increased if they are taken with other agents.

Tetracyclic antidepressants

Mianserin, **maprotiline** and **mirtazapine** are tetracyclic rather than tricyclic in molecular structure. Sometimes this group is referred to as the second-generation antidepressants. These drugs are also part of the first-line therapy of depression.

■ MECHANISM OF ACTION

The action of mianserin is not like that of the TCAs (see Figure 35.2). It has been suggested that it allows the synaptic amine levels to increase by blocking presynaptic α_2 receptors and noradrenaline reuptake. It may possibly also affect serotonin action. Maprotiline acts by producing a stronger inhibition of reuptake of noradrenaline than serotonin.

Mirtazapine, like mianserin, is an antagonist at presynaptic α_2 receptors; it blocks postsynaptic serotonin, histaminergic (H_1) and α_1 receptors. Mirtazapine has been shown to be as effective as other antidepressants in relieving the symptoms of depression and is reported to be more efficacious than mianserin.

◆ COMMON ADVERSE EFFECTS

Common adverse effects include headache, drowsiness, dry mouth and fatigue. Some of these unwanted effects are common as therapy starts but wane as treatment continues. The common adverse effects of mirtazapine include somnolence, orthostatic hypotension, increased appetite, weight gain and constipation.

✚ CLINICAL CONSIDERATIONS

At present, the risk of haematological toxicity has restricted these agents to situations where the use of TCAs is contraindicated, such as in heart and bladder disease. Some practitioners claim that the incidence of toxicity is relatively low compared with their benefits and advocate a much wider use of the tetracyclics. Interestingly, the half-life of mirtazapine is 20–40 hours, with a tendency towards a longer half-life in women.

The effects of the tetracyclic antidepressants are shown in Figure 35.3.

In view of the potential for haematological toxicity, a full blood examination should be undertaken at the start of therapy, and then every 4 weeks during the first 3 months of therapy. Similarly, baseline and subsequent liver function tests should be conducted to test for any disturbance in liver function. In cases of overdose, tetracyclic antidepressants are more serious than SSRIs but less serious than TCAs.

Non-selective and irreversible monoamine oxidase inhibitors

■ MECHANISM OF ACTION

MAOIs act to raise the synaptic levels of endogenous amines by preventing the degradation of excess transmitter after its release (see Figure 35.2). Examples of well-established MAOIs are **phenelzine** and **tranylcypromine**. These drugs are irreversible inhibitors of MAO. The effects of the non-selective MAOIs, both therapeutic and adverse, can persist for as long as 2 weeks after therapy ceases.

◆ COMMON ADVERSE EFFECTS

Common adverse reactions to the MAOIs are less serious than those observed during TCA therapy. They consist of antimuscarinic and antiadrenergic effects. The effects of non-selective MAOIs are shown in Figure 35.3. The MAOIs are contraindicated in people with epilepsy, liver disease and serious cardiovascular disease.

✚ CLINICAL CONSIDERATIONS

MAO is an important enzyme involved in the metabolism of amines present in food – in particular, a substance called **tyramine**, an indirect-acting sympathomimetic agent (see Chapter 26). Tyramine is taken up by the presynaptic amine pump and causes the release of neuronal stores of noradrenaline from peripheral nerves. MAO is responsible for the degradation of the released noradrenaline. In people taking MAOIs, the ingestion of food rich in tyramine has the potential to precipitate a widespread release of noradrenaline in the periphery that is unable to be broken down because MAO is inhibited. The consequence is life-threatening cardiovascular stimulation.

The older, non-selective MAOIs are used if the depressed patient displays intolerance or does not respond to first-line therapy. These drugs produce similar levels of improvement as the TCAs, but the older agents in this group can have life-threatening interactions with diet and other drugs, as mentioned above. A list of tyramine-containing foods is presented in Table 35.1.

The use of other sympathomimetic amines, such as nasal decongestants and vasoconstrictors, is not recommended during therapy with non-selective MAOIs. There are also interactions to be noted between MAOIs and both TCAs and narcotic analgesics in the form of CNS overexcitation (delirium, seizures). When changing therapy from one form of antidepressant to another, 2 weeks should be allowed to elapse before commencing the other type to avoid such interactions.

Reversible inhibitors of monoamine oxidase

■ MECHANISM OF ACTION

Two isoenzymes of MAO have been identified – type A (MAO-A) and type B (MAO-B) – with distinct specificities

TABLE 35.1 TYRAMINE-CONTAINING FOODS

Fermented foods
- Beer
- Cheese
- Liqueurs
- Red wine

Meat/yeast extracts
- Bovril
- Marmite

Pickled foods
- Herring

Sauces
- Sour cream
- Soy sauce

Aged/cured meats
- Bacon
- Game
- Hot dogs
- Salami

Foods containing stock cubes
- Dehydrated foods
- Packet soups

Coffee substitutes

Fruit/vegetables
- Avocado

and anatomical distribution. MAO-A accounts for 30 per cent of the MAO within the brain and is also located within the intestinal wall, peripheral adrenergic nerves and placenta. MAO-A appears to control the synaptic concentrations of noradrenaline and serotonin, which have been implicated in depressive illness. MAO-B seems to be more predominant within the liver and brain and is also found in platelets. This subtype controls the synaptic levels of dopamine. This finding has important implications for antidepressant therapy. Relatively specific MAO-A inhibitors have been developed with a lower risk of producing life-threatening interactions with ingested tyramine. **Moclobemide** is an example of a relatively selective MAO-A inhibitor; its effects are reversible.

As an aside, MAO-B inhibitors, which increase the synaptic concentration of dopamine, are important anti-parkinsonian drugs. (This is elucidated further in Chapter 36.)

◆ COMMON ADVERSE EFFECTS

Common adverse reactions of RIMAs include nausea, insomnia and dizziness. RIMAs are contraindicated in cases of known hypersensitivity and acute confusional states. The effects of the RIMAs are shown in Figure 35.3.

✚ CLINICAL CONSIDERATIONS

Moclobemide has a short half-life of about 4 hours; its effects last for up to 18 hours. It has been shown to be well tolerated, with little evidence of toxicity to the liver or heart. Its low toxicity has led to its inclusion as a first-line drug in the treatment of depression. Its clinical effectiveness is poor compared with that of other antidepressants, however.

A low tyramine diet is not usually needed in patients taking RIMAs if the maximum dose is not exceeded. RIMAs are relatively non-toxic in overdose and do not usually cause impaired alertness, unlike irreversible MAO inhibitors, which can cause drowsiness and insomnia.

Noradrenaline–serotonin reuptake inhibitors

■ MECHANISM OF ACTION

Venlafaxine represents a novel class of antidepressant drug: It is an NSRI. Venlaxfaxine is a phenethylamine, and its mechanism of action most closely resembles that of the TCAs. As its family name suggests, venlafaxine reportedly blocks the reuptake of noradrenaline, serotonin and, to some extent, dopamine from the synaptic gap (see Figure 35.2). The inhibition of serotonin reuptake appears to be greater than that of noradrenaline reuptake.

◆ COMMON ADVERSE EFFECTS

Common adverse effects of venlafaxine include nausea, headache, anorexia, sedation and dizziness. The effects of the NSRIs are shown in Figure 35.3.

✚ CLINICAL CONSIDERATIONS

Clinical studies have demonstrated a number of differences in the effects of venlaxfaxine compared with the TCAs. Venlafaxine is at least as efficacious as the TCAs, but it produces less sedation and fewer cardiovascular and antimuscarinic side effects. Moreover, venlaxfaxine produces its therapeutic effects within the first 2 weeks of therapy. There is also some evidence that venlafaxine may be more effective than the SSRI fluoxetine in some cases of moderate to severe depression.

Selective noradrenaline reuptake inhibitors

Reboxetine has been approved recently for the treatment of major depression in the UK.

■ MECHANISM OF ACTION

Reboxetine blocks the reuptake of noradrenaline (see Figure 35.2) but does not significantly affect the reuptake

of serotonin or dopamine. Clinical trials have shown it to have similar efficacy to the TCA imipramine and the SSRI fluoxetine.

◆ COMMON ADVERSE EFFECTS

Common adverse reactions with reboxetine include headache, dry mouth, tachycardia, hypotension, urinary retention, constipation and insomnia. Caution is suggested when considering this treatment for patients with cardiovascular disease, a history of seizures, urinary retention or prostatic hypertrophy. The effects of the SNRIs are shown in Figure 35.3.

✚ CLINICAL CONSIDERATIONS

Reboxetine is absorbed rapidly from the oral route and has a bioavailability greater than 90 per cent. It is subject to significant hepatic metabolism and has a half-life of 13 hours. A significant interaction with carbamazepine is expected, such that doses of reboxetine may need to be increased in patients taking carbamazepine.

ANTIDEPRESSANT TREATMENT CONSIDERATIONS

There are a number of important general considerations concerning antidepressant therapy. First, significant therapeutic benefits of treatment will not manifest immediately following the commencement of therapy; it may take 3–4 weeks before the benefits are evident. The adverse effects may arise immediately or shortly after starting treatment, however. This indicates that the therapeutic effects are not induced by simply activating or blocking central receptors. These drugs appear to be associated with altered synaptic function and receptor sensitivity in pathways controlling mood. Understandably, the implications of a delay in clinical benefit may well affect the compliance of patients with the course of treatment.

Another consideration is the timing of drug administration during the day. Antidepressants that produce sedating effects are best administered at bedtime to promote sleep and to avoid disrupting daily activities. Some antidepressants have activating effects and should be taken in the morning or early afternoon to avoid disruption of sleep.

Finally, a combination of drugs from different antidepressant classes in order to manage depression is contraindicated. Toxic reactions are likely to arise from such combinations, especially if an MAOI is involved. It is safer practice to change the medication when the the patient's response is inadequate. When changing antidepressants, however, the patient must undergo a 10- to 14-day 'drug holiday' between stopping the old treatment and starting the new treatment. This washout period avoids toxic drug interactions.

OTHER PSYCHIATRIC CONDITIONS THAT RESPOND TO ANTIDEPRESSANT DRUGS

Sometimes, depressive illness underlies the manifestation of a few anxiety disorders, namely panic disorder, obsessive–compulsive disorder and social phobias. Antidepressant drugs have application in the treatment of these conditions, usually in conjunction with other therapeutic agents. Panic disorder is characterised by extreme fear, which induces a number of sympathetic nervous system responses (e.g. sweating, palpitations, shortness of breath, faintness, feelings of loss of control). Obsessive–compulsive behaviour is characterised by its components: An obsession manifests as recurrent and persistent thoughts, which the affected person tries to suppress; compulsions manifest as repetitive behaviours, which the patient performs in a ritualistic fashion. Social phobias are characterised by a persistent fear of social situations, whereby the affected person may be subject to scrutiny by others or fears that he or she may do something that results in humiliation or embarrassment.

TCAs, MAOIs, SSRIs and the benzodiazepine **alprazolam** (see Chapter 34) have been used for the prophylaxis of recurrent panic attacks in panic disorder. The MAOIs and the SSRIs have been used to treat people with social phobias. The SSRIs form the second-line therapy in obsessive–compulsive disorder.

MOOD STABILISERS

Mania is the antithesis of depression. It is characterised by an elevation of mood lasting more than a week. The affected person is hyperactive and talkative. He or she experiences insomnia, increased sexual drive and an increased flow of ideas and thoughts. At the synaptic level, amine neurotransmitter release, particularly of noradrenaline, is enhanced.

The affected person often cycles between mania and depression. Sometimes, cycles occur four or more times a year; this is known as rapid-cycling bipolar affective disorder. An affected person's moods are best stabilised by pharmacological agents such as **lithium carbonate**, **carbamazepine**, **sodium valproate** and **clonazepam**, as discussed below. In an acute attack of mania, treatment with an antipsychotic drug (see Chapter 33) may be required.

LITHIUM CARBONATE

Lithium carbonate is used mainly as a mood stabiliser to prevent mania and cyclic depressive states.

■ MECHANISM OF ACTION

Lithium has been reported to enhance the action of the amine-reuptake pump and hence to inhibit noradrenaline

release. This results in a depletion of neurotransmitter within the synapse. This is the opposite action to that of TCAs.

Within the body, lithium is treated like sodium. Chemically, these substances are similar: they are both metals, and as ions they have a charge of +1. Lithium lies above sodium in the periodic table of the elements. The action of lithium is most likely mediated by altering the normal sodium–potassium pump. Lithium distributes itself in both intracellular and extracellular fluid, like sodium, but lithium is handled poorly by the sodium–potassium pump. It may be that lithium replaces sodium in the pump and thus slows down the rate of sodium and potassium transfer between body compartments, although recent evidence indicates that this is probably not the case. As the sodium–potassium pump is important in all body cells, the effects of lithium are widespread, affecting many body systems, including the CNS. Another possibility is that lithium changes levels in the brain of inositol phosphate (IP_3) by blocking its recycling. IP_3 is an important second messenger involved in both α-adrenergic and muscarinic transmission and there is a consequent disturbance of intracellular calcium function following lithium administration.

◆ COMMON ADVERSE EFFECTS

Common adverse reactions to lithium include gastrointestinal irritation, tremor, muscle weakness and polyuria. As lithium has a very narrow therapeutic range (therapeutic index less than 2), impending toxicity manifests as an exacerbation of the above adverse effects, with tinnitus, blurred vision, ataxia, muscle twitches and altered consciousness. Serious adverse reactions include cardiac dysrhythmias, convulsions and renal failure. Lithium can also lead to hypothyroidism and nephrogenic diabetes insipidus, with its resultant polydipsia and polyuria. Contraindications for treatment include renal and cardiac insufficiency and sodium imbalance.

✚ CLINICAL CONSIDERATIONS

Lithium is the drug of choice for the treatment and prevention of acute mania. Remember that it is the blood concentration rather than the dosage of drugs that leads to complications. Due to the low therapeutic index of lithium, patients on lithium need plasma concentrations monitored closely, especially during the initial stages of treatment.

The patient should be aware of the signs of lithium toxicity, which include thirst, vomiting, frequent urination, nausea and sweating. In view of the effect of lithium on the kidneys and thyroid gland, renal and thyroid function tests are completed at initiation of therapy and then every 3–6 months thereafter. The lithium dose should be titrated gradually according to response in order to avoid a relapse.

Lithium interacts with oral diuretic agents and non-steroidal anti-inflammatory agents in a way that reduces lithium excretion and may thus cause lithium toxicity.

Anticonvulsants

Carbamazepine, sodium valproate and clonazepam are anti-seizure drugs that are also useful in the treatment of bipolar affective disorder. They are usually employed when an individual fails to respond to lithium alone or in situations of rapid-cycling manic–depressive illness.

■ MECHANISM OF ACTION

The mode of action of anticonvulsants in this condition is not well understood; however, an enhancement of gamma-aminobutyric acid (GABA) activity has been proposed. It is possible that these drugs act to stabilise the erratic firing pattern of nerves involved in controlling mood.

Carbamazepine is actually a tricyclic substance related to imipramine and has some intrinsic antidepressant activity. It is used in the treatment of mania and as a prophylactic agent. If used in combination with lithium, it can increase the toxicity of the lithium ion by elevating its plasma concentration.

Sodium valproate is particularly effective as a prophylactic agent, but it is also used in the treatment of rapid-cycling bipolar affective disorder.

The advantage of using a benzodiazepine such as clonazepam is that it is well tolerated and has a large margin of safety. Its use is limited to that of an adjunct to lithium therapy. It acts to reduce the incidence of manifestations of mania, such as altered speech and motor function. (The common adverse reactions, other uses, contraindications and clinical considerations are detailed in Chapter 37.)

CLINICAL MANAGEMENT

Antidepressants

Assessment

- Assess the patient's baseline observations. These should include lying and standing blood pressures, radial and apical pulses with description of rate, rhythm and quality, fluid input and output, bowel habits and weight. Sleep patterns and behavioural aspects of depression should also be assessed. Compare with subsequent observations.
- Check the patient's liver and renal function, including liver function enzyme levels, serum creatinine and urea levels, and ensure urine output is greater than 600 ml/day. Severely impaired liver and renal function are contraindications.
- Obtain a history of depression or manic depression.
- Assess whether the patient is taking other central nervous system depressant drugs, which could cause an additive effect with these agents.
- Tricyclic antidepressants cause antimuscarinic effects and therefore are contraindicated in patients with narrow-angle glaucoma and prostatic hypertrophy.
- Patients with a history of cardiac disease, hyperthyroidism and epilepsy need to exercise caution when taking antidepressants, as these conditions may be aggravated.
- Take care with patients who have suicidal tendencies: such patients are particularly at risk, because these drugs cause serious toxic effects at excessive doses.

Planning

- Following a course of antidepressants and non-pharmacological therapy, the patient's depression will be lessened.
- The patient will experience minimal adverse effects from the therapy.

Implementation

- Closely observe the patient for manifestations of depression and the way these may alter during therapy. These manifestations include insomnia, apathy, withdrawal, and lack of interest in activities.
- If the patient is taking antiseizure drugs concurrently, observe the effect on seizures. The doctor may need to increase the dose of antiseizure drugs, as antidepressants can lower the seizure threshold.
- The antimuscarinic effects of tricyclic antidepressants include dry mouth, increased heart rate, urinary retention, constipation and blurred vision. Monitor for sexual impairment in erection, ejaculation and responsiveness problems.
- Monitor the patient for suicidal tendencies if severe depression is present.
- Administer the drug at night if the patient becomes very drowsy during the daytime.
- Monitor renal and hepatic function during therapy.
- Ensure that the patient swallows the medication to prevent use in a possible future suicide attempt.

Patient teaching

- Inform the patient that the drug's effectiveness occurs after about 2 weeks of compliance. Antidepressant treatment needs to continue even after recovery because of the potential for a relapse.
- It is not appropriate for a patient to stop taking tricyclic antidepressants abruptly. The tetracyclic antidepressants mianserin and mirtazapine may be stopped abruptly without adverse withdrawal effects. High-dose selective serotonin reuptake inhibitors may be tapered off over a 2-week period to avoid a withdrawal syndrome. Advise the patient to report withdrawal symptoms, which include abdominal pain, diarrhoea, nausea, headache, myalgia, sweating and insomnia.
- The patient should be informed to move from a lying to standing position very slowly to prevent effects of postural hypotension (see Table 11.20 in Chapter 11 for further information).
- Tell the patient to take great care when driving and operating machinery while on antidepressant therapy, especially during the initial stages of treatment.
- Inform the patient that selective serotonin reuptake inhibitors should be taken in the morning to minimise the incidence of insomnia.
- Alcohol should be avoided because of the additive central nervous system depressant effect.
- To cope with the effects of dry mouth (an antimuscarinic effect), advise the patient to suck boiled sweets and ice chips. Adequate fluid intake and oral hygiene should also be maintained (see Table 11.9 in Chapter 11 for further information).
- Instruct the patient about the importance of checking with the doctor and pharmacist before taking over-the-counter medications.

- Advise patients on fluvoxamine or venlafaxine to take the preparation with food to prevent stomach upsets.
- Inform patients on paroxetine to swallow the tablet whole with food to minimise stomach upsets.
- If daytime sedation is a problem with nefazodone, the bulk of the dose can be taken at night.

Evaluation

- Observe for the therapeutic effect on depression. An improved condition will be indicated by the patient's greater interest in the immediate environment, physical appearance and interpersonal relations.
- Evaluate the presence of adverse effects. The doctor may need to be contacted to prescribe an altered dose or medication.

Monoamine oxidase inhibitors and reversible inhibitors of monoamine oxidase

Assessment

- Assess for a history of hyperthyroidism, cardiovascular and cerebrovascular disease, phaeochromocytoma, hepatic and renal impairment, hypertension and glaucoma. Check with the doctor, as monoamine oxidase inhibitors are usually contraindicated in these conditions.
- Assess for baseline observations such as blood pressure, pulse and respirations. Compare with subsequent observations.
- Note that concurrent use with other drugs is usually contraindicated because of the large number of drug interactions.

Planning

- The patient's depressant behaviour will improve.
- The patient will experience minimal adverse effects.

Implementation

- Closely observe the patient for manifestations of depression and the way these may alter during therapy. These manifestations include insomnia, apathy, withdrawal and lack of interest in activities.
- Regularly monitor blood pressure, pulse and respirations. Monoamine oxidase inhibitors tend to increase sympathomimetic effects through a rise in amine levels.
- Monitor for adverse effects such as postural hypotension, insomnia, headache, muscle twitching, constipation and impaired sexual function.
- Monitor for the presence of a hypertensive crisis, as indicated by tachycardia, stiff neck, high blood pressure and chest pain.
- Monitor the patient for suicidal tendencies if severe depression is present.
- Ensure the patient swallows the medication to prevent use in a possible future suicide attempt.
- Assist the patient with ambulation during the first stages of therapy.

Patient teaching

- Instruct the patient about tyramine-containing foods that may cause a hypertensive crisis if taken with phenelzine or tranylcypromine. Provide the patient with a list of these foods. Note that reversible inhibitors of monoamine oxidase such as moclobemide are not usually affected by tyramine-containing foods. It is advisable to avoid large quantities of tyramine-rich foods such as mature cheese, however, if hypertension is a problem and with high doses of moclobemide.
- Inform the patient that the drug's effectiveness occurs after about 2 weeks of compliance. Antidepressant treatment needs to continue even after recovery because of the potential for a relapse.
- Inform the patient about the potential problems in taking over-the-counter preparations with phenelzine and tranylcypromine. Several over-the-counter preparations contain sympathomimetics. Note that reversible inhibitors of monoamine oxidases such as moclobemide are not affected by over-the-counter preparations containing sympathomimetics.
- Instruct the patient not to consume alcohol with a monoamine oxidase inhibitor due to the additive depressant effects.

Evaluation

- Observe for the therapeutic effect on depression. An improved condition will be indicated by the patient's greater interest in the immediate environment, physical appearance and interpersonal relations.
- Evaluate the presence of adverse effects. The doctor may need to be contacted to prescribe an altered dose or medication.

Mood stabilisers (lithium)

For clinical management of other mood stabilisers, see Chapter 37.

Assessment

- Assess the patient's history for organic brain syndrome and cardiovascular, cerebrovascular, thyroid and renal disease. If any of these conditions is present, clarify the prescription with the doctor.
- If the patient has a severe infection associated with sweating, fever, diarrhoea or vomiting, the lithium dose may need to be reduced in order to prevent toxicity from dehydration.
- Assess whether a female patient of childbearing age is using contraception, as lithium can cause harm to the fetus, especially in the first trimester. Similarly, lithium should not be used in breastfeeding mothers, as it can lead to lithium toxicity in the infant.
- Before giving the initial dose, establish the patient's baseline weight and vital signs. Determine sleeping patterns and behaviour exhibited. Assess fluid input/output and total balance. Compare with subsequent observations.
- Establish a baseline serum level of lithium. Compare with subsequent observations of serum levels.

Planning

- Following a course of mood stabilisers and non-pharmacological therapy, the patient's manic depression will be lessened.
- The patient will experience minimal adverse effects from the therapy.

Implementation

- Administer after meals to prevent gastric irritation.
- Ensure that the patient has an adequate fluid intake of about 2–3 l each day. Regularly monitor fluid input, output and total balance during the early stages of therapy.
- Regularly monitor body weight and vital signs during therapy. Monitor the drug's effect on sleeping patterns and behaviour.
- Monitor electrolyte levels in the early stages of therapy (check for hyponatraemia and hypophosphataemia). Loss of fluid and electrolytes can also cause dysrhythmias.
- Perform renal and thyroid function tests at baseline and then every 3–6 months.
- Regular serum levels of lithium should be taken every 2–3 months while the patient is in remission. Levels above 1.5 mmol/l necessitate withholding lithium and clarifying the dose with the doctor. The lithium concentration should be monitored more often during illness, manic and depressive phases and changes in diet and weather, with concomitant medications (e.g. diuretics) and in pregnancy.
- Monitor fine and gross muscle tremors.
- In a severely manic patient, a benzodiazepine or antipsychotic agent may need to be considered in addition to lithium treatment. Anticonvulsants may also be helpful.

Patient teaching

- Instruct the patient on the importance of compliance. Withdrawal of therapy will cause manic symptoms to reappear. Toxicity problems will warrant withdrawal of therapy, however (refer to the next point).
- Advise the patient to watch for signs of lithium toxicity, including extreme thirst, frequent urination, nausea and vomiting. A patient is prone to toxicity problems during periods of illness and low fluid intake. If these signs occur, inform the patient to stop taking the medication and to see the doctor immediately.
- Inform the patient to maintain an adequate fluid and sodium intake. A normal diet should be maintained, with more fluid consumed in hot weather.
- Alertness may be impaired in the initial stages of therapy, so advise the patient to avoid activities requiring coordination and concentration, such as driving and operating machinery.

Evaluation

- Observe for the therapeutic effect on manic depression.
- Evaluate the presence of adverse effects.

SUMMARY

- Depression is a state of profound sadness. It can be reactive, in response to a life event, or endogenous, without an apparent trigger.
- The synaptic hypothesis of depression proposes that a depletion in the synaptic levels of noradrenaline and serotonin underlies the condition.
- Antidepressant drugs act by raising the levels of one or both of these neurotransmitters. This is achieved by blocking the presynaptic reuptake of one or both transmitters (i.e. tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), noradrenaline–serotonin reuptake inhibitors (NSRIs) and selective noradrenaline reuptake inhibitors (SNRIs)), blocking presynaptic α_2 receptors (tetracyclic antidepressants), inhibiting the transmitters' degradative enzyme (monoamine oxidase inhibitors, MAOIs) or blocking a subtype of postsynaptic serotonin receptors (SSRIs).
- Antidepressant effects may not be observed for up to 4 weeks after treatment commences.
- Continue treatment for 4–12 months for a single episode of major depression.
- Cognitive behavioural therapy can augment pharmacological treatment.
- Combination therapy should be avoided because of adverse reactions.
- Mood stabilisers are used in the management of mania and cyclic depressive states.
- Lithium carbonate is a mood stabiliser that acts to deplete synaptic noradrenaline levels. It has a low therapeutic index and thus requires close monitoring.
- Some antiseizure drugs are also used to stabilise mood. They may act to stabilise erratic firing patterns in the pathways controlling mood.

1 Define the following affective disorders:
(a) reactive depression;
(b) a panic disorder;
(c) mania;
(d) obsessive–compulsive behaviour;
(e) bipolar affective disorder.

2 State the proposed synaptic aberrations underlying the following conditions:
(a) depression;
(b) mania.

3 State the mechanism of action of each of the following drug groups:
(a) tricyclic antidepressants;
(b) lithium carbonate;
(c) non-selective monoamine oxidase inhibitors;
(d) selective serotonin reuptake inhibitors;
(e) noradrenaline–serotonin reuptake inhibitors.

4 Compare and contrast the general characteristics of the following drug groups:
(a) the tricyclic antidepressants (TCAs) and the selective serotonin reuptake inhibitors (SSRIs);
(b) the non-selective monoamine oxidase inhibitors (MAOIs) and the reversible inhibitors of monoamine oxidase (RIMAs);
(c) the TCAs and the tetracyclic antidepressants;
(d) the TCAs and the non-selective MAOIs;
(e) the SSRIs and the noradrenaline–serotonin reuptake inhibitors (NSRIs).

5 Which drugs/drug groups may form a part of the therapy in the following conditions?
(a) obsessive–compulsive disorder;
(b) mania;
(c) severe depression;
(d) social phobias.

6 Why should the urinary output and neurological signs be monitored closely in a patient receiving lithium?

7 Mark Dasmussen, a 50-year-old man, is newly diagnosed with depression. He complains of difficulty sleeping at night. What type of antidepressant would be suitable for Mr Dasmussen? Provide a rationale for your answer.

8 Mary Rogers, a 65-year-old patient, has manic depression, which is treated with lithium. After experiencing severe pain in her back, she decides to take some aspirin in an attempt to alleviate the pain. What is the problem with this combination?

9 Theo Durr is a 35-year-old with rapid-cycling manic-depressive illness. He has not responded well to lithium therapy and is now receiving treatment with sodium valproate. What adverse effects should be monitored for during this therapy?

10 Your patient is taking tranylcypromine. What would you advise the patient about foods?

11 Peta McMuster is a 20-year-old woman with migraine who has sought treatment. She has been taking sumatriptan as a nasal spray to improve her condition. She recently became quite depressed and required treatment. Her doctor started her on therapy with the selective serotonin reuptake inhibitor fluoxetine. She soon experienced sweating, hyperreflexia, muscle twitching and abnormal foot movements. What complication of this antidepressant therapy is she experiencing? How has this come about? (*Hint*: you might want to refer to Chapter 30 to find out more about sumatriptan's mechanism of action.) What is the treatment?

12 Why would you advise a patient not to consume alcohol while on antidepressant therapy?

13 As significant therapeutic benefits of antidepressant therapy are not apparent for some weeks, compliance with treatment may be a problem. Outline some approaches that could be used to promote compliance with drug therapy.

35 DRUG SUMMARY TABLE: ANTIDEPRESSANTS AND MOOD STABILISERS

FAMILY NAME	GENERIC NAME	TRADE NAME(S)
Tricyclic antidepressants (TCAs)	Amitriptyline	Triptafen
	Clomipramine	Anafranil
	Dosulepin (dothiepin)	Prothiaden
	Doxepin	Sinequan
	Imipramine	
	Nortriptyline	Allegron
	+Flufenazine	Motival
	Trimipramine	Surmontil
Tetracyclic antidepressants	Maprotiline	Ludiomil
	Mianserin	
	Mirtazapine	Zispin Soltab
Noradrenaline–serotonin reuptake inhibitors (NSRIs)	Venlafaxine	Efexor
Selective serotonin reuptake inhibitors (SSRIs)	Citalopram	Cipramil
	Escitalopram	Cipralex
	Fluoxetine	Prozac
	Fluvoxamine	Faverin
	Paroxetine	Seroxat
	Sertraline	Lustral
Non-selective monoamine oxidase inhibitors (MAOIs)	Phenelzine	Nardil
	Tranylcypromine	
Reversible inhibitors of monoamine oxidase (RIMAs)	Moclobemide	Manerix
Selective noradrenaline reuptake inhibitors (SNRIs)	Reboxetine	Edronax
Mood stabilisers	Carbamazepine	Tegretol
		Carbagen SR
	Clonazepam	Rivotril
	Lithium carbonate	Camcolit
		Priadel
		Liskonum
	Sodium valproate	Epilim
Panic disorder therapy	Alprazolam	Xanax

DRUGS USED IN NEURODEGENERATIVE DISORDERS

36

CHAPTER THIRTY-SIX

OBJECTIVES

After completing this chapter, the reader should be able to:

- **describe the pathophysiology of Parkinson's disease, Alzheimer's disease, Huntington's disease, motor neuron disease and multiple sclerosis;**
- **differentiate between primary and secondary parkinsonism;**
- **explain the pathophysiological basis for the use of the varied drugs in the treatment of Parkinson's disease;**
- **outline the treatment approach in Parkinson's disease;**
- **outline the use of antimuscarinic and dopaminergic drugs in Parkinson's disease;**
- **outline the use of drugs in Alzheimer's disease, Huntington's disease, motor neuron disease and multiple sclerosis.**

KEY TERMS

Parkinson's disease
Basal ganglia
Dementia
Alzheimer's disease
Multiple sclerosis
Motor neuron disease

DEGENERATION OF THE NERVOUS SYSTEM CAN CAUSE GREAT morbidity and mortality. The aetiology of these conditions is not understood well, although some, such as Huntington's disease, are determined genetically. Others may be due to autoimmunity triggered by a viral infection, such as multiple sclerosis (MS) and Sydenham's chorea (St Vitus' dance),

which can occur in children as a result of rheumatic fever. Most of these degenerative disorders produce a progressive deterioration in neuronal function and tend to be irreversible. Temporary and sometimes long-term remissions are not unusual. Treatment is supportive rather than curative. Generally, neurodegenerative conditions can be divided into two groups: those affecting movement and those affecting memory and cognition.

In this chapter, we examine the pathophysiology and treatment of the following important neurodegenerative disorders: Parkinson's disease, Alzheimer's disease, Huntington's disease, motor neuron disorders and MS. The two most common diseases of this type are Parkinson's disease and Alzheimer's disease.

PARKINSON'S DISEASE

Pathophysiology

Parkinson's disease is a disease with a mean age of onset around 60 years, although it can develop at a younger age. In most patients, rigidity of voluntary muscle, slowness of movement (bradykinesia) and postural instability (the affected person may break into a run in order to stop themselves from falling – termed festination) are the main characteristics.

The incidence of Parkinson's disease is about 1–2 per cent in people over 60 years of age, and so it is not an uncommon disease. The cause of Parkinson's disease is unknown, but a considerable amount is known about the central nervous system (CNS) defect that leads to the illness. A reasonable understanding of the pathophysiology of the disease will help in the understanding of the many types of pharmacological treatment used to alleviate some of the symptoms.

The defect in Parkinson's disease is in the basal ganglia portion of the midbrain in a region known as the substantia nigra ('black substance'), so-called because it contains melanin-pigmented neurones. This part of the brain is important in the initiation and control of muscular movement, especially fine muscle movement. The substantia nigra is connected to another part of the basal ganglia called the corpus striatum via the nigrostriatal pathway. This is part of the extrapyramidal pathway, whose role is to modify the activity of the pyramidal pathway to ensure that the muscle movement is smooth and coordinated and that muscle tension (tone) is appropriate. The nigrostriatal pathway is inhibitory and involves dopaminergic fibres. Disruption of dopamine in this pathway may explain many of the characteristics of Parkinson's disease. The mechanism of degeneration may be associated with the development of proteinaceous inclusions (Lewy bodies) within the cytoplasm of dopamine neurons. Neurons using other neurotransmitters and modulators (e.g. gamma-aminobutyric acid (GABA), serotonin, acetylcholine) may also be damaged.

Loss of the inhibitory dopamine influence may also lead to an apparent excitatory excess mediated through cholinergic pathways. The homeostatic control between excitatory muscarinic and inhibitory dopaminergic activity can be likened to a seesaw, as shown in Figure 36.1. Normally the seesaw is balanced, but it can sway to and fro, depending on the skeletal muscular activity of the body. In Parkinson's disease, the dopaminergic fibres and/or the dopamine receptors degenerate, causing excessive muscarinic activity. The seesaw remains unbalanced, as the dopaminergic activity is never sufficient to keep the seesaw in balance.

The usual way to treat the condition is to try to rebalance the seesaw using drugs; surgical treatment is still experimental. This can be addressed using two methods: by decreasing the muscarinic activity (by using antimuscarinic drugs) and/or by increasing the dopaminergic activity (by increasing dopamine levels, blocking the breakdown of dopamine or mimicking dopamine's action). The common adverse effects of the antiparkinsonian drugs are shown in Figure 36.2.

Parkinsonian-like symptoms can be produced by drugs, poisons and traumatic lesions to the basal ganglia. When the cause is known, the disease is termed 'secondary parkinsonism' as opposed to idiopathic or primary parkinsonism. Secondary parkinsonism is sometimes only temporary if the symptoms are due to drugs such as the antipsychotic phenothiazines (see Chapter 33). Secondary parkinsonism is not called Parkinson's disease.

Decreasing muscarinic activity

Antimuscarinic drugs were the first compounds to be used in the treatment of Parkinson's disease when it was noticed that belladonna preparations improved the condition. Since the advent of synthetic antimuscarinics, newer compounds have replaced the use of **atropine**. Antimuscarinics are of no use in hypokinesia, but they help to control the tremor and rigidity of Parkinson's disease. Because of the nature of their side effects, these drugs are not the first choice of therapy in elderly people, but they may be useful in the treatment of the early stages of the disease in younger patients or, sometimes, in combination with dopaminergic drugs, when tremor is otherwise uncontrollable.

MECHANISM OF ACTION

By inhibiting the muscarinic receptors in the basal ganglia, the imbalance between the extrapyramidal and pyramidal pathways is lessened. The dominance of the acetylcholine side of the seesaw is reduced (see Figure 36.1).

FIGURE 36.1 DIAGRAMMATIC REPRESENTATION OF NORMAL (A) AND ABNORMAL (B) NIGROSTRIATAL PATHWAY FUNCTIONING

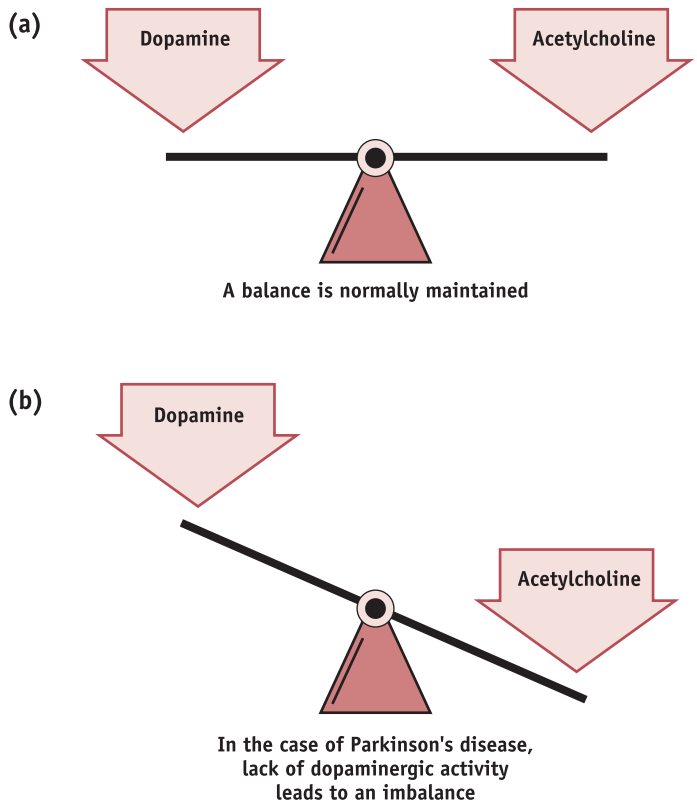
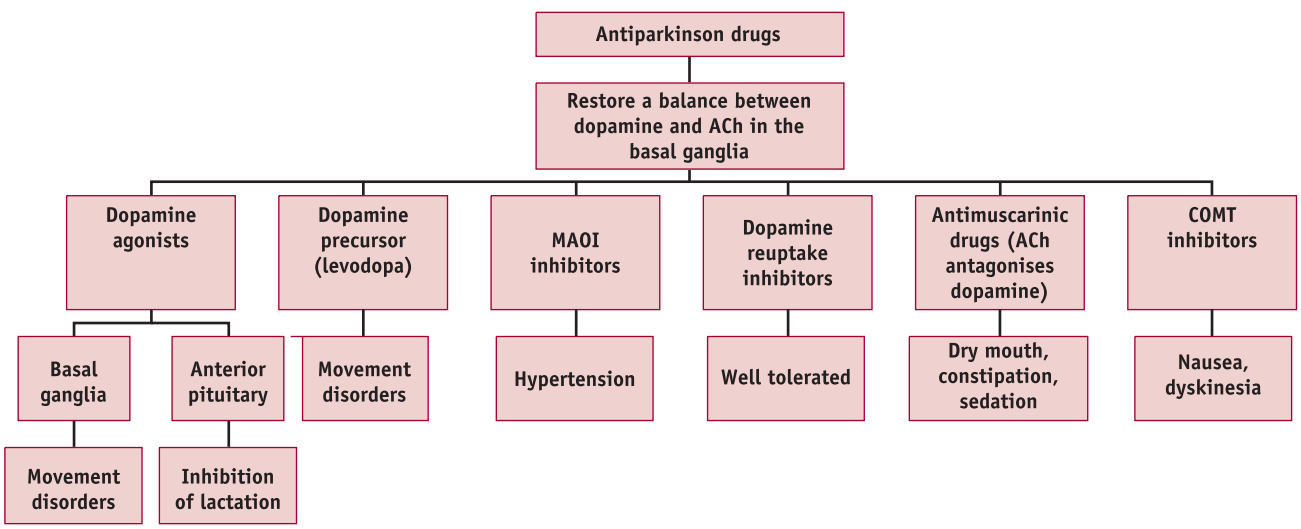


FIGURE 36.2 ANTIPARKINSONIAN DRUGS AND THEIR COMMON ADVERSE EFFECTS



ACh, acetylcholine; COMT, catechol-O-methyltransferase; MAOI, monamine oxidase inhibitor.

◆ COMMON ADVERSE EFFECTS

The side effects are those that are usual for antimuscarinic drugs (see Chapter 27) and include difficulty in micturition, confusion and hallucinations, which are very undesirable in elderly patients.

✚ CLINICAL CONSIDERATIONS

There are many antimuscarinics available, the commonly used ones being **benztropine**, **benzhexol**, **procyclidine** and **orphenadrine**. There is little to choose between these drugs; choice depends on the physician's preference and the patient's response. Benzhexol and procyclidine occasionally produce euphoric symptoms, which have led to their abuse, but in view of their adverse-effects profile (see Chapter 27) this is surprising. Orphenadrine is of value in the treatment of skeletal muscle pain and nocturnal cramps (see Chapter 37) and can be combined with paracetamol for this purpose. When the antimuscarinic drugs have served their usefulness in the treatment of Parkinson's disease, their withdrawal should be gradual to avoid exacerbation of the symptoms of the disease. Antimuscarinics are the only drugs useful in the treatment of secondary parkinsonism (i.e. that caused by antidopaminergic drugs).

Increasing dopaminergic activity

INCREASING DOPAMINE LEVELS

LEVODOPA

As the major defect in Parkinson's disease is the lack of dopamine activity in the substantia nigra, it seems logical to try to increase the dopamine activity in this area. If dopamine itself is administered, however, it does not cross the blood–brain barrier. Consequently, this approach causes only peripheral dopamine effects (see Chapter 26). The immediate precursor of dopamine is a chemical named **levodopa** or L-dopa, which can cross the blood–brain barrier, where it is converted into dopamine.

■ MECHANISM OF ACTION

Levodopa has been used widely for the treatment for Parkinson's disease, but it has serious drawbacks as it is also converted into dopamine by peripheral mechanisms.

Large doses of levodopa have to be given to ensure that a sufficient amount gets into the CNS before being converted into dopamine. By giving large doses, however, the levodopa and the dopamine produced peripherally trigger fairly severe peripheral adverse effects. To try to avoid these effects, pharmacologists have come up with a clever solution: the enzyme that converts levodopa to dopamine is a decarboxylase. Several inhibitors of this enzyme have been found, and at least two of them are unable to cross the blood–brain barrier – **carbidopa** and **benserazide**. By adding one of these compounds to levodopa preparations, the peripheral conversion of levodopa to dopamine is inhibited, allowing more levodopa to cross the blood–brain barrier. As the inhibitors cannot cross the blood–brain barrier, the CNS conversion of levodopa to dopamine can proceed unhindered. This combination of active drug plus the enzyme inhibitor reduces the incidence of adverse effects from about 80 per cent to less than 15 per cent, a tremendous boost to the patient. Adverse effects are still common with this combination, but most patients would rather put up with these effects than suffer the full-blown symptoms of Parkinson's disease.

◆ COMMON ADVERSE EFFECTS

Side effects of levodopa are common and include:

- nausea, which may be treated by incorporating **domperidone** in the drug regimen;
- depression, which may require antidepressant therapy;
- involuntary movements of the extremities, head, lips and tongue;
- agitation and confusion – although these are sometimes due to the disease itself;
- increased sexual activity;
- hypotension;
- delusions;
- dysrhythmias.

Some of these adverse effects, particularly the disorders of movement, can be avoided to some extent by using slow-release preparations, which maintain more constant blood levels, thus avoiding concentration peaking. It is also important to distinguish drug-induced movements from the disease itself. The early addition of the dopamine agonist **bromocriptine** may help to delay or prevent the onset of these involuntary movements.

✚ CLINICAL CONSIDERATIONS

The effect of levodopa in Parkinson's disease tends to decrease with time, until a point when no effect is produced at all. This may take years to develop. In the initial stages of the drug losing its effect, dosing has to become more frequent, with the drug being needed as often as once-hourly. This progressive loss of drug activity is probably due to the continued degeneration of the dopaminergic neurons.

An unusual event occasionally results from long-term levodopa therapy, referred to as the 'on–off phenomenon'. This can be quite marked and is characterised by the patient having more or less normal movement until severe symptoms of the disease suddenly develop. These symptoms last for varying lengths of time (anything from 30 minutes to several hours) before partial normality returns. The attacks can occur at any time but are usually confined to periods when the patient is awake. The cause of these attacks is not known, but the subcutaneous injection of **apomorphine**

is useful in their control (see below). As this drug is a strong emetic, domperidone should be administered for 2 days before starting such treatment. Levodopa should be taken at the same time each day, and always with or before food to ensure uniform blood concentrations of levodopa. A controlled-release formulation is often useful for the on–off phenomenon. During this time, a conventional formulation is still usually needed for the morning dose because of its faster onset of action.

OTHER PERIPHERAL INHIBITORS OF LEVODOPA CONVERSION

Entacapone and **tolcapone** belong to a class called catechol-O-methyltransferase (COMT) inhibitors. They are useful in further preventing the conversion of levodopa to dopamine in the periphery as an adjunct to the decarboxylase inhibitors.

■ MECHANISM OF ACTION

COMT is an enzyme present at adrenergic and dopaminergic synapses and in the liver and kidney. This enzyme, like monoamine oxidase (MAO), metabolises certain neurotransmitters and substances belonging to the catecholamine chemical group (see Chapter 26). Substances such as dopamine, levodopa and noradrenaline belong to this group. Entacapone and tolcapone, like benserazide and carbidopa, do not cross the blood–brain barrier and, therefore, affect only peripheral COMT. These drugs, when given with levodopa, increase the amount of levodopa available to cross the blood–brain barrier for subsequent conversion into dopamine.

◆ COMMON ADVERSE EFFECTS

The adverse effects of entacapone (e.g. nausea, diarrhoea, dyskinesias) are due to an increase in dopaminergic activity. Patients should be told that their urine may turn a reddish-brown colour during treatment. As many drugs are metabolised by COMT, drug interactions can be common. This necessitates care in the administration of different drugs, and patients should be advised to check with their doctor or pharmacist before taking over-the-counter preparations. For example, iron complexes with entacapone, thus preventing the absorption of the latter. Liver enzymes may increase with administration of COMT inhibitors. Neuroleptic malignant syndrome (NMS) may occur, but this is rare (see Chapter 33).

✚ CLINICAL CONSIDERATIONS

The concurrent use of the decarboxylase inhibitors (benserazide and carbidopa) with entacapone or tolcapone enhances the effect of levodopa. Liver function tests should be performed every 2 weeks for the first 3 months and monthly thereafter. If iron is required, administration of the drugs should be separated by 2–3 hours.

INHIBITING THE BREAKDOWN OF DOPAMINE

Another approach is to prolong the action of the dopamine released from the nigrostriatal nerves.

■ MECHANISM OF ACTION

In Chapter 35, a class of antidepressants called monoamine oxidase inhibitors (MAOIs) are discussed, which inhibit the enzyme MAO responsible for degrading noradrenaline. This enzyme is also responsible for degrading dopamine in the substantia nigra; thus, by inhibiting the activity of this enzyme, dopamine levels will rise. You may remember that members of this class of drugs usually have severe problems associated with their use, particularly dietary restrictions and the problem of drug–drug interactions. The enzyme present in the substantia nigra however, is not the same as that in the gut, liver and higher centres of the brain and is termed MAO-B, as opposed to the other enzyme MAO-A.

Selegiline is an MAO-B inhibitor and inhibits MAO-A only if given in large quantities. Selegiline, given concurrently with levodopa, enables a smaller dose of the latter to be administered, thus avoiding many of the adverse effects associated with levodopa.

◆ COMMON ADVERSE EFFECTS

Dyskinesias still occur with supplemental selegiline, but with less frequency than when levodopa is used alone, and the symptoms can often be resolved by reducing the dose of levodopa. Selegiline is remarkably free of adverse effects, dry mouth being the only one of possible significance; unlike with most other MAOIs, the diet does not need to be restricted to tyramine-free foods (see Chapter 35). It has been reported that selegiline actually inhibits the hypertensive effect of tyramine, even when its breakdown is prevented.

✚ CLINICAL CONSIDERATIONS

Selegiline is usually added to levodopa therapy only when levodopa is no longer offering significant or prolonged relief to the patient. Some clinicians, however, argue that selegiline may retard the progression of the disease and should be introduced early in the drug regimen.

STIMULATING RELEASE OF DOPAMINE

Amantadine was originally developed as an antiviral agent and is still used in the prophylaxis of influenza (see Chapter 73). Serendipitiously, it was found to be useful in the treatment of Parkinson's disease.

■ MECHANISM OF ACTION

The action of amantadine in alleviating the symptoms of Parkinson's disease was discovered when a patient with Parkinson's disease showed a marked improvement when being treated with amantadine for influenza. Its action in Parkinson's disease is indirectly dopaminergic. Dopamine reuptake by the presynaptic neuron is decreased and dopamine synthesis and release are increased. Furthermore,

slight antimuscarinic effects are apparent with amantadine. Amantadine is much less efficacious than levodopa but, when used in combination, a potentiation of levodopa's effect is seen. Amantadine also potentiates the effects of the antimuscarinic drugs.

◆ COMMON ADVERSE EFFECTS

Amantadine is generally tolerated well compared with levodopa, but it can cause postural hypotension, ankle oedema, insomnia, livedo reticularis and hallucinations.

✚ CLINICAL CONSIDERATIONS

Amantadine is useful in diminishing tremor in the early stages of Parkinson's disease, particularly if combined with antimuscarinic drugs. The beneficial effect often wanes after 6–12 months.

MIMICKING DOPAMINE'S ACTION

Bromocriptine is related to ergotamine (see Chapter 30) and can be classified as a dopamine agonist. Like amantadine, bromocriptine is best used in conjunction with levodopa, whose action it potentiates. **Lisuride** (lysuride), **cabergoline** and **pergolide** are similar drugs to bromocriptine and are also ergot derivatives. The more recently introduced agents **pramipexole**, **ripinirole** and **rotigotine** also have a direct action on dopamine receptors. These agents are also used with levodopa in more advanced cases of Parkinson's disease. Rotigotine is licensed for use as monotherapy in early-stage Parkinson's disease.

Apomorphine is an emetic substance and, as the name suggests, is a synthetic derivative of morphine. It has a structural similarity to and action resembling that of dopamine – hence its use in Parkinson's disease. It is a non-ergot dopamine agonist.

■ MECHANISM OF ACTION

Dopamine agonists mimic the effects of dopamine on the pyramidal pathway by stimulating dopamine receptors.

◆ COMMON ADVERSE EFFECTS

Bromocriptine, during the initial stages of therapy, may cause nausea, but this may disappear with time and can be alleviated using domperidone. It is a pity that both amantadine and bromocriptine are not so effective as levodopa, as their adverse-effects profile is so much better than that of levodopa.

Lisuride has been associated with severe psychiatric effects, such as delusions, confusion and hallucinations. Other common adverse effects are nausea, vomiting, diplopia and dysrhythmias. Both the patient and his or her carers need to be told of these effects. Cabergoline can cause pleural effusion, fibrosis, depression, gastrointestinal upset and neurological symptoms. Pergolide can cause hypotension, hallucinations, confusion, dyskinesias, somnolence, insomnia, gastrointestinal upset, retroperitoneal fibrosis, rhinitis, dyspnoea, diplopia, atrial premature contractions and NMS.

Pramipexole may lead to hypotensive reactions in some patients. This can occur during the first few days of treatment. Pramipexole has also been associated with attacks of sudden onset of sleep.

Apomorphine is a very powerful emetic, hence the danger of overdosing; even at therapeutic doses, antiemetics such as domperidone (see Chapter 55) are administered concurrently. The phenothiazine antiemetics are contraindicated in Parkinson's disease.

Other adverse effects of apomorphine are respiratory depression, euphoria (but its abuse potential is very low because of its emetic effect), hypotension and uraemia. An unusual effect in men is penile erection, and it is being used in the treatment of erectile dysfunction (see Chapter 45).

✚ CLINICAL CONSIDERATIONS

The treatment of new patients is often started with dopamine receptor agonists. Doses of dopamine receptor agonists should be increased and withdrawn gradually according to response and tolerability.

These drugs are useful when used in conjunction with levodopa preparations to suppress the incidence of on–off problems fairly quickly until effectiveness is shown without the appearance of severe adverse effects. Withdrawal of pergolide from treatment regimens must be done slowly, as abrupt withdrawal often precipitates attacks of severe hallucinations and confusion, particularly when given in conjunction with levodopa. Abrupt withdrawal has also been associated with NMS (see Chapter 33). Drug-induced hypotension can be prevented with **fludrocortisone**.

Initialisation of therapy with these drugs should be by giving small doses and increasing to the optimum dose slowly. This approach may help to avoid adverse effects.

Bromocriptine is occasionally used in the suppression of lactation, but this use is frowned on by many and does not now appear on the list of indications provided by the manufacturer. It appears that prolactin inhibitory factor (PIF) is, in fact, dopamine; thus, bromocriptine inhibits the production of prolactin and causes lactation to cease. In the treatment of hyperprolactinaemia, bromocriptine is the drug of choice.

The dopamine agonists have been used in the prevention and suppression of lactation. Bromocriptine and pergolide suppress the production of growth hormone and can be used as an adjunct to surgery and radiotherapy in the treatment of acromegaly (see Chapter 56).

In Parkinson's disease, pergolide can be used in the normal management, but it is particularly useful in the control of the on–off effect associated with levodopa. Although apomorphine can be administered orally, it is given only by subcutaneous injection in most countries, its onset of therapeutic effect then being apparently faster and the dosage easier to control. The dose of apomorphine is critical and

varied and usually is titrated against the therapeutic effect by experimentation to determine the optimum lowest dose. Initiation of apomorphine treatment is undertaken in hospital under medical supervision to observe for therapeutic and adverse effects. The subcutaneous injection sites are rotated to prevent problems with absorption. Tolerance to the gastrointestinal effects of apomorphine develops rapidly, thus enabling the domperidone dose to be reduced and gradually withdrawn over several weeks.

The drug can be self-administered or given by a responsible carer.

Combination therapy

It is normal for combined therapy to be used in Parkinson's disease, and monotherapy today being uncommon. Many neurologists and geriatricians, however, are concerned about the potential for polypharmacy.

ALZHEIMER'S DISEASE

Pathophysiology

Alzheimer's disease is classified primarily as a form of dementia characterised by profound brain shrinkage, enlarged ventricles and significant histological changes to brain tissue. Almost half of all cases of dementia are due to Alzheimer's disease. There is a progressive deterioration of intellectual and cognitive functioning. Impairment of memory and loss of insight are early manifestations. At first, the affected person is forgetful, and then confused and later demented. Hyperexcitability, aphasia, apraxia, agnosia and changes of gait develop as the condition advances. The cause or causes of Alzheimer's disease are yet to be identified clearly. Diagnosis is usually made by eliminating other possible causes and is confirmed by postmortem examination. The current prognosis is poor: The affected person deteriorates over 5–10 years and the condition ends in death.

Within the brain, the concentrations of most neurotransmitters and other neuromodulators decrease as Alzheimer's disease progresses. One of the brain transmitter mechanisms particularly affected is the cholinergic system. A reduction in levels of acetylcholine and acetylcholinesterase occurs early in the development of the disease. This information has provided an opportunity to trial drug treatments that may halt or slow the disease's progression. The current drug therapy for Alzheimer's disease is with the anticholinesterase group.

Anticholinesterases

The anticholinesterases **rivastigmine**, **galantamine**, **memantine** and **donepezil** are now used in the treatment of people with mild to moderate Alzheimer's disease. In addition, galantamine has acetylcholinergic (nicotinic) activity.

■ MECHANISM OF ACTION

In the early stages of Alzheimer's disease, the brain levels of acetylcholine are decreased. The role of acetylcholine in cognition and memory formation is well established (see Chapter 27). The rationale for this therapy is that by blocking the degradative enzyme for acetylcholine, more transmitter will be available and its action prolonged. Interestingly, and perhaps paradoxically, the muscarinic agonist **pilocarpine** has been shown to exacerbate Alzheimer's disease. Donepezil is more selective for brain cholinesterases, particularly acetylcholinesterase, and has less peripheral activity.

◆ COMMON ADVERSE EFFECTS

Donepezil and rivastigmine produce a number of common adverse effects, which include nausea, vomiting, elevated liver enzyme levels, diarrhoea, dizziness, anorexia, myalgia and dyspepsia. These adverse effects are sometimes severe enough to make the patient cease drug therapy. They are contraindicated in patients with active liver disease, untreated peptic ulcer, hypersensitivity and pregnancy. These drugs can also be problematic for patients with severe asthma, seizures, bradycardia and cardiac conduction disorders. Drug interactions of note include concomitant treatment with a cholinomimetic drug. They may prolong the effects of neuromuscular blocking agents such as **suxamethonium** and enhance **theophylline** clearance.

Galantamine can cause gastrointestinal upset, weight loss, anorexia, somnolence, CNS disturbances, rhinitis, urinary tract infection and fatigue.

✚ CLINICAL CONSIDERATIONS

Clinical studies of anticholinesterase treatment in Alzheimer's disease have produced controversial results; some trials have shown some improvement in cognitive function and quality of life, but others have not. These drugs do not affect the underlying pathophysiological process, but when effective they appear to halt the cognitive decline for between 6 months and 2 years. After this time, the cognitive function of people receiving therapy continues to deteriorate.

Donepezil requires only once-a-day administration. Its half-life is approximately 70 hours. It appears to be tolerated well, with few patients stopping therapy because of adverse effects, and it induces no notable abnormalities in laboratory values. Donepezil can also have positive effects on dementia caused by vascular disease. It has not yet been demonstrated whether or not galantamine and rivastigmine have any advantages over donepezil.

HUNTINGTON'S DISEASE

Pathophysiology

Huntington's disease, also known as Huntington's chorea and Huntington's syndrome, is a genetic disease characterised

by involuntary muscle movements and dementia. A person who possesses the Huntington gene on one of their autosomes (non-sex chromosomes) will develop the disease because the disease is an autosomal dominant condition. The onset of the manifestations of this disease is usually between 40 and 60 years of age.

The early manifestations of Huntington's disease include slight uncontrollable muscle movements, lack of coordination, clumsiness, short-term memory losses and changes in emotional state (depression and sometimes antisocial or aggressive behaviour). The condition then degenerates further, leading to involuntary writhing movements, cognitive impairment, loss of speech and swallowing and, ultimately, death.

The abnormal gene programmes for the production of a protein with an expanded polyglutamine aspect called huntingtin. The abnormal huntingtin protein causes cell death through as yet undefined mechanisms. There is a widespread loss of CNS neurons, particularly in the basal ganglia and the cerebral cortex. This accounts for the observed clinical manifestations of Huntington's disease. There appear to be losses of nerve fibres that release acetylcholine and GABA in particular. The loss of GABA nerves in the basal ganglia appears to lead to an overactivity of the dopaminergic nigrostriatal pathway. What we see is the opposite of Parkinson's disease, at least in this aspect of the pathophysiology. The dopaminergic extrapyramidal pathway now dominates the muscarinic pyramidal pathway. The seesaw in Figure 36.1 is now reversed. This explanation accounts for the involuntary writhing movements. Indeed, supportive evidence for this account comes from observation of giving a person with Parkinson's disease an overdose of levodopa, when involuntary writhing movements develop.

Treatment

A drug that can be used specifically in the treatment of Huntington's disease is **tetrabenazine** (see Chapter 37). The antipsychotic agents (see Chapter 33) may also be useful. Surgical implantation of undifferentiated tissues, such as stem cells, is also being trialled as treatment for this condition.

■ MECHANISM OF ACTION

Tetrabenazine appears to act by inhibiting the storage of dopamine in the neuronal neurotransmitter vesicles, thus decreasing dopamine activity. The antipsychotic agents block central dopamine receptors.

◆ COMMON ADVERSE EFFECTS

The main adverse effect is parkinsonism. Other adverse effects of tetrabenazine are drowsiness, depression, impaired alertness and dysphagia.

Common adverse effects of the antipsychotics include motor disturbances, endocrine disruption and allergic reactions.

MOTOR NEURON DISEASE

There are several types of motor neuron disease. The most famous person with the condition is the astrophysicist Professor Stephen Hawking. Many readers will have observed Professor Hawking on television and seen the distress caused by this condition – a remarkable brain locked in a useless body. There is no cure for motor neuron disease, and death usually ensues within several years. Professor Hawking has defied these odds for many years, but his survival is exceptional.

Symptoms of motor neuron disease include muscle fasciculation, hypotonia, muscle wasting and paradoxical reflexes. Treatment is generally to relieve the many symptoms, although in one type of the disease, amyotrophic lateral sclerosis (ALS), there is a drug, **riluzole**, that specifically but temporarily treats the condition.

Treatment

RILUZOLE

■ MECHANISM OF ACTION

The neurons of a patient with ALS accumulate glutamate, which may be the cause of the paralysis. Riluzole appears to inhibit the release of glutamate into the neurons, leading to a slowing down of the paralysis.

◆ COMMON ADVERSE EFFECTS

Common adverse effects include asthenia, nausea and decreased lung function.

✚ CLINICAL CONSIDERATIONS

Riluzole can prolong the active life of people with ALS by only a matter of months, but it does improve their quality of life. Riluzole is not effective against ALS when the onset of the disease affects the limbs.

Supportive therapy

The following agents are used to relieve the symptoms of motor neuron disorders:

- tricyclic antidepressants for depression (see Chapter 35);
- oxygen therapy for hypoxia from poor respiratory muscle function (see Chapter 51);
- antimuscarinics to reduce dribbling and salivation (see Chapter 27);
- **baclofen** and/or **diazepam** for spasticity (see Chapter 37).

MULTIPLE SCLEROSIS

Pathophysiology

MS is a relatively common disease of the nervous system involving demyelination of the nerves of the brain and/or

spinal cord. The accepted view is that MS is an autoimmune disorder that may be precipitated by a viral infection of the CNS. Lymphocytes enter the CNS tissues and become trapped. These cells start to attack the myelin sheath and the cells that make the myelin (oligodendrocytes). As a consequence to the loss of myelin, CNS neural transmission becomes slowed, distorted or blocked. Multiple plaques of non-functional scar tissue form throughout the CNS, giving rise to the name 'multiple sclerosis'.

The age of onset of MS is usually around 20–40 years; it affects more women than men. It is interesting to examine the epidemiology of the condition, as MS is more common in temperate climates and there are some ethnic groups with low incidence rates of MS (Inuits, Asians, indigenous Americans).

The disease follows an unpredictable course with variable severity and remission periods. There is a wide variation in clinical manifestations and prognosis. Broadly, there are two types of MS: the progressive form, which worsens continually, with no remission; and the more common relapsing–remitting form, characterised by a series of attacks followed by complete or partial remission.

There are four common syndromes of symptoms that reflect the parts of the CNS affected: spinal, brain stem, cerebral and cerebellar syndromes. The most common is the spinal syndrome, which is characterised by muscle weakness, stiffness and slowness, preferentially affecting the limbs. Paraesthesias, pain, muscle spasms and spasticity are also observed. In the other syndromes, cranial nerve function, emotions, memory, cognition, vision, motor coordination and gait may be affected.

The survival time from diagnosis can be well over 20 years; therefore it is important to offer patients assistance to improve their quality of life in the acute phases of the disease. As the cause of MS is probably autoimmune, the best causative treatment involves use of immunosuppressive drugs, which are dealt with in detail in Chapters 58 and 75.

TABLE 36.1 DRUGS USED IN THE SYMPTOMATIC TREATMENT OF MULTIPLE SCLEROSIS

Symptom	Drug
Spasms, spasticity	Diazepam, baclofen
Infection	Aggressive antibiotic therapy
Neuralgia	Carbamazepine
Depression, pain	Tricyclic antidepressants
Urinary urgency	Propantheline
Incomplete bladder emptying	Bethanechol, α-blockers
Fatigue	Amantadine

The two specific immunosuppressive drugs used in MS are **glatiramer** and **interferon beta-1b**. Both of these drugs can reduce the number of relapses and delay the development of new lesions. Corticosteroids, such as **prednisone** and **methylprednisolone**, can also be effective in acute phases of the disease, but they are not as effective as the other drugs, although they are considerably cheaper to buy. **Corticotrophin** is used occasionally. Other immunosuppressants are of no value. Table 36.1 details the drugs that can be used to treat the various chronic conditions and symptoms that may arise in patients with MS.

CLINICAL MANAGEMENT

Drugs for neurodegenerative disorders

Assessment

- Assess the patient for clinical manifestations of parkinsonism, including shuffling gait, masked facies, resting tremor and stooped-forward posture.
- Assess the patient for clinical manifestations of Alzheimer's disease, including memory loss, forgetfulness and reduced cognitive ability.
- Assess the patient for clinical manifestations of motor neuron disease, including muscle fasciculation, hypotonia, muscle wasting and paradoxical reflexes.
- Assess the patient for clinical manifestations of Huntington's disease, including involuntary muscle movement.
- Assess the patient for clinical manifestations of multiple sclerosis, including muscle weakness.
- Assess the patient for a history of glaucoma, heart disease, peptic ulcers, renal and hepatic disease, depression and cardiac dysrhythmias.
- Assess vital signs on initial administration of levodopa and bromocriptine. Take lying and standing blood pressures. Compare with subsequent observations.

Planning

- The patient will experience relief of parkinsonian symptoms.
- The patient will experience reduced symptoms of Alzheimer's disease.
- The patient will experience reduced symptoms of motor neuron disease.
- The patient will experience reduced symptoms of Huntington's disease.
- The patient will experience a reduction in the frequency of relapses in symptoms associated with multiple sclerosis.
- The patient will experience minimal adverse effects from the therapy.

Implementation

- Regularly monitor vital signs and electrocardiogram (ECG) during the initial stages of antimuscarinic therapy. Antimuscarinics can cause tachycardia.
- Monitor the effect of therapy on the clinical manifestations of parkinsonism, including shuffling gait, masked facies, resting tremor and stooped-forward posture.
- Postural hypotension is common in the early stages of therapy with levodopa and bromocriptine. Therefore, ensure that the patient rises slowly from a lying position (see Table 11.20 in Chapter 11 for further information).
- Administer a levodopa and a decarboxylase inhibitor combination with a low-protein diet. High-protein diets interfere with dopamine transport into the central nervous system.
- Provide the patient with assistance with walking during the initial stage of therapy.
- Take care in the administration of dopamine agonists such as bromocriptine and pergolide, as these may cause confusion and hallucinations, especially in elderly and demented patients, and at high doses. These effects must be monitored closely.
- Selegiline can increase the incidence of adverse effects produced by levodopa. When used in combination, a decrease in dose of levodopa is required.
- When entacopone and selegiline are used in combination, there is the risk of producing serotonin syndrome. If this combination is used, selegiline should be at the lower level of its dose range.
- When using acetylcholinesterase inhibitors in Alzheimer's disease, a careful monitoring of benefits should occur following 3 months of treatment. Treatment should be discontinued if there is no improvement in the condition or if there is poor adherence or significant adverse effects.
- During glatiramer therapy, patients usually develop antibodies, with maximal levels obtained at 3 months of therapy.

Patient teaching (antimuscarinics)

- Instruct the patient that constipation can occur, and to consume a high-fibre diet (see Table 11.4 in Chapter 11 for further actions and prevention of constipation).
- Advise the patient to avoid alcohol consumption, as this combination may intensify the central nervous system depressant effects.
- Instruct the patient that a dry mouth is a common adverse effect. Relief can be obtained by sucking boiled sweets or ice chips or using an artificial saliva (see Table 11.9 in Chapter 11 for further action that may be taken).
- Advise the patient to void before taking the medication to prevent problems with urinary retention.
- As drowsiness is a common effect of these drugs, advise the patient to avoid driving and operating machinery.

Patient teaching (levodopa)

- Advise the patient to take levodopa with food to avoid gastrointestinal irritation. Food also slows down the absorption rate.
- Inform the patient that urine and perspiration may be discoloured. These are not harmful effects of the drug, but clothes may become stained.
- Advise the patient to avoid foods rich in vitamin B_6 such as beans and cereals, and to avoid vitamin supplements containing vitamin B_6.
- Explain to the patient that a therapeutic effect may not be apparent for several months.
- The medication should never be stopped abruptly, as rebound parkinsonism may occur.

Patient teaching (amantadine, bromocriptine, pergolide)

For bromocriptine, see also reference to antimuscarinics.

- Inform the patient that reduced benefit occurs after 4–12 weeks of therapy. Complete compliance is important for full benefit.
- Advise the patient not to drink alcohol with these medications, as this will result in an increased central nervous system depressant effect.
- Instruct the patient not to stop taking the medication abruptly.
- As bromocriptine can cause postural hypotension, advise the patient to rise slowly from a lying position (see Table 11.20 in Chapter 11 for further action that may be taken).
- As bromocriptine can inhibit salivation, regular dental visits are important to prevent dental problems.

Patient teaching (acetylcholinesterase inhibitors)

- Advise the patient or the carer to omit one or more doses if adverse effects such as abdominal pain, nausea, vomiting or diarrhoea occur.
- Advise the patient to take donepezil in the evening before bedtime to alleviate problems relating to fatigue and dizziness.

Patient teaching (glatiramer)

- Advise the patient to rotate the site of the subcutaneous injection to reduce irritation and pain. Body areas used may include the arms, abdomen, hips and thighs.

Evaluation

- The patient will demonstrate improved mobility, with reduced tremor and rigidity in Parkinson's disease.
- The patient will demonstrate improved cognitive ability in Alzheimer's disease.
- The patient will demonstrate improved movement in motor neuron disease.
- The patient will demonstrate improved movement in Huntington's disease.
- The patient will demonstrate improved movement in multiple sclerosis.
- Evaluate adverse effects. The doctor may need to alter the dose or combination of medications to achieve a lower incidence of adverse effects.

SUMMARY

- Parkinson's disease is a movement disorder caused by lack of dopaminergic activity in the basal ganglia of the brain.
- There is no cure for Parkinson's disease, but symptoms can be relieved with dopaminergic and/or antimuscarinic drugs.
- The activity and effectiveness of antiparkinsonian drugs usually wanes over a period of years.
- Combination pharmacotherapy may prolong the effectiveness of antiparkinsonian drugs.
- Antiparkinsonian drugs can produce adverse effects similar to those of the disease itself.
- Alzheimer's disease is characterised by a lack of acetylcholine activity in the brain.
- The symptoms of Alzheimer's disease can be treated temporarily with drugs that prolong the action of acetylcholine in the brain.
- The treatment of movement disorders such as spasticity and the choreas is symptomatic only.
- Multiple sclerosis (MS) can often be held in check for many years by using immunosuppressive drugs.
- Treatment of motor neuron diseases is supportive only, although amyotrophic lateral sclerosis (ALS) can be suppressed for several months with riluzole.

1 Why is domperidone the preferred antiemetic in controlling the nausea and vomiting sometimes caused by antiparkinsonian drugs?

2 Explain the function of the decarboxylase inhibitor that is usually included with levodopa preparations.

3 Differentiate between hypokinesia, bradykinesia, akinesia and dyskinesia.

4 Would selegiline be useful in the treatment of depression?

5 Why, unlike with some monoamine oxidase inhibitor (MAOI) drugs, are dietary restrictions not necessary when using selegiline?

6 Why, in the treatment and/or prevention of nausea and vomiting associated with apomorphine treatment of Parkinson's disease, are the phenothiazines and antiemetics such as metoclopramide contraindicated?

7 A 70-year-old patient with Parkinson's disease is taking levodopa. Why would you advise the patient to avoid over-the-counter cough and cold preparations containing sympathomimetic decongestants?

8 Bromocriptine is a highly protein-bound drug (95 per cent protein-bound) and undergoes extensive liver metabolism. Would the dose be increased or decreased or remain the same in a patient with liver disease compared with a patient without liver disease? Why?

9 Mary Jackson, a 75-year-old, has recently been diagnosed with Parkinson's disease. She is taking levodopa and carbidopa for her condition. What patient education would you provide Ms Jackson about her medications?

10 Mary Jones has been on a combination of levodopa and benserazide for Parkinson's disease over the past 6 months. What evaluation would you make to determine whether there is any improvement in Mrs Jones' condition?

11 Provide a rationale for the advice to take levodopa with food.

12 Describe the adverse effects that may lead to the cessation of therapy with the anticholinesterases used in Alzheimer's disease.

13 What factors are taken into account when treating multiple sclerosis with immunomodulating agents?

14 Discuss the role of the immune system in the aetiology of multiple sclerosis.

15 Why are immunomodulating drugs useful in multiple sclerosis?

16 Discuss why many patients cease therapy with the anticholinesterases used in Alzheimer's disease.

36 DRUG SUMMARY TABLE: NEURODEGENERATIVE DISORDERS

FAMILY NAME	GENERIC NAME	TRADE NAME(S)
Antimuscarinics	Trihexyphenidyl (benzhexol)	Broflex
	Benzatropine (benztropine)	Cogentin
	Orphenadrine	Biorphen
		Disipal
	Procyclidine	Arpicolin
		Kemadrin
Dopamine agonists	Amantadine	Symmetrel
Direct and indirect dopamine agonists	Apomorphine	APO-go
	Bromocriptine	Parlodel
	Cabergoline	Cabaser
	Entacapone	Comtess
	Levodopa	
	+Benserazide (co-beneldopa)	Madopar
	+Carbidopa (co-careldopa)	Sinemet
	Lisuride	
	Pergolide	Celance
	Ropinirole	Requip
	Selegiline	Eldepryl
		Zelapar
	Tolcapone	Tasmar
Dopamine antagonist	Tetrabenazine	Xenazine
Anticholinesterases	Donepezil	Aricept
	Galantamine	Reminyl
	Memantine	Ebixa
	Rivastigmine	Exelon
Glutamate inhibitor	Riluzole	Rilutek

ANTISEIZURE DRUGS AND MUSCLE RELAXANTS

37

CHAPTER THIRTY-SEVEN

OBJECTIVES

After completing this chapter, the reader should be able to:

- **define epilepsy and state the difference between partial and generalised seizures;**
- **demonstrate familiarity with the characteristics of some common seizure types;**
- **identify the four groups of antiseizure drug, describe their mechanisms of action and state the general adverse reactions associated with therapy;**
- **identify important pharmacokinetic considerations associated with antiseizure drug therapy;**
- **describe the three modes of action of spasmolytic agents, identify representative drugs from each group and state some common adverse reactions of them.**

KEY TERMS

Convulsions
Epilepsy
GABA
Glutamate
Muscle spasms
Nerve membrane excitability
Seizures
Sodium channels

ANTISEIZURE DRUGS ARE USED IN THE TREATMENT OF seizures and, in particular, the condition characterised by recurrent seizures – epilepsy. Antiseizure drugs are widely known as anticonvulsants. The term 'anticonvulsant' is somewhat misleading, however, because some seizures do not manifest as convulsions. As you will discover in this chapter, seizures can

manifest as abnormal behavioural patterns and as a state of unresponsiveness. Therefore, 'antiseizure drug' is a more appropriate term.

Muscle relaxants are used to counter painful muscle spasms associated with conditions such as multiple sclerosis (MS) and fractures. At first glance, the antiseizure drugs and the muscle relaxants might seem like disparate drug groupings, but there is some overlap between the actions of the two groups.

The two drug groups are discussed separately. For each group, there is a brief discussion of the associated pathophysiology, followed by an examination of the mechanisms of action, adverse reactions, contraindications and other clinical considerations.

EPILEPSY

Epilepsy is a condition characterised by the continued recurrence of seizures. A seizure is the manifestation of an intense, uncontrolled, transient electrical discharge across the surface of the cerebral cortex. It is analogous to a fierce electrical storm moving across the surface of the earth. The discharge may be constrained to one region of the cortex (i.e. focal) or arise in a discrete cortical region and spread to involve a greater area on one or both sides of the brain (i.e. diffuse). The cause of a seizure may be either a biochemical imbalance (e.g. electrolytes, glucose, pH) or a structural abnormality (e.g. tumour, injury, disease).

Epilepsy is a term used to indicate that an individual experiences recurrent seizures, but it does not describe the nature of the seizure itself. There are many types of seizure, and they are classified according to the region of the cortex in which they arise and how they spread. A simple partial seizure is defined as one that arises in only one hemisphere and does not involve a loss of consciousness. A generalised seizure arises in both hemispheres simultaneously and always results in unconsciousness. A complex partial seizure arises in one hemisphere, involves an impairment of consciousness and may progress to a generalised seizure. Descriptions of some common types of seizure are provided in Table 37.1. It should be noted that a person with epilepsy may suffer more than one type of seizure.

Status epilepticus is a potentially life-threatening form of epilepsy. In this condition, there is no spontaneous recovery from a seizure, and the affected person moves immediately from one seizure into another. Status epilepticus is commonly associated with patient non-compliance during antiseizure drug therapy, but it may also arise as a result of interactions between antiseizure drugs and other drugs.

Table 37.2 gives information about the medication groups and specific medications that may produce seizure-like symptoms.

ANTISEIZURE DRUGS

The categorisation of antiseizure drugs that follows is based on chemical structure and mechanism of action. Chemical groupings include the hydantoins, succinimides, benzodiazepines and barbiturates.

TABLE 37.1 COMMON SEIZURE TYPES AND THEIR MAJOR CHARACTERISTICS

Seizure	Partial/generalised	Characteristics
Absence (petit mal)	Generalised	Sudden but transient loss of consciousness; manifests as a blank state, child unresponsive, altered posture, lip-smacking, eyelids flutter
Aura	Partial	Usually person experiences sensation without stimulus present (olfactory, visual, aural)
Clonic	Generalised	Convulsive movements of body
Jacksonian	Partial	Muscle spasms characterised by sequential involvement of body parts
Psychomotor	Partial	Person displays transient aberrant behaviour; examples include alterations in mood, apparent 'drunkenness', psychotic behaviour
Tonic	Generalised	Body forced into rigid and fixed position by violent muscle contractions
Tonic–clonic (grand mal)	Generalised	Person collapses and becomes rigid; may become incontinent; followed by violent convulsions; after clonic phase, person remains unconscious in deep sleep

TABLE 37.2 DRUGS THAT MAY PRODUCE SEIZURE-LIKE SYMPTOMS

Medication group	Specific medications
Adrenocortical and gonadal agents	Hormone replacement therapy, oral contraceptives, desmopressin, prednisone
Anaesthetics	Halothane, isoflurane, ketamine, propofol
Antidepressants	Tricyclic antidepressants, selective serotonin reuptake inhibitors, antimicrobials (amphotericin, fluconazole, quinolones, zidovudine, penicillins)
Antipsychotics	Butyrophenones, clozapine, olanzapine, phenothiazines, risperidone
Bronchodilators	Aminophylline, theopylline
Contrast media	Meglumine, metrizamide
Immunosuppressants	Ciclosporin
Stimulants	Amphetamines, pseudoephedrine

■ MECHANISMS OF ACTION

Antiseizure drugs suppress the overexcitability of cortical neurons by one of the following means: directly stabilising the nerve membrane, altering the movement of sodium through its membrane channels, enhancing the activity of other transmitters such as gamma-aminobutyric acid (GABA) and glycine, or inhibiting the action of glutamate. Some antiseizure drugs act through a combination of these effects.

◆ COMMON ADVERSE EFFECTS

Common adverse reactions generally associated with antiseizure drug therapy include gastrointestinal disturbances (nausea, vomiting, altered appetite), ataxia, headache, nystagmus, mental confusion, allergic skin rash, myelosuppression (inhibition of blood-cell production) and sedation. Some of these reactions, such as gastrointestinal upset, are transient problems that manifest as therapy starts. Others, such as sedation, are dose-related. Hypersensitivity to any of these drugs is a contraindication to therapy. An increased risk of birth defects in children born to women with epilepsy is well known. Most of the antiseizure drugs, with the exception of the benzodiazepines, are suspected teratogens. The risk of malformations is compounded by drug therapy, especially if antiseizure drug combinations are used. This is offset, however, against a far greater risk to mother and fetus associated with the onset of uncontrolled seizures.

Drugs affecting movement of sodium across the membrane

PHENYTOIN

Sodium **phenytoin** is the sole clinical representative of this group in use as an antiseizure drug. Phenytoin is most suitable for the treatment of tonic–clonic seizures. It is also useful in the treatment of partial and other generalised seizures, excluding absence seizures.

Phenytoin also has other uses: as an antidysrhythmic agent (see Chapter 48) and as a co-analgesic in the treatment of neuralgias (see carbamazepine later in this chapter). Phenytoin is not the drug of first choice in either of these conditions, however. Phenytoin is classified as a class IB antidysrhythmic, but its use is quite limited. It is most effective against digitalis-induced dysrhythmias.

■ MECHANISM OF ACTION

Phenytoin acts to promote the intracellular removal of sodium ions during the refractory period of the action potential. As a result, it stabilises cortical nerves against hyperexcitability, especially those located in the motor cortex, and prevents discharging neurons from repeated firing.

◆ COMMON ADVERSE EFFECTS

Additional adverse reactions pertinent to phenytoin therapy include gum overgrowth (gingival hyperplasia) and liver damage. More rarely, hirsutism has been reported. Gum overgrowth can be minimised by good oral care. White and red blood cell levels and liver function must be monitored regularly.

When phenytoin is administered parenterally, it tends to cause significant local reactions at the injection site, such as pain and burning, which may interrupt intravenous infusion.

✚ CLINICAL CONSIDERATIONS

It is important to check the phenytoin concentration and decrease the dose if neurological symptoms occur. Patients

are encouraged to see their doctor if symptoms such as fever, sore throat, mouth ulcers, bruising or bleeding occur. Regular visits to the dentist will assist in preventing gingival hypertrophy associated with phenytoin therapy. Female patients should be advised to use non-hormonal forms of contraception because phenytoin decreases the effectiveness of the oral contraceptive pill.

CARBAMAZEPINE

Carbamazepine is a tricyclic compound related to **imipramine**. It has an antiseizure action not dissimilar to that of phenytoin. Carbamazepine is used in the treatment of partial and generalised seizures, excluding absence and myoclonic seizures. It is the drug of choice in symptomatic partial seizures.

Carbamazepine is also the drug of choice in the treatment of neuralgias, particularly trigeminal neuralgia (tic douloureux). This condition occurs as a result of an aberration of function of the sensory fibres of the trigeminal nerve, which detects facial pain. Without any noxious stimulus being present, these sensory fibres fire messages to the brain, causing the perception of severe pain originating from the facial surface. The condition is characterised by episodes of pain that increase in frequency over time. It is rarely seen in people under 50 years of age and may be associated with an alteration of blood flow to the trigeminal nerve. Phenytoin has also been used successfully for this purpose.

■ MECHANISM OF ACTION

Carbamazepine promotes sodium efflux across the nerve membrane. As a consequence, carbamazepine reduces neuronal excitability, especially repeated firing of the same neuron. Unlike phenytoin, carbamazepine leaves the motor cortex relatively unaffected.

◆ COMMON ADVERSE EFFECTS

Severe cardiovascular disturbances, altered micturition, and liver and kidney dysfunction are adverse effects of carbamazepine, in addition to those generally associated with antiseizure drugs. Absolute contraindications for use are hypersensitivity and cardiac or liver impairment.

✚ CLINICAL CONSIDERATIONS

Patients are advised to inform their doctor if they experience symptoms such as fever, sore throat, rash, bruising or bleeding, as these may be associated with aplastic anaemia or hypersensitivity syndrome. The dose should be increased slowly when commencing treatment to improve compliance by minimising drowsiness until tolerance to this effect occurs. A full blood examination is taken every 2 weeks for the first 1–3 months of treatment.

OXCARBAZEPINE

Oxcarbazepine is a relatively recent addition to this grouping of antiseizure drugs. It is recommended for use in the treatment of partial and generalised tonic–clonic seizures. It is licensed for use as monotherapy or combination therapy in adults and children over the age of 6 years.

■ MECHANISM OF ACTION

Oxcarbazepine blocks voltage-gated sodium channels. The consequence of this is that hyperexcitable neurons are stabilised, nerve impulse transmission is reduced and repetitive firing is inhibited. There is also evidence that oxcarbazepine enhances potassium efflux and reduces calcium influx, which may also contribute to the desired drug action.

◆ COMMON ADVERSE EFFECTS

Common adverse effects tend to occur at the start of therapy and are transient, diminishing once the treatment becomes stabilised. Reactions include hyponatraemia, hepatitis, fatigue, skin eruptions and gastrointestinal disturbances.

✚ CLINICAL CONSIDERATIONS

A number of clinical trials have indicated that oxcarbazepine is comparable in efficacy to a number of important antiseizure agents (phenytoin, carbamazepine, valproic acid) for partial and generalised tonic–clonic seizures but is better tolerated in terms of adverse reactions and compliance with therapy. Oxcarbazepine has a lower potential for drug interactions than carbamazepine, but it interacts with oral contraceptives.

As oxcarbazepine may induce hyponatraemia, any circumstances that may promote sodium loss during treatment require vigilance. For example, drugs such as the non-steroidal anti-inflammatory agents (NSAIDs) induce sodium loss and therefore require monitoring.

Oxcarbazepine inhibits the cytochrome P450 enzyme CYP2C19, which can cause the accumulation of substrates such as phenytoin, some barbiturates, some tricyclic antidepressants and **diazepam** if administered concurrently with the former.

Drugs that stabilise nerve membranes directly

SUCCINIMIDES

There is only one member of this group still used in clinical practice: **ethosuximide**. This is indicated in the treatment of childhood absence seizures.

■ MECHANISM OF ACTION

Ethosuximide acts to stabilise neuronal excitability, thereby raising the threshold to uncontrolled cerebral discharges, especially within the motor cortex.

◆ COMMON ADVERSE EFFECTS

Alopecia and muscle weakness have been associated with ethosuximide therapy.

✚ CLINICAL CONSIDERATIONS

In view of the potentially serious adverse effects of ethosuximide, including Stevens–Johnson syndrome and toxic epidermal necrolysis, it is useful to monitor blood levels of this medication. Monitoring is also useful in patients who have hepatic or renal impairment.

Drugs affecting GABA activity

BENZODIAZEPINES

A number of benzodiazepines (see Chapter 34) are used as antiseizure drugs, including **clobazam**, **clonazepam** and diazepam. Diazepam is used to control status epilepticus; the others are used in the treatment of generalised seizures, especially absence and myoclonic seizures.

■ MECHANISM OF ACTION

The mechanism of action of these agents is to inhibit the firing of hyperexcitable neurons through enhancement of the action of the inhibitory transmitter GABA. This transmitter is active at all levels of the central nervous system (CNS) (see Chapter 32).

◆ COMMON ADVERSE EFFECTS

In addition to the general adverse effects of antiseizure drugs, the benzodiazepines used in epilepsy commonly induce fatigue, muscle weakness, hypersalivation and vertigo.

✚ CLINICAL CONSIDERATIONS

These agents are not particularly useful for long-term treatment of epilepsy because of their sedative effects and tendency to produce tolerance. If no therapeutic benefit is observed, then treatment should be discontinued. In this case, reduction in dose should be gradual in order to avoid withdrawal seizures.

BARBITURATES

The only barbiturate used as an antiseizure drug in the UK is the long-acting phenobarbital (**phenobarbitone**). Barbiturates are used as hypnotics (see Chapter 34) and intravenous general anaesthetics (see Chapter 41); however, the antiseizure activity of phenobarbital is greater than its sedating action. Phenobarbital is no longer the first drug of choice in epilepsy, but occasionally it is useful in tonic–clonic and partial seizures. It is of no value in treating absence seizures.

A related drug, **primidone**, has antiseizure drug activity and also has active metabolites: phenobarbital and **phenylethylmalonamide**.

■ MECHANISM OF ACTION

These drugs depress neuronal excitability by enhancing the action of the inhibitory transmitter GABA. Primidone has been shown to be more effective than phenobarbital alone.

◆ COMMON ADVERSE EFFECTS

Adverse reactions of primidone are characteristic of antiseizure drugs in general. The barbiturates have a narrow therapeutic index; that is, they are quite toxic. Overdosage often leads to death, especially when the drug is taken in combination with other CNS depressants such as alcohol and antihistamines.

The toxic effects of barbiturates include respiratory depression, circulatory shock and renal and hepatic damage. Physical and psychological dependence can arise with continued use. Paradoxical excitement may also be observed in some individuals, especially elderly patients. There are reports of impaired intellectual development in children receiving prolonged barbiturate therapy. Contraindications to therapy include severe liver and kidney disorders and hyperactivity in children.

✚ CLINICAL CONSIDERATIONS

During intravenous treatment with phenobarbital, assisted mechanical ventilation is required because of the risk of respiratory depression. As barbiturates have a low therapeutic index and may produce serious adverse effects, it is useful to consider monitoring of plasma concentration during therapy.

OTHER DRUGS AFFECTING GABA ACTIVITY

VIGABATRIN

Vigabatrin use is restricted to adjunctive therapy for patients with epilepsy, particularly those with complex partial seizures that are not controlled well by other drugs.

■ MECHANISM OF ACTION

Vigabatrin is an irreversible inhibitor of the enzyme that degrades GABA. As a result of therapy, brain concentrations of GABA are enhanced.

◆ COMMON ADVERSE EFFECTS

Weight gain is a common adverse effect. Aggressive and psychotic behaviours have also been reported.

✚ CLINICAL CONSIDERATIONS

Vigabatrin may produce visual-field defects. Vision should be tested by perimetry before commencing drug therapy and then every 3–6 months. In view of this potential problem, vigabatrin is not used until other therapies have been considered first.

TIAGABINE

Tiagabine is used in combination with other drugs to control partial seizures with or without secondary generalisation in adults and children over the age of 12 years.

■ MECHANISM OF ACTION

Tiagabine blocks reuptake of GABA and therefore prolongs the effects of the inhibitory transmitter. Tiagabine is absorbed well from the gut and should be taken with food. It is subject to significant liver metabolism; its half-life is around 8 hours. It should be noted that drugs such as phenytoin and carbamazepine are liver-enzyme inducers and, in combination with tiagabine, can shorten the latter's duration of action.

◆ COMMON ADVERSE EFFECTS

Common adverse effects of tiagabine include dizziness, tiredness, nervousness and diarrhoea.

✚ CLINICAL CONSIDERATIONS

As the dose of tiagabine is increased, a form of status epilepticus may be observed. If this occurs, the dose should be reduced or the treatment stopped.

Miscellaneous antiseizure drugs and drugs with combined mechanisms of action

SODIUM VALPROATE

Sodium valproate has efficacy against a broad range of seizures and is the drug of first choice for symptomatic and idiopathic generalised seizures, juvenile myoclonic epilepsy and childhood absence seizures. It is also available as valproic acid, which is licensed for acute mania associated with bipolar disorder.

■ MECHANISM OF ACTION

Its mechanism of action is to trigger the release of GABA within the brain and inhibit sodium channels that respond to changes in voltage during depolarisation.

◆ COMMON ADVERSE EFFECTS

The major concern associated with this drug is its hepatotoxicity: liver function must be monitored during therapy. Liver impairment is a contraindication for use. Other side effects include increased appetite and weight gain, transient hair loss, ataxia and tremor.

✚ CLINICAL CONSIDERATIONS

Sodium valproate is fairly hygroscopic (absorbs moisture) and is packaged in aluminium foil for protection. When a half-tablet is the prescribed dose, the unused half must be discarded because it will be inactivated quickly by moisture in the air. Sodium valproate should be taken with food because of its tendency to produce gastrointestinal irritation. Enteric-coated tablets may also help with the symptoms of gastrointestinal irritation.

Treatment must be stopped if there is loss of seizure control or if symptoms of hepatitis or pancreatitis (e.g. nausea, vomiting, anorexia, jaundice) occur. In addition, if spontaneous bleeding or bruising occurs, which may be indicative of thrombocytopenia, treatment should be stopped.

ACETAZOLAMIDE

This drug is a carbonic anhydrase inhibitor. It is a second-line drug for both tonic–clonic and partial seizures. It has been suggested that carbon dioxide accumulates within the brain as a consequence of the enzyme-dependent reaction. Suh a state depresses neuronal excitability.

LAMOTRIGINE

Lamotrigine is indicated in the treatment of partial and generalised seizures that are controlled poorly by other agents. Lamotrigine was launched in 1991 and licensed for monotherapy in 1995, but not in children under 12 years of age. Combination therapy is licensed for both adults and children over the age of 2 years.

■ MECHANISM OF ACTION

Studies suggest that the action of lamotrigine is two-fold. It inhibits the passage of sodium through voltage-sensitive channels and reduces the release of the excitatory neurotransmitter glutamate, also implicated in the pathophysiology of seizures. As a result, the uncontrolled and repetitive firing of neurons within the affected area of the cortex is suppressed. The major advantage of lamotrigine over older drugs lies in the reduction of debilitating adverse reactions, such as sedation and impaired motor coordination.

◆ COMMON ADVERSE EFFECTS

A common adverse reaction is the appearance of a rash. When used in combination with other antiseizure drugs, dizziness, headache and double vision have been associated with lamotrigine. Drug hypersensitivity is a contraindication for use.

✚ CLINICAL CONSIDERATIONS

Severe skin reactions, such as Stevens–Johnson syndrome and toxic epidermal necrolysis, occur in a high percentage of individuals taking lamotrigine (1 in 50 children, 1 in 1000 adults). There is an increased risk of skin reactions with concurrent administration of sodium valproate. The patient should be advised to stop treatment if a rash occurs.

GABAPENTIN

Gabapentin is approved for use only in combination with other antiseizure drugs in the control of partial seizures.

■ MECHANISM OF ACTION

Gabapentin is a structural analogue of GABA. Its mechanism of action has yet to be clearly established. It does not seem to bind with the transmitter systems already linked to antiseizure drug activity, such as GABA, benzodiazepine, glutamate or glycine. Moreover, it does not affect sodium channels in the same way as phenytoin or carbamazepine.

◆ COMMON ADVERSE EFFECTS

Common adverse effects of gabapentin include somnolence, dizziness and ataxia.

✚ CLINICAL CONSIDERATIONS

Gabapentin is not subject to metabolism and is mostly eliminated from the body in urine. In patients with renal impairment and haemodialysis, the dose is strictly regulated, depending on the estimated creatinine clearance and the time following dialysis.

TOPIRAMATE

Topiramate is used as an adjunct to other antiseizure drugs in the management of partial seizures in adults with or without secondary generalised seizures. It is also licensed as monotherapy in adults and children over the age of 6 years with newly diagnosed epilepsy who have generalised tonic–clonic seizures or partial seizures.

■ MECHANISM OF ACTION

The action of topiramate is similar to that of lamotrigine in that it reduces seizure activity by blocking sodium channels and inhibiting a type of glutamate receptor in the brain. Topiramate, however, also appears to increase the activity of GABA. Topiramate is absorbed well from the gut and most of the drug is eliminated unchanged in the urine. Its half-life is 21 hours. Phenytoin and carbamazepine interact with topiramate, lowering the plasma concentration of the latter.

◆ COMMON ADVERSE EFFECTS

Common adverse effects of topiramate include ataxia, confusion, dizziness, fatigue, impaired concentration and altered thinking patterns.

✚ CLINICAL CONSIDERATIONS

Topiramate is avoided in patients with a history of psychosis, as it can aggravate psychotic symptoms. Dose reduction may be required in renal impairment. During treatment with topiramate, the patient should not drive or operate machinery because of problems relating to fatigue and impaired concentration. Topiramate interacts with oral contraceptives.

LEVETIRACETAM

Levetiracetam is licensed for the combination treatment of partial seizures with or without secondary generalisation. It is not recommended for use in children younger than 16 years.

■ MECHANISM OF ACTION

The mechanism of action of levetiracetam is unknown. It is a novel drug, as it does not appear to act at any of the sites of other antiseizure agents.

◆ COMMON ADVERSE EFFECTS

Somnolence, dizziness, asthenia and aggression are common adverse effects of levetiracetam. It has no reported drug interactions.

✚ CLINICAL CONSIDERATIONS

Levetiracetam should not be used in breast-feeding women. It should be used cautiously in pregnant women and in children younger than the recommended age. Dosage adjustment may be required in patients with renal failure.

Drug withdrawal should occur gradually. Patients who experience somnolence or dizziness should be advised to avoid using machinery and driving.

Pharmacokinetic considerations

Phenytoin, valproic acid and the benzodiazepines bind strongly to plasma proteins and displace other highly bound drugs such as **warfarin**, some NSAIDs, and each other if combined therapy is indicated. The consequences are that the plasma levels of these drugs will be higher than normal, and the subsequent effects stronger.

Drug interactions are very important in combination antiseizure drug therapy. Phenytoin, carbamazepine and the barbiturates are hepatic enzyme inducers (see Chapter 14 for further discussion), and drugs with a similar metabolism will be cleared from the body faster when used in combination with these enzyme inducers. As a consequence, blood drug concentrations are lower than expected, as are the resultant drug effects.

Most antiseizure drugs have long half-lives (on average, greater than 12 hours). As explained in Chapter 14, the steady state for plasma drug levels will not be achieved for at least five half-lives (in this case, greater than 60 hours). It may thus take at least 3 days, but more commonly a week or so, before therapeutic effects develop. Half-lives also have implications for the patient if toxic effects emerge. Even if therapy ceases immediately, it will take at least five half-lives for the plasma drug levels to become negligible.

With the exception of phenytoin, the patient should start antiseizure drug therapy gradually, increasing the dose slowly until the seizures are controlled or toxicity emerges. This minimises the incidence of the transient adverse reactions. If toxic effects are observed before the seizures are controlled, then combination antiseizure drug therapy is used. With phenytoin, a loading dose takes plasma levels closer to the therapeutic range more quickly, followed by daily maintenance doses. Seizure management with a single antiseizure drug (i.e. monotherapy) is the ultimate goal, as it lowers the possibility of drug interactions and reduces the magnitude and number of adverse effects, and patient compliance is improved. Unfortunately, this is not always possible.

Status epilepticus

Management includes positioning of the patient to avoid injury and support of respiration by the administration of oxygen. Hypoglycaemia should be corrected if present. If alcohol abuse is suspected, thiamine should be administered by injection.

The drug of choice for treatment is a benzodiazepine – intravenous or rectal diazepam may be used. Diazepam is administered as an emulsion (Diazemuls™) when given intravenously. This reduces the risk of thromboembolism with intravenous use of the drug. Lorazepam is sometimes used in hospital, as it has a longer duration of antiepileptic action; a single dose of midazolam may also be used, given by the buccal rouute (unlicensed action). If the seizures recur or fail to respond after about half an hour, then phenytoin sodium or phenobarbital may be used.

Paraldehyde may also be of value in resistant cases. This may be given rectally and causes very little respiratory depression, making it safe to administer if no resuscitation facilities are available.

If all of the above fail, it may be necessary to anaesthetise the patient with thiopental or propofol. The patient is cared for with intensive care support.

MUSCLE RELAXANTS

For the purposes of this discussion, muscle relaxants refer to drugs that act to inhibit contraction in skeletal muscle, as distinct from agents that relax visceral and cardiac muscle. Agents that relax involuntary muscles are named according to their specific uses (e.g. bronchodilators, uterine relaxants, antihypertensives, antianginal agents, antispasmodics) and are discussed elsewhere in this book.

We can subdivide skeletal muscle relaxants into those used before surgery for the purposes of intubation (i.e. surgical muscle relaxants) and those used to inhibit acute or chronic muscular spasms (i.e. spasmolytic agents). Surgical muscle relaxants (or, more accurately, neuromuscular blocking agents) and depolarising and non-depolarising nicotinic antagonists are dealt with in Chapter 27. The focus here is on spasmolytic agents. Skeletal muscle spasm can arise as a result of a variety of causes, including musculoskeletal trauma (e.g. sprain, strain, fracture, dislocation, spinal injury), diseases such as multiple sclerosis (see Chapter 36), and the position of limbs during sleep (e.g. nocturnal cramps). The spasm is characterised by repetitive nerve stimulation of particular muscle groups. Inhibition of skeletal muscle contraction can occur at any number of levels along the motor pathway – from the brain, down the spinal cord, along the efferent nerves, through the neuromuscular junction and to within the muscle fibre itself. Drugs are grouped here according to the level at which they act (see Figure 37.1). The choice of drug depends on the level at which the cause of the spasm has arisen.

Centrally acting muscle relaxants

■ MECHANISM OF ACTION

In seizure management, GABA-ergic transmission plays an important role. This is also true for inducing muscle relaxation. Benzodiazepines such as diazepam are effective spasmolytic agents. By enhancing the action of the inhibitory transmitter GABA, they act to suppress hyperexcitable motor pathways within the brain and spinal cord. **Baclofen** acts by stimulating GABA receptors in the spinal cord. As a consequence, the reflex muscle contractions associated with some forms of muscle spasm are suppressed. Another therapeutic effect is analgesia. This is brought about by blocking the release of an important spinal chemical mediator of pain transmission, substance P (see Chapter 39).

Orphenadrine is a centrally acting antimuscarinic agent (see Chapter 27) that can be used as a muscle relaxant. This action suppresses the activity of the pyramidal pathway responsible for skeletal muscle innervation.

◆ COMMON ADVERSE EFFECTS

The adverse effects of diazepam and baclofen derive from a general reduction in CNS activity brought about by GABA. Daytime sedation, ataxia, dizziness, mental confusion and drowsiness are often noted with these agents.

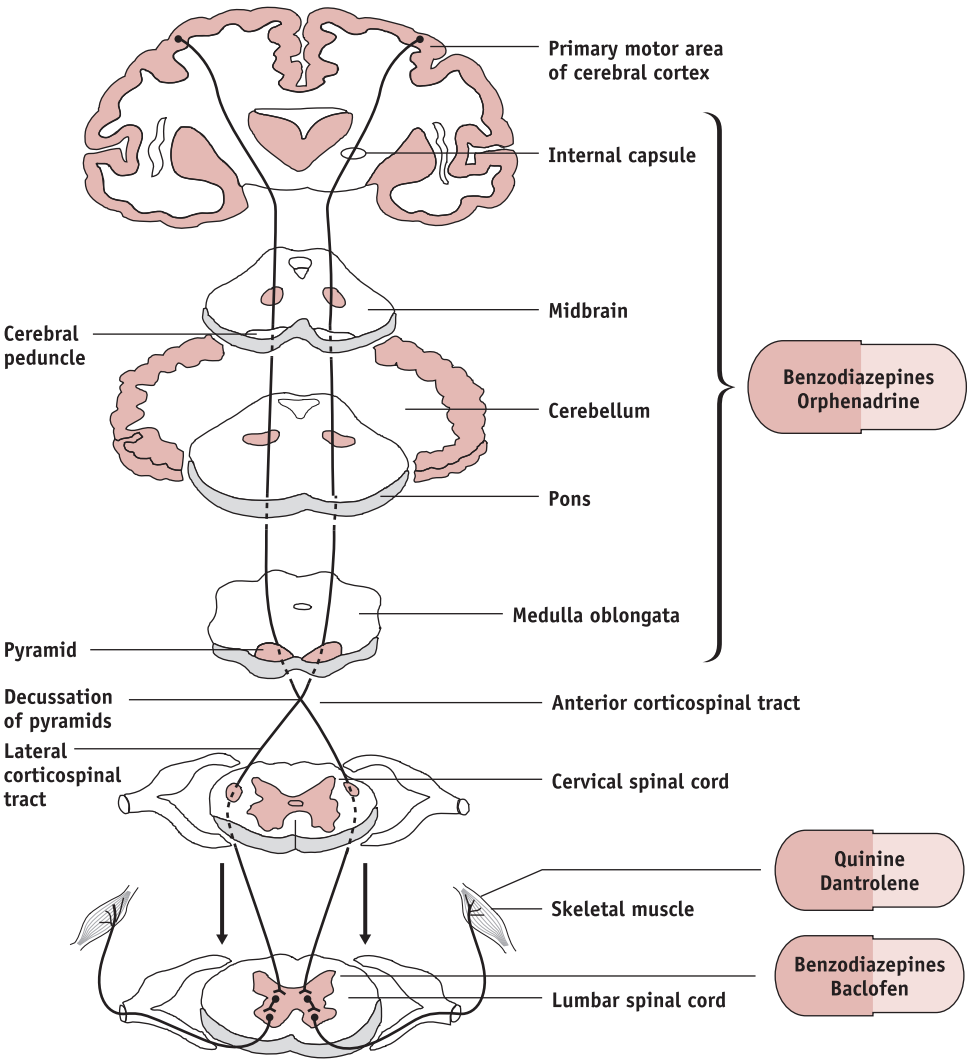
As orphenadrine is an antimuscarinic agent, common adverse reactions include drowsiness, dry mouth and blurred vision. These effects are dose-related and diminish when the dose is reduced. Contraindications for use are glaucoma, urinary obstruction and myasthenia gravis.

✚ CLINICAL CONSIDERATIONS

When taking baclofen, the patient should be advised not to drive or operate machinery if the drug causes drowsiness. Intrathecal administration may be successful in patients who do not tolerate high oral doses or do not respond to oral administration.

FIGURE 37.1 SITES OF ACTION OF MUSCLE RELAXANTS

This diagram shows the sites at which various muscle relaxants interfere with neuromuscular physiology along the pyramidal pathways to the skeletal muscle itself.



Orphenadrine should be avoided in elderly patients and in patients with poor cognitive ability. Orphenadrine is not often used because of its extensive adverse effects and poor efficacy.

Drugs affecting muscle excitability

The antimalarial agent **quinine** can be used as a spasmolytic agent. It is used for nocturnal leg cramps and reduces their frequency by about 25 per cent in ambulatory patients.

■ MECHANISM OF ACTION

Quinine diminishes the excitability of the plasma membrane of the muscle itself, reducing the responsiveness to the repetitive nerve stimulation underlying muscle cramps. It does this by increasing the impulse refractory period and raising the threshold for stimulation. It may take up to 4 weeks for improvement to become apparent.

◆ COMMON ADVERSE EFFECTS

The most common adverse reaction is cinchonism, characterised by sensory and gastrointestinal disturbances. Hearing and balance are particularly affected, resulting in tinnitus, loss of high-frequency hearing and vertigo. Visual impairments range from blurred vision, photophobia and altered colour perception to blindness. Gastrointestinal manifestations consist of nausea and vomiting, due to central stimulation of the vomiting centre, abdominal pain and diarrhoea, which result from local irritation of the tract

tissue. Quinine is very toxic in overdosage and fatalities have occurred in children. Immediate advice should be sought from a poisons centre if overdose is suspected.

Quinine is contraindicated during pregnancy, if hypersensitivity is apparent, and in patients suffering tinnitus or optic neuritis.

Intramuscularly acting muscle relaxants

Dantrolene is a muscle relaxant that acts on the muscle fibres.

■ MECHANISM OF ACTION

Dantrolene interferes with the release of calcium from the sarcoplasmic reticulum, which is necessary for contraction. Ostensibly, dantrolene does not affect nerve transmission to muscle or depolarisation of the muscle membrane itself. Dantrolene is a hydantoin derivative, like phenytoin.

◆ COMMON ADVERSE EFFECTS

The most common adverse effects involve the CNS and include dizziness, drowsiness, fatigue, malaise and weakness. Gastrointestinal disturbances, particularly diarrhoea, may also be experienced. Treatment with dantrolene is contraindicated if liver disease is evident, due to the drug's hepatotoxicity.

✚ CLINICAL CONSIDERATIONS

Dantrolene treatment should be decreased slowly and then stopped if diarrhoea is severe. The patient's liver function is monitored at the beginning of therapy and every 1–2 months thereafter. If there are abnormalities in liver function tests, the drug should be stopped.

CLINICAL MANAGEMENT

Antiseizure drugs

Assessment

- Assess the patient for history of severe respiratory disease and porphyria, as use in these conditions is contraindicated.
- Assess the patient for history of renal and hepatic disease and diabetes. Caution should be exercised with antiseizure drug use in these patients.
- Assess the following information about the seizures: frequency, types of movement, sequence of progression, duration, presence and description of aura or aggravating factors, whether patient is incontinent during the seizure, postictal status, changes in pupil size, changes in conscious state, apnoea and cyanosis.
- Assess vital signs before starting therapy, and compare with subsequent observations.

Planning

- The patient will not experience seizures.
- Adverse effects with antiseizure drug therapy will be minimal.

Implementation

- Monitor the effect of therapy on characteristics of the seizure.
- Monitor vital signs regularly and following any seizure.
- Keep oxygen and suction at the bedside.
- Protect the patient from hazards such as sharp objects during a seizure.
- Keep the bed in a low position, with padded and raised cot sides.
- Administer oral medication with food to minimise gastrointestinal irritation.
- Note that drug monitoring with blood levels is required only with phenytoin and if there may be a problem regarding compliance. The therapeutic index of other antiseizure drugs, such as the newer drugs (lamotrigine, vigabatrin, gabapentin, tiagabine, topiramate), is so large that little information is obtained by performing blood-level analyses.
- An attempt to withdraw antiseizure drug therapy may be considered after 2–3 years of treatment without seizures. Good prognostic signs include a history of infrequent seizures, a younger age of achieving seizure control and normal neurological examinations.
- If the patient experiences jaundice, oedema, ataxia or impaired consciousness while on sodium valproate, antiseizure drug treatment should be altered, as these symptoms may be indicative of hepatitis.
- If the patient experiences spontaneous bleeding or bruising while on sodium valproate, it is important to change the antiseizure drug therapy, as these symptoms are indicative of thrombocytopenia.

- Severe cutaneous reactions have been associated with lamotrigine, including Stevens–Johnson syndrome and toxic epidermal necrolysis. There is also an increased risk with concomitant administration of sodium valproate. Treatment should be stopped immediately if a rash occurs.

Patient teaching

- Inform the patient to take the medication at equal intervals during the day and not to omit doses. The drug should never be withdrawn abruptly, as rebound seizures can occur.
- As several antiseizure drug preparations can induce liver enzymes and increase the metabolism of many drugs, there is a high risk of failure with the contraceptive pill. Female patients should be advised to use a non-hormonal form of contraception.
- Female patients who want to become pregnant should speak to their doctor, as some antiseizure drugs, such as phenytoin and sodium valproate, can have a teratogenic effect on the fetus. Seizure frequency tends to increase during pregnancy because of increased metabolism. These patients must be closely monitored during pregnancy. Female patients should also be counselled to withdraw antiepileptic treatment if they wish to plan for a pregnancy and they have been seizure-free for at least 2 years.
- Instruct the patient to institute safety precautions at home, such as keeping sharp objects in storage enclosures and ensuring that floor space is not cluttered with unnecessary objects.
- When first put on antiseizure drug therapy, the patient should not drive or operate machinery. Until the patient adapts to the drug, drowsiness and dizziness are likely to occur.
- For patients with diabetes who are taking phenytoin, advise that the blood glucose level should be checked more closely as phenytoin can inhibit insulin release.
- Advise patients taking phenytoin that urine may discolour to a pink or red-brown. This discoloration is harmless.
- For patients taking phenytoin, advise on the importance of oral hygiene and regular dental check-ups to prevent gingivitis and gingival hyperplasia.
- Instruct the patient to avoid alcohol, as this can precipitate a seizure.
- The patient should never take baths and should avoid hot showers, as the tactile stimulus from hot water can provoke a seizure.
- Phenytoin can interfere with folic acid metabolism, so the patient should have an adequate folic acid and vitamin D intake.
- Patients taking carbamazepine should be informed about the possibility of blood dyscrasias and advised to report any signs of sore throat, mucosal ulceration, petechiae or bruising of unknown cause.
- Use of controlled-release carbamazepine tablets may help to improve tolerance. The dose may need to be increased, however, if changing to a controlled-release formulation.
- Advise patients on vigabatrin that visual fields should be tested before commencing therapy and at yearly intervals.

Evaluation

- Evaluate the effectiveness of the antiseizure drug in controlling seizures.
- Evaluate the incidence of adverse effects. Dosage may need to be altered or alternative therapy implemented.
- Continue to monitor phenytoin levels regularly to ensure that they remain in the desired range.

Muscle relaxants

Assessment

- Obtain patient history of gait, range of motion, coordination, reflexes, posture, and muscle strength and tone.
- Assess the patient for impaired renal and hepatic function, respiratory depression and age (very young, elderly). Caution should be exercised in these cases when administering such medications.
- Document baseline vital signs and compare with subsequent observations.
- Obtain history of narrow-angle glaucoma or myasthenia gravis. Orphenadrine is contraindicated in these conditions.

Planning

- The patient will achieve a higher level of dexterity and lower incidence of muscular spasms.

Implementation

- Monitor the patient's gait, range of motion, co-ordination, reflexes, posture, and muscle strength and tone.
- Baclofen is administered with food to minimise gastrointestinal irritation.
- Intrathecal administration of baclofen may be tried in a patient who fails to respond to oral administration or who experiences unpleasant adverse effects with oral therapy.
- For patients taking dantrolene, liver enzyme levels should be monitored.
- For reconstituted intravenous dantrolene solution, protect the preparation from light and use within 6 hours.
- For patients on dantrolene, monitor liver function at the commencement of treatment and at 1–2 months thereafter. Treatment should be stopped if there are any abnormalities with liver function.
- Dantrolene may cause severe diarrhoea; if this continues after dosage adjustment, or after stopping and recommencing therapy, treatment should be stopped permanently.

Patient teaching

- Inform the patient that full benefit from the medication does not occur for several weeks.
- Caution the patient to avoid driving and using heavy machinery until the effect is stabilised, as the drugs are prone to causing drowsiness and dizziness.
- Advise the patient to avoid taking alcohol, as this combination will potentiate central nervous system depression.
- The patient should seek advice from the pharmacist and doctor before taking over-the-counter medications.
- As dantrolene can cause photosensitivity, advise the patient to use sunblock and wear protective clothing while outdoors (see Table 11.19 in Chapter 11 for further information).
- Advise the patient that orphenadrine, a centrally acting muscle relaxant, is used for about 2–3 weeks only because of the problems associated with its prolonged use.
- Instruct female patients that these drugs should not be used during pregnancy or while breast feeding.
- As orphenadrine causes antimuscarinic effects, teach the patient how to limit its adverse effects of constipation and dry mouth. These measures include maintaining good oral hygiene and a high-fibre diet. (Refer to Tables 11.4 and 11.9 in Chapter 11 for additional measures to counteract these adverse effects.)

Evaluation

- Evaluate the effectiveness of treatment by the decreased incidence of spasms and improved range of motion.
- Evaluate the incidence of adverse effects of these drugs.

SUMMARY

- In terms of action, antiseizure drugs act to suppress the overexcitability of cortical neurons by one of the following means: directly stabilising the nerve membrane, altering the movement of sodium through its membrane channels, enhancing the activity of other transmitters such as gamma-aminobutyric acid (GABA) and glycine, inhibiting the action of glutamate, or through a combination of these effects.
- It is recommended that treatment commences with one drug for a particular type of epilepsy, increasing the dose gradually.
- Check the patient's compliance, as this is a common reason for lack of seizure control.
- If insufficient control is achieved with one drug, ensure maximal dose is given without onset of adverse effects and then add a second drug. Decrease the dose of the first drug when optimal dosage of the second drug is achieved.
- As several antiseizure drugs affect the oral contraceptive pill, female patients are advised to use a non-hormonal form of contraception.
- Many antiseizure drugs are suspected teratogens. A woman taking these drugs who is planning a pregnancy should seek counselling regarding the risk of fetal abnormalities.
- Monitoring of plasma concentration is useful for phenytoin, valproate, carbamazepine, phenylbarbitone and ethosuximide. Plasma concentration monitoring of other antiseizure drugs is not useful.
- Muscle relaxants refer to drugs that act to inhibit contraction in skeletal muscle.

- Spasmolytic agents are muscle relaxants used to inhibit acute or chronic muscular spasms.
- Inhibition of skeletal muscle contraction can occur at any number of levels along the motor pathway – from the brain, down the spinal cord, along efferent nerves, through the neuromuscular junction and to within the muscle fibre itself. Drugs are grouped in this chapter according to the level at which they act: either centrally or on the muscle itself. The choice of drug depends on the level at which the cause of the spasm has arisen.
- Treatment should be withdrawn if the patient shows no benefit within 6–8 weeks.
- Adverse effects can be minimised by starting from a low dose and increasing gradually. Avoid an abrupt decrease in dose to prevent withdrawal syndrome.
- It is recommended that the patient does not drive or operate machinery while taking these medications.

1 For the following types of seizure, outline their major characteristics and classify them as either partial or generalised:
(a) tonic–clonic;
(b) psychomotor;
(c) absence;
(d) myoclonic.

2 Describe the mechanisms of action of the following drugs/drug groups:
(a) hydantoins;
(b) carbamazepine;
(c) benzodiazepines;
(d) valproic acid;
(e) gabapentin;
(f) oxcarbazepine.

3 State four common adverse reactions associated with antiseizure drugs.

4 Outline the three major modes of action of spasmolytic drugs.

5 Compare and contrast the central spasmolytic actions of baclofen, diazepam and orphenadrine.

6 In hospital, one of the main ways of determining the effectiveness of antiseizure drug therapy is to document the incidence of and describe the patient's seizures on a seizure chart. What information would be required on such a chart?

7 Michelle Duponte, a 25-year-old patient, and her partner have decided they want to start a family. Michelle has been on phenytoin since her early teens for a seizure disorder. She would like to discontinue the phenytoin before getting pregnant. What points would need to be discussed with Ms Duponte and her partner before a final decision is made to wean her from the medication?

8 Michelle Duponte develops stomatitis during phenytoin treatment. What action would you give for this condition? Provide rationales for your answer. (See Table 11.14 in Chapter 11 for assistance.)

9 Francis McHenry, 53 years old, has developed partial seizure epilepsy as a consequence of a serious head injury. His seizures have not been controlled well with carbamazepine and sodium valproate. His doctor adds lamotrigine and later gabapentin to his therapy. His seizures are now controlled well. What are the possible problems associated with the multidrug treatment of Mr McHenry's epilepsy?

10 Leonora Alexandro is a 40-year-old patient with multiple sclerosis. After commencement on orphenadrine, she complains to you about developing a dry mouth. What action would you take? (See Table 11.9 in Chapter 11 for assistance.)

11 Tammy Edsel is a 60-year-old resident in a nursing home. She has recently suffered a series of strokes. She has developed spasticity of the right arm. Tammy is taking dantrolene for the spasticity and is suffering from severe diarrhoea. What action would you take in this situation?

12 A common adverse effect of lamotrigine is rash. What patient education would you offer to alleviate the discomfort associated with the rash? (See Table 11.8 in Chapter 11 for assistance.)

37 DRUG SUMMARY TABLE: ANTISEIZURE DRUGS AND MUSCLE RELAXANTS

FAMILY NAME	GENERIC NAME	TRADE NAME(S)
Benzodiazepines	Clobazam	Frisium
	Clonazepam	Rivotril
	Diazepam	Diazemuls
		Stesolid
Hydantoin	Phenytoin	Epanutin
Succinimide	Ethosuximide	Emeside
		Zarontin
Barbituates and related drugs	Phenobarbital	
	Primidone	Mysoline
Miscellaneous antiseizure agents	Acetazolamide	
	Carbamazepine	Tegretol
		Carbagen SR
	Gabapentin	Neurontin
	Lamotrigine	Lamictal
	Levetiracetam	Keppra
	Oxcarbazepine	Trileptal
	Tiagabine	Gabitril
	Topiramate	Topamax
	Valproate	Epilim
	Valproic acid	
	Vigabatrin	Sabril
Muscle relaxants (spasmolytics)	Baclofen	Baclospas
		Lioresal
	Chlordiazepoxide	
	Dantrolene	Dantrium
	Diazepam	Diazemuls
		Stesolid
	Orphenadrine	Biorphen
		Disipal
	Quinine	

CENTRAL NERVOUS SYSTEM STIMULANTS

38

CHAPTER THIRTY-EIGHT

OBJECTIVES

After completing this chapter, the reader should be able to:

- **discuss attention deficit disorder (ADD) and attention deficit hyperactivity disorder (ADHD) and their treatment;**
- **outline other therapeutic uses for stimulant drugs;**
- **discuss the abuse of amphetamines.**

KEY TERMS

Attention deficit disorders

Narcolepsy

CENTRAL NERVOUS SYSTEM STIMULANTS ARE USED IN A variety of conditions, including attention deficit and attention deficit hyperactivity disorders and narcolepsy. Although these drugs have been maligned in the past, they do have an important role to play in normalising an individual's behaviours and sleep patterns in pathological conditions.

ATTENTION DEFICIT DISORDER AND ATTENTION DEFICIT HYPERACTIVITY DISORDER

Attention deficit disorder (ADD) and attention deficit hyperactivity disorder (ADHD) are clinical disorders that mainly affect children, although occasionally they also affect adults, which is not widely realised. The disorders were described in the 1930s, but they have attracted a great deal of attention, often controversial, only recently from both the medical profession and the public. The diagnosis of hyperkinetic disorder (HKD) is sometimes used by UK clinicians; this defines a subgroup of ADHD where all three core signs – inattention, hyperactivity and impulsiveness – are present before the age of 7 years. Many symptoms of ADD and ADHD are similar, but people with ADHD are hyperactive (always on the go, acting before thinking, disruptive, etc.); people with ADD do not have this manifestation. The symptoms common to both disorders are numerous and include forgetfulness, obsessiveness, frustration, lack of interest, impulsiveness, daydreaming, uncooperativeness, aggressiveness and the inability to work independently. Diagnosis depends on expert opinion, usually by a specialist paediatrician or psychiatrist, regarding these and many other symptoms. Scores are given for each symptom and then totalled to give a number, which, if high enough, helps to confirm the diagnosis. It is estimated that approximately 5 per cent of schoolchildren and adolescents have one of these conditions (equivalent to 366 000 children and adolescents in England and Wales). Boys are much more susceptible than girls. The condition often persists into adulthood. The causes of the conditions are unknown but may involve a biochemical disorder of neurotransmitter processes in the brain.

The principal drugs used in the treatment of both ADD and ADHD are surprising and paradoxical, especially in the case of ADHD. Central nervous system (CNS) stimulants have been shown to be of help in the treatment but not the cure of about 75 per cent of cases. In the UK, the National Institute for Health and Clinical Excellence (NICE) recommends three drugs for use when drug treatment is considered appropriate: **methylphenidate**, **atomexetine** and **dexamfetamine**. Drug treatment is initiated only by a doctor with expertise in ADHD and is based on a comprehensive clinical assessment and diagnosis. Other forms of treatment include a range of social, psychological and behavioural interventions. Much of the controversy in ADD concerns not only the aetiology and diagnosis but also the treatment. Specialist opinion regarding the diagnosis and the treatment is divided. This, in part, accounts for variations in drug treatment in different countries.

METHYLPHENIDATE AND DEXAMFETAMINE

■ MECHANISM OF ACTION

Methylphenidate and dexamfetamine (also called dextroamphetamine) are CNS stimulants. Their mechanism of action in ADD and ADHD is unknown. As stimulants, they appear to have various modes of action, all directed to increasing catecholamine (both noradrenaline and serotonin) activity at CNS synapses. This can lead to many effects, including euphoria, reduction in appetite (see Chapter 60), insomnia and wakefulness. These properties lead to much abuse of CNS-stimulating drugs, and both psychological and physical addiction can occur. Dexamfetamine is the more efficacious stimulant and thus has the higher abuse potential. None of these actions explains the effect of this type of drug in ADD and ADHD. The drugs are non-addictive in both children and adults when used in properly diagnosed conditions. They are both Schedule 2 controlled drugs. Methylphenidate is not licensed for use in children under 6 years; dexamfetamine is not licensed for use in children under 3 years. Children on these drugs require regular monitoring. Treatment may be discontinued, under careful specialist supervision, when improvement has occurred.

◆ COMMON ADVERSE EFFECTS

Adverse effects of methylphenidate include headache, palpitations, cardiac dysrhythmias (not so severe with dexamfetamine) and hypertension (and occasionally hypotension). It is important not to give the drug for at least 4 hours before bedtime because of the potential to induce insomnia. Retardation of growth can occur in children, and 'drug holidays' should be used, during which the drug is withheld (e.g. weekends, school holidays). Food tends to increase the absorption of the drug, thus making it more rapidly effective if given at mealtimes.

✚ CLINICAL CONSIDERATIONS

Overdose can lead to a rise in sympathetic nerve activity and to psychotic effects. The latter effects are often seen in people who abuse these drugs. For example, the abuser may believe that they can control a car at speeds much above their actual capability, leading to serious crashes and deaths.

Prescription of methylphenidate and dexamfetamine has to comply with UK legislation relating to psychostimulant drug administration (refer to Chapter 3 for further information); both are Schedule 2 controlled drugs. Administration should not be continued if no obvious benefit is seen following titration of dose to behaviour – there should be a response within 1 month. Children's growth should be monitored regularly (see above). In the

USA, 10 per cent of those taking ADHD drugs are over 50 years of age; there are concerns regarding this increased use of mehylphenidate in adults and the possibility of dangerous effects on the heart.

ATOMEXATINE

■ MECHANISM OF ACTION

Atomexatine is a selective noradrenaline reuptake inhibitor. Its precise mechanism by which it works in ADHD is not known. It is licensed for the treatment of ADHD in children aged 6 years and older and has been marketed in the UK since July 2004.

◆ COMMON ADVERSE EFFECTS

Adverse effects of atomexatine include abdominal pain, decreased appetite, nausea and vomiting, early-morning awakening, irritability and mood swings. Seizures are a potential risk.

Increased heart rate and small increases in blood pressure have been observed in clinical trials and reports of QT interval prolongation have been received.

There has been concern regarding increased risk of suicidal thoughts and behaviour in people taking this drug. A Europe-wide review has concluded that the overall balance of risks and benefits remains positive in the treatment of ADHD. Patients should be monitored for signs of depression and suicidal thoughts.

OTHER USES OF AMPHETAMINES

Another use of stimulant drugs is in the treatment of narcolepsy, a rare disease in which the patient falls asleep at any time, often at inopportune moments. This condition must not be confused with fatigue syndromes, general tiredness and lack of energy. Narcolepsy and somnolescence can be treated by the drug **modafinil**.

MODAFINIL

■ MECHANISM OF ACTION

The mechanism of action of modafinil is unknown, but it has no effect on noradrenaline, dopamine or serotonin receptors. Modafinil is a psychostimulant and can produce euphoria; therefore, abuse could be a problem. Modafinil is better than placebo for the treatment of narcolepsy; however, trials of the drug have been limited, and its use for the long-term treatment of narcolepsy is still under investigation.

◆ COMMON ADVERSE EFFECTS

Adverse effects of modafinil are relatively common and include headache, nervousness and nausea. As this drug is an inducer of the cytochrome P450 enzymes, the potential for drug–drug interactions must be borne in mind.

ABUSE OF AMPHETAMINES

Amphetamines were initially developed as a treatment for asthma, but their strong stimulant properties were soon recognised. In the Second World War, 75 million amphetamine tablets were used by British troops to improve their alertness and confidence and for their energising effects. Interestingly, Adolf Hitler may have been addicted to amphetamines, which may have contributed to his irrational and unrealistic optimism towards the end of the war in Germany. Amphetamines also suppress hunger, and they were used widely as an appetite suppressant during the middle decades of the twentieth century. Stimulant drugs have commonly been used to induce wakefulness and have been taken by students before examinations in order to remain awake after studying all night; unfortunately, these drugs can mislead the user into thinking they have answered examination questions well when they have actually written gibberish. Today, the only clinically recognised use of amphetamines is in the treatment of narcolepsy, as described above.

Being stimulants, amphetamines are abused in sport, as described in Chapter 24; they are also widely abused for recreational purposes. Their use among drug abusers is mainly for the sense of elation produced and their energising effects. As insomnia is a side effect of amphetamines, abusers may use sedatives/hypnotics to counter this effect when sleep is desired. Long-term abuse of amphetamines leads to a psychosis not unlike that of schizophrenia.

Withdrawal effects of amphetamines are depression, lethargy and tiredness.

CLINICAL MANAGEMENT

Central nervous system stimulants

Assessment

- Establish baseline vital signs, including blood pressure, pulse rate and rhythm. Compare with subsequent observations.

Planning

- Through a combined programme of medication and counselling, the behaviour of a child with attention deficit disorder (ADD) or attention deficit hyperactivity disorder (ADHD) will be pacified.
- The patient will not experience the adverse effects attributed to central nervous system stimulants.
- The incidence of narcolepsy will decrease following use of a central nervous system stimulant.

Implementation

- Monitor the patient for effects of central nervous system stimulant on behaviour modification.
- Monitor the patient for effects of central nervous system stimulant on narcolepsy.

Patient teaching (methylphenidate and dexamfetamine for ADD and ADHD)

- Advise the patient that when taking central stimulants for a prolonged period, withdrawal symptoms can occur. A gradual decrease is essential to prevent withdrawal effects.
- Encourage the family of a child with attention deficit disorder to seek counselling for support and reassurance. Drug treatment alone is an insufficient form of therapy.

Evaluation

- Evaluate the effectiveness of the drug to pacify behaviour.
- Evaluate the tendency of the drug to produce adverse effects, especially those of a central stimulatory nature.
- Evaluate the effectiveness of the drug to reduce the incidence of narcolepsy.

SUMMARY

- Stimulants of the central nervous system (CNS) are used in the treatment of attention deficit disorder.
- Mechanism of action of these drugs in attention deficit disorder is still unknown.
- Central nervous system stimulants have the potential for abuse.
- Amphetamines are abused in sports and recreationally.
- Overdose of central nervous system stimulants leads to increased activity of the sympathetic nervous system and psychotic effects.
- In older adults, central nervous system stimulants may have a detrimental effect on the heart.

1 Why do drug abusers commonly take amphetamines?

2 Differentiate between attention deficit disorder (ADD) and attention deficit hyperactivity disorder (ADHD).

3 Jack Jobbins, an 8-year-old boy, is prescribed methylphenidate for the treatment of attention deficit disorder (ADD). How would you evaluate Jack to determine whether there is clinical improvement from the treatment?

38 DRUG SUMMARY TABLE: CENTRAL NERVOUS SYSTEM STIMULANTS

FAMILY NAME	GENERIC NAME	TRADE NAME(S)
ADHD drugs	Dexamfetamine (dexamphetamine) Methylphenidate	Dexedrine Ritalin Concerta Equasym XL
Miscellaneous	Modafinil Atomexetine	Provigil Strattera

CASE STUDY VIII.1

Mr RT, aged 39 years, has been taking phenelzine for several months for the treatment of depression. His doctor has recently changed his therapy to moclobemide, of which Mr RT takes 450 mg twice daily. In the past, Mr RT has needed to watch the food he ate when taking phenelzine. His doctor has informed him that he will not need to worry about the foods he consumes when taking moclobemide, even though it is a similar kind of drug to phenelzine.

QUESTIONS

1 *Although moclobemide is similar to phenelzine, in what ways is it different?*

2 *What kinds of food would Mr RT have to avoid while taking phenelzine?*

3 *What precautions will Mr RT have to exercise with respect to alcohol? Explain why.*

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WEB RESOURCES

ADHD www.nimh.nih.gov/publicat/adhd.cfm

ADHD eBook www.pediatricneurology.com/adhd.htm

AdhdNews www.adhdnews.com/

American Epilepsy Society www.aesnet.org

Antidepressants http://abc.net.au/health/depression/anti.htm

Anxiety and Panic Disorders http://panicdisorder.about.com/cs/tricyclics/

CzKids program www.addtoc3kids.com

Depression drug database www.coreynahman.com/antidepressantdrugsdatabase.html

Epilepsy Action www.epilepsy.org.uk

National Institute of Mental Health (NIMH): Depression www.nimh.nih.gov/publicat/depression.cfm#ptdep5

Neuroscience for Kids (Explore the Nervous System and Neurological Diseases)
http://faculty.washington.edu/chudler/introb.html

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DRUGS USED TO RELIEVE PAIN AND PRODUCE ANAESTHESIA

Auntie, did you feel no pain
Falling from that willow tree?

HARRY GRAHAM – *RUTHLESS RHYMES FOR HEARTLESS HOMES*

Pain has long been the bugbear of medicine, and yet some people still believe that pain is something that must be borne with many diseases. One still hears stories regarding the inadequacy of pain relief by health-care professionals. Compassion and empathy are important aspects of all health care, and the treatment of pain should be encompassed within these attitudes. Whether the pain is postoperative or due to disease, anyone dealing with its control should have a thorough understanding of the drugs that are used. This section deals with these drugs, including their advantages and disadvantages.

One of the reasons some patients and health-care professionals are reluctant to use painkillers may be that they are a commonly abused group of drugs. Used properly and under controlled supervision, however, they seldom pose problems (see Chapters 39 and 40).

Pain during surgery is controlled by either local or general anaesthetics. The administration of these drugs is normally carried out only by people qualified in their use. Other health-care professionals are often intimately involved in such procedures, however; therefore, part of this section is devoted to the local and general anaesthetics (see Chapters 41 and 42).

IX

NARCOTIC ANALGESICS

39

CHAPTER THIRTY-NINE

OBJECTIVES

KEY TERMS

Pain
Visceral pain
Nociception
Opioids
Opiates
Narcotics
Euphoria
Palliative care

After completing this chapter, the reader should be able to:

- **describe the function of naturally occurring opioids and their receptors;**
- **explain the rationale behind the use of narcotic analgesics;**
- **delineate the problems associated with the use of narcotic analgesics;**
- **list the varied uses of opiates and opioids.**

NARCOTIC ANALGESICS WERE ORIGINALLY DERIVED FROM crude extracts of the opium poppy and have been known since antiquity. It is a common misconception that the opium poppy originated in the Far East. In fact, the plant originated in Greece and spread slowly eastwards to India and China. Today, most licit and illicit opium poppy cultivation takes place in Asia. The 'Golden Triangle' region of Thailand is notorious for producing much of the world's illicit narcotics.

Opium contains many different compounds, which have profound effects on the human body. **Morphine** is the main compound that has analgesic properties, but the analgesic **codeine** is also present. Morphine comes from opium, which is the dried exudate of the opium poppy, whose Latin name is, aptly, *Papaver somniferum* – the 'sleep-bearing poppy'.

Thomas Sydenham, a physician, had this to say in 1680 about opium: 'Among the remedies which it has pleased Almighty God to give to man to relieve his sufferings, none is so universal and so efficacious as opium.' Many people today would dispute this statement because of the sufferings that the abuse of opium has brought to humanity; nevertheless, morphine and its derivatives, when used therapeutically, remain some of the best drugs available to relieve pain, cough and diarrhoea.

The other two principal compounds of opium are noscapine, which is not used in the UK, and **papaverine**, which has been used as an antispasmodic. Papaverine has been reported to relieve ischaemia in senile dementia by relaxing the smooth muscles in arterial walls; however, there is little evidence that it has any real value in this condition.

This chapter is concerned with the analgesics derived from opium and related compounds. Compounds derived directly from morphine and its analogues are often termed opiates. Those made synthetically are called opioids. **Heroin**, for example, is easily prepared from morphine by acetylation and is often known as diacetylmorphine or diamorphine. Clandestine laboratories in many parts of the world are aware of the ease with which morphine can be converted into heroin. Opioids often have no structural relationship to morphine but have similar actions on the central nervous system (CNS). **Pethidine**, a common narcotic, is manufactured by purely synthetic means.

Narcotic analgesics are occasionally called strong painkillers, and aspirin-like drugs mild painkillers. To a certain extent this is true, but it is rather a glib and misleading statement. In general, the narcotics are the preferred treatment for moderate to severe pain, but in some instances, for example bone pain, the non-narcotic analgesics have a better pain-relieving effect. Pain of neuropathic origin very often does not respond to any of the classic analgesics but can respond well to drugs not normally associated with pain relief, such as some of the antidepressants and antiseizure drugs. When other drugs not usually classified as analgesics are combined with true analgesics to better control pain, they are termed adjuvants or co-analgesics; the antipsychotics are good examples of such.

PAIN

Pain is a symptom of many conditions and is often what prompts patients to seek medical help. As well as being a presenting symptom, pain is often induced medically, especially when surgical intervention is required. Not so long ago, pain was considered to be a necessary part of an illness, and postoperatively many patients received only nominal pain relief from the medical profession. Today, it is realised that pain is what patients fear and, if present, what often hinders the healing process. Pain relief is now considered to be of utmost importance in patient care. The use of narcotics in pain relief has been limited to some extent by the fear that patients may become addicted to the drug. This fear is mainly unfounded, as addiction to narcotics after surgery is rare owing to their only short-term use. In palliative care, if addiction does occur, the benefits of continuing treatment are usually considered greater than the problem of addiction.

In the context of pain and its treatment, it is important to consider the two main types of pain. The first type is *productive pain*, which occurs immediately on tissue damage. This is a warning type of pain to which one can sometimes react, thereby avoid deteriorating sequelae. For example, if you touch something hot, you react to the pain by withdrawing your hand, thus avoiding further tissue damage. The second type of pain is termed *non-productive pain*; even though this is often caused by tissue injury, one has minimal control over this type of pain. Non-productive pain occurs, for example, when a stomach ulcer perforates. The pain produced is excruciating, but there is nothing much the patient can do about it. Productive pain commonly leads to non-productive pain.

Whatever the cause of pain, it is a protective response of the body to warn the individual that something is wrong. Analgesics of any type do not have much effect against productive pain. Non-narcotic analgesics have little, if any, effect on visceral pain. Visceral pain emanates from the internal organs of the torso. Other types of pain are termed musculoskeletal and respond well to non-narcotic analgesics. Some types of pain require treatment with drugs not normally considered to be analgesics – for example, **phenytoin** or **carbamazepine** may be used to treat trigeminal neuralgia (see Chapter 37).

Pain results from the stimulation of small afferent nerve fibres termed nociceptive neurons. These nerves are usually activated only by relatively strong stimuli. For example, warm water stimulates heat receptors in the skin to record the sensation of warmth, but scalding water leads to tissue damage and only then are the nociceptive fibres stimulated. In other words, pain receptors have a higher threshold for activation than purely thermal (or mechanical-type) receptors. The cell bodies of these afferent fibres lie in the dorsal root ganglia just outside the spinal cord. These ganglia may be resected to produce a nerve block in chronic severe pain.

The stimulation of nociceptive nerves by mechanical means can lead to pain even after the stimulus is withdrawn. This is because the transmission of the pain message is induced by chemicals released due to trauma. There are many of these chemicals, the most active being the kinins, such as bradykinin and kallidin. These kinins can be potentiated by prostaglandins – hence, the importance of prostaglandin inhibitors in the control of many types of peripheral pain. As yet, there are no therapeutic substances available to inhibit the action of kinins (although there are some at the research stage); therefore, pain suppression is generally available only through the use of inhibitors of prostaglandin synthesis or drugs that act on the central transmission of the pain messages.

Interestingly, the substance **capsaicin**, the hot ingredient of chilli peppers, is nociceptive, but, unlike other nociceptive substances, its effect wears off after several

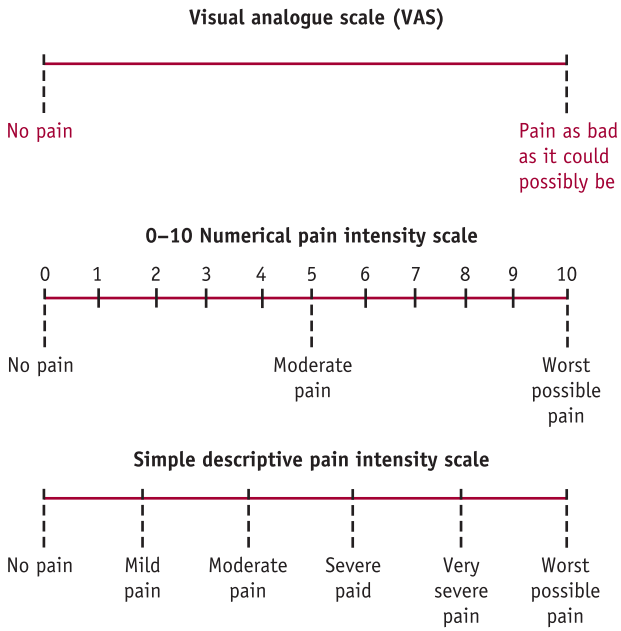
minutes. Capsaicin, however, remains on the receptors and effectively blocks the pain transmission, producing analgesia. The stimulation of the small nociceptive fibres, the C fibres, is via the release of a compound known as substance P and other pain-producing neuropeptides. Capsaicin stimulates the release of substance P; on continued application of capsaicin, substance P stores are exhausted and no more pain transmission can occur. Capsaicin found in products such as chilli and curry powders can produce severe burning sensations on the tongue, as anyone who has tasted a hot curry knows. This is due mainly to the release of substance P. If one continues to consume the hot food, substance P stores get depleted and the burning sensations decrease. This may explain how in chilli-pepper-eating competitions, the contestants appear to consume hundreds of hot peppers with impunity. The same physiological mechanism renders capsaicin useful as a skin application, and it has proved to be beneficial in the treatment of some extremely painful superficial conditions, as discussed in Chapter 40. Capsaicin has been included in rubefacients for a long time without its effect being understood properly (see Chapter 78).

Pain assessment

Pain is a very individual and complex experience influenced by many factors, including culture, prognosis, diagnosis, coping strategies, values, fear and anxiety. Self-reports are commonly used as indicators of pain severity (see Figure 39.1). The approach commonly used for post-operative patients is the categorical rating scale. Different descriptors can be used to rate the patient's pain. These include no pain, mild pain, moderate pain, severe pain, very severe pain and worst possible pain. The visual analogue scale (VAS) uses a 10-cm line rated from no pain to worst pain possible and asks the patient to mark their pain on this continuum. The VAS score is the distance from the no-pain point to the patient's estimate. The verbal numerical rating scale asks the patient to rate the pain from no pain (0) to worst pain possible (10). Although health-care professionals usually assess vital signs such as blood pressure, pulse and respirations regularly, pain assessment is sometimes not examined routinely. If patients experience acute or chronic pain, then it is important that they are assessed during movement, activity and rest, and that the effects of analgesics are evaluated closely for alleviation of pain.

Self-reports of pain form part of a pain history, which should be documented for all patients who have any form of acute or chronic pain. This history should be included with the patient's observation and medication order charts and consulted regularly in order to evaluate the effectiveness of analgesic medication and non-pharmacological treatments. Table 39.1 contains information about what is included in a pain history, such as the quality of pain, location, and factors that trigger and relieve the pain. In

FIGURE 39.1 SELF-REPORTING MEASURES FOR THE INTENSITY OF PAIN



Source: *Medical-Surgical Nursing: Critical Thinking in Client Care*, by P Le Mone & KM Burke, Addison Wesley, Menlo Park, 1996, p. 89.

TABLE 39.1 PAIN HISTORY

Circumstances associated with pain onset, e.g. walking, showering
Primary site of pain
Radiation of pain to other body areas
Character of pain, e.g. sharp, stabbing, aching, burning, stinging, crushing, gnawing
Intensity of pain (use self-report measures)
At rest
On movement
At present
Precipating and alleviating factors affecting pain
What makes it worse?
What makes it better?
Timing of pain
When does it begin?
For how long does it last?
Effect of pain
On activities
On sleep
Medications taken for pain relief
Use of non-pharmacological treatments

FIGURE 39.2 ANALGESIC CHART FOR DOCUMENTING PAIN ASSESSMENT AND MANAGEMENT

ANALGESIC CHART

NAME: JOHN SMITH
ID NO. 123456

Patient's goal for pain rating: 2 or less

Date Time Initials	Analgesic dose route	Pain rating (0–10)	Vital signs Pulse	Respiration	Blood pressure	Level of activity	Other comments (e.g. quality of pain)
1.6.07 1400 EM	Morphine 10 mg IV	9	92	20	150/80	Agitated	Central abdominal stabbing pain
1.6.07 1450 EM		6		16			Pain decreasing
1.6.07 1600 RP		4				Relaxed	Pain almost fully relieved
1.6.07 1700 RP	Morphine 10 mg IV	7		15		Facial grimacing, shallow breathing	Pain increasing
1.6.07 1745 RP		4					
1.6.07 1800 RP		1	78	12	120/70	Sleeping	Pain almost gone. Able to cough and deep-breathe

assessing and managing the patient's pain, it is also important that information is documented on a dedicated analgesic chart. The exact details on the chart may differ between institutions, but it should contain information about the analgesic dose route, pain rating, vital signs, level of arousal and activity, and adverse reactions to the administered analgesic. This documentation helps to ensure that the patient's ongoing analgesic needs are effectively monitored and evaluated (see Figure 39.2).

PROPERTIES OF NARCOTIC ANALGESICS

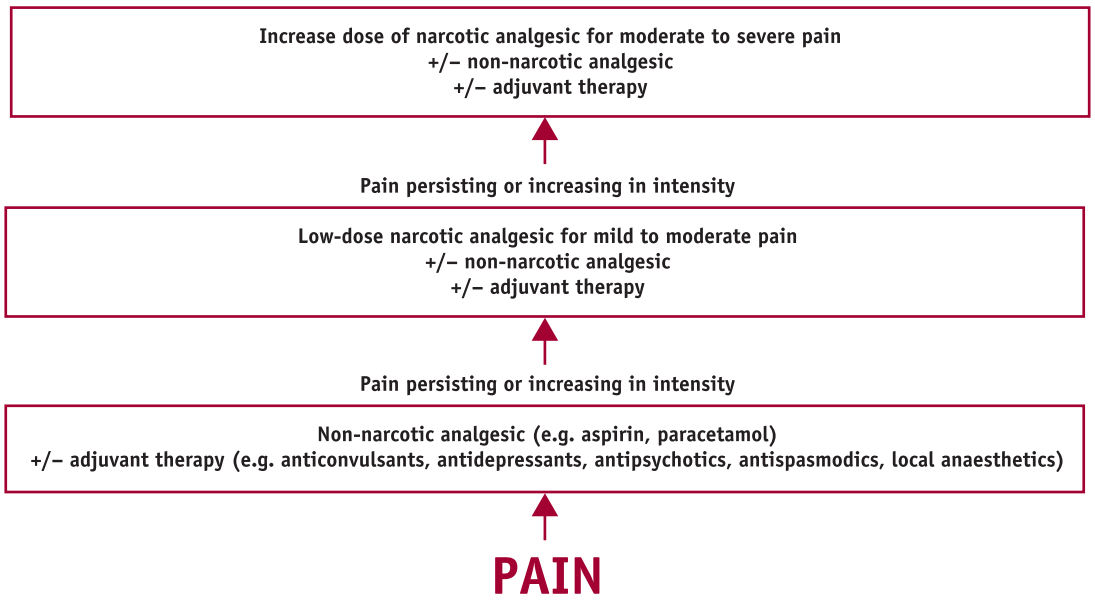
With regard to their pain-relieving qualities, narcotic analgesics have an action only on the CNS. The non-narcotics (see Chapter 40), on the other hand, have some direct effect on the pain-producing lesions, stopping the pain at its source. This is why, for certain types of pain, the non-narcotics are superior.

The World Health Organization's (WHO) 'ladder of analgesia' provides a useful means of determining the type of analgesic to be used for varying severities of pain. In this model, non-narcotic and narcotic medications are progressively administered until pain is relieved. The model effectively demonstrates the interactive nature of using different analgesics (see Figure 39.3).

MECHANISM OF ACTION

All centrally acting opioid analgesics stimulate opioid receptors within the CNS: they are opioid agonists. The presence of opioid receptors is due to the fact that we have naturally occurring compounds that can lessen our response to painful stimuli. The production of these compounds is noticeable under certain circumstances. Marathon runners, for example, are often not aware of the physical agonies that their bodies are suffering until after the end of a race; rugby players have been known to play to the end of a game, unaware of broken limbs; people in road accidents can be fully conscious but unaware of horrendous damage to their bodies. These situations arise because the body can produce natural compounds, called endogenous opioids, which suppress centrally controlled pain mechanisms. These substances are inhibitory neuromodulators, which suppress pain messages to the CNS from the periphery.

FIGURE 39.3 WORLD HEALTH ORGANIZATION LADDER OF ANALGESIA



Several of these compounds have been identified and given the general names endorphins, enkephalins and dynorphins. These compounds are all polypeptides and are distributed widely in and, to a lesser degree, outside, the CNS. For example, metencephalin is found in the myenteric plexus, where it is involved in inhibiting the release of acetylcholine. At least four different receptors for these compounds have been identified, and this helps to explain the differing properties of the opioids (see Table 39.2).

The presence of receptors in the limbic system of the brain (the part concerned with emotions) produces the euphoric effect of many of the opiates. Euphoria is of great advantage in the clinical situation, especially in terminally ill patients, as a feeling of wellbeing helps the patient forget about the future, or lack of. Euphoria is also the effect sought by drug abusers. Many patients, when given narcotic analgesics, are still very much aware of their pain but are not bothered by it. This feeling of euphoria pushes the pain away to another plane, reducing the pain to a minor irritation. This euphoria, combined with the drowsiness produced by many of the narcotics, allows the postoperative or terminally ill patient to curl up in bed and forget about pain, a desirable effect in these circumstances. This has led to the widespread use of narcotics in palliative care.

TABLE 39.2 ENDOGENOUS OPIOID RECEPTORS

Receptor type	Receptor site	Endogenous opioid	Major effect
δ (delta)	Limbic	Not known	Behavioural changes Hallucinations
ε (epsilon)	Hippocampus Amygdala	Enkephalin	Dysphoria Psychotic effects
κ (kappa)	Hypothalamus	Dynorphin	Hypothermia Miosis Sedation Analgesia
μ (mu)	Dorsal horn of spinal cord Thalamus	β-Endorphin	Analgesia Respiratory depression Euphoria

◆ COMMON ADVERSE EFFECTS

Unfortunately, narcotic analgesics have many adverse effects, and the problem of addiction creates dilemmas regarding their use. This fear of addiction in prescribers, administrators and recipients has led to the coining of the term 'opiophobia'. Some would say that the problem of addiction with the narcotics has been overstated and that when they are used for the conventional treatment of severe pain, addiction is not usually a problem. Many patients have taken narcotics for years and addiction has not been apparent when the drugs were withdrawn. When the narcotics are used solely for recreational purposes, however, the risk of addiction is of course very high, and many health-care professionals are reluctant to prescribe and administer narcotics because of their bad reputation. Perhaps this fear of turning the patient into an addict is an overreaction.

The chemoreceptor trigger zone (CTZ) is stimulated by many of the narcotics. This can lead to severe nausea, which is sometimes bad enough to incapacitate the patient and lead to non-compliance. This nausea is worse in the ambulant patient and may be avoided by the patient remaining in the recumbent position. Antiemetics can also be of help.

The morphine analogue **apomorphine**, if injected intravenously, causes violent vomiting. This action has been used in aversion therapy in individuals with an alcohol problem; the reasoning is that a neat whisky followed by apomorphine will deter alcohol consumption in the future.

The gastrointestinal tract has many opioid receptors. Stimulation of these receptors causes an increase in segmentation-type contractions and a simultaneous decrease in peristaltic movements. This leads to an increase in water absorption, with a consequent thickening of the bowel contents and resulting constipation. This can be a major problem in elderly and bedridden patients and, in severe cases, can lead to impacted faeces. Careful attendance to bowel habits is of the utmost importance when using these drugs, and the judicious use of laxatives is usually required. This action of the narcotics is utilised in the treatment of diarrhoea (see Chapter 54).

Narcotics contract biliary smooth muscle, which may result in a spasm in the biliary tract; thus, they are often contraindicated in the management of pain from biliary colic. The ureter can be similarly affected and renal colic can also be exacerbated. Some doctors still use opioids for both biliary and renal colic in a high enough dose to overcome the pain caused by the rise in the duct pressure. Pethidine has little action on smooth muscle and may be preferred in the treatment of the pain of smooth-muscle spasm. Because of its minimal effect on gastrointestinal smooth muscle, pethidine is devoid of a constipating effect.

Most of the common narcotics cause depression of cough and respiratory centres of the CNS. They act to reduce the responsiveness of the brain-stem respiratory centres to carbon dioxide. Respiratory depression is the main cause of death following narcotic overdose. Pethidine is less likely to cause respiratory depression and is of no value as a cough suppressant.

Tolerance is another problem associated with prolonged narcotic use. Following repeated dosing, the effects of the narcotic decrease. Tolerance develops fairly rapidly to the euphoric and analgesic properties of the narcotics but relatively slowly to the effects on the respiratory centre. This is a problem with addicts, who may increase the dose in order to attain the desired effect but then suffer from potentially fatal respiratory depression.

Miosis (pupillary constriction) occurs with the narcotic drugs and is indicative of an overdose. Tolerance does not develop to this miosis and drug abusers cannot disguise their constricted pupils.

The adverse effects of narcotics are summarised in Figures 39.4 and 39.5.

✚ CLINICAL CONSIDERATIONS

The dose of narcotic analgesic required may vary eight- to ten-fold between patients because of tolerance, the patient's previous experience of pain, the patient's threshold to pain and the condition being treated. When changing between analgesics, it is important to consider their equianalgesic

FIGURE 39.4 EFFECTS OF NARCOTICS

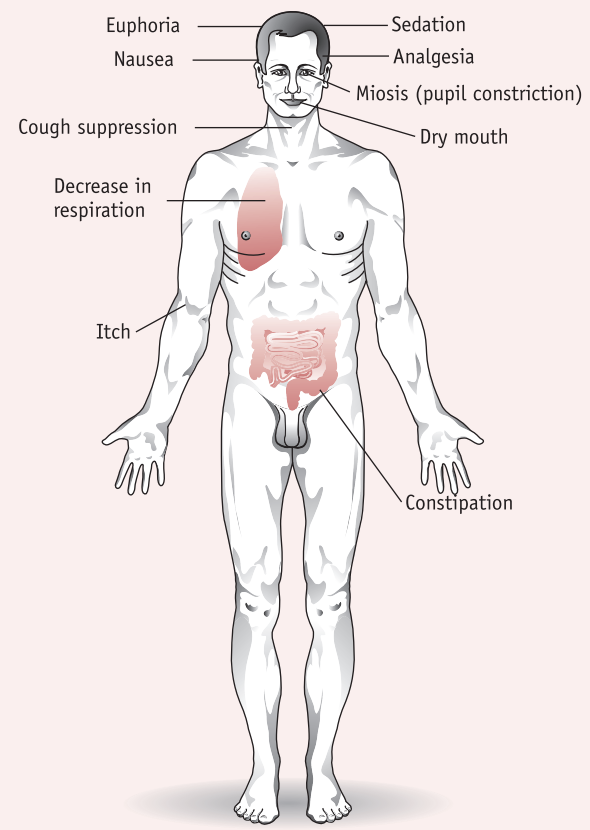
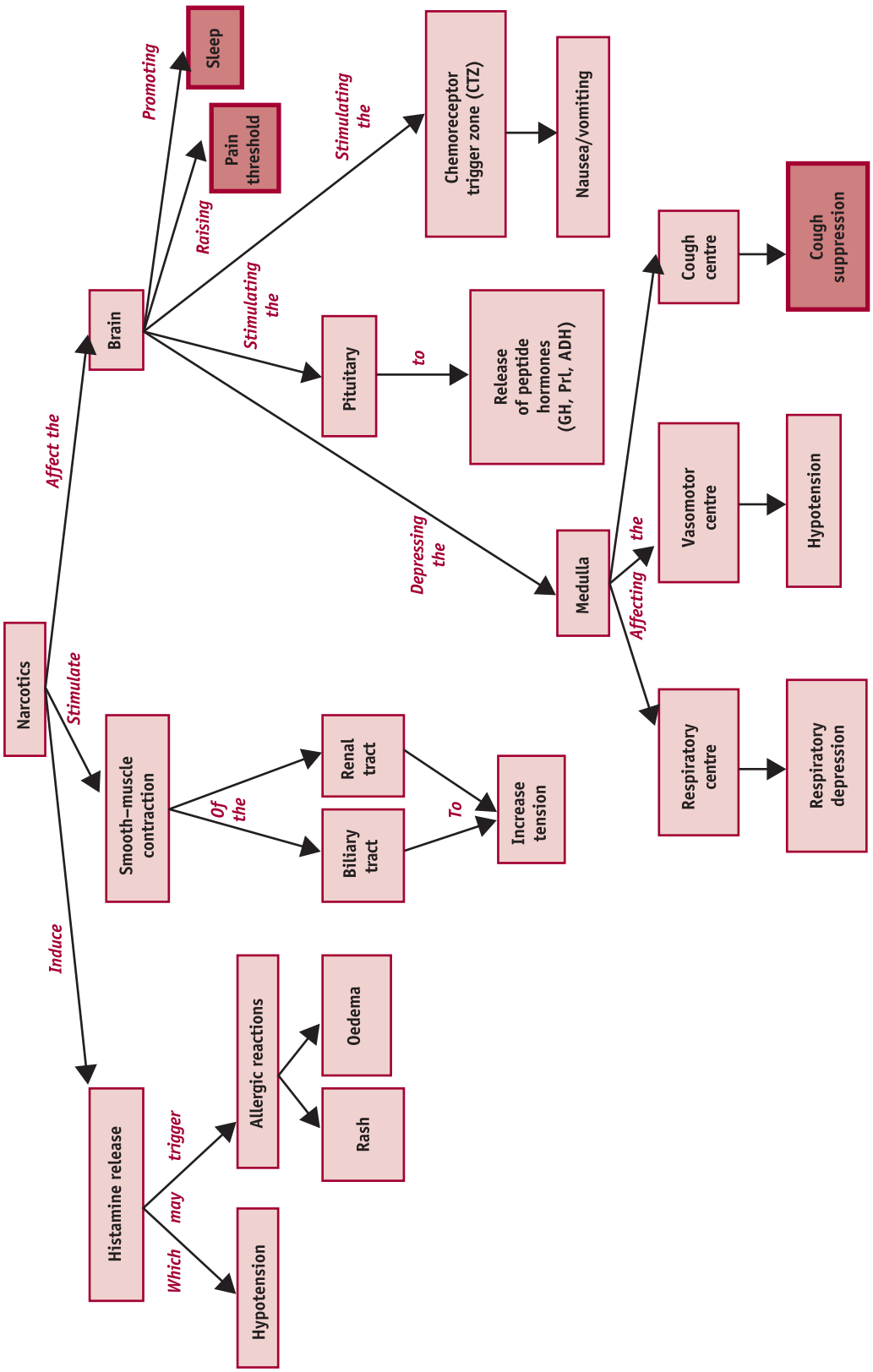


FIGURE 39.5 FLOWCHART SHOWING THE EFFECTS OF NARCOTIC ANALGESICS

Therapeutic effects are shown in the darker shaded boxes.



ADH, antidiuretic hormone; GH, growth hormone; Prl, prolactin.

dose compared to morphine. Usually, 10 mg of intramuscular or subcutaneous morphine is considered the parent drug to which others are compared. For instance, 10 mg of intramuscular or subcutaneous morphine is equivalent to 150–200 μg of subcutaneous or transdermal **fentanyl**, 75–100 mg of intramuscular or subcutaneous pethidine, and 30 mg of oral morphine (Table 39.3). It is generally wise to start with a slightly lower dose when changing between narcotic analgesics because of incomplete cross-tolerance. Morphine is often the preferred analgesic for moderate to severe pain. Other narcotic analgesics may be used if the adverse effects of morphine are tolerated poorly. A narcotic analgesic may be combined with a non-steroidal anti-inflammatory drug (NSAID) to treat specific problems, such as bone pain from tumour metastases and headache from a brain tumour.

TABLE 39.3 EQUIANALGESIC DRUG TABLE

Drug	Dose approximately equivalent with 10 mg IM/SC morphine	Duration of action (hours)	Active metabolite	Pharmacokinetic and clinical issues
Morphine	10 mg IM/SC/IV 30 mg oral	2–4 2–3 12–24 (controlled release)	Yes	Moderate-severe acute or chronic pain
Pethidine	75–100 mg IM/SC	2–3	Yes	Contraindicated in renal failure. Not suitable for severe continuing pain
Methadone	10 mg SC/IM 20 mg oral	8–24 (chronic dosing)	No	Accumulates in body, thus analgesic effect may increase
Dextropropoxyphene	65–100 mg oral	4–6	Yes	Avoid long-term use, as metabolite can cause toxicity
Tramadol	100–120 IM/IV 150 mg oral	3–6 3–6	Yes	For moderate to severe pain
Oxycodone	15–20 mg oral	3–4 12–24 (controlled release)	Yes	Moderate to severe acute or chronic pain
Fentanyl	100–150 μg IV/SC	0.5–1	No	Useful in severe renal impairment, as no active metabolite
Hydromorphone	1.5–2 mg SC/IM 6–7.5 mg oral	2–4 2–4	Yes	Moderate to severe acute or chronic pain

These comparisons are only approximate and patients should be carefully monitored after any change in dose or type of opioid analgesia. It is recommended that the BNF should be consulted for further information.

Adapted from Rossi, S. (ed.) (2007) *Australian Medicines Handbook 2007*, Adelaide (SA): Australian Medicines Handbook Pty Ltd.

IM, intramuscular; IV, intravenous; SC, subcutaneous.

Opiates

MORPHINE

Morphine was the first narcotic agent to be introduced as a single analgesic agent and it remains the mainstay analgesic, in spite of the availability of a succession of more potent agents. All analgesics are still compared to morphine. Morphine has a short half-life of about 4 hours, and so frequent dosing is required for conventional preparations. The advent of slow-release tablets and a similar suspension (which has to be made fresh from granules sold in individual sachets) has contributed to morphine's popularity as an analgesic. Some members of the medical profession continue to use an impure opium preparation containing morphine, codeine, noscapine and papaverine. This preparation is called **papaveretum**; the presence of papaverine may help in the better relief of pain involving smooth-muscle spasm. This is a mixture of four active drugs that should be avoided if possible, however, and the authors can see no real need to continue with the use of this preparation. If a spasmolytic is needed, it can be given separately.

CODEINE

Codeine is chemically closely related to morphine but is much less potent. Much of the analgesic activity of codeine may be related to its partial conversion into morphine in the liver. Approximately 10 per cent of the population are lacking the enzyme responsible for this conversion; this is an important point, as many patients who claim to gain little pain relief from high-dose codeine analgesic combinations may have a drug idiosyncrasy. Codeine may be given as codeine phosphate as an analgesic. It is also used as an antidiarrhoeal and antitussive. The analgesic activity of codeine potentiates the analgesic activity of both aspirin and paracetamol and is often combined with these drugs. These combinations are useful for moderate pain, and the minimal euphoric effect of codeine lessens the risk of addiction. The potential for abuse does exist, however, and the higher-dose combinations should not be used indiscriminately. The higher-dose preparations are usually identified by the term 'forte'.

DIHYDROCODEINE

This derivative of codeine has been available in many countries for several decades as a moderately potent analgesic. The proprietary nomenclature of this drug is interesting. In most countries it has been called, rather unusually, DF118. DF stands for an Edinburgh-based pharmaceutical company called Duncan and Flockart (now part of GlaxoSmithKline); it was given the number 118 as it was the one-hundred and eighteenth new drug synthesised by this company for potential pharmaceutical use. All potential drugs synthesised by pharmaceutical companies are given such numbers, but they are usually replaced by more conventional generic names on release.

Dihydrocodeine is a better analgesic than codeine and has fewer adverse effects and a lower abuse potential than morphine. Its rightful place and value in the opiate armamentarium are uncertain, however.

DIAMORPHINE

Diamorphine (heroin) was initially introduced as an alternative to morphine in cases of addiction, the premise being that diamorphine was less addictive. In fact, the opposite is true and, because of this, diamorphine is an illegal drug in many countries. In the UK, diamorphine is used as analgesia in chest pain associated with myocardial infarction and in terminal illness where its greater euphoric effect is beneficial. Diamorphine has greater solubility than morphine, which may be of considerable advantage in emaciated patients.

The half-life of diamorphine is slightly shorter than that of morphine. If it is taken orally, diamorphine is converted almost completely to morphine during the hepatic first pass; therefore, it is not given orally, except occasionally as an antitussive. Diamorphine crosses the blood–brain barrier very rapidly and produces an intense euphoria on injection in many individuals, hence its appeal to addicts. As diamorphine is more potent than morphine, less has to be given to achieve the desired effects and less has to be smuggled by drug traffickers in order to make a large profit.

Diamorphine is one of the most controversial of the opiates because of its addictive properties. Many drug-addiction experts assert that heroin is safer than both nicotine and alcohol. Nicotine and tobacco smoke cause millions of deaths throughout the world, and alcohol taken in excess causes untold misery in many families. It is suggested by some experts that recreational use of heroin does not necessarily interfere with one's normal lifestyle and correct dosing does not lead to long-term adverse effects.

Withdrawal symptoms from opiate dependence can be horrifying to both observers and addicts, but they are not as dangerous as the withdrawal symptoms of alcohol and barbiturate addiction. People undergoing abrupt withdrawal suffer from what is known as 'cold turkey'. Symptoms are variable but include an increase in flow of most body fluids, resulting in lacrimation, rhinorrhoea, diarrhoea and, sometimes, spermatorrhoea. The sufferer also experiences from severe psychological disturbances, which often necessitate psychiatric treatment.

Diamorphine is metabolised to monoacetylmorphine, a substance that can be detected in urine and is generally

indicative of heroin rather than morphine use or abuse. Proof of illegal use of diamorphine is obtained by detecting monoacetylmorphine in the urine. There have been some cases of this compound being detected when no heroin has been utilised, however; this can happen, for example, when morphine has been prescribed legitimately and aspirin has been taken concurrently. Aspirin can acetylate other compounds, and this is its mechanism of action when used as an antiplatelet drug (see Chapter 46); morphine can be acetylated in vivo to monoacetylmorphine.

Opioids

PETHIDINE

Pethidine, like morphine, has a high hepatic first pass and thus the parenteral dose is lower than the oral dose. The analgesic activity of pethidine is not as strong as that of morphine, but pethidine is used widely for moderate to severe pain because it causes less constipation and less respiratory depression than morphine. Pethidine is a useful analgesic in labour, as it does not suppress uterine contractions; it must be remembered, however, that the fetal respiratory rate may be affected. In renal and biliary colic and following abdominal surgery, pethidine is less likely than the other narcotics to increase smooth-muscle spasms as it has an additional antimuscarinic action; this action may, however, cause dry mouth and blurring of vision as side effects. The sustained use of pethidine as an analgesic is inadvisable and not recommended, not only because of the potential risk of addiction but also due to the accumulation of one of its metabolites, norpethidine, in the body. Norpethidine has a longer half-life than pethidine, and the concentration of this metabolite can rise to toxic levels during frequent dosing over several days. Norpethidine acts as a CNS stimulant and can lead to the development of potentially serious convulsions in susceptible individuals. Pethidine should not be given with other proconvulsant drugs such as some of the selective serotonin reuptake inhibitors (SSRIs) (see Chapter 35). Monoamine oxidase inhibitors (MAOIs), occasionally used in the treatment of depression, also interact with pethidine to cause severe hyperpyrexia, restlessness, coma and hypotension.

METHADONE

Methadone is used mainly as a substitute for the more abused narcotics in the control of heroin and morphine addiction. It may seem senseless to replace one drug of addiction with another, but there is method in using methadone as a morphine or heroin substitute. The effect of methadone is similar to that of the other narcotics, but it has fewer adverse effects and produces fewer withdrawal symptoms and it is thought to be easier to wean addicts off methadone, although the addiction may be more powerful. Methadone has a long half-life of about 24 hours, which helps to explain its weaker withdrawal symptoms. As methadone binds strongly to the opiate receptors, an injection of heroin after methadone administration does not produce the immediate 'high' due to lack of empty receptors. This, combined with its long half-life, discourages the use of heroin in cooperative addicts. Methadone is administered orally, reducing the use of syringes and lowering the risk of the drug user developing infectious diseases such as human immunodeficiency virus (HIV) infection and acquired immunodeficiency syndrome (AIDS) and hepatitis.

If breakthrough pain occurs when methadone is used therapeutically in the control of pain, an opiate with a shorter half-life can be given.

DEXTROPROPOXYPHENE

Dextropropoxyphene has a similar profile to that of codeine and is often combined with **paracetamol** as **co-proxamol**. In view of dextropropoxyphene's similarity to codeine and the fact that it can cause severe respiratory depression following overdose, it is difficult to understand why this drug has gained so much popularity. This respiratory depression on overdose can lead to death before life-saving treatment can be instigated because dextropropoxyphene is absorbed quickly from the gastrointestinal tract and can cause death within 1–2 hours of ingestion. In 2005, the Medicines and Healthcare Products Regulatory Agency (MHRA) announced a phased withdrawal of co-proxamol in the UK following evidence of 300–400 intentional and accidental fatal overdoses each year. This gradual phasing out gives patients taking the drug regularly time to discuss alternatives with their doctor. Co-proxamol should no longer be prescribed, except to patients already taking it.

PENTAZOCINE

There have been many attempts to produce powerful analgesics with little potential for abuse. **Pentazocine** is one analgesic that has had some success. Pentazocine is known as an agonist/antagonist analgesic as it is agonistic at the κ receptors but antagonistic at the μ and δ receptors. (At low doses, there may be partial agonism at the μ receptors, which accounts for the drug's slight euphoric effect.) High doses result in dysphoria, and hallucinations may occur. If pentazocine is administered to people addicted to pure agonists, withdrawal symptoms are likely to be produced. Addiction is known to occur with pentazocine, especially with parenteral administration.

TRAMADOL

Tramadol is a centrally acting synthetic opioid used therapeutically in the control of moderate to severe pain. Tramadol is less likely than most other opioids to produce euphoria, tolerance and addiction when given in normal doses. Tramadol produces analgesia by two mechanisms. It has relatively weak agonist activity at all opioid receptors but particularly at the μ receptor. Additionally, it inhibits the reuptake of noradrenaline and enhances serotonin release within central pain pathways. Its relatively short half-life necessitates the use of three to four doses per day by mouth, intravenously or intramuscularly. Sustained-release preparations are available. The usefulness of tramadol is due to its efficacy in many types of pain, except for that of neurogenic origin, combined with a low potential for addiction and less respiratory depression than typical opioid drugs. It is a popular drug in pain management, either used on its own or given in combination with paracetamol or NSAIDs, but it is less effective for severe pain than morphine. Tramadol is only partially reversed by naloxone; it should not be given to opioid addicts, as it produces acute withdrawal symptoms. Tramadol is not used intraoperatively as it has been associated with a raised incidence of intraoperative recall, but it is useful postoperatively. Its side-effects profile is similar to that of the other narcotics, with perhaps more nausea in the initial stages of therapy but with a much lower incidence of respiratory depression. Like pethidine, tramadol may have proconvulsant properties, and so it should not be used in conjunction with other proconvulsant drugs or in epileptiform conditions. There is also a risk of developing serotonin syndrome (see Chapter 35) following concomitant use of tramadol with selective serotonin reuptake inhibitors.

Other narcotic analgesics

Several other narcotic analgesics are available, all of which are similar in many respects to those already mentioned. As is the case for any class of drugs, individual idiosyncrasies may make some of these other narcotics better for some patients than the more commonly used narcotics. Their properties, which may be of benefit in certain situations, are given below; more information can be found in the drug summary table at the end of the chapter.

Oxycodone has less of a hepatic first pass and a longer half-life than morphine, as the pectinate is relatively well absorbed from the rectum. As a suppository, oxycodone is useful for overnight analgesia. Oxycodone is relatively popular as a narcotic analgesic and is available in slow-release tablets. It is said to have a lower abuse potential than morphine, but it should be pointed out that its abuse in the USA is common, with many addicts grinding up slow-release preparations for injection.

Hydromorphone is more potent than morphine, which enables it to be injected subcutaneously. This is useful under certain circumstances, as subcutaneous injections are less painful than intramuscular injections. For patients tolerant to narcotics, a high-potency (HP) preparation is available. Extreme care must be used in determining whether patients should be given the HP preparation, as narcotic-naive patients could easily be overdosed. Abuse potential is high.

Fentanyl is a synthetic opioid with agonist action at the μ receptor. It is commonly used in neuroleptoanalgesia (see Chapter 41) because of its short duration of therapeutic action. This enables the patient to recover speedily from the drug's effects after short medical or surgical procedures. It has high lipid solubility (it is nearly 600 times more lipid-soluble than morphine), which explains its rapid onset of action following intravenous injection. Fentanyl is available for transdermal delivery; the patches last about 3 days. Fentanyl is very useful in chronic pain disorders, especially due to cancer. Breakthrough pain can, as usual, be dealt with using fentanyl lozenges, oral morphine solution or another fast-acting preparation. Fentanyl delivered transdermally has less risk of causing constipation, but care should be taken if the patient has a fever, as the fentanyl absorption from the patch may increase.

Fentanyl combined with the local anaesthetic **ropivacaine** is particularly useful in severe postoperative pain after surgery where an epidural has been given; an infusion of fentanyl into an indwelling epidural catheter can be maintained for up to 72 hours. Its high lipid solubility means that it diffuses rapidly from the cerebrospinal fluid into the spinal cord, thus decreasing the risk of delayed respiratory depression.

Alfentanil is also a synthetic μ agonist that is used for short-term analgesia and by infusion for sedation in some operative procedures. Although alfentanil is less lipid soluble than fentanyl, the former has a faster onset of action due to it being 89 per cent unionised at the plasma pH of 7.4. Only 9 per cent of fentanyl is unionised at this pH.

Buprenorphine is a very potent narcotic with a relatively long half-life; its therapeutic effect lasts for 6–8 hours. Buprenorphine has a high hepatic first pass but, because of its potency, it can be given sublingually. It is only a partial endorphin agonist, which lessens its abuse potential. The adverse effects of dizziness and nausea are more pronounced than those of morphine, which restricts its use. The effects of buprenorphine on the respiratory centre are not easily reversed with **naloxone**. If the patient responds well to buprenorphine, it is valuable in the treatment of terminal cancer pain. Buprenorphine has been found to be very useful in treating opiate addiction, as described above for methadone.

Information on other narcotic analgesics is available in the drug summary table at the end of this chapter.

NARCOTIC ANTAGONISTS

NALOXONE

Naloxone is classified as a pure antagonist at the natural opioid receptors and is therefore not of much use in its own right. As it has a much stronger affinity for the receptors than most of the agonists, however, it can be used to reverse their action in cases of overdose (see Chapter 22). Intravenous naloxone reverses the effects of opioids in 1–3 minutes, but it has a shorter duration of action than the opioids and so may need repeat administration. Naloxone works antagonistically with most of the narcotics, but with buprenorphine, which binds rather tenaciously to the receptors, the results are not so dramatic.

Paediatric naloxone is available to counteract respiratory depression that can occur in the newborn due to analgesic use in labour.

Interestingly, naloxone blocks the analgesic effects of acupuncture, confirming the value of this form of complementary medicine. It is suggested that the acupuncturist's needles somehow stimulate endorphin release, the effect of which is blocked by naloxone.

Low-dose naloxone is increasingly being used to treat some of the adverse effects seen with the use of epidural opioids. When titrated carefully, side effects such as itching, nausea and vomiting may be eliminated without removing the analgesic effects of the epidural opioid.

✚ CLINICAL CONSIDERATIONS

Patients who have taken an opioid overdose and receive naloxone should be observed for about 2–3 hours following treatment to ensure they do not relapse. This concern is particularly important in cases of methadone overdose, where the effects of narcosis can extend for more than 24 hours. Although naloxone is effective in treating the sedation and respiratory depression associated with narcotic analgesic use, it does not reverse other adverse effects of the metabolites of these drugs, such as seizures associated with norpethidine and cardiac dysrhythmias due to nordextropropoxyphene.

Naloxone should be administered with caution in people with cardiovascular disease, as serious cardiovascular effects have occurred, including hypotension, hypertension, ventricular tachycardia, ventricular fibrillation and cardiac arrest.

NALTREXONE

Like naloxone, **naltrexone**, is an opioid antagonist that can be given orally and is therefore a useful drug in the management of narcotic withdrawal in addicts. In the UK, naltrexone is used as an adjunct to prevent relapse in detoxified formerly opioid-dependent patients who have remained opioid-free for at least 7–10 days. In some countries, e.g. Israel and Mexico, naltrexone is given by infusion while the patient remains anaesthetised for several days in order that withdrawal effects are not experienced. This long-term anaesthesia is not without risks and is banned in most countries. By using the oral preparation of naltrexone high doses can completely block the receptors from heroin agonism for several days. This type of administration will, of course, lead to withdrawal symptoms, which may be severe but not life-threatening. Many of these symptoms can be relieved partially by the appropriate use of other drugs to treat the withdrawal effects, for example benzodiazepines to abolish anxiety and help with sleep, quinine to help with muscle cramps, NSAIDs to treat joint pain and clonidine to decrease central output of sympathetic activity. Naltrexone is also of use in treating alcohol addiction but not with other addictive drugs. It is not known why naltrexone helps in alcoholism. Naltrexone appears to be a relatively safe drug at normal dosages but is hepatotoxic in high doses; therefore, care is needed in patients with a history of liver disorders, a common problem in drug addicts. Patients on naltrexone who require severe pain relief need specialised treatment, such as a modified type of neuroleptoanalgesia.

✚ CLINICAL CONSIDERATIONS

Liver function in patients receiving naltrexone must be monitored before starting treatment and then monthly for the first 3 months. If liver function is normal, monitoring should continue at 3-monthly intervals. Following narcotic withdrawal, the patient must be advised that they are at high risk of having a fatal overdose if they stop taking naltrexone and start using heroin again.

CLINICAL MANAGEMENT

Narcotic analgesics

Assessment

- Assess for characteristics of pain, including precipitating factors, aggravating factors, location, quality, intensity and duration of pain. Assess characteristics before and after pain relief is administered.
- Obtain baseline vital signs and compare with observations obtained after narcotic analgesic administration.
- Obtain a history from the patient of conditions that are contraindicated for narcotic use, including respiratory distress, head injury, epilepsy and diabetic acidosis. Narcotics can be used, with caution, in elderly people and patients with obstructive airway conditions such as asthma or emphysema, and heart disease.
- Assess the patient about to commence naltrexone for concomitant hepatic disease, as naltrexone may be hepatotoxic in high doses.
- Transdermal fentanyl patches should not be used for acute or postoperative pain in patients not previously exposed to narcotic analgesics because of the risk of life-threatening respiratory depression.

Planning

- The patient will be free of pain or will experience only minimal pain after analgesic use.

Implementation

- Monitor observations and the way these are affected by the pain or narcotic analgesic. Pain tends to cause tachycardia, increased respiratory rate, raised blood pressure, cold and clammy skin, diaphoresis, restlessness, and splinting or holding a painful body part. Narcotic analgesics should not be administered if the respirations are less than 12 per minute or the systolic blood pressure is less than 110 mmHg.
- Observe the patient for adverse effects of the drug, including respiratory depression, low blood pressure, drowsiness, confusion, urinary retention, constipation and pupillary constriction.
- Administer the narcotic before the pain reaches a maximal level in order to allow for the full benefit of the drug.
- Monitor the vital signs at regular intervals to determine changes in respiration or blood pressure. Changes are likely to occur about 7–8 minutes after an intravenous injection, 30 minutes after an intramuscular injection, and about 90 minutes after a subcutaneous injection.
- Monitor urinary output: output should be at least 600 ml per day.
- Auscultate for bowel sounds for reduced peristalsis (refer to Table 11.4 in Chapter 11 for information on the methods to deal with constipation).
- Maintain safety precautions after administration. Put cot sides up, put the bed in a low position and place the call bell within easy reach of the patient.
- If the patient has a tendency to become nauseated with a narcotic, administer with an antiemetic, such as prochlorperazine or metoclopramide.
- Non-pharmacological measures can assist with pain relief, including back rubs, changing position, massage and aromatherapy.
- Monitor for signs of overdose of narcotic analgesics (when abused), such as pinpoint pupils, coma and respiratory depression. Have naloxone available for administration.
- Monitor liver function tests for the patient receiving naltrexone in the management of narcotic withdrawal.
- Apply transdermal patches to dry, non-hairy skin on the upper arm or the torso area. The patch should be removed after 72 hours and placed in a new area.
- The most serious adverse effect of narcotic analgesics is respiratory depression. This effect is best monitored by the degree of sedation. A fall in respiratory rate is an unreliable sign and should be considered a late indicator.

Patient teaching

- Instruct the patient to comply with the prescribed drug regimen, and explain that indiscriminate use may lead to dependence.
- Alcohol and other central nervous system depressants should be avoided.
- Advise the patient to report any urinary retention and constipation.
- Advise the patient to rise slowly from a lying position to prevent postural hypotension (see Table 11.20 in Chapter 11 for further information).
- The patient should avoid smoking immediately after administration.
- Reassure the patient that frequent administration of narcotics in the context of pain relief rarely leads to addiction.

- For the patient who is taking a narcotic for chronic pain (e.g. in palliative care), regular administration of the drug creates a better effect than taking it 'as required'.
- The patient with chronic pain should be reassured that with the use of narcotic analgesics in palliative care, dependence and tolerance are not important issues to consider.
- Advise the patient receiving palliative care that the effects of nausea, vomiting and drowsiness usually settle within the first week of treatment.
- Patients receiving palliative care require regular use of a laxative. Docusate sodium with senna is good to start with, as it tends to be effective and produces minimal adverse effects.

Evaluation

- Observe for the therapeutic effect of the narcotic, either alleviating or reducing the pain.
- Evaluate for adverse effects, such as low blood pressure and decreased respirations.

SUMMARY

- Narcotic analgesics act on receptors in the brain and spinal cord to control pain. They produce analgesia and euphoria, reduce anxiety, promote sleep, inhibit coughing and may be used to treat diarrhoea.
- Narcotic analgesics mimic naturally occurring peptides to control pain.
- These receptors are found scattered in both the central nervous system and peripheral organs and account for the many other pharmacological effects of narcotics.
- Narcotic analgesics are better for the control of visceral pain rather than musculoskeletal pain.
- The euphoria produced by narcotics is important, especially in pain control in palliative care.
- Adverse effects associated with the narcotics include respiratory depression, nausea and vomiting, constipation, physical dependence and tolerance.
- Individual responses to narcotic analgesics can vary ten-fold. Dose titration is required to ensure adequate effect.
- Breakthrough doses of analgesic may be needed to establish effective pain relief.
- Lower dosage is often required when administering narcotic analgesics by the epidural or intrathecal route. Systemic adverse effects may also be reduced.
- Narcotic antagonists are useful not only in managing narcotic overdoses but also in the treatment of narcotic addicts, as are partial agonists.
- Patients should not try to overcome the blockade effect of naltrexone by using higher doses of heroin, because of the possibility of an overdose.
- Liver function needs to be monitored regularly in patients on naltrexone.
- Some narcotic drugs, such as codeine, pethidine, morphine, oxycodone and dextropropoxyphene, as well as their active metabolites, have delayed excretion. Extended treatment with naloxone may be needed to reverse their effects.
- Naloxone may be used to determine whether the patient is opioid-free. Check for withdrawal symptoms such as rhinorrhoea, yawning, sweating, lacrimation and vomiting during naloxone administration.

1. Suggest why football players have been known to continue playing after having cracked a bone, normally a very painful event.
2. Why does naloxone affect the efficacy of acupuncture in the control of pain?
3. Pentazocine may precipitate withdrawal symptoms in a morphine addict. Why?
4. Why is prochlorperazine sometimes administered with opiate drugs?
5. Why is methadone, itself an addictive drug, used in the treatment of heroin addiction?
6. What precautions must be taken when naloxone is used as an antidote for morphine overdose?
7. What is meant by 'cross-tolerance'?
8. Itch may develop after the injection of morphine. Why?

9 A patient on morphine may have difficulty in reading a telephone directory. Why?

10 Amilia Jayasinghe has just undergone a hip replacement. She has received morphine 10 mg intravenously for pain relief. Over the course of half an hour, her blood pressure drops to 80/60 mmHg from 110/80 mmHg, and her respiration rate drops to 12 from 15 breaths/min. What actions would you take? Provide rationales for your answer. (See Tables 11.1 and 11.6 in Chapter 11 for assistance.)

11 Provide a rationale for the use of pethidine instead of morphine following gastrointestinal surgery.

12 Soo Ling, a 15-year-old netballer, has been taking a preparation containing paracetamol and codeine to provide pain relief for her right knee. After visiting the community health centre, she complains of not having opened her bowels for 3 days. What is the cause of the constipation? What action would you take to treat the constipation?

13 According to drug legislation, to what schedule do most narcotic analgesics belong? What implications does this schedule have for administration of narcotic analgesics?

14 What changes in vital signs would indicate to you that a patient's pain is resolving after a morphine injection?

39 DRUG SUMMARY TABLE: NARCOTIC ANALGESICS

FAMILY NAME	GENERIC NAME	TRADE NAME(S)
Opioids	Alfentanil	Rapifen
	Buprenorphine	Subutex
	Dextropropoxyphene	
	+ Paracetamol	Co-proxamol
	Fentanyl	Sublimaze
	Meptazinol	Meptid
	Methadone	Physeptone
	Pentazocine	Fortral
	Pethidine	
	+ Promethazine	Pamergan P100
	Tramadol	Tramake
		Dromadol SR
		Larapam SR
		Zydol SR
		Zamadol SR
	+ Paracetamol	Tramacet
Opiates	Codeine	
	Hydromorphone	Palladone
	Morphine	Morphgesic
		Morcap
		MXL
		Oramorph
		MST Continus
		Sevredol
		Zomorph
	+ Cyclizine	Cyclimorph
	Oxycodone	Oxycontin
		Oxynorm
Opiate and opioid antagonists	Naloxone	Narcan
	Naltrexone	Nalorex

NON-STEROIDAL ANTI-INFLAMMATORY, ANTIPYRETIC AND ANALGESIC DRUGS

40

CHAPTER FORTY

OBJECTIVES

After completing this chapter, the reader should be able to:

- **describe the role of prostaglandins in inflammation and the use of prostaglandin inhibitors in the control of pain;**
- **list the antipyretic properties of anti-inflammatory and analgesic drugs;**
- **explain the difference in action between paracetamol and other prostaglandin inhibitors;**
- **outline the dangers of aspirin and paracetamol use;**
- **list the uses and side effects of anti-inflammatory drugs;**
- **list the uses of non-prostaglandin inhibitors in the treatment of rheumatoid arthritis.**

KEY TERMS

Inflammation
Prostaglandins
Cyclo-oxygenase
Reye's syndrome
Disease-modifying anti-rheumatic drugs (DMARDs)

INFLAMMATION OF TISSUES GENERALLY RESULTS IN PAIN, which can be treated with analgesics (painkillers). Many of the analgesics available also have anti-inflammatory properties, and therefore they are suitable for use in inflammatory conditions such as rheumatoid arthritis. Analgesics with no anti-inflammatory properties are not very useful in the treatment of inflammatory conditions. Some of the anti-inflammatory drugs have little or no painkilling activity and are of little use in the treatment of painful conditions where inflammation is not a problem.

Most of the drugs that are used as both analgesics and anti-inflammatories are prostaglandin inhibitors; that is, they inhibit enzymes involved in prostaglandin biosynthesis. The reason for their diversity of action is that prostaglandins occur throughout the body in all tissues, and only some drugs may be able to access these tissues. The joint capsule is a site of many inflammatory processes, but not all drugs are able to gain entry to this site. Another reason is that many different types of prostaglandin are found in the body. Some drugs, given at a constant dose, are more effective at inhibiting the biosynthesis of one prostaglandin than another. Prostaglandin synthesis in different tissues may involve isoenzymic variants of the enzymes involved.

The drugs commonly referred to as non-steroidal anti-inflammatory drugs (NSAIDs) are prostaglandin inhibitors. The term 'non-steroidal' is used as these drugs do not bear any structural resemblance to the corticosteroids, which are also important anti-inflammatory compounds. The mechanism of action of the NSAIDs is also different from that of corticosteroids in that they do not mediate their effect through interference with the immune response. (See Chapter 58 for a fuller discussion on the corticosteroids.)

INFLAMMATION, PROSTAGLANDINS AND PROSTAGLANDIN INHIBITORS

Inflammation was aptly described in Roman times as *rubor et tumor cum calor et dolor*, which, roughly translated, means 'redness and swelling with heat and pain'. The pathological conditions leading to this are varied. These can be minor sprains and strains, the extreme agonies that can accompany an acute attack of gout, or the continued agony of arthritic joints. Whatever the pathological condition, the causative factors at the site of the inflammatory response are similar; that is, prostaglandins are present in excess at the site of the inflammation. Infections, injuries and an abnormal immune response can all lead to the release of prostaglandins from some of the immunocompetent cells.

Prostaglandins have several roles to play as mediators of inflammation. They augment the action of histamine and other naturally occurring compounds in causing vasodilation and increasing vascular permeability to fluids. These two processes result in the classic symptoms of inflammation. Furthermore, some of the prostaglandins act directly on pain receptors, relaying the pain message to the brain. Recent research into the production of prostaglandins has led to a radical rethinking of inflammatory responses and has revolutionised the treatment of inflammatory conditions. At least two enzymes are involved in the synthesis of prostaglandins, both of which are cyclo-oxygenases (COX). One of these COX enzymes is constitutive and is involved in the synthesis of prostaglandins for homeostatic responses; this enzyme is COX-1, and its inhibition results in most of the adverse effects of the NSAIDs. The other enzyme is COX-2, which is inducible and is found in inflammatory conditions and some types of carcinoma. The development of drugs that act only on the COX-2 type has led to a new group of anti-inflammatory drugs devoid of many of the serious adverse effects of the NSAIDs.

Prostaglandins are found in the hypothalamus and are involved in raising the body's temperature in some infections. Most prostaglandin inhibitors are, therefore, useful in lowering raised body temperature. This is termed an antipyretic effect, and drugs with this effect are termed antipyretics.

As inflammation involves many other processes of the immune system, it is not surprising that prostaglandin inhibitors act only to relieve the symptoms of inflammation and are in no way a cure for such conditions.

There is mounting evidence that the NSAIDs have other effects on the immune system that are completely unrelated to prostaglandins and their function. These effects are directed towards the cell membranes, especially the immunocompetent cells called neutrophils. These membrane effects at the biochemical level are varied and are the subject of many ongoing research studies. The significant end result of these effects appears to be a decrease in the adhesiveness of the neutrophils to vascular endothelium, thus reducing the accumulation of the cells at pro-inflammatory sites and, therefore, decreasing the inflammatory response.

The main use of anti-inflammatory drugs is in the treatment of pain resulting from rheumatoid arthritis and osteoarthritis. Rheumatoid arthritis is an inflammatory condition of connective tissue, especially within the joint capsule. It may be described as an autoimmune disease, whereby the body's own immune system starts to destroy the synovial membrane. This may eventually lead to complete destruction of the joint and its associated structures. Osteoarthritis can result from mechanical damage to the joint and leads to degeneration of the articular cartilage; the hip joint is commonly affected.

There are many other joint, ligament, muscle and tendon diseases, which may be of autoimmune origin or due to physical trauma, that respond to treatment with anti-inflammatory drugs. This makes these drugs used widely by sportspeople.

There are several adverse effects of prostaglandin inhibitors that are generally common to them all – their effects on the stomach and kidneys. The effects on the stomach are two-fold. Most prostaglandin inhibitors are acidic drugs that can directly irritate the gastric mucosa. This can be severe, and in rare instances, especially if the drug is given to a patient with a pre-existing pathological condition of

the stomach, massive haematemesis can occur. It is usual to detect occult blood in the faeces after ingestion of NSAIDs. This is normally of no concern, unless obvious melaena occurs. The effect of these drugs on stomach secretions is of the most concern: in particular, hydrochloric acid and pepsin secretion is raised. As with most systems of the body, homeostatic mechanisms control gastric function. Prostaglandins in the stomach lead to a decrease in gastric secretions; therefore, inhibiting the synthesis of prostaglandins leads to an increase in secretions. This can lead to ulcer formation, a not uncommon occurrence in patients on long-term NSAID therapy. Some NSAIDs are worse offenders than others. Generally, the better the anti-inflammatory properties of a drug, the more severe the gastric problems. There is also tremendous individual variation in response to NSAIDs. If a patient suffers from gastric problems with an anti-inflammatory agent, then it is useful to try another NSAID, which may be less severe in its adverse effects in that patient. In some cases, it may be possible to give prostaglandin analogues with the NSAID in order to avoid gastric problems (see Chapter 53 for more details).

Prostaglandins are involved in the control of renal blood flow and, therefore, the glomerular filtration rate. Inhibition here may cause a reduction in glomerular filtration, giving rise to fluid and sodium retention, which can lead to hypertension. In athletes, this has been known to lead to renal failure.

Other effects of the NSAIDs on the body, related to their inhibitory effects on prostaglandins, are a prolongation of bleeding time (see Chapter 46) and delayed parturition and/or dystocia. The action of NSAIDs on the pregnant uterus has been used in the past to slow down or stop premature labour. Prostaglandins have a role to play in causing dysmenorrhoea; this makes NSAIDs valuable in the treatment of this type of uterine pain.

A recent trend in the application of anti-inflammatories is to make use of percutaneous absorption. If the drug is applied topically to the skin above an inflamed area, the drug reaches that area directly through the skin, being present in a high concentration exactly where needed; in theory, this produces fewer adverse effects, which seems to be the case in practice, particularly in sports-related injuries. **Aspirin** as an alcoholic solution and salicylic acid and/or derivatives are occasionally incorporated in topical preparations. Several other NSAIDs have also been formulated as gels and sprays for topical application. The anti-inflammatory compound **benzydamine** is used only for topical application.

The prostaglandin inhibitors used as anti-inflammatories are classified according to their chemical nature. Their categorisation is somewhat complicated to non-chemists, but this is the only convenient way to present them. Table 40.1 contains information about the half-lives and frequency of administration for common NSAIDs and paracetamol. This information is useful in determining the duration of action of a particular analgesic and the appropriate dosage schedule for a patient. Patient assessment is a very important aspect of pain management in order to ensure adequate and appropriate interventions (see Chapter 39).

Salicylates

ASPIRIN

Included in the salicylates is one of the most widely used of all drugs, aspirin, which is sometimes referred to by its chemical name, acetylsalicylic acid. A study carried out in Connecticut, USA, showed that aspirin was present in 37 per cent of blood samples obtained from blood-donor centres; approximately 400 000 tons of the drug are consumed each year in the world. This mass production makes aspirin a very cheap drug.

Aspirin has good analgesic, anti-inflammatory, antipyretic and antiplatelet properties. Aspirin's action as an antiplatelet drug is different from the other anti-inflammatory drugs in that it acts as a non-competitive inhibitor of platelet prostaglandins; **indometacin** and the other NSAIDs act as competitive inhibitors. (See Chapter 46 for a fuller explanation of this.) Aspirin is one of the older known analgesics. It is derived from willow bark in the form salicylic acid (the Latin word for willow is *salix*, hence 'salicylic'). Aspirin, which is prepared from synthetic salicylic acid, takes its name from another Latin term, *Spiraea ulmaria* (meadowsweet), which is another natural source of salicylates. The initial 'a' refers to the acetyl group. To some extent, aspirin can be considered a prodrug, as it undergoes a high hepatic first-pass metabolism to produce salicylic acid. Salicylic acid is just as effective an analgesic as aspirin but has no antiplatelet activity. Historically, salicylic acid was used before aspirin as an analgesic; owing to its taste and irritant properties, however, it did not gain wide acceptance as a drug.

Today, aspirin is promoted in a multitude of different formulations, from fast-release soluble tablets to enteric-coated and slow-release forms. The formulation used depends on the indication and the circumstances of administration. Aspirin is readily hydrolysed in aqueous solutions and consequently is limited in its use as a liquid oral preparation. Liniments containing aspirin dissolved in alcoholic solutions are available to treat sports and other traumatic joint and tissue injuries.

Being weakly acidic, aspirin taken by mouth and entering the stomach is lipophilic. In this state, it can be absorbed through the stomach wall for systemic effects. If taken on a full stomach, aspirin is dispersed with the other stomach contents and thus acts fairly rapidly. Taken on an empty stomach, especially in a solid form, there is a risk of inducing gastric erosions. Under all circumstances, it is prudent to use the buffered or soluble variety of aspirin.

TABLE 40.1 PHARMACOKINETIC CHARACTERISTICS OF NON-STEROIDAL ANTI-INFLAMMATORY DRUGS, ANALGESICS AND ANTIPYRETIC AGENTS

Chemical class	Half-life (hours)	Frequency of administration during the day
Salicylates		
Aspirin	0.25	3–4
Diflunisal	5–20	2
Propionic acid derivatives		
Flurbiprofen	3.8	2–4
Ibuprofen	2	3–4
Ketoprofen	1.8	2–4, 1*
Naproxen	14	2, 1*
Tiaprofenic acid	2–3	2–3
Indoleacetic acids		
Indometacin	2.4–6	2–4
Ketorolac trometamol	4.5	4
Sulindac	15	1–2
Fenamates		
Diclofenac	1.1	2–3
Mefenamic acid	3	3–4
Oxicams		
Piroxicam	48	1–2
Tenoxicam	42–98	1
COX-2 inhibitors		
Celecoxib	4–15	1–2
Etoricoxib	25	1
Paracetamol	3–4	4–6

* Controlled-release preparation.

The soluble, effervescent aspirin preparations are much faster at producing a therapeutic action than the other preparations. Some tablets are available as chewable flavoured tablets and gums in order to improve patient compliance. Aspirin in the small intestine has lipophobic properties but, in view of the enormous surface area of the ileum, absorption is not a problem. For the sake of argument, assume aspirin crosses the gastric mucosa at a rate of 100 molecules per second and at a rate of only two molecules per second in the ileum. The area of the stomach is maybe 1000 cm^2, whereas the ileum has a surface area of 250 000 cm^2. It is easy to see, then, that aspirin absorption is relatively fast in the intestine.

Always bear in mind that aspirin is a prostaglandin inhibitor and can be ulcerogenic by other mechanisms (see Chapter 53).

◆ COMMON ADVERSE EFFECTS

Considering that aspirin is such a widely used drug worldwide, its incidence of complications, as a percentage, is low; some of the complications can be serious, however. Aspirin is often used to treat the pyrexia of febrile diseases such as influenza and chickenpox. There are strong indications that Reye's syndrome may result from such treatment in children and young teenagers. Reye's syndrome is a rare form of encephalopathy with concomitant liver damage, the incidence of which rises when aspirin is used in viral-type diseases in children. This condition occurs in 1 in 2000 treatments. It appears that aspirin induces a further rise in body temperature instead of the expected decrease. The febrile state can induce convulsions, leading to encephalopathy. Aspirin is thus contraindicated in the treatment of febrile and viral infections in children and young teenagers under the age of 16 years. It is also contraindicated during breast feeding.

For normal use as a simple analgesic, aspirin is a fairly safe drug as long as bleeding and/or ulcerative problems do not occur. There is convincing evidence that when combined with caffeine, aspirin's analgesic effect is enhanced. There is also evidence that long-term use of

aspirin to relieve minor aches and pains can cause renal damage. Used in large quantities, for example in rheumatoid arthritis, aspirin can cause tinnitus, which is a sign of overdosing. Like many drugs, aspirin can promote allergic reactions in atopic individuals. This action of aspirin may be due to the fact that, by inhibiting the conversion of arachidonic acid to prostaglandins, the biosynthetic pathway is diverted towards the leukotrienes (see Chapter 30). Aspirin in low doses decreases the renal excretion of uric acid and should be avoided by people with gout, as their symptoms can intensify. Paradoxically, however, large doses of aspirin can increase the renal excretion of uric acid.

Chronic ingestion of aspirin and other NSAIDs can cause papillary necrosis, leading to irreversible renal failure. This type of kidney disease is termed analgesic nephropathy. It is interesting to note that people with rheumatism sometimes ingest 20+ kg of aspirin in their lives. When looked at in the light of these figures, it is not surprising that the body sometimes reacts adversely.

Aspirin has reputedly been shown to prevent bowel cancer when taken regularly, and it has been suggested that aspirin could be useful in the treatment of bowel cancer, but evidence for this is still inconclusive. The NSAID **sulindac** (see below) may also have this property. Pre-eclampsia may be prevented by the consumption of aspirin tablets in the third trimester of pregnancy, although this is still being debated. Usually aspirin is not given late in pregnancy, as it may cause premature closure of the fetal ductus arteriosus.

The effects of the NSAIDs are summarised in Figures 40.1 and 40.2.

ASPIRIN POISONING

Chronic aspirin poisoning can occur in patients using several grams of aspirin per day for conditions such as rheumatoid arthritis. Ear problems such as tinnitus and deafness are indicators of overdosing. If the patient presents with these symptoms as well as epigastric discomfort, sweating, hyperventilation and mental confusion, the dose should be reduced or the drug discontinued.

Acute overdose of aspirin can lead to all of the above symptoms as well as mania, convulsions and, eventually, coma. In overdose, aspirin stimulates the respiratory centre, producing hyperventilation. This leads to respiratory alkalosis, a compensatory metabolic acidosis and dehydration. Fever, tachypnoea, tachycardia and hypoglycaemia may occur. Death is usually due to cardiovascular collapse, respiratory failure or overstimulation of the central nervous system. There is no antidote, but metabolic acidosis may be treated with bicarbonate, which also aids excretion of salicylate by alkalinising the urine. Haemodialysis may be necessary in the severely ill patient.

OTHER SALICYLATES

Diflunisal is a derivative of salicylic acid that causes less gastric distress than aspirin and is of use in inflammatory conditions. Unfortunately, diarrhoea is often a problem with this drug.

Methyl salicylate, or oil of wintergreen, is a common ingredient of liniments used in muscle and joint injuries. If you have used a changing room in a sports stadium, you will probably be familiar with its smell. Methyl salicylate is toxic if given by mouth.

Copper salicylate has been incorporated in creams for the topical relief of arthritic pain in the unproven belief that copper may moderate the course of the disease.

✚ CLINICAL CONSIDERATIONS

With chronic use, it is important to monitor for gastrointestinal bleeding and renal and hepatic dysfunction. The adverse effects of salicylates relating to gastrointestinal bleeding and peptic ulceration are aggravated when administered together with corticosteroids. This combination should, therefore, be avoided.

Propionic acid derivatives

Propionic acid, which is closely related to acetic acid, has been derivatised to produce several common NSAIDs. These are usually easily identified by their generic names, which have the suffix '-profen' or similar (e.g. **ibuprofen**, **ketoprofen**, **tiaprofenic acid**). **Naproxen** is the exception to this naming protocol. With the exception of tiaprofenic acid, the drugs in this group are very similar. Often, the patient's response determines which to use. Tiaprofenic acid is reported to be concentrated in the capsular space of the joints. This may lessen circulating levels of the drug and, thus, reduce adverse systemic effects. Naproxen has a longer half-life than the other propionic acid derivatives and has to be administered only twice a day compared with four times a day. Because of their shorter half-life, sustained or extended-release (ER) forms are available for prolonging the action and lessening the dosage rate of these drugs.

◆ COMMON ADVERSE EFFECTS

The adverse effects of the propionic acid derivatives are gastrointestinal upset (including ulceration), tinnitus, oedema, dizziness, headache, nervousness and rash. Gastrointestinal risk may be less than that with aspirin, and Reye's syndrome has not been reported with these drugs; hence, ibuprofen is now available in syrup form for children. Note that headaches can be an adverse effect of these drugs – which are sometimes used to treat headaches.

✚ CLINICAL CONSIDERATIONS

These drugs are better tolerated than other NSAIDs. As the propionic acid derivatives are metabolised in the liver,

FIGURE 40.1 FLOWCHART SHOWING THE EFFECTS OF NON-STEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDS)

Therapeutic effects are shown in the darker shaded boxes.

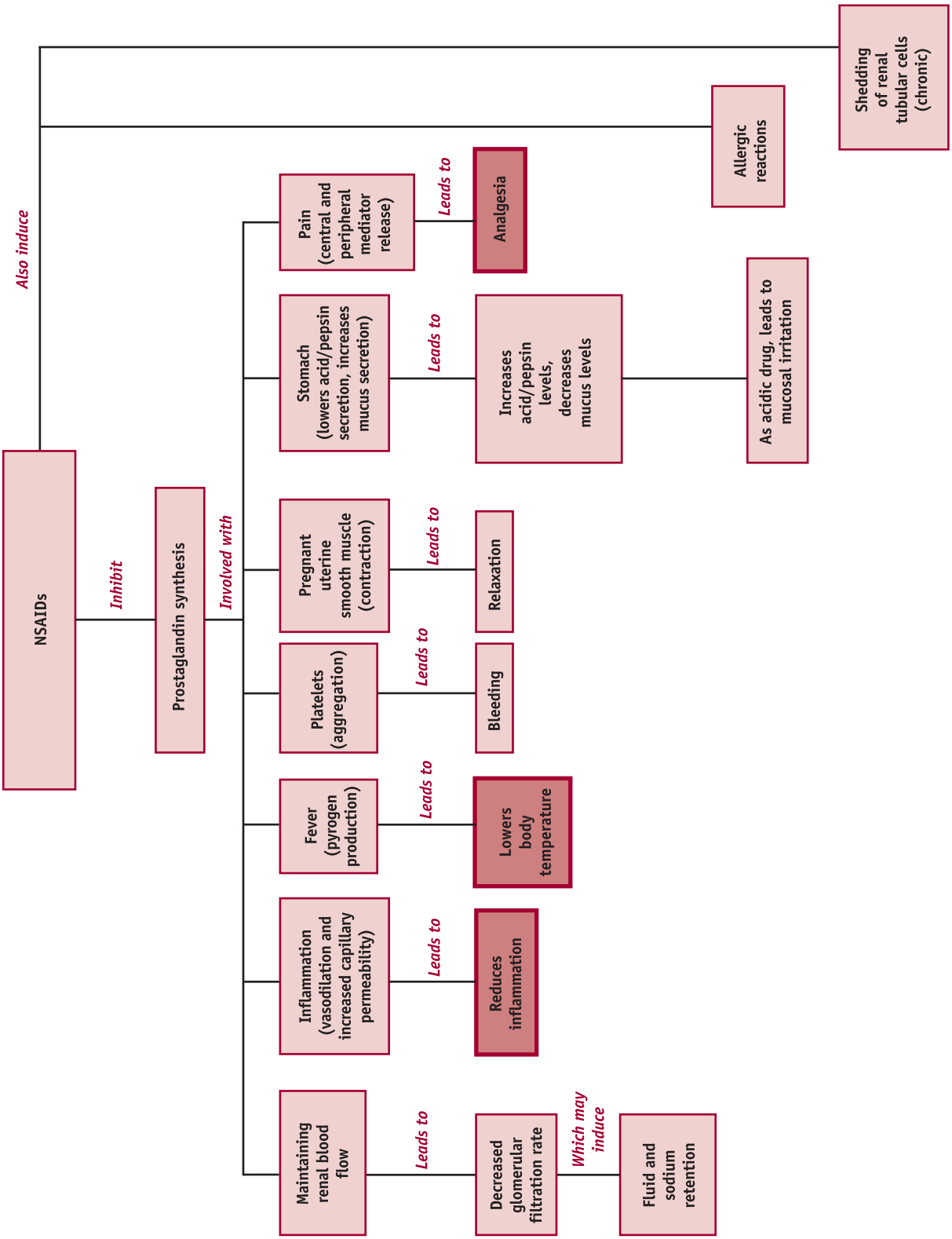
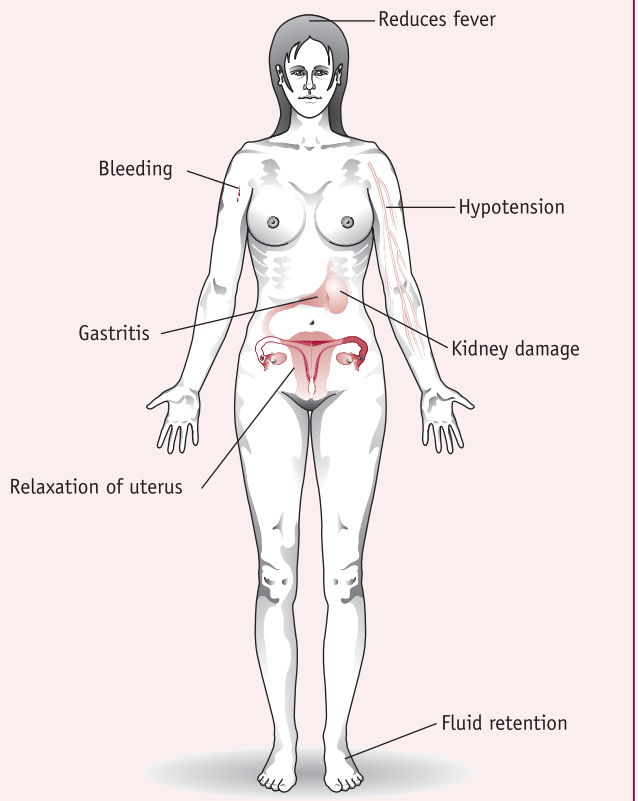


FIGURE 40.2 EFFECTS OF NON-STEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDS)



a lower dose is required in patients with liver conditions. Controlled-release preparations are often taken at bedtime to improve nocturnal and morning symptoms of arthritic pain. Ibuprofen and naproxen are available as oral liquids, which are useful for children with inflammatory disease or fever because the exact dose can be administered.

Indoleacetic acids

This group includes indometacin and sulindac. Sulindac is an example of a prodrug that is inactive itself but is metabolised to its active form in the body.

Related to this group of anti-inflammatories is **ketorolac trometamol**. This is an unusual anti-inflammatory: when administered intramuscularly, it can be as effective as morphine and pethidine in the control of postoperative pain and other prostaglandin-mediated pains. Ketorolac has the added advantage of a longer duration of action and does not induce physical dependence.

◆ COMMON ADVERSE EFFECTS

These drugs are among the most effective of the prostaglandin inhibitors with regard to their anti-inflammatory activity. Not surprisingly, their adverse-effects profile is, therefore, higher. The incidence of gastrointestinal disturbances is in the order of 30 per cent. Central nervous system (CNS) adverse effects occur often with these drugs, especially in elderly patients. The effects include headache, dizziness, confusion and other psychic disturbances. Sulindac is less liable to cause hypertension than other NSAIDs.

Ketorolac has been known to precipitate acute renal failure in some patients, particularly in younger people. There is mounting evidence that this drug is a potent gastric prostaglandin inhibitor and should, therefore, be used with caution in patients with a history of gastritis and/or peptic ulcer.

✚ CLINICAL CONSIDERATIONS

To prolong their action, these drugs can be given as suppositories. Suppository insertion is particularly useful when going to bed, so that the drug is still active when the patient arises the next morning. Suppository insertion is useful in treating acutely painful conditions involving smooth-muscle spasm such as renal colic, especially if given in the early stages of an attack. (Remember that prostaglandins are involved in causing smooth-muscle spasms.)

In view of the high incidence of gastrointestinal problems associated with these medications, patients are strongly advised to take them with meals. Patients who have predisposing gastrointestinal conditions, such as gastric ulceration or bleeding, should carefully monitor the use of these medications. If the patient has black or blood-stained bowel motions or vomits something resembling coffee grounds, the patient must stop taking the medication and contact the doctor.

Fenamates

There are two fenamates in common use – **mefenamic acid** and **diclofenac**. Diclofenac is used often for pain associated with muscle and connective tissue injuries and for rheumatoid arthritis and osteoarthritis. Diclofenac can also be used as an adjunct to other therapies in painful inflammatory infections. Diclofenac has been combined with **misoprostol**, a prostaglandin analogue, which helps to reduce the incidence of peptic ulcer and is recommended for use in patients with a history of peptic ulcer or upper gastrointestinal tract problems (see Chapter 53).

Mefenamic acid is used in the treatment of painful conditions emanating from the uterus, such as dysmenorrhoea. Some gynaecologists state that this drug should be the first-line treatment in such conditions. It is also useful in the treatment of pain resulting from tooth extractions and toothache.

◆ COMMON ADVERSE EFFECTS

Mefenamic acid has little effect on the gastric prostaglandins and at normal dosages gastric problems are rare. Most other anti-inflammatory drugs are likely to result in constipation as an adverse effect, but mefenamic acid commonly

produces diarrhoea. The occurrence of severe diarrhoea warrants discontinuance of the drug. Mefenamic acid is not used very often in severe inflammatory conditions. This is mainly because long-term therapy has caused a fall in haematocrit and haemoglobin levels in blood and because of the high incidence of diarrhoea. Diclofenac is often involved in gastrointestinal effects.

✚ CLINICAL CONSIDERATIONS

In view of the relatively low incidence of gastrointestinal problems with these drugs, they may be considered for patients who suffer from gastrointestinal bleeding or ulceration. Diclofenac is available as a suppository formulation, which can be administered at bedtime to control nighttime and morning pain. Patients taking mefenamic acid are advised to monitor the incidence of diarrhoea and to stop taking the medication if it occurs.

Oxicams

The available oxicams, **piroxicam** and **tenoxicam**, have the advantage of long half-lives, especially tenoxicam, whose half-life is over 1 week. This requires less frequent dosing, but it takes longer for blood levels to attain a steady state.

◆ COMMON ADVERSE EFFECTS

Piroxicam has a half-life of about 2 days, and steady-state levels are attained in about 10 days. One might think that by giving a loading dose of these drugs, steady-state levels could be obtained quickly in the bloodstream. If this is done with tenoxicam, however, toxic effects are frequent due to sudden overloading of the system with the drug. Because of this, it is more prudent to initialise the patient on a once-daily regimen. This is of great importance, as this group of drugs is renowned for causing gastric problems. Other effects are increased bleeding time, dizziness, headache and ocular changes, for example blurred vision.

✚ CLINICAL CONSIDERATIONS

As piroxicam and tenoxicam have very long half-lives compared with other NSAIDs (30–50 hours and 42–98 hours, respectively), they need to be taken only once daily. This dosage frequency may be important for patients who need to take several medications or who have busy activity schedules.

Cyclo-oxygenase (COX-2) inhibitors

This new class of NSAIDs was fast becoming an important alternative treatment for inflammatory conditions until the safety of the drugs was questioned following trials showing an increased risk of thrombotic events with rofecoxib compared with placebo. Rofecoxib (Vioxx™) was voluntarily withdrawn worldwide by the manufacturer in September 2004.

■ MECHANISM OF ACTION

The enzyme that the NSAIDs inhibit is a COX. COX is present in the body as isoenzymes: that found in the stomach, intestine and platelets is COX-1 and that in the joints and tissues is COX-2. The COX enzymes are similar as far as their function is concerned, but their active centres are dissimilar, hence the different names (such enzymes are termed isoenzymes). COX-2 inhibitors, at therapeutic concentrations, have little or no inhibitory effect on the COX-1 enzyme. This breakthrough was thought to be advantageous, because the COX-2 inhibitors do not, in theory, cause peptic ulcers as they have no effect on gastric secretions, but they will help to relieve the inflammation and pain associated with rheumatoid arthritis and osteoarthritis and probably all other types of musculoskeletal pain and inflammation.

The COX-2 inhibitors **celecoxib**, **etoricoxib**, **meloxicam** and **parecoxib** are beneficial in all types of musculoskeletal pain, and are perhaps superior to the NSAIDs, although parecoxib is recommended only for postoperative pain and inflammation. Parecoxib is a prodrug, as it is metabolised in the body to its active form, valdecoxib. Meloxicam is an oxicam but, unlike tenoxicam and piroxicam, it is relatively selective for the COX-2 enzyme.

◆ COMMON ADVERSE EFFECTS

The incidence of severe gastrointestinal problems with COX-2 inhibitors is low and comparable with placebo, but mild problems akin to dyspepsia are common. As these drugs can inhibit some of the cytochrome P450 system enzymes, concomitant use of other drugs can be problematic; current contraindications should be checked before use, and adverse effects with other drugs should be considered possible. This should always be the case with new drugs (as with established ones). COX-2 inhibitors are contraindicated in patients with a history of peptic bleeding/ulcers and liver disorders. Long-term effects on the kidney and other systems are unknown.

The isoenzyme COX-2 is responsible for the production of prostacyclin in the endothelium of blood vessels. If this is inhibited, then the platelet adhesion to the vessel wall is likely to be greater. As the COX-2 inhibitors do not affect platelet function or offer any anti-thrombotic cardiovascular protection, this may increase the risk of heart attacks and strokes in susceptible patients.

✚ CLINICAL CONSIDERATIONS

For patients who have coexisting cardiovascular disease, the use of non-selective NSAIDs rather than selective COX-2 inhibitors, such as celecoxib, is preferable. This is because selective agents do not reduce platelet aggregation and may also increase prothrombotic activity, therefore aggravating a cardiovascular condition. As selective COX-2

inhibitors are metabolised in the liver, hepatic impairment can increase the blood concentration of these agents; it is preferable to use a low starting dose in patients with hepatic impairment. Selective COX-2 inhibitors should be used in preference to standard NSAIDs only when indicated specifically (e.g. if there is a high risk of gastrointestinal ulcers) and after an assessment of cardiovascular risk. They should not be given to patients with a history of ischaemic heart disease. Parecoxib is available only for intramuscular and intraveous injection and is useful for postoperative pain. Celecoxib appears to be prophylactic in adenomatous polyps of the colon.

Other analgesics

PARACETAMOL

Paracetamol (known as acetaminophen in the USA) is an analgesic agent. It has no significant anti-inflammatory activity or antiplatelet activity. It does have antipyretic properties, however, which makes it a useful analgesic in febrile illnesses such as influenza.

Paracetamol is often advertised as being gentle to the stomach. This is because other analgesics with anti-inflammatory properties are usually acidic in nature and, by inhibiting stomach prostaglandin synthesis, lead to excessive production of hydrochloric acid and pepsin (see Chapter 53). As an analgesic, paracetamol is best taken on an empty stomach for fast action, as a full stomach will lead to slower absorption rates. As it is not associated with Reye's syndrome, it is the preferred analgesic in the symptomatic treatment of children with viral infections.

■ MECHANISM OF ACTION

The mechanism of action of paracetamol is now thought to be via COX-3 inhibition. This recently discovered isoenzyme is present in the brain and the spinal cord and is selectively inhibited by paracetamol. Paracetamol has no significant action on COX-1 or COX-2, which explains its lack of anti-inflammatory action and gastric side effects. The central action of paracetamol explains its antipyretic effect and its lack of other peripheral adverse effects associated with the NSAIDs.

◆ COMMON ADVERSE EFFECTS

In spite of the favourable aspects of paracetamol, it is in many respects more dangerous than other NSAIDs if taken in excess. The therapeutic index of paracetamol can be as low as 15, and overdosing with it is insidious. In the early years of its introduction (the 1950s), people who overdosed on paracetamol were admitted to hospital, perhaps had gastric lavage, were kept under observation overnight and discharged apparently well the next day. Three days later they were dead. The cause of death was acute liver failure. This is still the case if appropriate treatment is not initiated within 8–12 hours of overdose. There was a case in 1998 of a young woman dying of liver failure after the ingestion of only ten tablets of paracetamol. The therapeutic index of paracetamol has been placed as low as 1.7 in children under 4 years old. These two incidences should be considered carefully when using paracetamol, especially in babies and young children, and paracetamol should never be thought of as a safe drug. (See Chapter 22 for a detailed discussion of the treatment of paracetamol poisoning.)

Heavy alcohol drinkers are more susceptible than non-drinkers to paracetamol poisoning; this may be due to the fact that the enzyme-inducing properties of ethanol increase the rate of conversion of paracetamol to its toxic metabolite.

Aspirin and paracetamol are often combined with the narcotics codeine and dextropropoxyphene, which reputedly are synergistic combinations. This type of combination is not always desirable, especially with dextropropoxyphene (being withdrawn slowly in the UK). The half-lives of the drugs are vastly different (aspirin ~4 hours, dextropropoxyphene ~12 hours). The effect of the aspirin thus wears off before that of the dextropropoxyphene, which may mean the patient repeats the dose of the mixture long before blood levels of dextropropoxyphene have dropped significantly. This may lead to excessively high levels of dextropropoxyphene in the blood, with resultant respiratory depression, which could prove fatal.

✚ CLINICAL CONSIDERATIONS

As several brands of paracetamol are available, individuals need to exercise extreme care in checking the strength of the particular preparation and the correct dose. A lack of awareness of the different strengths of paediatric preparations may lead to overdose and liver damage. Parents and caregivers need to exercise extreme diligence to ensure the appropriate dose is given according to the child's body weight. Other than the potential problem relating to liver damage, which can be controlled easily by keeping to an appropriate dosage schedule, paracetamol is preferable to other NSAIDs for mild to moderate pain relief.

In relation to febrile symptoms, paracetamol effectively reduces fever, but it does not affect the cause or prevent febrile convulsions. In fact, a febrile response indicates that the body's immune system is working to combat microorganisms. Thus, a low-grade fever of about 37.5–38.5 °C does not warrant paracetamol treatment unless the child is feeling particularly uncomfortable. Other non-pharmacological measures should be instigated, including providing fluids, tepid sponges, and loose lightweight clothes. The usual adult dose of paracetamol is 4 g

daily. For the best response, the dose is taken as two tablets or capsules (e.g. 500 mg for each tablet or capsule) and repeated every 4–6 hours.

NEFOPAM

Nefopam is a centrally acting analgesic completely unrelated to all other analgesics. In many respects, it is similar to the antimuscarinic drugs, especially with regard to its side effects. Nefopam can be given parenterally or by mouth and has a rapid onset of action. It is useful in the treatment of many types of acute pain, such as post-operative and traumatic pain.

MISCELLANEOUS DRUGS USED IN INFLAMMATORY CONDITIONS

The NSAIDs, including the COX-2 inhibitors, are the first-line treatment in the relief of symptoms of rheumatoid diseases. If symptoms and degeneration continue unabated, other drugs may be considered, although some rheumatologists emphasise that the alternative drugs are underutilised. These drugs are sometimes referred to as slow-acting antirheumatic drugs (SAARDs) or disease-modifying antirheumatic drugs (DMARDs). A description of these drugs is given below.

CHLOROQUINE AND HYDROXYCHLOROQUINE

Both **chloroquine** and **hydroxychloroquine** are used in the treatment and prevention of malaria. They were found accidentally to improve some of the arthritic conditions found in systemic lupus erythematosus (SLE). Their mechanism of action is not known.

◆ COMMON ADVERSE EFFECTS

These drugs, especially chloroquine, have a high incidence of adverse effects if given for long periods, and it is sometimes recommended that they are not given for more than 1 year. Prolongation of treatment with these drugs is sometimes achieved by stopping the drug for 3 months every half-year – that is, giving the occasional 'drug holiday'. The adverse effects are mainly ocular, and regular ophthalmic examinations are advised.

✚ CLINICAL CONSIDERATIONS

It is preferable to use hydroxychloroquine rather than chloroquine in musculoskeletal conditions because the former has a lower incidence of ocular toxicity. Before treatment is commenced, it is important to undertake a baseline ocular examination in patients over the age of 40 years and in those who have a family history of eye disease. Visual acuity should be checked once a year during treatment.

GOLD COMPOUNDS

■ MECHANISM OF ACTION

Gold compounds appear to modify the immune response by affecting the migration of immunocompetent cells to sites of inflammation and by stabilising the lysosomal membranes. Although the gold compounds are relatively toxic, their advantage is that they may alter the course of some forms of rheumatoid arthritis. Their effect is of very slow onset (about 3–4 months), and concurrent therapy with NSAIDs is advisable. If no response is noticeable after this length of time, there is usually no point in continuing with the treatment. There are two forms of gold commonly used. Sodium **aurothiomalate** is an injectable form, usually given as a weekly injection at least initially. **Auranofin** is an oral preparation that may be as good as the aurothiomalate and may, eventually, completely supersede the injectable compound, as its adverse-effects profile is less severe.

◆ COMMON ADVERSE EFFECTS

Approximately 30 per cent of patients on gold therapy may have to discontinue the drug because of adverse effects. The common adverse effects are related mainly to lesions of the skin and mucous membranes. Blood dyscrasias can occur, and blood tests should be performed on patients taking gold therapy regularly. Another problem is proteinuria due to renal damage. This can be tested for easily by performing regular urinalysis. Patients should be instructed to report any untoward effects immediately, as continuing treatment may result in irreversible damage to the haemopoietic, renal and hepatic systems and the CNS.

✚ CLINICAL CONSIDERATIONS

Before the patient receives oral or intramuscular gold therapy, various tests need to be performed, including urinalysis, complete blood examination and platelet count. These tests are repeated regularly during treatment. Gold therapy is ceased if the patient has significant proteinuria or haematuria. Similarly, if the patient has a low platelet count or if signs of thrombocytopenia, such as bleeding or bruising, are apparent, then the gold therapy should be ceased. Sun exposure can lead to dermatitis, and the patient should be encouraged to take precautions in the sun.

PENICILLAMINE

Penicillamine is a compound often used as a chelating agent in cases of heavy-metal poisoning. Penicillamine is used to treat toxicities that may occur during gold therapy for rheumatoid diseases, as well as being used to treat those conditions. Like the chloroquines, the use and value of penicillamine is in rheumatoid diseases, mainly rheumatoid arthritis. It is of little use in SLE, but it is useful in

the treatment of ankylosing spondylitis. Penicillamine is pharmacologically unrelated to penicillin and is a derivative of the amino acid cysteine. It is formed as a breakdown product of penicillin.

■ MECHANISM OF ACTION

Penicillamine's action is probably due to the suppression of immunoglobulin production by B-lymphocytes. It may also have an immunosuppressive effect on T-cells.

◆ COMMON ADVERSE EFFECTS

Like gold, penicillamine has a broad spectrum of adverse effects, which limits its use. Rashes, gastrointestinal problems and allergy to penicillamine commonly cause patients to discontinue taking this drug. Blood dyscrasias and renal damage should be checked for regularly by routine blood and urine examinations. Breast engorgement can occur in women. It has been noted that SLE, a rheumatoid disease, and some other autoimmune diseases can be induced by penicillamine.

✚ CLINICAL CONSIDERATIONS

A full blood examination and urinalysis are performed about every 2 weeks until the penicillamine dose is stabilised. In view of the potential of pencillamine to cause blood dyscrasias, the drug is stopped if the white blood cell count or platelet count drops, if proteinuria or haematuria occurs, or if fever or a rash is present. A baseline neurological examination is also carried out to determine any pre-existing problems in this area. Patients are advised to stop treatment after 6 months if there is no apparent benefit, because of its broad range of serious adverse effects.

SULFASALAZINE

Sulfasalazine is dealt with more fully in Chapter 54, its main use being in the treatment of inflammatory bowel diseases. In rheumatoid arthritis, the drug must be given in fairly high doses compared with those for ulcerative colitis; even so, it is generally tolerated well. The most common problem with sulfasalazine is dyspepsia. Blood dyscrasias and hepatotoxicity have been noted, and it is prudent to perform blood counts and liver function tests regularly in patients taking sulfasalazine.

IMMUNOSUPPRESSIVE DRUGS

Apart from **etanercept**, immunosuppressive drugs are dealt with fully in Chapters 58 and 75. As a few of these drugs are used in the treatment of severe rheumatoid arthritis, a brief mention of them is given here. The corticosteroids are very potent anti-inflammatory compounds that can be used to relieve the pain of rheumatoid arthritis. They modify the course of the disease only at high doses. High doses of corticosteroids have considerable adverse effects, which preclude them from use as DMARDs. The corticosteroids used in rheumatoid arthritis are usually **prednisone** and **prednisolone**. Generally, corticosteroids are used only if NSAIDs are problematic, although intralesional corticosteroid therapy may have long-term action in synovitis. The longer-acting and more potent corticosteroids tend to be associated with more problems and generally are avoided, unless deemed absolutely necessary.

In patients refractory to all other drugs, and if the condition warrants it, treatment may be given using immunosuppressive drugs usually reserved for the treatment of neoplasia. Those commonly used are **methotrexate**, **azathioprine**, **chlorambucil** and **cyclophosphamide** (see Chapters 75 and 76). Methotrexate is the preferred agent, as it has a lower incidence of adverse effects; whichever drug is used, the patient must be observed closely for potentially serious adverse effects on the haemopoietic, pulmonary and hepatic systems.

ETANERCEPT

■ MECHANISM OF ACTION

One of the natural mediators of immunity is tumour necrosis factor (TNF), which is found in the synovial fluid of patients with rheumatoid arthritis. Etanercept is a modified receptor for TNF, which is prepared by recombinant DNA technology. It binds specifically to TNF, thus inactivating it.

◆ COMMON ADVERSE EFFECTS

Adverse effects include an increased risk of infections, especially of the upper respiratory tract in children, and worsening of congestive heart failure and allergic reactions.

✚ CLINICAL CONSIDERATIONS

The dose regimen of immunosuppressive drugs can be quite complex. For instance, methotrexate is usually given as a weekly dose. Patients should, therefore, be provided with comprehensive details about the dose, time and day of administration. Due to the long-term adverse effects associated with corticosteroids, such as osteoporosis and difficulty in weaning, their use should be monitored carefully.

Etanercept is given only when the response to DMARDs has been negative. It may be given with methotrexate for a better response and is given only by intramuscular injection.

MISCELLANEOUS ANALGESIC AGENTS

CAPSAICIN

Capsaicin is prepared from hot peppers and has been used since ancient times as a local anaesthetic. Some of its pharmacology was considered in Chapter 39, as its

mechanism of action helps to explain the transmission of painful stimuli. Some superficial conditions can cause extreme pain, for example post-herpetic neuralgia as a result of shingles, and diabetic neuropathy. These two conditions do not respond well to conventional analgesia using either narcotics or peripheral-acting analgesics; Capsaicin applied topically, however, is often very effective. Initial application of capsaicin produces hyperalgesia, but with continued application this disappears – along, usually, with the original pain. It is important that the preparations are applied regularly and frequently (three to four times a day), otherwise the therapeutic effect may not be attained initially or sustained after reaching therapeutic control; this is because levels of substance P will start to rise during missed applications. Compliance in the early stages of treatment is often poor due to the hyperalgesia, burning and stinging sensations produced. (Note that these reactions may detract from the real pain due to the counterirritant theory discussed in Chapter 78.) Sometimes this initial reaction is so bad that a local anaesthetic such as lidocaine gel has to be applied concurrently. These preparations must not be applied to broken or inflamed skin, or to the lesions of active herpes zoster (shingles). There do not appear to be any long-term effects of capsaicin on the body, but intravenous injection in animals has produced neurotoxic reactions. The significance of this in humans is at present unknown. As many peoples around the world have been consuming vast amounts of capsaicin-containing foods for most of their lives without any signs of neurotoxicity or other adverse effects, it is likely that none will be forthcoming with the use of capsaicin in clinical practice. This is not to say that vigilance should be dropped, however. The cough sometimes seen with capsaicin application is probably due to the inhalation of dried material from the application site. Capsaicin also has proven benefit in the relief of arthritic pain.

✚ CLINICAL CONSIDERATIONS

As there is a risk of photosensitivity with the use of topical preparations containing capsaicin, patients should be advised to avoid exposure of affected areas to sunlight. Additional first-aid treatment of soft-tissue injuries during the first 72 hours includes rest, ice, compression and limb elevation.

CLINICAL MANAGEMENT

Non-steroidal anti-inflammatory, antipyretic and analgesic drugs

Assessment

- Assess for the patient's specific complaint, which may involve arthritis, headache, menstrual cramps, post-operative pain or musculoskeletal injury. For patients with arthritis, assess joint function and ability to perform activities.
- Assess baseline vital signs and compare with subsequent observations.
- Determine whether there is any history of gastric bleeding, gastric irritation or liver disease. Several of these drugs are prone to causing gastric irritation. Caution should also be used when administering in patients with cardiovascular or renal impairment. Note, however, that paracetamol does not cause gastric irritation or alter platelet stickiness or clotting times.
- Blood tests confirm the diagnosis and monitor the progression of rheumatoid arthritis. These tests include erythrocyte sedimentation rate (ESR), rheumatoid factor and antinuclear antibody (ANA).
- Establish the patient's history for allergies before administration. In patients with a documented history of hypersensitivity, a possible anaphylactic reaction could be life-threatening.
- Assess female patients for pregnancy. Aspirin should not be taken in the third trimester of pregnancy.

Planning

- The patient will have relief from pain and show improvement in the ability to perform activities. It is also important to determine ways of preventing or treating recurrences.
- For patients with rheumatoid arthritis, the aim is to improve joint function.
- For the patients taking this drug for an infection, the patient will have a reduced fever. The underlying cause of the fever will be determined and treated, if possible.

Implementation

- Monitor the drug's effect on the patient's specific condition.
- Administer the medication with a full glass of water and ask the patient to remain sitting upright for 15–30 minutes to prevent the tablets from becoming lodged in the oesophagus.
- Administer tablets with a meal in order to minimise gastric irritation. Note that paracetamol does not produce gastric irritation.
- If the patient is taking the drug for fever, monitor the patient's temperature regularly. Also note the presence of diaphoresis, chills and level of consciousness.

- For patients taking the drug for fever, maintain an adequate fluid intake and monitor fluid input and output in order to ensure the patient is not experiencing a negative fluid balance.
- For patients taking the drug for fever, determine the sites of infection that could give rise to the elevated temperature.
- As these agents have an effect on reducing clotting (except for paracetamol), the patient should be monitored for manifestations of bleeding, including epistaxis, bleeding gums and bruising. Haemoglobin and haematocrit levels should also be checked periodically.
- Implement comfort measures for fever, including tepid sponges and light clothing. Change linen regularly.
- Monitor temperature every 4 hours for a fever.
- Rectal administration through suppositories is useful in children and in individuals for whom the oral route is not possible.
- Aspirin should be stopped 7 days before surgery to fully restore platelet production and function.

Patient teaching

- Encourage the patient to comply with the prescribed regimen.
- The doctor should be notified immediately if bleeding, rash, flu-like symptoms, swelling of legs or feet, gastrointestinal distress, dizziness, reduced urine output, visual disturbance or tinnitus occurs. These are toxic effects of aspirin and other non-steroidal anti-inflammatory drugs. The most common adverse effect associated with paracetamol is rash.
- Instruct the patient to take the medication with meals or with milk to minimise gastric irritation; this is not a problem with paracetamol.
- Inform the patient to check with the pharmacist or doctor before taking any over-the-counter medications.
- Advise the patient to avoid alcohol and drugs that are highly protein-bound, such as anticoagulants. Aspirin and other non-steroidal anti-inflammatory drugs displace highly protein-bound drugs from protein sites, causing more free anticoagulant. Bleeding time therefore increases, and haemorrhage may occur.
- Instruct parents not to administer aspirin for flu-like symptoms in children under 12 years. Reye's syndrome, associated with delirium, vomiting, lethargy, hepatic injury, encephalopathy and coma, may occur. Paracetamol is considered a safe alternative for viral conditions in children.
- Instruct the patient to report any manifestations of allergy, such as hives, rash and itching.
- Sustained-release and enteric-coated preparations must be swallowed whole.
- Instruct the patient that aspirin tablets and capsules should be removed from the packaging immediately before use. Aspirin degrades quickly in the presence of air and moisture.

Evaluation

- Evaluate the effectiveness of the drug to reduce pain, inflammation and fever.
- Determine whether the patient is experiencing any adverse effects from the drug.

SUMMARY

- Pain and inflammation are caused by some of the prostaglandins.
- Drugs that inhibit (the synthesis of) prostaglandins associated with pain and inflammation are called non-steroidal anti-inflammatory drugs (NSAIDs).
- Most of the NSAIDs inhibit prostaglandins in the gastric mucosa and can cause peptic ulcers.
- Some of the newer NSAIDs do not inhibit gastric prostaglandins and are termed cyclo-oxygenase 2 (COX-2) inhibitors.
- Paracetamol is a COX-1 prostaglandin inhibitor but, as it is non-anti-inflammatory, it is not considered an NSAID.
- Drugs that suppress the immune system and are useful in rheumatoid arthritis are termed disease-modifying rheumatoid arthritis drugs (DMARDs).
- DMARDS have diverse mechanisms of action.
- Aim for early and proactive control of pain. Preventing pain should be the goal of care rather than treating pain already present.
- Regular fixed-dose scheduling is preferable to as-required scheduling.
- Take medications with meals to decrease gastrointestinal irritation.
- Do not administer aspirin with other NSAIDs because of the potential for increasing the incidence of adverse effects.
- Oral analgesics are suitable for moderate acute pain if the patient is able to swallow. The oral route is also preferable for patients with chronic pain because of the lower risk of potential complications.

1. Why would aspirin be an unsuitable analgesic after a tonsillectomy?
2. List five disadvantages of aspirin use.
3. A bottle of aspirin tablets is labelled 'Aspirin 300 mg', yet on being weighed the tablet is 360 mg. Would this be correct?
4. What is meant by 'buffered aspirin'?
5. Why are asthmatic people usually not able to take aspirin?
6. What are three advantages of paracetamol over aspirin?
7. What are three advantages of aspirin over paracetamol?
8. Why could paracetamol prove to be problematic if given to an alcoholic patient?
9. Indometacin and other non-steroidal anti-inflammatory drugs are often administered rectally, and yet stomach ulcers can still occur. Why?
10. Why are salicylates often present in liniments for sports injuries?
11. What advantage would the use of an indometacin topical spray have over oral therapy in treating the pain of a pulled muscle?
12. What are two major adverse effects of hydroxychloroquine?
13. Why are full blood counts performed routinely on patients undergoing therapy with the slow-acting drugs used in the treatment of rheumatoid arthritis?
14. Edgar Siodmark, a 25-year-old patient, complains of pain following removal of a toenail. What type of analgesic would you advise, and why? What analgesics would be contraindicated, and why?
15. Matilda Riggs, an 80-year-old patient with rheumatoid arthritis, complains of gastrointestinal irritation following ingestion of indometacin tablets. What alternative type of indometacin formulation would you recommend? How would this formulation assist in decreasing gastrointestinal irritation?
16. Tomichi Hashimoto, a 55-year-old executive director, takes aspirin 100 mg orally each morning for treatment of atherosclerosis. Explain how aspirin produces this effect.
17. Nick Erbakan, a marathon runner, often uses a preparation containing methyl salicylate and aromatic compounds on a nagging calf injury. Why would you advise him to wash his hands before handling his baby son, James?
18. Emily Hickey, a 75-year-old patient with rheumatoid arthritis, is ordered ibuprofen sustained-release tablets. She asks you whether she could crush the tablets and mix them with peanut butter before swallowing. What would be your reply to her, and why?
19. Why is aspirin contraindicated in a patient who is taking warfarin following a heart-valve replacement?

40 DRUG SUMMARY TABLE: NON-STEROIDAL ANTI-INFLAMMATORY, ANTIPYRETIC AND ANALGESIC DRUGS

FAMILY NAME	GENERIC NAME	TRADE NAME(S)
Salicylates	Aspirin	Caprin
		Nu-Seals Aspirin
		Disprin
	Methyl salicylate + Aromatic	Deep Heat
Non-steroidal anti-inflammatory agents	Diclofenac	Diclomax
		Motifene
		Voltarol
	+ Misoprostol	Arthrotec
	Diflunisal	Dolobid
	Etodolac	Lodine SR
	Fenbufen	Lederfen
	Fenoprofen	Fenopron
	Flurbiprofen	Froben SR
	Ibuprofen	Brufen
		Fenbid
	+ Codeine	Codafen Continus
	Indometacin (indomethacin)	Flexin Continus
	Ketoprofen	Orudis
		Oruvail
	Ketorolac	Toradol
	Mefenamic acid	Ponstan
	Nabumetone	Relifex
	Naproxen	Naprosyn
		Synflex
	+ Misoprostol	Napratec
	Piroxicam	Brexidol
		Feldene
	Sulindac	Clinoril
	Tenoxicam	Mobiflex
	Tiaprofenic acid	Surgam
COX-2 inhibitors	Celecoxib	Celebrex
	Etoricoxib	Arcoxia
	Meloxicam	Mobic
	Parecoxib	Dynastat
Miscellaneous	Acetylcysteine	Parvolex
	Auranofin	Ridaura
	Aurothiomalate	Myocrisin
	Azathioprine	Imuran
	Benzydamine	Difflam
	Capsaicin	Axsain
		Zacin
	Chlorambucil	Leukeran
	Chloroquine	Avloclor
		Malarivon
		Nivaquine

FAMILY NAME	GENERIC NAME	TRADE NAME(S)
	Cyclophosphamide	Endoxana
	Etanercept	Enbrel
	Hydroxychloroquine	Plaquenil
	Methionine	
	Methotrexate	
	Nefopam	Acupan
	Paracetamol	Calpol
		Medinol
		Paldesic
		Panadol
	Penicillamine	Distamine
	Prednisolone	
	Sulfasalazine	Salazopyrin

GENERAL ANAESTHESIA

41

CHAPTER FORTY-ONE

OBJECTIVES

After completing this chapter, the reader should be able to:

- **outline the effects of general anaesthetics;**
- **describe the use of anaesthetics in the induction and maintenance of general anaesthesia;**
- **explain the action of anaesthetics within the central nervous system;**
- **list the stages of anaesthesia;**
- **give the rationale for the use of neuromuscular blocking agents in anaesthesia;**
- **define the importance of premedications before anaesthesia.**

KEY TERMS

Neuroleptanalgesia
Pharmacokinetics
Premedication
Routes of administration
Stages of anaesthesia

THROUGHOUT THE CENTURIES, PEOPLE HAVE STRIVEN TO conquer pain, especially that caused during surgical procedures. Operative procedures were always limited in their success by two main factors: postoperative infections and the agonising pain that occurred during the procedure. If the patient did not succumb to the operative procedure, then death from a postoperative infection usually ensued. For several centuries, the opiates and/or alcohol were the mainstay of 'anaesthetists' in their control of pain. These substances had limited success, but they were probably better than nothing. Their main limitation was that, to produce insensitivity to pain, deep sleep or unconsciousness was necessary, and the amount of the substances needed to do this would be potentially fatal.

It was not until the 1840s that surgical anaesthesia became possible, with the introduction of three agents in quick succession: **chloroform**, **ether** and **nitrous oxide**. These three substances, following inhalation, quickly lead to unconsciousness, and surgical anaesthesia is produced. Nitrous oxide is still a widely used gaseous anaesthetic, and diethyl ether (ether) is used occasionally. Chloroform is used rarely today because of its toxicity, but other, newer halogenated hydrocarbons, such as **isoflurane**, are extremely common.

Inhalation anaesthetics are the principal agents used in the maintenance of anaesthesia, but intravenous agents are most commonly used in the induction of anaesthesia.

Surgical anaeshesia is a reversible state of unconsciousness produced by drugs, with sufficient depression of the reflexes to allow an operation to be performed. Before a patient reaches surgical anaesthesia, they go through several stages (see below). These were described by Guedel in 1937 in unpremedicated patients breathing diethyl ether in air. With modern techniques and equipment, the stages may occur too rapidly to be recognised or distinguished.

STAGES OF ANAESTHESIA

Stage 1: analgesia

Pain is the first sense to be abolished and consciousness is still retained. This type of anaesthesia is often used in childbirth and in trauma in the form of Entonox™, which is a mixture of nitrous oxide and oxygen. The patient inhales the gas until pain recedes, but not enough to reach the unconscious state, thus maintaining some control over the situation. The sense of hearing is often enhanced in this stage. Operating-room personnel should be aware of this when induction with anaesthetic gases is used: The patient may appear to be unconscious, and probably is to a certain extent, but he or she can still hear. Comments passed between staff may be recalled later by the patient, which could cause embarrassment on both sides. Normal reflexes are present and stage 1 ends with loss of the eyelash reflex and unconsciousness.

Stage 2: excitement (delirium)

As the name suggests, this may not be a pleasant stage of anaesthesia. The patient can suffer from fitting and become violent. A sense of extreme fear may be felt, which could produce a phobic response to any suggestion of anaesthetics in the future. There may be irregular breathing and struggling, the pupils are dilated, and vomiting, coughing and laryngospasm may occur. It is important that the passage from stage 1 to stage 3 be attained as quickly as possible. Stage 2 ends with loss of the eyelid reflex.

Stage 3: surgical anaesthesia

This stage is characterised by progressive muscular relaxation and is subdivided into four planes. Muscle relaxation is important during many surgical procedures, as reflex movements can occur when a scalpel slices through the tissues. This muscular relaxation ends in respiratory paralysis and, unless the patient is attached to a ventilator, death ensues fairly quickly. Reflexes are abolished with high delivery rates of gaseous anaesthetics, but the dividing line between the desired state and respiratory paralysis is narrow. This required careful judgement by early anaesthetists. The knowledge of when to reduce the amount of anaesthetic given to maintain surgical anaesthesia, but not enough to return to stage 2, was gained only through experience. Various reflexes of the body, such as corneal reflexes and pupillary size, could be used as indicators of when this stage was reached.

Neuromuscular blocking agents (surgical muscle relaxants) are available (see Chapter 27) to make anaesthesia much safer, as less anaesthetic has to be given.

Stage 4: medullary paralysis (overdose)

This stage begins with respiratory failure and can lead to circulatory collapse. Through careful monitoring, this stage is avoided. If this stage is reached, it is termed an 'anaesthetic accident'.

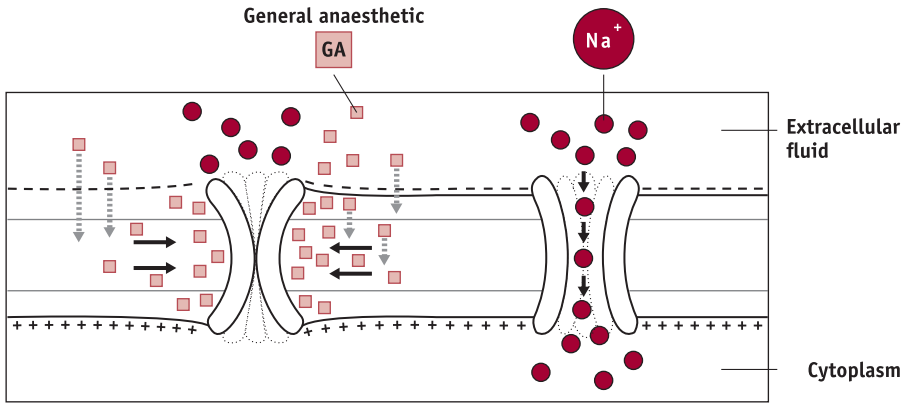
In the induction of anaesthesia with intravenous anaesthetic agents, stages 1–3 merge so quickly into one another that they are not apparent. In the emergence from anaesthesia, the stages may be seen in reverse order.

MECHANISM OF ACTION OF GENERAL ANAESTHETICS

In many respects, the mechanism of action of general anaesthetics is thought to be similar to the action of local anaesthetics, except that the action of the former is confined principally to the central nervous system (CNS). A common property of general anaesthetics is that they are all very lipophilic. This is essential, as the drug must cross the blood–brain barrier to be effective. Cell membranes are, by nature, both lipophilic and hydrophilic, depending on the site in the membrane. The lipid layers are interspersed with islands of proteins, and it is thought that the sodium channels are present in these protein islands. When the lipophilic anaesthetic enters the lipid membrane, the whole membrane is slightly distorted and squeezes the sodium channels, causing a marginal blockage. This then prevents neural conduction. This is shown diagrammatically in Figure 41.1.

Different parts of the CNS are more sensitive to this action than others; conveniently, those of the respiratory centre are less sensitive. This does not explain everything, as many very lipophilic compounds do not act as general anaesthetics and some anaesthetics are not fat-soluble. Those that are not fat-soluble probably exert their action by other mechanisms, as is the case with the benzodiazepines

FIGURE 41.1 EFFECT OF GENERAL ANAESTHETICS ON SODIUM CHANNELS



Note the swelling next to the channels

(see Chapter 34). Some of the general anaesthetics that are liquid at room temperature are so lipophilic that they would be useful as stain removers or could be used in dry cleaning.

PHARMACOKINETICS OF INHALATION ANAESTHETICS

As these drugs are gases or volatile liquids, and absorption is from the lungs, their pharmacokinetic properties are rather different from those of most drugs, and their administration cannot be measured in conventional dose forms. Even using the percentage concentration of the anaesthetic gas or vapour in the administered mixture does not give an exact indication of how much of the anaesthetic will be absorbed into the body. (Recall from respiratory physiology that the transfer of gases from the alveolar sacs into the bloodstream depends on the partial pressures of the constituent gases.) The absorption of anaesthetics from the lungs into the tissues depends on their partial pressures. This means that in an intubated patient, if the pressure of the gas delivered is increased, there will be an increase in its absorption rate and, hence, its effect. This may be done without altering the relative concentrations of the gases. Once absorbed, the anaesthetic is dissolved in the plasma and its speed of action depends on its solubility. The more water-soluble the drug, the slower its rate of transfer across the blood–brain barrier; the less soluble, the faster its transfer. Ether is highly soluble in blood, whereas nitrous oxide is not; therefore, induction with nitrous oxide occurs faster than that with ether. Recovery from these anaesthetics is the reverse; that is, the patient will return to consciousness from a nitrous oxide anaesthetic much faster than from an ether anaesthetic. This may lead one to think that nitrous oxide and the more insoluble anaesthetics would have a large advantage over the less soluble anaesthetics; this is not strictly true, however, as when induction is ceased with nitrous oxide the gas quickly diffuses back into the alveoli and reduces the relative concentration of oxygen, sometimes to such an extent that anoxia ensues. This is termed diffusion anoxia and can be avoided by administering more oxygen to the patient before cessation of the procedure.

INHALATION ANAESTHETICS

NITROUS OXIDE

Nitrous oxide was one of the first anaesthetic gases. As moderate doses dramatically reduced a person's inhibitions, nitrous oxide was called 'laughing gas'. In the early days of its discovery, parties were held at which balloons full of nitrous oxide were distributed to the guests for inhalation, in much the same way as cocktails would be served today. Nitrous oxide is a sweetish-smelling gas that is non-flammable but is capable of supporting combustion; this prohibits the use of naked flames in the vicinity of its use. (You may recall chemistry classes at school when a smouldering cigarette immersed in a jar of oxygen caught fire and burnt quickly; nitrous oxide is similar to oxygen in this respect.)

Nitrous oxide is used for maintenance of anaesthesia, and, in sub-anaesthetic concentrations, for analgesia. As an anaesthetic, nitrous oxide lacks potency, but its analgesic properties are good. This is one reason why, during anaesthesia, nitrous oxide is combined with another general anaesthetic agent. The other reason is that less of the more potent anaesthetics has to be given in order to produce an acceptable level of anaesthesia, thus making the procedure safer. In fact, to obtain efficient anaesthesia with nitrous

oxide, it would have to be given 100 per cent pure, at which concentration death rather than anaesthesia would ensue. Used alone, nitrous oxide can be used to relieve pain postoperatively, during labour, when surgical dressings are being removed and in casualties at the site of accidents. When used as such, it is usually given in a premixed form containing 50 per cent oxygen (Entonox), which helps to prevent anoxia. As an anaesthetic agent, this combination is relatively safe, causing minimal respiratory and cardiovascular depression.

◆ COMMON ADVERSE EFFECTS

Prolonged exposure to nitrous oxide may result in megaloblastic anaemia owing to interference with the action of vitamin B_{12}. For this reason, exposure of operating-theatre staff to nitrous oxide should be minimised. Nitrous oxide has also been shown to inhibit DNA synthesis, which may be why theatre staff have a higher incidence of spontaneous abortions than the general public. Nitrous oxide may also be teratogenic because of this effect. Nitrous oxide can diffuse into body cavities, with a resultant increase in pressure, and has, on rare occasions, produced or enlarged a pneumothorax.

HALOTHANE, ISOFLURINE AND OTHER HALOGENATED HYDROCARBONS

Halothane, a fluorinated hydrocarbon, is a volatile liquid anaesthetic with the advantages of being potent and non-irritant. Halothane is used less widely nowadays because of its association with hepatotoxicity (see below). It is used in combination with nitrous oxide. At a concentration of less than 2 per cent, deep anaesthesia can be maintained.

◆ COMMON ADVERSE EFFECTS

Unlike the earlier halogenated hydrocarbons, halothane produces minimal irritation to the respiratory tract and thus does not usually initiate the cough reflex. This made halothane a good agent for gas induction in children. Administration of **adrenaline** (epinephrine) and sympathomimetic drugs should be avoided in patients anaesthetised with halothane, as ventricular arrhythmias may result.

Halothane also causes respiratory depression, resulting in elevation of arterial carbon dioxide tension and, sometimes, ventricular arrhythmias.

Halothane is metabolised to an extent of about 20 per cent by the liver, which can lead to damage to the hepatocytes, resulting in 'halothane hepatitis'. This is more common with repeated administration, and it is recommended that patients should not be anaesthetised with halothane at less than 2- to 3-month intervals. The mechanism of halothane hepatitis is unclear, but it may be immunological in origin. Halothane hepatitis is rare but, owing to its serious nature, all patients in whom the use of halothane is contemplated must be asked when they last received a general anaesthetic.

Other fluorinated hydrocarbons in use are **desflurane**, **isoflurane** and **sevoflurane**. Isoflurane is a less potent anaesthetic than halothane but is used widely as there is a lower risk of hepatotoxicity.

✚ CLINICAL CONSIDERATIONS

As these agents produce marked myocardial and respiratory depression, it is important to regularly monitor vital signs and cardiac rhythm during and following surgery. The patient must be assessed carefully to determine the presence of contraindications that may preclude the use of certain inhalation anaesthetics. These drugs have a depressant effect on the hypothalamus, leading to disrupted regulation of body temperature. Inhalation agents can decrease glomerular filtration and increase tubular reabsorption. Urinary output needs to be monitored regularly.

INJECTABLE GENERAL ANAESTHETICS

The use of intravenously administered anaesthetics has revolutionised the induction of anaesthesia. The action of these drugs is extremely rapid, especially if the injection is given quickly. Induction can take place in about 10 seconds without the patient being aware of the onset of unconsciousness. These anaesthetics are powerful drugs, and their use should be restricted to experienced personnel. Patients injected with fast-acting anaesthetics pass extremely rapidly through the different stages of anaesthesia, and the stage of respiratory cessation may be reached in a matter of seconds.

THIOPENTAL SODIUM

■ MECHANISM OF ACTION

Thiopental sodium (thiopentone sodium) is a barbiturate and one of the most widely used intravenous anaesthetics; it is also one of the original intravenous anaesthetics. It has no analgesic properties. Thiopental sodium is used for induction of anaesthesia and occasionally in status epilepticus to control fitting. Induction is generally smooth and rapid but, owing to its potency, overdosage with cardiorespiratory depression may occur. Barbiturates exert their action on the gamma-aminobutyric acid (GABA) receptor complex, as described in Chapter 34.

◆ COMMON ADVERSE EFFECTS

Even though thiopentone has a comparatively short half-life in plasma of about 2.5 minutes, its residual effects can be prolonged. This is because it is quickly redistributed to the tissues, from where it can slowly re-enter the blood,

making the patient drowsy. After equilibration, the half-life is about 8 hours.

Hypersensitivity reactions to thiopental sodium can occur, and severe anaphylaxis is seen in about 1 in 20 000 administrations.

When giving this drug intravenously, great care must be taken to ensure that extravasation does not occur, as this can lead to tissue necrosis, with sloughing of the dermis and epidermis. If nerves are accidentally perfused, as can happen with the medial nerve on antecubital injection, permanent damage to the nerve can result. Intra-arterial injection can lead to thrombosis, which may necessitate prophylactic treatment with heparin.

✚ CLINICAL CONSIDERATIONS

Patients receiving these drugs may be restless and irrational during the initial recovery phase if they are in pain because of their negligible analgesic effect. The propensity of these agents to cause respiratory depression points to the need to maintain and evaluate the adequacy of airway management. Rapid injection may lower the blood pressure. The monitoring of cardiovascular status is very important.

PROPOFOL

Propofol is an intravenous anaesthetic with an even shorter half-life than thiopentone (of the order of about 2 minutes in the blood and about 1 hour in the tissues). It is associated, therefore, with rapid recovery without a hangover effect, and it is used very widely. The short half-life prevents untoward sequelae and enables patients to return home, with assistance, soon after minor surgery. Propofol is the main induction agent used at present. It is also administered as an infusion for maintenance of anaesthesia. It is given for sedation of ventilated patients in intensive care. Propofol is very lipophilic and is presented as an emulsion in soybean oil and purified egg phospholipids (egg allergy is not a contraindication).

◆ COMMON ADVERSE EFFECTS

Propofol is a respiratory depressant and can cause apnoea and cardiac depression. Convulsions and anaphylaxis have occurred after administration; as the onset of convulsions can be delayed, the Commission on Human Medicines has advised special caution after day surgery. Bradycardia and hypotension are common and, intravenous administration of an antimuscarinic drug may be necessary to prevent this.

✚ CLINICAL CONSIDERATIONS

When administering propofol, signs of respiratory and cardiovascular depression should be checked, such as decreased blood pressure and respiratory rate. The incidence of involuntary movements should be carefully looked for and documented. Its effects are rapid and dissipate quickly when used as an induction agent, and thus the patient is likely to be in pain on recovery. During the recovery period, analgesics are titrated to produce pain relief. As propofol can produce local pain on intravenous injection, it is preferable to use a large vein for infusion.

KETAMINE

Ketamine is related to the hallucinogen **phencyclidine** (PCP, angel dust) and, not surprisingly, often causes vivid dreams and hallucinations during emergence from anaesthesia produced by it. Ketamine is commonly used in veterinary surgery. It has become a drug of abuse as a hallucinogen, and there are frequent burglaries of veterinary clinics to gain supplies of the drug. Ketamine in low doses produces 'dissociative anaesthesia'. In dissociative anaesthesia, not all parts of the brain are depressed and muscle tone and respiration remain normal, with relative protection of the airway. Although a patent airway is often maintained, this is not always the case, as increased muscle tone associated with the jaw may lead to airway obstruction. Intense analgesia and amnesia are also produced. Ketamine is unlike any other induction agent as it produces stimulation of the sympathetic nervous system, with increased levels of adrenaline. This increases the heart rate, cardiac output, blood pressure and myocardial oxygen demand.

◆ COMMON ADVERSE EFFECTS

As ketamine can induce slight hypertension, it should be used with caution in patients with cardiovascular disease, but it is suitable for patients with hypotension. Laryngeal and pharyngeal reflexes are not abolished, which makes ketamine useful in emergency surgery if the patient has eaten recently; however, laryngeal spasm has occurred in rare instances. Recovery from ketamine anaesthesia often causes delirium, confusion and hallucinations. These experiences are often described as unpleasant, but they can be reduced by the concurrent use of benzodiazepines or opioids.

✚ CLINICAL CONSIDERATIONS

Ketamine can be administered intramuscularly, which is advantageous in some situations. In view of the drug's tendency to produce hallucinations, tactile, verbal and visual stimuli are minimised during recovery to minimise unpleasant reactions. Ketamine is useful in reactive airways disease such as asthma, because it reduces airway resistance. Complete recovery from ketamine administration may take several hours. Regular monitoring for vital signs and conscious state should be carried out during this time.

FENTANYL, REMIFENTANIL AND ALFENTANIL

These drugs are opioids (see Chapter 39). They are often used in combination with propofol or another pure

anaesthetic. They are used only rarely as premedication and are more likely to be administered at induction. As adjunct analgesics in anaesthesia, they can be useful in painful procedures in which high doses of pure anaesthetics are contraindicated.

◆ COMMON ADVERSE EFFECTS

Adverse effects include respiratory depression, muscle rigidity, bradycardia, hypotension, gastrointestinal upset and laryngospasm.

PREMEDICATION

Before general anaesthesia, it used to be customary to give medication to alleviate the patient's anxiety. This is no longer common practice, although premedicating drugs are still used in certain circumstances.

The narcotic analgesics (see Chapter 39) were used to make the patient slightly euphoric, which allayed anxiety and offered some postoperative analgesia in operations of short duration. Narcotics are now more usually administered at induction of anaesthesia.

The benzodiazepines (see Chapter 34) are occasionally used to reduce anxiety levels and promote some amnesia without any effect on the respiratory system.

Antimuscarinic drugs (see Chapter 27) were once used to reduce salivary, gastric and respiratory tract secretions. This helped to avoid inhalation of these secretions into the lungs during operative procedures, which could lead to aspiration pneumonia or asphyxiation. Some sedation may result from the use of these drugs, and **hyoscine** may induce retrograde amnesia. Atropine is now used only rarely for premedication, but it has a role in emergencies in the treatment of vagotonic side effects.

H_2-receptor antagonists (proton-pump inhibitors) increase the pH and reduce the volume of gastric fluid. This reduces the complication of regurgitation and aspiration of gastric contents during operative procedures. Muscle relaxants used in anaesthesia are the neuromuscular blocking drugs; these drugs are discussed specifically in Chapter 27. Blockade of the neuromuscular junction enables lighter levels of anaesthesia to be employed while yet achieving adequate relaxation of the muscles of the abdomen and diaphragm. The relaxation of the vocal cords allows the passage of a tracheal tube.

NEUROLEPTANALGESIA

Many invasive procedures are carried out more satisfactorily with a cooperative patient. This is unachievable with general anaesthesia but, using a combination of anxiolytics, antipsychotics and narcotic analgesics, the patient can be rendered cooperative without suffering any distress. Procedures in which neuroleptanalgesia is used are some of the various endoscopies, extracorporeal shock-wave lithotripsy (ECSWL) and removal of cataracts. The effects of using these combinations of drugs are short-lived. This means that most patients can have such procedures performed as day cases, thus reducing hospitalisation. The drugs commonly used are the benzodiazepine **midazolam**, which causes amnesia and sedation (see Chapter 34), and the opioids fentanyl, alfentanil and remifentanil (see Chapter 39). For some procedures that involve little trauma, midazolam alone may suffice. All these drugs can cause marked sedation and respiratory depression and, as with all drugs used in any type of anaesthetic practice, they should be administered only by experienced and specialist personnel.

CLINICAL MANAGEMENT

General anaesthetics

Assessment

- The patient is assessed by the anaesthetist preoperatively for the presence of any conditions that could produce adverse effects, especially cardiac and respiratory conditions.
- As anaesthetics depress the respiratory, cardiovascular and central nervous systems, vital signs and conscious state must be assessed regularly. Specifically, the following observations are assessed:
  - temperature, as these agents have a depressant effect on the hypothalamus, and serious heat loss can occur during prolonged surgery and through exposure of viscera;
  - respiration rate, depth, equality of bilateral lung expansion and rhythm;
  - blood pressure;
  - colour and warmth of peripheries and colour of nail beds and lips, as an indication of peripheral perfusion;

- level of consciousness, orientation to time, place and person, and pupillary response and size;
- urinary output greater than 30 ml/hour through a urinary catheter;
- emergence of the patient from anaesthesia compared with the amount of anaesthetic used.

Planning

- After administration of anaesthetic(s), a state of balanced anaesthesia is achieved. This is where loss of consciousness, analgesia, amnesia and muscle relaxation are achieved. Usually, a combination of anaesthetics and neuromuscular blocking agents are required to achieve this balance.
- Parameters will continue to remain within acceptable levels during and after anaesthesia.

Implementation

- Continue to monitor parameters regularly, as described in the assessment. Various agents may need to be administered to overcome any drop in blood pressure or changes in cardiac rhythm. These agents may include antidysrhythmic drugs or sympathomimetics.

Evaluation

- Promote patient safety during the emergence from anaesthesia. The patient should be placed in a semi-Fowler's position, ensuring that all limbs are within the confines of the stretcher and the bed rails are in the upright position.
- Turn the head to one side to prevent aspiration of vomit. Suction secretions from the mouth and oropharynx to maintain a patent airway.
- Ensure adequate ventilation using oxygen via a face mask for the immediate recovery period. This will also prevent nitrous oxide diffusion hypoxia.
- Keep the patient covered to prevent heat loss and hypothermia.
- Continue to regularly evaluate vital signs, conscious state, urinary output and skin condition.
- Ensure adequate pain relief, but monitor respirations carefully while the patient is attempting to regain consciousness.
- Ensure patient's fluid status is adequate. Hypovolaemia can lead to low blood pressure and bradycardia.

SUMMARY

- Inhalation anaesthetics are used to maintain surgical anaesthesia.
- Observe carefully for cardiovascular and respiratory depressant effect.
- Injectable anaesthetics are generally used for the induction of anaesthesia.
- During the recovery period, observe for underventilation by monitoring for respiratory apnoea. It is important to watch elderly patients and patients with pre-existing respiratory insufficiency.
- Vital signs are monitored continuously due to the depressant effect on the vasomotor centre in the medulla oblongata.

1. What are the advantages of the shorter-acting intravenous anaesthetics?
2. Why is halothane normally given with nitrous oxide and oxygen?
3. Why should vital signs be monitored closely after general anaesthesia?
4. What is balanced anaesthesia? Provide a rationale for its use.
5. Millie Rushton, a 52-year-old patient, has been admitted to hospital for an abdominal hysterectomy. On the evening before surgery, you explain the preoperative routine and what to expect after surgery. She asks you why she needs to have an injection before she goes to theatre. What would you say to her?
6. What evaluation would you make of a patient after injection of a typical premedication?

41 DRUG SUMMARY TABLE: GENERAL ANAESTHESIA

FAMILY NAME	GENERIC NAME	TRADE NAME(S)
Intravenous agents	Alfentanil	Rapifen
	Ketamine	Ketalar
	Midazolam	Hypnovel
	Propofol	Diprivan
	Remifentanil	Ultiva
	Thiopental	
Gaseous agents	Halothane	
	Isoflurane	Aerrane
	Sevoflurane	
	Desflurane	Suprane

LOCAL ANAESTHESIA

42

CHAPTER FORTY-TWO

OBJECTIVES

KEY TERMS

Nerve conduction
Pain
Potassium channels
Routes of administration
Sodium channels

After completing this chapter, the reader should be able to:

- **explain the mechanism of action of local anaesthetics;**
- **list the problems associated with the use of local anaesthetics;**
- **describe the common local anaesthetics and their uses.**

LOCAL ANAESTHETICS ARE DRUGS THAT BLOCK THE transmission of nerve impulses between the peripheral nervous system and the central nervous system (CNS). Their main purpose is to prevent pain impulses from nociceptors (pain receptors) reaching the higher centres. They are used mainly in minor surgical procedures and are especially common in dentistry. Many minor surgical procedures, such as suturing, excision of superficial growths and removal of cataracts, are commonly performed using a local anaesthetic injected intradermally or subcutaneously. Even deeper-excision operations, such as for hernias, occasionally are performed using local anaesthetics.

For major operations, local anaesthetics can be injected epidurally or, rarely, intrathecally. When given thus, all structures supplied by nerve roots originating below the site of injection are rendered temporarily inactive.

Epidural anaesthesia is a particular type of nerve block in which the local anaesthetic is injected into the epidural space to affect the nerve roots in the injected region, which may be thoracic, lumbar or sacral (caudal). This type of procedure is commonly used in obstetrics. The main dangers of this type of injection are nerve damage and the potential for introduction of foreign substances (microorganisms) into the cerebrospinal fluid.

Intrathecal (subarachnoid) anaesthesia is obtained when the local anaesthetic is injected into the cerebrospinal fluid below the arachnoid tissue. Here, the nerves are not protected by the perineurium, and profound anaesthesia results from minimal amounts of local anaesthetic.

Injection of a local anaesthetic near a nerve or a nerve plexus proximal to a surgical site is termed a nerve block. An example is a brachial plexus block for surgical procedures to the upper limb. Nerve blocks affect both motor and sensory nerves and thus produce relaxation of the muscles in the appropriate region.

Intravenous local anaesthesia is used to treat upper-limb injuries at the site of accidents and in hospital to enable speedy discharge of the patient. (The lower limb can also be treated in this way, but intravenous local anaesthesia is less commonly used in this part of the body.) The arm is elevated to drain most of the blood, and a tourniquet or blood-pressure cuff is applied above arterial pressure to occlude the blood supply. The veins are then filled with local anaesthetic to enable the surgical procedure to be carried out. It is of the utmost importance that the cuff is not deflated until the effects of the local anaesthetic have decreased, otherwise cardiac arrest and/or convulsions may ensue.

Local anaesthetics can be applied topically to relieve the minor irritations of itching and superficial pain. Their application to mucous membranes can be particularly effective. Their use in invasive procedures such as catheterisation is common. The use of local anaesthetics in ophthalmic, respiratory and dermatological preparations is dealt with more thoroughly in Chapters 79, 52 and 78, respectively.

PERIPHERAL NERVE PHYSIOLOGY

The conduction of messages along nerve fibres depends on the interchange of ions between the inside and outside of the cell. Under normal conditions, the main ion of intracellular fluid is potassium and that of extracellular fluid is sodium. When a neurotransmitter binds to its receptor at a synapse, a complex series of biochemical reactions is set up, which results in sodium ions entering the neuronal cytoplasm through sodium channels. When this happens, potassium channels open and the potassium ions leave the cytoplasm. This interchange progresses down the length of the neuron until its end, at which point a neurotransmitter is released to carry the message onwards, either to another nerve cell or to an effector organ. As the message travels down the cell, the end that initially received the message reverts to its original state, the sodium ions are pumped back into the extracellular fluid and the potassium re-enters the cytoplasm. Figure 42.1 shows this process diagrammatically.

■ MECHANISM OF ACTION

Local anaesthetics are thought to work by inhibiting the movement of sodium through channels in the plasma membrane of a neuron. By doing this, they inhibit the transmission of nerve impulses. The action of the local anaesthetics is dose-dependent; that is, the more drug there is present, the greater the inhibition, until a complete block is produced. In unmyelinated nerves all of the nerve-membrane sodium channels are blocked, whereas in myelinated fibres only the nodes of Ranvier are affected. The exact mechanism of action is unclear, but it appears that the drug enters the membrane and distorts the channels, thus preventing sodium entry. All local anaesthetics are ionisable molecules, and their action depends on the pH of the medium. The cationic form of the drug is more effective than the unionised form.

Local anaesthetics can also affect sodium channels in other parts of the body, such as the conduction system of the heart. This can lead to an abnormal heartbeat; thus, systemic distribution of local anaesthetics is best kept to a minimum. (See Chapter 48 for details on the use of local anaesthetics as antidysrhythmics.) For this reason, **adrenaline** is often incorporated in injections of local anaesthetic. Adrenaline constricts the peripheral blood vessels, lessening the distribution of the local anaesthetic and, consequently, its potential effects on the heart. Owing to this vasoconstriction, a relatively bloodless field is maintained at the site of injection, which may make surgical procedures easier.

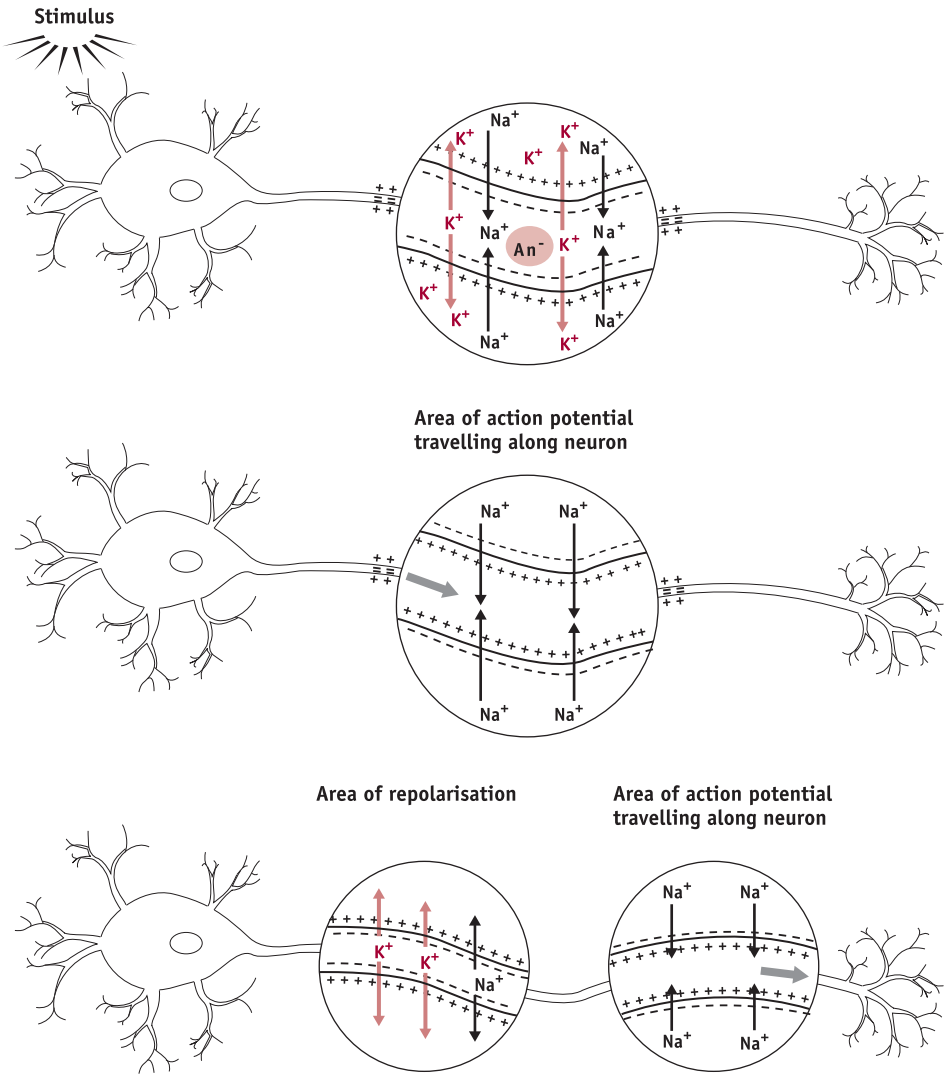
In areas where blood supply is poor, it can be dangerous to include adrenaline in the injection, as necrosis of the tissues may ensue. These areas include the extremities such as the fingers and toes. Adrenaline can be replaced by other vasoconstrictors, such as the polypeptide **felypressin**. Felypressin, which is related to antidiuretic hormone, has the advantage of causing fewer cardiac problems.

◆ COMMON ADVERSE EFFECTS

Entry of large amounts of local anaesthetic into the CNS could cause untold havoc with neural transmission. When given as a spinal anaesthetic into the subarachnoid space, usually at level L4 of the spine in pelvic and lower-limb surgery, a very dense solution is injected to prevent the drug's distribution towards the upper regions of the CNS. This type of solution is termed 'heavy'.

The common adverse effects of local anaesthetics are the result of their effects on the CNS and cardiovascular system. These may occur with uptake of the drug into the peripheral circulation, causing stimulation and restlessness. At high doses, convulsions may occur, and these can result

FIGURE 42.1 PHYSIOLOGY OF NERVE TRANSMISSION



An^-, anion; K^+, potassium ion; Na^+, sodium ion.

in death. Stimulant effects are particularly prevalent with cocaine, hence the greater potential for abuse with this drug. A decrease in the excitability of heart muscle can lead to asystole. This is to be expected, as **lidocaine** is used as an antidysrhythmic (see Chapter 48).

Hypersensitivity can occur following topical application of local anaesthetics. This adverse reaction may go unnoticed because of the suppression of the pain.

✚ CLINICAL CONSIDERATIONS

Problems associated with local anaesthetics relate to the possibility of systemic absorption following administration. The rate of systemic absorption is associated with the vascularity of the injection site. For instance, the intercostal site is the most vascular, followed by the epidural, brachial plexus and subcutaneous areas. Local anaesthetics generally cause vasodilation, but their duration of action can be prolonged by the addition of adrenaline, which produces vasoconstriction and reduces blood flow.

COMMONLY USED LOCAL ANAESTHETICS

Local anaesthetics are often divided into two groups, which are related to their chemical structure. The amides – lidocaine (lignocaine), **prilocaine**, **cinchocaine**, **bupivacaine**, **levobupivacaine** and **ropivacaine** – have a prolonged action, as their metabolism is slow. The esters are metabolised much more rapidly and so have a shorter duration of action; they are also more likely to provoke

TABLE 42.1 COMPARISON OF LOCAL ANAESTHETICS

Anaesthetic	Relative potency	Onset of action	Duration of action	Toxicity	Indications
Esters					
Cocaine	1	Medium	Short	Very high	Topical; ENT
Procaine	0.5	Slow	Short	Low	Infiltration, nerve block
Tetracaine	4	Slow	Long	High	Topical
Amides					
Prilocaine	1	Rapid	Medium	Low	Infiltration, nerve block
Levobupivacaine	1	Medium	Long	Medium	Infiltration, nerve block, epidural, spinal
Lidocaine	1	Rapid	Medium	Medium	Infiltration, topical, nerve block, IV regional anaesthesia
Mepivacaine	1	Rapid	Medium	Medium	Infiltration
Bupivacaine	4	Medium	Long	Medium	Infiltration, nerve block, epidural, spinal
Ropivacaine	3	Medium	Long	Medium	Nerve block, epidural

ENT, ear, nose and throat
Source: Adapted from Rossi, S (ed.) (2007) *Australian Medicines Handbook 2007*. Adelaide (SA): Australian Medicines Handbook Pty Ltd.

hypersensitivity reactions. The esters are **cocaine**, **procaine**, **tetracaine** (amethocaine) **proxymetacaine** and **benzocaine**. Note the suffix -caine is a common feature in the naming of local anaesthetics. The properties of local anaesthetics are compared in Table 42.1.

BUPIVACAINE

Although bupivacaine is one of the more toxic local anaesthetics, it has gained widespread use because of its properties. When buvicaine gains entry to the peripheral circulation, it becomes highly protein-bound, which lessens its toxic effect. If given during childbirth, it does not appreciably cross the placental barrier, and hence its lack of effect on the fetus. Bupivacaine has a long duration of action and is useful for spinal blocks for the prolonged maintenance of local anaesthesia. Its onset of action is slow, being about 5–20 minutes after injection and taking up to 30 minutes for full effect. There is a greater danger of myocardial depression with bupivacaine than with lidocaine, and this is more persistent and resistant to treatment as bupivaciane is ten times slower at dissociating from cardiac sodium channels.

ROPIVACAINE

Ropivacaine is similar in many respects to bupivacaine. It has more action on sensory nerve transmission than on motor nerve transmission. This could be useful in some surgical procedures, for example where the mobility of a treated limb is required. More importantly, ropivacaine has less action on the cardiovascular system, thus rendering this drug safer if systemic levels are raised due to overdose or unintentional intravascular injection. Like bupivacaine, ropivacaine is used for both regional blocks and epidurals.

CINCHOCAINE

Cinchocaine has a fast onset and long duration of action. It is used topically in anorectal conditions.

COCAINE

Cocaine hydrochloride, being potentially very toxic, is not used except for topical application. Its use is confined mainly to ear, nose and throat (ENT) surgery as it is a potent vasoconstrictor. This lessens the bleeding from highly vascularised sites. Cocaine has a great potential for abuse because of its central effects, which are not related to its anaesthetic properties, and this further restricts its clinical use. Cocaine creates a powerful habit that is difficult to cease. Its attraction as a drug of abuse derives from its stimulant properties. It is usually ingested by nasal absorption or smoked as the free base (crack). Frequent use can lead to permanent stuffiness of the nose and, eventually, deterioration of the nasal septum and associated mucous membranes.

LEVOBUPIVACAINE

Levobupivacaine is the L-stereoisomer of bupivacaine and has similar properties to bupivacaine. Levobupivacaine, however, is markedly less cardiotoxic.

LIDOCAINE

Lidocaine is perhaps the most common of the local anaesthetics. It has a rapid onset of action and intermediate duration. Most of the other local anaesthetics, apart from cocaine, are derived from lidocaine. Lidocaine is available in a variety of preparations, including spinal anaesthetic preparations, injectable forms, and jellies, creams and ointments. Lidocaine is often used in dental surgery, with or without the addition of adrenaline. An interesting reported use of lidocaine is in the treatment of premature ejaculation. When sprayed on the head and shaft of the penis 5–15 minutes before sexual intercourse, lidocaine desensitises the receptors and delays ejaculation. This can be a very effective treatment, although some men have said that they felt that their penis had 'disappeared' and had to look to check it was still there. Lidocaine is used intravenously as an antidysrhythmic as well as a local anaesthetic (see Chapter 48).

PRILOCAINE

Prilocaine is less toxic than lidocaine and has similar uses. Mixed with lidocaine, it is available as Emla™ cream, which, when applied topically under an occlusive dressing provided by the manufacturer with the cream preparation, penetrates the skin well and produces an efficient surface anaesthesia. This is useful for the insertion of venous cannulae, especially in children. Emla cream is useful for some minor surgical procedures, such as the removal of localised lesions and split skin grafting. This local anaesthetic mixture appears to be very safe, with few adverse effects having been reported. It must be remembered that allergic reactions, including anaphylactic shock, can result from the topical application of local anaesthetics, although such reactions are rare.

BENZOCAINE

Benzocaine is poorly soluble in water and has low potency and toxicity. It is of use only in the treatment of topical pain. It is often included in creams for sunburn, sprays and gargles for sore throats, lozenges for mouth ulcers and ear drops. A novel use for benzocaine has been as a lozenge for appetite suppression, the theory being that numbing the tongue makes it insensitive to taste and therefore the patient eats less. Benzocaine, like other local anaesthetics, can produce hypersensitivity reactions in susceptible patients.

CLINICAL MANAGEMENT

Local anaesthetics

Assessment

- Check the history for drug sensitivity to local anaesthetics. Localised allergic effects include burning, tenderness, swelling and redness, which may lead to necrosis. Systemic allergic effects include rash, urticaria, oedema and anaphylaxis.
- Assess vital signs and conscious state before application of local anaesthetic and compare with subsequent observations.
- Assess sensory and motor neurological function of body parts anaesthetised – for example, the movement and sensation of extremities.
- Assess patient's hydration status before application of anaesthesia.

Planning

- The patient will have relief from pain and discomfort.
- The patient will not experience bladder distension if these muscles are affected by the local anaesthetic.

Implementation

- Monitor vital signs and conscious state regularly. Local anaesthetics can cause cardiac depression, leading to hypotension and dysrhythmias. Central stimulation can lead to tremors, restlessness and, ultimately, convulsions.
- Continue to monitor sensory and motor neurological function of anaesthetised body parts.
- Regularly monitor fluid balance by documenting input and output. As local anaesthetic causes vasodilation, a low circulating blood volume can decrease blood pressure.
- Vasoconstrictors such as adrenaline can be used to prolong the duration of action of local anaesthetics.
- Resuscitation equipment should be readily available to manage adverse effects of local anaesthetics.

Plexus

- This approach can lead to a pneumothorax, as shown by pain in the chest, absent or decreased breath sounds, decreased expansion on the affected side and dyspnoea. Treatment involves oxygen, positioning of an intercostal catheter and analgesia.

Spinal and epidural

- Position the patient with good body alignment to decrease the incidence of muscular injury.
- Avoid rapid position changes, as these can lead to decreased blood pressure. Give vasopressors (e.g. adrenaline, phenylephrine) if low blood pressure persists.
- Administer oxygen until all motor and sensory functions have returned. Encourage the patient to cough and deep-breathe every 15 minutes to decrease the incidence of atelectasis.
- Check the patient for bladder distension caused by the decreased bladder tone of anaesthesia. Encourage the patient to void, otherwise an indwelling urinary catheter may need to be inserted.

Evaluation

- Evaluate the anaesthetised areas for sensation and movement, and continue until movement and sensation returns after anaesthesia is ceased.
- Continue to evaluate vital signs and conscious state, and compare with baseline levels.
- Lay the patient flat for approximately 12 hours following a spinal block or epidural to prevent the leakage of cerebrospinal fluid, which may increase the risk of a postanaesthetic headache.

SUMMARY

- Local anaesthetics interfere with the conduction of nerve impulses in sensory neurons.
- Local anaesthetics can be administered locally to ease topical pain.
- Some local anaesthetics can be given parenterally for localised severe pain and operative procedures.
- For regional local anaesthesia of the upper limb, local anaesthetics can be used for nerve block.
- For regional anaesthesia of the lower part of the body, local anaesthetics can be given by epidural injection or spinal block.
- Parenteral use of local anaesthetics can cause cardiac muscle-conduction problems.
- Resuscitation equipment, medications and oxygen should be kept close by during administration of local anaesthetics in order to treat adverse effects.
- Vasoconstrictors such as adrenaline and felypressin can be used to prolong the action of local anaesthetics and reduce the incidence of adverse effects.
- Vasoconstrictors should be avoided in the extremity areas, such as fingers, toes and ears.

1. What problems may present with local anaesthetic use?
2. Is there a relationship between the use of lidocaine as an antidysrhythmic and as a local anaesthetic?
3. Cocaine is often abused by nasal sniffing. It is not used to desensitise the nasal mucosa. Why, therefore, is it abused?
4. When considering the use of local anaesthesia for a vasectomy, would you use a local anaesthetic containing adrenaline? Why?
5. What nursing care would you provide for a patient's anaesthetised limb to prevent injury?
6. After local anaesthesia of the nasopharyngeal area, how would you test the adequacy of a patient's gag reflex?
7. How would you manage and care for a patient after administration of a spinal anaesthetic of bupivacaine?
8. If a local anaesthetic preparation is used topically in the nose or throat, what instructions would you provide the patient about eating and drinking?

42 DRUG SUMMARY TABLE: LOCAL ANAESTHESIA

FAMILY NAME	GENERIC NAME	TRADE NAME(S)
Local anaesthetics	Tetracaine (amethocaine)	Minims Local Anaesthetic
		Ametop gel
	Bupivacaine	Marcain preparations
	Cinchocaine	Proctosedyl
	Levobupivacaine	Chirocaine
	Lidocaine (lignocaine)	Mimims Local Anaesthetic
		Xylocaine preparations
	Mepivacaine	
	Oxybuprocaine	Minims Local Anaesthetic
	Prilocaine	Citanest
	+Lidocaine	Emla cream
	Procaine	
	Proxymetacaine	Minims Proxymetacaine
	Ropivacaine	Naropin

CASE STUDY IX.1

Ms RA was admitted to hospital with acute right hypochondrial and shoulder pain. She was diagnosed as having acute cholecystitis and immediate surgery was performed, which confirmed the diagnosis. Before being taken to the operating room, Ms RA was given an injection of diazepam, papaveretum and metoclopramide. Anaesthesia was initiated with thiopentone and maintained with nitrous oxide and halothane. Just after induction, she was given an injection of suxamethonium followed by atracurium. More atracurium was administered by the anaesthetist during the operation. Before the surgeon closed up the incision, atropine followed by neostigmine was given.

After some time in the recovery room, Ms RA was returned to the ward fully conscious but somewhat drowsy. She had some pain at the site of the incision and was given morphine and prochlorperazine intramuscularly. This was repeated every 4 hours for 24 hours postoperatively, and Ms RA was discharged 3 days later. Ms RA made an uneventful recovery.

QUESTIONS

1. *Ms RA was found to have gall stones. What pharmacological treatment could have been used that might have prevented the need for surgery?*
2. *Ms RA was given three drugs preoperatively. Why?*
3. *Why was suxamethonium given immediately after the induction of anaesthesia?*
4. *Why was suxamethonium not given concurrently with thiopentone?*
5. *Why was atracurium administered?*
6. *Why was neostigmine administered, and why was atropine given just before this?*
7. *Why was morphine given with prochlorperazine?*
8. *How would you know from Ms RA's appearance that morphine had been administered?*
9. *Would it be appropriate to mix morphine with prochlorperazine before administration?*

CASE STUDY IX.2

Ms RF, aged 56 years, is admitted to hospital with a rectosigmoid tumour. She is scheduled to have a laparotomy and left hemicolectomy. At the start of the operation, she receives a combination of midazolam 5 mg, fentanyl 100 mg and propofol 140 mg. During the operation, she also receives fentanyl 100 mg and 8 ml of 0.75% ropivacaine. Following the operation, the anaesthetist commences an epidural infusion containing ropivacaine 0.2% and fentanyl 4 mg/ml in 100 ml normal saline, running at 6 ml/h.

QUESTIONS

1. *What is the purpose of midazolam, fentanyl and propofol administered at the induction of surgery?*
2. *What is the purpose of combining ropivacaine and fentanyl during surgery?*
3. *What clinical management would be required of the epidural infusion in the surgical ward?*

CASE STUDY IX.3

Ms JJ, aged 56 years, has been taking piroxicam 20 mg once daily in the morning for a few months. She initially required the non-steroidal anti-inflammatory drug because she strained her shoulder while helping a friend lift a cupboard up a flight of stairs. She comments that the shoulder hurts only occasionally if she does not take the tablets. After visiting her local doctor, he suggests that she stop taking the piroxicam, to treat the shoulder with paracetamol 500 mg, up to a maximum of 4 g daily, and to have physiotherapy.

QUESTIONS

1. *Why has the doctor decided to stop the piroxicam therapy?*
2. *How would Ms JJ have taken the piroxicam in relation to food? Explain your answer.*
3. *What is the mechanism of action of piroxicam compared with that of paracetamol?*
4. *What potential problems are associated with paracetamol if Ms JJ exceeds the recommended dose?*

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WEB RESOURCES

Anaesthesia & Analgesia http://intl.anesthesia-analgesia.org

Analgesia and Anti-inflammatory Drug Information www.fda.gov/cder/drug/Analgesia_antiinflam/default.htm

Intute www.intute.ac.uk/healthandlifesciences

Joint Commission on Accreditation of Healthcare Organizations www.jointcommissioninternational.com/international.asp?durki=7656

Over-the-Counter Analgesic Guide www.fda.gov/cder/offices/otc/whatwedo.htm

Patient-Controlled Analgesia www.pslgroup.com/dg/Anaesthesianews.htm

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MODULATION OF OXYGENATION AND PERFUSION

And now I see with eye serene
The very pulse of the machine;
A being breathing thoughtful breath,
A traveller betwixt life and death;

WILLIAM WORDSWORTH – *SHE WAS A PHANTOM OF DELIGHT*

A functioning heart, the very pulse of the human machine, ensures the difference between life and death. Together with a working set of lungs and a patent vasculature, tissues and cells are perfused with oxygenated blood essential for life. In disease states that affect these organs, drugs have an important role to play in maintaining adequate tissue perfusion and oxygenation.

In this section, we examine the effects of drugs used in the therapy of cardiovascular conditions (Chapters 43–46, 48 and 50), fluid and electrolyte imbalances (Chapters 47 and 49) and respiratory conditions (Chapters 51 and 52). This is an important area of pharmacology because these disorders figure prominently within the ten most commonly reported chronic conditions causing disability in our community. As the use of these drugs is widespread, a good grasp of their properties is desirable.

Many of the drug groups discussed here are described in detail elsewhere in the book. Drug groups such as adrenergic agonists and antagonists, cholinergic antagonists, narcotics, antihistamines and corticosteroids have applications in the treatment of the conditions affecting oxygenation and perfusion.

X

DRUGS USED TO LOWER BLOOD LIPIDS

43

CHAPTER FORTY-THREE

OBJECTIVES

KEY TERMS

Hyperlipidaemia
Hypercholesterolaemia
Hypertriglyceridaemia
Atherosclerosis
Lipoproteins

After completing this chapter, the reader should be able to:

- **define the various types of hyperlipidaemia;**
- **explain the aetiology of atherosclerosis;**
- **describe the mechanisms of action of drugs used to lower blood lipids.**

ATHEROSCLEROSIS IS THE MOST COMMON CAUSE OF DEATH in most developed countries. The disability caused by this disease costs the community a great deal in health care for both drug therapy and major surgical procedures, such as coronary bypass surgery. Yet in many cases, this condition can be avoided by dietary and lifestyle changes. This chapter is concerned mainly with the drug therapy for this condition, but a short discussion on moderating non-pharmacological measures is included.

The word 'atherosclerosis' is derived from three Greek words *athere* (gruel), *oma* (mass) and *scleros* (hard). This describes the lesions commonly called plaques that occur in the body's arterial system. These consist of an accumulation of lipid, cholesterol, collagen fibres and modified monocytes (foam cells) in the inner lining of the arteries. The evidence points to blood-borne cholesterol leading to the pathological changes. These lesions cause a narrowing of the arteries. In the coronary arteries, myocardial oxygen insufficiency due to this can cause the pain of angina pectoris (see Chapter 45). There will be an increased chance of small emboli occluding damaged arteries due to the decrease in the diameter of the lumen. The smaller-diameter vessels also lead to an increase in cardiac output, with a consequent rise in blood pressure, which can further increase arterial damage. The loss of some of the elasticity of the vessels contributes to the high blood pressure (see Chapter 44). In addition, people prone to atherosclerosis often have an increase in platelet adhesiveness, which can lead to clot formation (see Chapter 46).

Cholesterol is considered to be one of the principal causes of atheroma formation, although other fats such as triglycerides may be implicated in the aetiology of this condition. Cholesterol is an essential lipid that is necessary for the formation of cell membranes and the synthesis of the steroid hormones, including vitamin D. The human body has no problem in synthesising cholesterol from carbohydrate, protein and lipids, and so dietary deficiency is almost impossible. The problem with cholesterol is that it is found in high quantities in many foodstuffs and, more importantly, some other lipids encourage its formation, especially saturated fats. Most cholesterol in the diet is derived from animal sources, and hence vegetarians have a lower incidence of hypercholesterolaemia. Some fats of plant origin, such as coconut oil and palm-nut oil, may be cholesterologenic.

Another important consideration in cases of hypercholesterolaemia is that of heredity, whereby some people just produce too much cholesterol. For these people, dietary modification is less successful in dealing with the problem, and drug intervention is often necessary.

The biochemistry of the movement of lipids in the bloodstream and the factors that increase lipid deposition in arteries is extremely complex. The transport of lipids involves many enzymes and substances known as lipoproteins, which act as carriers. As far as cholesterol is concerned, the two lipoproteins most concerned with its transport are the high-density lipoproteins (HDL) and the low-density lipoproteins (LDL). These are so-named because, on centrifugation, LDL remains suspended in the preparation while HDL separates towards the bottom. LDL is often termed 'bad cholesterol', as it transports cholesterol to the cells, where it is deposited, even though it may not be required. This is the type of cholesterol associated with atherosclerosis. HDL is referred to as 'good cholesterol' as it transports the cholesterol to the liver, where it can be removed from the body. The older method of measuring blood cholesterol levels is therefore not a very accurate measure of the patient's susceptibility to atheromatous plaque formation. LDL and HDL measurements should also be taken to give a more accurate picture of the problem. The ratio of HDL to LDL should be high. Normally, it is found that high cholesterol levels are associated with high LDL levels, but having a high HDL may compensate for this. Figure 43.1 shows a simplified model of cholesterol transport in the body. (This is an oversimplification of the cholesterol problem, and more can be learned by consulting the references at the end of this section.)

An excess of triglycerides in plasma is considered to be harmful, although not as harmful as an excess of cholesterol. The presence of above-normal amounts of triglycerides probably predisposes people to diabetes mellitus and a higher risk of cardiovascular disease. Like cholesterol, triglycerides are transported in the bloodstream, bound to lipoproteins, called very-low-density lipoproteins (VLDL).

There have been at least six types of hyperlipidaemia, described according to the lipoproteins involved in the defect. Three of these are rare and three are relatively common. The common types are described here.

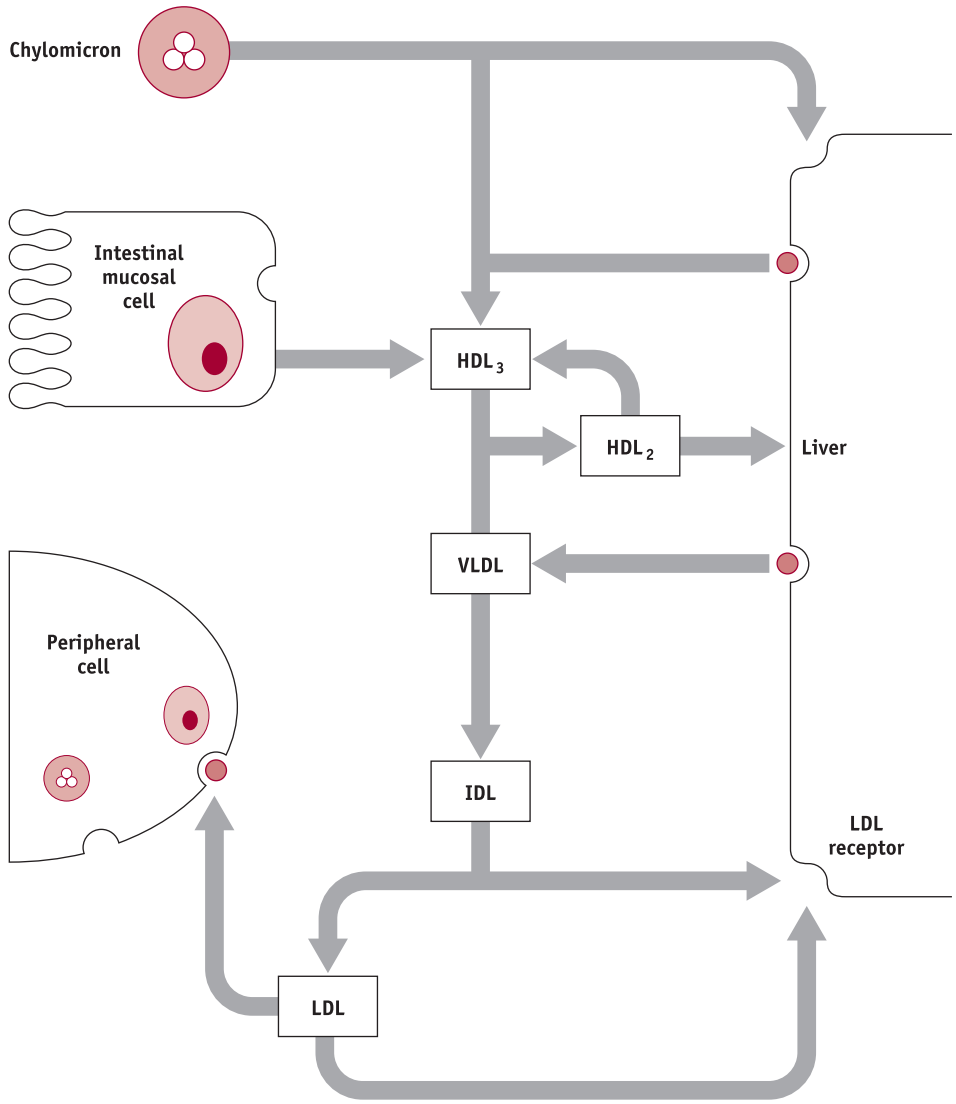
Type IIa hyperlipidaemia is associated with high levels of cholesterol and LDL in the blood. Ischaemic heart disease is common in this type. The condition may be hereditary and is then termed familial hypercholesterolaemia. This can result in severe premature coronary heart disease and tendon xanthomata. If genetic in origin, this condition almost always requires the use of drugs, even in the absence of any clinical features; in other cases, dietary modification is often successful.

Type IIb hyperlipidaemia is characterised by high VLDL and LDL and, therefore, high triglyceride and cholesterol blood levels. Ischaemic heart disease may result. This type may be related to high alcohol intake, obesity, diabetes mellitus and overeating. Dietary modification is usually all that is required, but drugs may be necessary in resistant cases.

Type IV hyperlipidaemia is characterised by high VLDL and hypertriglyceridaemia. Causes are similar to that of type IIb, but both peripheral vascular disease and ischaemic heart disease can be found in patients. Treatment is as for type IIb.

Before discussing the drugs used in the treatment of hyperlipidaemias, we will look at factors other than avoidance of foods high in cholesterol and saturated fats, which can sometimes beneficially modify these conditions. Alcohol causes a rise in HDL levels, which may be beneficial, but only if it is consumed in moderation. Excess alcohol intake is dangerous. Alcoholics do not

FIGURE 43.1 CHOLESTEROL TRANSPORT



HDL, high-density lipoprotein; IDL, intermediate-density lipoprotein; LDL, low-density lipoprotein; VLDL, very-low-density lipoprotein.

normally suffer from atherosclerosis but die prematurely from liver or cardiac abnormalities. Exercise is also beneficial, as this helps to lower LDL and raise HDL. A diet high in fish, especially fatty fish such as sardines and herring, may also help to maintain beneficial lipoprotein concentrations. This was first noted in Inuit people, who have a diet rich in fatty fish and an extremely low incidence of atherosclerosis. This is due to the presence of highly unsaturated fatty acids in some fish oils, including a fatty acid with five double bonds known as eicosapentaenoic acid (EPA). Monounsaturated fatty acids may be of benefit – principally linoleic acid, an essential fatty acid found in high quantities in olive oil. This may help to explain why Italians have a lower incidence of cardiovascular disease than the Scots and Finns, who consume a diet high in saturated fats. Some other secondary causes of hyperlipidaemias are obesity (especially central obesity), diabetes mellitus, nephrotic syndrome, alcohol abuse, and the use of oral contraceptives, diuretics and beta-blockers.

Evening primrose oil contains significant amounts of linoleic acid and its relative, linolenic acid, and is promoted by health-food manufacturers as being beneficial for various ailments. These include such diverse diseases as psoriasis, mastalgia (breast pain) and Parkinson's disease. Its role in helping these conditions is unproven, but there is some evidence of its efficacy. Evening primrose oil should

be avoided in people with epilepsy or a past history of epileptic seizures.

DRUGS USED IN HYPERTRIGLYCERIDAEMIA

Any drug treatment of hypertriglyceridaemia should be accompanied by dietary measures to lower the intake of fatty foods.

Fibrates

The fibrates were the first drugs used to successfully treat hyperlipidaemias. Many fibrates have been superseded by newer drugs, but some still have their place in the management of certain hyperlipidaemias, particularly in type IV. Fibrates act mainly by decreasing serum triglycerides and have variable effects on LDL cholesterol.

BEZAFIBRATE

■ MECHANISM OF ACTION

Bezafibrate increases lipolysis in the tissues, which leads to an increase in the conversion of VLDL to LDL (remember that VLDL is associated with triglycerides and LDL with cholesterol). This rise in LDL is not usually desirable but is offset partially by a rise in HDL and is normally short-lived. The rate of reduction of triglycerides is often remarkable with bezafibrate, and it is of particular use in cases of cutaneous xanthomata (accumulation of lipids in the skin leading to nodular eruptions). Other beneficial effects of bezafibrate are inhibition of platelet aggregation and an increase in fibrinolysis, both effects being useful in atherosclerosis.

◆ COMMON ADVERSE EFFECTS

The rate of removal of cholesterol from the liver via the bile is increased when using bezafibrate, which poses a problem with the drug: there is a rise in the incidence of gall stones in patients on this drug. Other side effects of bezafibrate, are abdominal pain, diarrhoea, myalgia (muscle pain) and, rarely, alopecia. All fibrates can cause a myositis-like syndrome, especially in patients with impaired renal function.

✚ CLINICAL CONSIDERATIONS

It is important that the patient is assessed regularly for the incidence of gall stones while on bezafibrate therapy.

GEMFIBROZIL

In most respects, **gemfibrozil** is similar in action to bezafibrate, but gemfibrozil may have certain advantages. There is a lower incidence of cholelithiasis (gall stones) with gemfibrozil and, being non-halogenated, it may have less long-term toxicity. It has been suggested that the main beneficial effect of gemfibrozil is not its triglyceride-lowering effect but its ability to raise HDL levels by up to 25 per cent and to lower LDL cholesterol levels. Other adverse effects are as for bezafibrate, with gastrointestinal upsets being the most common.

✚ CLINICAL CONSIDERATIONS

Gemfibrozil should be taken about half an hour before food unless gastrointestinal side effects occur; this action improves the bioavailability of the drug. If abdominal pain occurs, the drug may be taken with food to improve tolerance. A full blood count and liver function test should be undertaken before and during treatment. The patient should be advised to speak to their doctor if they experience muscle pain, tenderness or weakness, as these signs may be indicative of myalgia.

Other lipid-lowering drugs

NICOTINIC ACID

Nicotinic acid (also known as niacin) belongs to the B_3 group of vitamins and as a vitamin can be replaced with **nicotinamide** (also known as niacinamide). As a hyperlipidaemic agent, there can be no substitution, as the role of nicotinic acid as an antihyperlipidaemic agent is completely unrelated to its function as a vitamin.

The use of a natural vitamin in the treatment of hyperlipidaemias has not gone unnoticed by naturopaths, who have promoted this vitamin for the self-treatment and prophylaxis of hyperlipidaemic conditions. Nicotinic acid is useful only in type IV hyperlipidaemia, however, and must be given in mega-doses of up to 1–3 g per day. At its highest dose, this is about 200 times the dietary amount needed to prevent pellagra. Such high doses, as will be seen, are not without adverse effects.

■ MECHANISM OF ACTION

The action of nicotinic acid in lowering triglyceride levels is not understood completely, but it probably decreases the formation of free fatty acids in adipose tissue, thus decreasing VLDL synthesis. Esterification of fatty acids to triglycerides in the liver is also decreased. This is also reflected by a fall in LDL cholesterol and a rise in HDL cholesterol. Triglyceride levels can decrease by as much as 30 per cent with high doses of the acid. When taken in conjunction with a fibrate, mortality from some hyperlipidaemias is lowered.

◆ COMMON ADVERSE EFFECTS

Nicotinic acid in high doses causes various adverse effects, the most apparent being a massive vasodilation shortly after ingestion. This can lead to intense flushing and itching of the skin and can be accompanied by faintness. Some people show an idiosyncratic response in this respect,

their peripheral vascular resistance decreasing so much that circulatory collapse occurs. The vasodilation caused by nicotinic acid is short-lived but has led to nicotinic acid being used for vascular disorders such as chilblains, Raynaud's disease and hypertension. Its value in these conditions is doubtful because of the short duration of the effect. Tolerance to the vasodilation develops quickly and, in the initial stages of therapy, can be reduced by taking **aspirin** 30 minutes before the nicotinic acid. Administration after meals also decreases the vasodilating effect. Patients should be warned of this potential effect, which can occur minutes after ingestion of the tablets. Other adverse effects include hyperuricaemia, hyperglycaemia and hepatic disorders. Gastrointestinal upsets are common and paradoxically worse with the slow-release preparations designed to lessen the vasodilating effect.

✚ CLINICAL CONSIDERATIONS

Adverse effects of nicotinic acid relating to flushing and abdominal pains usually resolve after 2–6 weeks of therapy; however, they may reappear if doses are missed. Adverse effects can be decreased by dividing the daily dose, increasing the dose gradually or taking the drug with food. Liver function and blood glucose levels should be monitored carefully, especially at the commencement of therapy. As nicotinic acid may produce myalgia, the patient should be advised to speak to their doctor if they experience muscle pain, tenderness or weakness.

ACIPIMOX

■ MECHANISM OF ACTION

Acipimox, which is related to nicotinic acid, reduces lipolysis in adipose tissue and increases the catabolism of VLDL, thus reducing plasma triglycerides. HDL levels are usually raised, which further reduces atherogenesis.

◆ COMMON ADVERSE EFFECTS

This drug, like nicotinic acid, can cause flushing due to its vasodilatory effect, but this is usually less pronounced and tolerance to the effect normally occurs fairly rapidly. Other adverse effects are not common, and in general acipimox is better tolerated than nicotinic acid.

FISH OIL

■ MECHANISM OF ACTION

Some highly unsaturated fatty acids (principally omega-3), which are present in some fish and marine oils, have anti-hyperlipidaemic effects. The two acids are eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), which have five and six double bonds, respectively. The efficacy of **fish oil** in hyperlipidaemias seems to be restricted to the rare type V hyperlipidaemia, which is characterised by raised chylomicron, VLDL and triglyceride levels. The dose needed for the treatment of this condition is about 10 g per day, which is equivalent to 250 g fatty fish. Extremely high doses are needed to lower cholesterol levels. Other beneficial effects of fish oil are a decrease in platelet adhesiveness and a decrease in prostaglandin formation, which may help in rheumatoid arthritis. The main problems with fish oil treatment are its cost and patient compliance with the high doses (which can impart a fishy odour to the breath and body), rather than its adverse effects. High doses are also high in kilojoules, and some brands may be high in vitamins A and D and therefore could lead to hypervitaminosis (see Chapter 61).

◆ COMMON ADVERSE EFFECTS

The adverse effect of most significance is a rise in LDL in some patients. Some people might find there is an objectionable fishy smell in the sweat and breath.

✚ CLINICAL CONSIDERATIONS

Fish oil is available as 1-g capsules, which largely prevent problems occurring associated with unpleasant fish odour. The patient should be examined regularly for signs of toxic levels of vitamin A and D (see Chapter 61). In a systematic review looking at the risks and benefits of omega-3 fats for mortality and cardiovascular disease published in the *British Medical Journal* in 2006, there was substantial variation between study results, and it was not clear whether there were long-term benefits from the consumption of long-chain or short-chain omega-3 fats. The review concludes that guidelines to eat more oily fish should continue at present but be reviewed as new evidence becomes available.

Table 43.1 shows the effects of various lipid-lowering drugs on lipid concentration in hypertriglyceridaemia.

DRUGS USED IN HYPERCHOLESTEROLAEMIA

Any drug treatment of hypercholesterolaemia should be accompanied by dietary measures to lower the intake of fatty and other cholesterologenic or cholesterol-containing foods.

Anion exchange resins

■ MECHANISM OF ACTION

The mechanism of action of the anion exchange resins is interesting when it is realised that they are not absorbed from the gastrointestinal tract. Their mechanism is simple and is based on the fact that bile salts excreted via the bile are synthesised from cholesterol. Bile salts are normally reabsorbed from the ileum and recycled back to the liver by the hepatic portal system for re-excretion into

TABLE 43.1 DRUG EFFECTS ON LIPID LEVELS IN HYPERTRIGLYCERIDAEMIA

Drug	LDL cholesterol	Triglyceride	HDL cholesterol
Gemfibrozil	↑ 15%	↓ 60%	↑ 20%
Nicotinic acid	↓ 22%	↓ 60%	↑ 22%
Fish oil	↑ 5%	↓ 45%	Varied response

HDL, high-density lipoprotein; LDL, low-density lipoprotein.
Source: Adapted from Rossi, S. (ed.) (2002) *Australian Medicines Handbook 2002*, Adelaide (SA): Australian Medicines Handbook Pty Ltd, p. 247.

the bile. This recycling is known as the enterohepatic cycle (discussed in Chapter 13). Anion exchange resins bind irreversibly to bile salts, thus removing the salts from the body. As these salts are required continuously for the emulsification and absorption of dietary fats, there is a resultant increase in the liver's LDL receptors, which further remove LDL cholesterol at an increased rate from the blood. Consequently, more cholesterol is converted into bile salts, which then depletes the body's cholesterol stores, resulting in a lowering of blood cholesterol levels. The rate-controlling enzyme in cholesterol biosynthesis, 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMG-CoA), is also increased. This causes the liver to synthesise more cholesterol, and in some patients this increase negates the faecal loss of bile salts. Patients who have a genetic defect in the formation of LDL receptors will not respond to anion exchange therapy.

The action of anion exchange resins to lower LDL cholesterol takes several weeks to become apparent. There may be a concurrent rise in VLDL, which normally returns to the original levels, but in patients with high VLDL this may take a long time. This makes these resins suitable for the treatment of type IIa hyperlipidaemias. There are two anion exchange resins in common use, the prototype being **colestyramine** (cholestyramine) and the more recently released **colestipol**.

COLESTYRAMINE

Colestyramine is a polymer related to polystyrene, with quaternary ammonium groups attached. These ammonium groups contain a chloride ion, which is easily replaced by ionic bile salts, hence the term 'exchange'. As these polymers are of a large molecular size, there is no absorption into the body and, therefore, no direct systemic effects of the drug.

COLESTIPOL

Colestipol is a polymer unrelated to cholestyramine but with an identical mechanism of action. Its associated problems are also identical, however, and the only advantage it may offer is that some patients find it easier to ingest.

◆ COMMON ADVERSE EFFECTS

The major problem associated with resins is patient compliance, as large amounts must be taken daily to maintain their cholesterol-lowering effect. The dose may be in excess of 20 g per day. The resin is suspended in water, fruit juice or cordial for ingestion, but even after disguising the taste it is still like drinking suspended cement. Constipation and a bloated feeling are frequent adverse effects of high doses. Concomitant administration of laxatives may be necessary in some cases. In fact, colestyramine can be used to treat diarrhoea when other measures have failed (see Chapter 54). Bile acids are not the only compounds to which colestyramine can bind. Acidic vitamins, such as folic acid, and acidic drugs, such as **thyroxine**, barbiturates and some anti-inflammatories, can have their absorption impaired by colestyramine. The absorption of the fat-soluble vitamins A, D, E and K can also be impaired; an increased bleeding tendency has been reported associated with vitamin K deficiency.

✚ CLINICAL CONSIDERATIONS

Colestyramine is mixed with water, juice or other liquid to dissolve the preparation. Its gritty texture may be reduced by mixing the dose with fluid and standing it overnight in the refrigerator. Any drug that has to be administered to patients on cholestyramine therapy should be taken at least 1 hour before or 4 hours after the cholestyramine dose. Children on colestyramine may need iron and folate supplements. Clinical considerations of colestipol are similar to those of cholestyramine.

Other drugs used in hypercholesterolaemia

NEOMYCIN

■ MECHANISM OF ACTION

Neomycin is an aminoglycoside antibiotic with cationic groups on the molecule, which have the ability to combine with anionic micelles of cholesterol and bile salts in the gut.

This prevents the absorption of cholesterol from the gut, thus lowering its blood level. There is some controversy as to whether HDL is lowered or raised, but there is no doubt that LDL levels are lowered. The use of neomycin in hyperlipidaemias is not common, but the drug is used in some countries, being reserved for use when all else has failed.

◆ COMMON ADVERSE EFFECTS

Although neomycin is absorbed relatively poorly, there have been cases of ototoxicity, leading to deafness, especially if the patient's renal function is impaired. Diarrhoea is a common side effect, owing to an upset in the normal bowel flora; therefore, the consequences of long-term treatment could be deleterious. (See also Chapter 68.)

THYROXINE

Thyroxine, as used for hypothyroidism, is discussed in detail in Chapter 57, and so only a brief description of its possible use as an antihyperlipidaemic agent is given here. It acts by increasing LDL receptors in the liver and therefore lowering plasma cholesterol levels. There is no effect on HDL or on VLDL levels. Side effects are numerous and are due to its ability to generally raise the metabolic rate.

PLANT FIBRES

The mucilage produced from *Psyllium* extract can bind cholesterol in the gut and lessen its absorption. (See Chapter 54 for more details regarding plant mucilages.)

HMG-CoA reductase inhibitors: statins

It has been suggested that these drugs are to hypercholesterolaemias what penicillin was to bacterial infections. This statement is even more profound when one considers that this group of drugs are of fungal origin, like penicillin. There are several drugs available worldwide in this group, of which **atorvastatin**, **fluvastatin**, **pravastatin**, **rosuvastatin** and **simvastatin** are available in the UK. In July 2004, simvastatin became available as an over-the-counter medicine in the UK at a dose of 10 mg/day. It is licensed to reduce the risk of a first major coronary event in people at moderate (10–15 per cent) risk of coronary heart disease. Pharamacists are being trained to identify patients at risk with the aid of a questionnaire and must be involved in all initial sales.

In the UK, the National Institute for Health and Clinical Excellence (NICE) has provided guidance for the use of statins for the prevention of cardiovascular disease. These are available on their website at www.nice.org.uk.

■ MECHANISM OF ACTION

HMG-CoA reductase is the rate-limiting enzyme in hepatic cholesterol synthesis, inhibition of which will lead to a reduction in plasma cholesterol. As the liver needs cholesterol for bile acid formation, if too little is produced the hepatocytes present themselves with more LDL receptors, which trap an increasing amount of LDL from the periphery. In patients with a homozygous genetic lack of LDL receptors, these drugs are of limited usefulness. The effect of these drugs on HDL levels is minimal. These drugs have similar uses to the anion exchange resins but are generally tolerated better by patients. There have been at least two large double-blind trials with the statins that have been suspended when it became clear that subjects in the placebo group had a significantly higher mortality than those in the statin group. By 1996 statins were being called 'miracle drugs', and in 2004 it was claimed that statins had already surpassed all other classes of medicine in reducing the incidence of death, heart attack and stroke. The benefits from statins in terms of risk reduction for CHD are apparent in people with normal LDL cholesterol levels as well as those with raised LDL, which raises the question of whether cholesterol lowering is their only beneficial effect. Statins may reduce the risk of breast cancer and have salutary effects in multiple sclerosis and Alzheimer's disease – a generalised anti-inflammatory action has been put forward to explain some of these effects. There isevidence to support a reduction in plaque size following administration of high dose statins.

◆ COMMON ADVERSE EFFECTS

Even with long-term therapy, which is normally the case, the statins have very few side effects, apart from headache and gastrointestinal upsets (including abdominal pain, flatulence, diarrhoea, nausea and vomiting) on the odd occasion. One serious problem that can occur is myositis (inflammation of voluntary muscles), the incidence of which is increased if other antihyperlipidaemic drugs are given concurrently, especially the fibrates and nicotinic acid. Severe muscle damage (rhabdomyolysis) is very rare, but the risk is higher in patients who have had transplants and are on ciclosporin therapy (see Chapter 75). As the statins may have some effect on steroid synthesis, they are contraindicated in children and in pregnancy. Pravastatin is more hydrophilic than simvastatin and therefore does not cross the blood–brain barrier and inhibit cholesterol synthesis there. This hydrophilicity may also explain the fact that the action of pravastatin is confined mainly to the liver, with little peripheral interference with cholesterol synthesis. This may be an advantage of pravastatin in that the synthesis of cholesterol (an essential compound) still proceeds in certain tissues. Biochemical abnormalities of hepatic function have been associated with the HMG-CoA reductase inhibitors, and it is recommended that all patients undergoing long-term treatment with these drugs have initial and then periodic liver function tests. Guidelines recommend that liver function tests be carried out before

a statin is commenced and within 1–3 months of starting treatment. Unless there are indications of hepatotoxicity, liver function tests need to be repeated every 6 months for a year. If serum transaminase concentrations rise and stay at three times the upper limit of the range, treatment should be discontinued. There have been reports of an increase in the incidence of cataracts in patients on statins, but the claims appear to be unfounded. Atorvastatin, fluvastatin and rosuvastatin are purely synthetic drugs, simvastatin is a semi-synthetic drug and pravastatin is a natural statin found in fungi.

✚ CLINICAL CONSIDERATIONS

To prevent gastrointestinal symptoms, the statins are taken in the evening with food. Because of potential problems associated with myopathy and rhabdomyolysis, the patient must see their doctor if muscle pain, weakness or tenderness occurs. Similarly, patients should observe for dark urine and yellowing skin and whites of the eyes for adverse conditions associated with the liver. Liver function is checked when administering statin treatment (see above).

Ezetimibe

■ MECHANISM OF ACTION

This drug localises at the brush border of the small intestine and selectively inhibits the absorption of cholesterol and related plant sterols. Statins reduce cholesterol synthesis in the liver and so together these actions complement each other.

◆ COMMON ADVERSE EFFECTS

Side effects of ezetimibe include headache, gastrointestinal disturbances, fatigue, myalgia and, rarely, rhabdomyelitis. There is more risk of myositis if ezetimibe is taken with a statin. Rarely, hypersensitivity reactions may occur.

✚ CLINICAL CONSIDERATIONS

Ezetimibe is licensed to be used in combination with a statin (or alone if a statin is inappropriate) in patients with familial hypercholesterolaemia.

As with all lipid-lowering drugs, ezetimibe should be used alongside dietary changes.

Table 43.2 shows the effects of various lipid-lowering drugs on lipid concentration in hypercholesterolaemia.

TABLE 43.2 DRUG EFFECTS ON LIPID LEVELS IN HYPERCHOLESTEROLAEMIA

Drug	LDL cholesterol	Triglyceride	HDL cholesterol
Gemfibrozil	↓ 10%	↓ 32%	↑ 10%
Nicotinic acid	↓ 22%	↓ 25%	↑ 27%
Anion exchange resins	↓ 20%	↑ 5%	↑ 5%
HMG-CoA reductase inhibitors (statins)	↓ 35%	↓ 15%	↑ 5%

HDL, high-density lipoprotein; LDL, low-density lipoprotein.
Source: Adapted from Rossi, S. (ed.) (2002) *Australian Medicines Handbook 2002*, Adelaide (SA): Australian Medicines Handbook Pty Ltd, p. 247.

CLINICAL MANAGEMENT

Drugs used to lower blood lipids

Assessment

- Obtain baseline levels for blood pressure, pulse and respiration rate. Compare with subsequent observations.
- Obtain the patient's dietary history and body weight.
- Assess the patient for biliary obstruction and severe liver and renal disease, as these conditions are normally contraindications.
- Assess the patient for obesity, diabetes, heart disease and hypertension. For the female patient, determine whether she is breast feeding or pregnant: these drugs should be not be used by such patients.

Planning

- The patient will select foods that are low in fat and cholesterol.
- The patient's cholesterol and triglyceride levels will reach a normal range within a few weeks.

Implementation

- Determine serum cholesterol, triglyceride, high-density lipoprotein (HDL) and low-density lipoprotein (LDL) levels. Measure lipids every 4–6 weeks while adjusting the dose of medication. Thereafter, measure the lipid levels every 6–12 months during the maintenance phase.
- Administer the drug with meals to prevent gastrointestinal irritation.

Patient teaching

- Most of these medications cause gastrointestinal irritation, of which the patient should be forewarned. Administration with meals should alleviate this adverse effect.
- Instruct the patient to maintain a diet that is low in cholesterol and fat.
- Encourage the patient to maintain healthy lifestyle habits, including moderate exercise, weight loss and smoking cessation.
- Explain about the need to remain on the therapy to lower blood lipids.
- Explain to the patient that it may take several weeks before blood lipid levels fall. Laboratory tests for blood levels will be ordered every 3–6 months.
- If there is a family history of hyperlipidaemia, it is advisable for children to have their blood lipid levels checked. Children should be encouraged to maintain a low-fat and low-cholesterol diet.

Cholestyramine and colestipol

- Instruct the patient to mix the powder well with water or juice. The powder should not be taken in dry form.
- As these drugs interfere with the absorption of fat-soluble vitamins, such as vitamins A and D, a supplementary vitamin preparation may be required.
- If the patient is taking other medications, examine the dosage schedule and arrange for a long time lapse between the antihyperlipidaemic drug and other medications. For example, other medications should be administered 1 hour before or 4–6 hours after resin medication.

Gemfibrozil

- Impotence and decreased libido may occur with this drug and should be reported; the drug dosage may then be changed or another drug ordered.
- Caution patients with diabetes to monitor blood glucose levels carefully. This drug may cause a rise in fasting glucose and a fall in glucose tolerance. Changes to insulin therapy or diet may be necessary.

HMG-CoA reductase inhibitors

- Advise the patient to have liver enzymes monitored regularly.
- Encourage the patient to have annual eye examinations to determine changes in visual acuity.
- Encourage the patient to take the medication in the evening with food.
- Advise the patient to see their doctor if muscle pain, tenderness or weakness occurs. These are possible symptoms of high liver enzyme concentrations.

Nicotinic acid

- Advise the patient that a flushed appearance is common with this drug, but the effect will diminish with continued use.

Evaluation

- Evaluate the effectiveness of the drug in falling cholesterol, triglyceride and low-density lipoprotein (LDL) levels.
- Ensure that the patient is on a low-fat and low-cholesterol diet.

SUMMARY

- Hypercholesterolaemia and, to a lesser extent, hypertriglyceridaemia are major risk factors in the development of atherosclerosis.
- The incidence of these conditions can be due to excess fats in the diet, but more commonly they are determined genetically.
- The treatment of these conditions is partially dietary, but drug intervention is usually needed with even moderately raised levels of triglycerides and cholesterol.
- Drug treatment of hypertriglyceridaemia changes the way the liver handles triglycerides, with a concomitant drop in blood levels.
- Drug treatment of hypercholesterolaemia involves either inhibiting the synthesis or increasing the removal of cholesterol (indirectly) via the bile.
- Drug treatment of hypercholesterolaemia is relatively free of adverse effects and reduces the risk of death from coronary heart disease.

1 (a) Colestyramine and colestipol are not absorbed from the gastrointestinal tract and yet are capable of lowering blood cholesterol levels. Why?
(b) Why is colestyramine contraindicated in cholestasis?

2 Why is it often necessary to supplement the diet with some vitamins during colestyramine therapy?

3 Blood coagulation problems have arisen during colestyramine therapy. Why?

4 Why is colestyramine sometimes used in the treatment of diarrhoea?

5 What general advice should be given to all patients on antihyperlipidaemic therapy?

6 Why are the fatty acids in fish oils used in the treatment of hyperlipidaemias termed omega-3 marine triglycerides?

7 What types of fish are high in omega-3 fatty acids?

8 Why are drugs such as pravastatin and simvastatin referred to as HMG-CoA reductase inhibitors?

9 What is the main advantage of gemfibrozil over bezafibrate?

10 Why are gall stones sometimes produced during bezafibrate therapy?

11 Why is diet alone usually not sufficient to reduce hyperlipidaemia?

12 Explain why low-density lipoprotein (LDL) is referred to as 'bad cholesterol' and high-density lipoprotein (HDL) as 'good cholesterol'.

13 Rose Goldstein, a 50-year-old patient who is taking colestipol, complains of constipation. What measures can you recommend to alleviate this problem? (See Table 11.4 in Chapter 11 for assistance.)

14 What evaluation would you perform to determine the effectiveness of a drug used to treat hypercholesterolaemia?

15 Yuri Makinov has been on colestyramine for 8 months. During his outpatient visit, he indicates to you that he has been experiencing nose bleeds. What do you think may be happening?

16 Julie Roberts is taking colestipol to treat her hypercholesterolaemia. She buys a nasal decongestant to alleviate the manifestations of an unpleasant cold. What will you tell her about the timing in taking both medications?

17 What type of blood test is recommended on a regular basis for a patient receiving simvastatin?

43 DRUG SUMMARY TABLE: DRUGS USED TO LOWER BLOOD LIPIDS

FAMILY NAME	GENERIC NAME	TRADE NAME(S)
Anion exchange resins	Colestyramine (cholestyramine)	Questran Questran Light
	Colestipol	Colestid
Fibrates	Bezafibrate	Bezalip
	Gemfibrozil	Lopid
HMG-CoA reductase inhibitors	Atorvastatin	Lipitor
	Fluvastatin	Lescol
	Pravastatin	Lipostat
	Simvastatin	Zocor
	Rosuvastatin	Crestor
Miscellaneous	Acipimox	Olbetam
	Fish oil	Maxepa Omacor
	Nicotinic acid	Niaspan
	Ezetimibe + Simvastatin	Ezetrol Inegy

ANTIHYPERTENSIVE DRUGS

44

CHAPTER FORTY-FOUR

OBJECTIVES

After completing this chapter, the reader should be able to:

- **state the blood-pressure readings considered to be the threshold for classification of hypertension;**
- **define the three forms of hypertension;**
- **describe the physiological processes involved in monitoring and influencing blood pressure;**
- **list the three factors that determine blood pressure;**
- **identify the main categories of antihypertensive agents;**
- **describe the mechanisms of action of all drug groups used in the treatment of hypertension;**
- **state the common adverse effects of the antihypertensive drug groups;**
- **briefly outline the approach used in treating the various forms of hypertension.**

KEY TERMS

Adrenergic receptors
Blood pressure
Calcium channels
Endocrine system
Hypertension
Sympathetic nervous system
Vasoactive chemicals
Renal system

HYPERTENSION IS A VASCULAR DISEASE CHARACTERISED BY consistently elevated average blood-pressure readings recorded over a period of time. The threshold for the diagnosis of hypertension is arbitrary, as individuals vary and blood pressure is distributed normally throughout the population. In most major published guidelines, an individual is regarded as

hypertensive if the average systolic blood pressure is 140 mmHg or greater and/or the average diastolic pressure is greater than 90 mmHg. Using this threshold, about 40 per cent of the adult population in the UK has raised blood pressure; the proportion increases with age. The British Hypertension Society (BHS) has produced a classification of blood-pressure levels within their guidelines for hypertension management (Table 44.1).

For many years, diastolic pressure was thought to be more important than systolic pressure but evidence from several studies has indicated that systolic pressure is the most important determinant of cardiovascular risk.

There are three hypertensive categories: *essential* (or *primary*), *secondary* and *malignant* hypertension. Essential hypertension often presents without any accompanying symptoms and is not related to any overt disease process. A specific underlying cause of hypertension cannot be found and the hypertensive state seems to be associated with age-related changes in nervous, cardiovascular and endocrine system function. When symptoms are noted, they are commonly nocturia and headache. More than 95 per cent of people with hypertension have this type.

Secondary hypertension arises as a consequence of some other condition, such as chronic renal disease (the most common), Cushing's syndrome, hyperaldosteronism, pheochromocytoma (benign tumour of the adrenal medulla), thyroid malfunction and acromegaly (overproduction of growth hormone)

Malignant hypertension develops quickly and reaches critical levels that can trigger lethal complications, such as cerebral oedema. This is defined as a blood pressure greater than 180/110 mmHg with signs of papilloedema and/or retinal haemorrhage. It may complicate hypertension of any aetiology and can be precipitated by a hypertensive crisis associated with the use of antidepressants called monoamine oxidase inhibitors (MAOIs) (see Chapter 35) and eclampsia.

Chronic hypertension results in damage to the walls of the blood vessels. Arteries and arterioles thicken in response to the high pressure and vasoconstriction, leading to a narrowing of the lumen. Accounting for these changes are hypertrophy (increase in the size of cells) and hyperplasia (increase in the number of cells) of the vascular smooth muscle. In addition, other layers of the wall undergo fibrosis. The damage to the vessel wall induces an inflammatory response that increases the permeability of the vascular endothelium. Sodium, calcium, water, plasma proteins and other substances from the blood permeate the vessel wall, exacerbating the thickening. The major consequence of untreated chronic hypertension is damage to a number of body organs and tissues.

Atherosclerosis, myocardial infarction, heart failure, renal failure, stroke, impaired mobility and generalised oedema are all associated with chronic hypertension. The aim of antihypertensive therapy is to lower blood pressure in order to prevent damage to major organs and other body tissues. This is rarely achieved through monotherapy (i.e. successful treatment with only one drug). Thus, the use of drug combinations to control high blood pressure is common (see later in this chapter) and can lead to an increase in the complexity of the drug regimens and in the incidence of adverse effects and development of non-compliance with therapy. (These issues are discussed broadly in Chapters 11 and 20.)

TABLE 44.1 BRITISH HYPERTENSION SOCIETY (BHS) CLASSIFICATION OF BLOOD-PRESSURE LEVELS

	Blood pressure (mmHg)
Optimal	< 120/80
Normal	< 130/85
High normal	130–135/85–89
Hypertension	
Mild (grade 1)	140–159/90–99
Moderate (grade 2)	160–179/100–109
Severe (grade 3)	> 180/> 110
Isolated systolic hypertension	
Grade 1	140–159/< 90
Grade 2	> 160/< 90

Source: Based on Williams B, Poulter NR, Brown MJ, *et al.* (2004) 'British Hypertension Society guidelines for hypertension management 2004 (BHS-IV) summary', *British Medical Journal*, 328, 634–40.

NORMAL REGULATION OF BLOOD PRESSURE

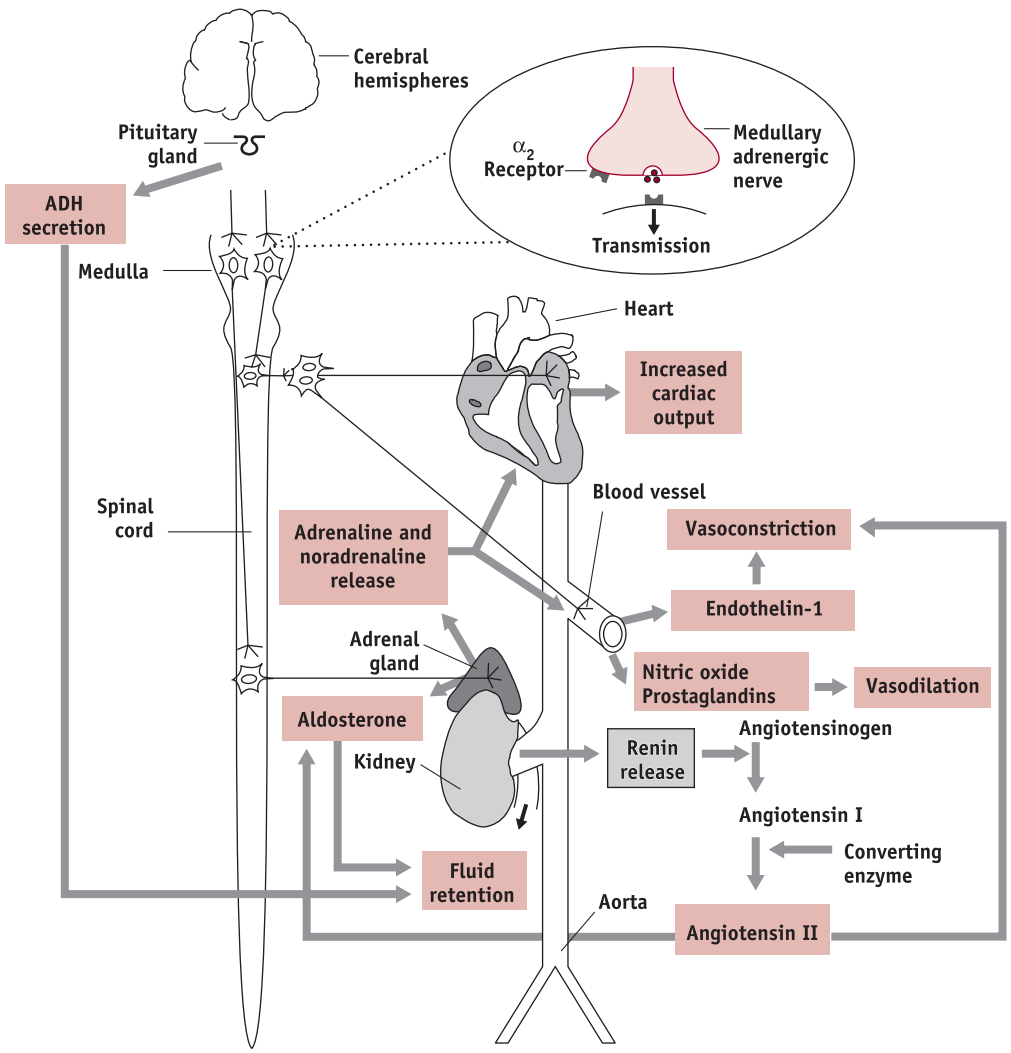
In order to understand the pathophysiology of hypertensive states and, in turn, the underlying rationale of drug therapy, an appreciation of the systems normally involved in monitoring and regulating blood pressure is required. Two factors that determine blood pressure are cardiac output (stroke volume × heart rate) and systemic vascular resistance (SVR) of the vasculature. Blood pressure is regulated by an interaction between nervous, humoral and renal systems. Figure 44.1 illustrates the interplay between these systems in blood pressure control.

Nervous control systems

Blood pressure is measured by sensory receptors located in the wall of arteries, which are sensitive to changes in pressure and blood chemistry (i.e. pH, pCO_2, pO_2). These receptors are found in the aortic arch and in the common carotid arteries. The receptors relay their information back to the vasomotor centre in the medulla via afferent fibres

FIGURE 44.1 BLOOD-PRESSURE CONTROL MECHANISMS

This figure shows the interplay between the nervous system, endocrine system, vasoactive substances and kidneys in the control of blood pressure. The nervous system influences cardiac output and blood-vessel diameter. The release of adrenaline and noradrenaline from the adrenal gland also influences these parameters and stimulates the release of renin into the blood from renal arterioles. Renin release leads to the production of angiotensin II, a potent vasoconstrictor, which in turn causes the secretion of aldosterone from the adrenal cortex. Aldosterone facilitates sodium and water retention, which increases blood volume and leads to an elevation in blood pressure. Indeed, renin release is triggered whenever renal blood flow is compromised. Antidiuretic hormone (ADH) from the pituitary also leads to an increase in blood volume through water retention. Vasoactive substances, such as nitric oxide, prostaglandins and endothelin-1 released from endothelial cells, also play a role in regulation of blood pressure.



primarily associated with the glossopharyngeal cranial nerve. The vasomotor centre is part of the sympathetic nervous system and its function is modulated by α_2-adrenergic receptors located there. Efferent fibres descend the spinal cord and enter the periphery between the T1 and L2 levels. These fibres stimulate vascular smooth muscle, causing a vasoconstrictive response that increases SVR and, thus, elevates blood pressure. The medulla also contains the cardiac centre, which controls heart rate and force of contraction. Sympathetic nerves arising from the medulla also stimulate the heart, which results in increased cardiac output and a corresponding rise in blood pressure.

Humoral control systems

The humoral influences on blood pressure comprise hormones and other vasoactive substances that either dilate

or constrict blood vessels. These substances are released into the circulation either from glands or directly from the blood-vessel wall itself. Some of these substances exert a systemic influence, while others act locally.

ENDOCRINE–RENAL INTERACTIONS

An important humoral mechanism is the renin–angiotensin system, which regulates renal blood flow. Renin is an enzyme released from renal arterioles when renal blood pressure drops. It converts the plasma protein angiotensinogen into angiotensin I. This is converted into the vasoactive substance angiotensin II by angiotensin-converting enzyme (ACE), which is present in the endothelium of the heart, brain, skeletal muscle and kidney but is particularly abundant in the endothelial cells of the pulmonary vasculature. Angiotensin II is one of the most potent known vasoconstrictive substances and has a marked effect on blood pressure, enhancing renal blood flow and urine production. Angiotensin II also triggers release of the mineralocorticoid aldosterone, which acts on the renal tubules to increase the active reabsorption of sodium via the sodium–potassium pump. The movement of water is greatly influenced by the osmotic influences of sodium and follows sodium passively back into the blood. A rise in blood volume elevates blood pressure. A consequence of this mechanism is that the excretion of potassium is increased.

Vasopressin, otherwise known as antidiuretic hormone (ADH), also increases the reabsorption of water and so, through an increase in blood volume, raises blood pressure. Adrenaline and noradrenaline released into the blood from the adrenal medulla during sympathetic stimulation have a direct effect on blood pressure through vasoconstriction.

Another hormone with a role in blood pressure control is atrial natriuretic factor (ANF). This is released in response to an increase in stretch of the right atrial chamber wall; this occurs when blood volume or blood pressure is increased significantly. ANF secretion results in increased sodium excretion (natriuresis) and water loss, which decreases blood volume and blood pressure.

ENDOTHELIAL VASOACTIVE SUBSTANCES

The endothelium of the blood vessel wall is another important source of vasoactive substances. The most important of these are the endothelins, prostaglandins and nitric oxide.

There appear to be three types of human endothelin (endothelin-1, endothelin-2, endothelin-3) and they are not limited to the vasculature. The roles of the endothelins are detailed in Chapter 31. Endothelin-1 is the only endothelin present in vascular endothelium and acts locally on the vasculature. It is the most potent vasoconstrictor substance yet described. Type A receptors largely mediate vasoconstriction and, in so doing, raise blood pressure. There is evidence that endothelin-1-mediated vasoconstriction is implicated in the regulation of normal blood pressure and in the pathophysiology of myocardial infarction, acute renal failure, Raynaud's phenomenon, subarachnoid haemorrhage, hypertension and heart failure. An endothelin receptor antagonist is now available for use in the management of pulmonary hypertension.

Prostacyclin (prostaglandin I_2), prostaglandin E_2 (PGE_2) and nitric oxide are locally acting vasodilators that have an influence on blood pressure. PGE_2 and prostacyclin are released in response to tissue injury and inflammation. Prostacyclin also inhibits thrombus formation by opposing platelet aggregation, an action for which it is probably better known (see Chapter 30).

Nitric oxide (see Chapter 31) acts on the venous and arterial vasculature. It can lower systemic blood pressure and increase local tissue perfusion. The action of nitric oxide on blood vessels underlies the clinical effects of nitrates such as glyceryl trinitrate and a drug used to treat impotence called sildenafil (Viagra™) (see Chapter 45).

In terms of fine control of the vascular response, there appears to be some modulation of the levels of these vasoconstrictors and vasodilators, mediated in part through the type B endothelin receptor (see Chapter 31).

Other factors influencing blood pressure

The onset of essential hypertension has been linked to inheritance, age-related structural changes in the blood-vessel wall, higher plasma renin levels, a diet rich in sodium salts and fats, and age-related changes in blood-pressure settings within the medullary centre (reset to higher levels). Indeed, from the above discussion, you should be able to see why each factor causes elevated blood pressure by its effects on stroke volume, heart rate and systemic vascular resistance.

ANTIHYPERTENSIVE THERAPIES

The drugs used in the treatment of essential hypertension produce the desired effect of lowering blood pressure to within normal limits by interfering with the systems described above. Before these drugs are discussed, it must be remembered that lifestyle changes alone may be sufficient to control blood pressure in people with mild hypertension and will usually be recommended first. These include a healthy diet (including a low salt intake) and regular aerobic exercise (brisk walking, cycling or jogging for 30–60 minutes, three to five times a week), providing this is safe for the patient. Both healthy eating and exercise can reduce blood pressure. Excessive alcohol consumption (more than 21 units (men) or 14 units (women) weekly) is associated with raised blood pressure, as is excessive caffeine consumption (more than five cups of coffee per day). The patient should be encouraged to stop smoking. There is no direct link between smoking and hypertension, but smoking is linked to cardiovascular disease.

In most patients with hypertension, drugs are needed eventually to maintain a substantial lowering of blood pressure. To simplify the learning of these drugs, a

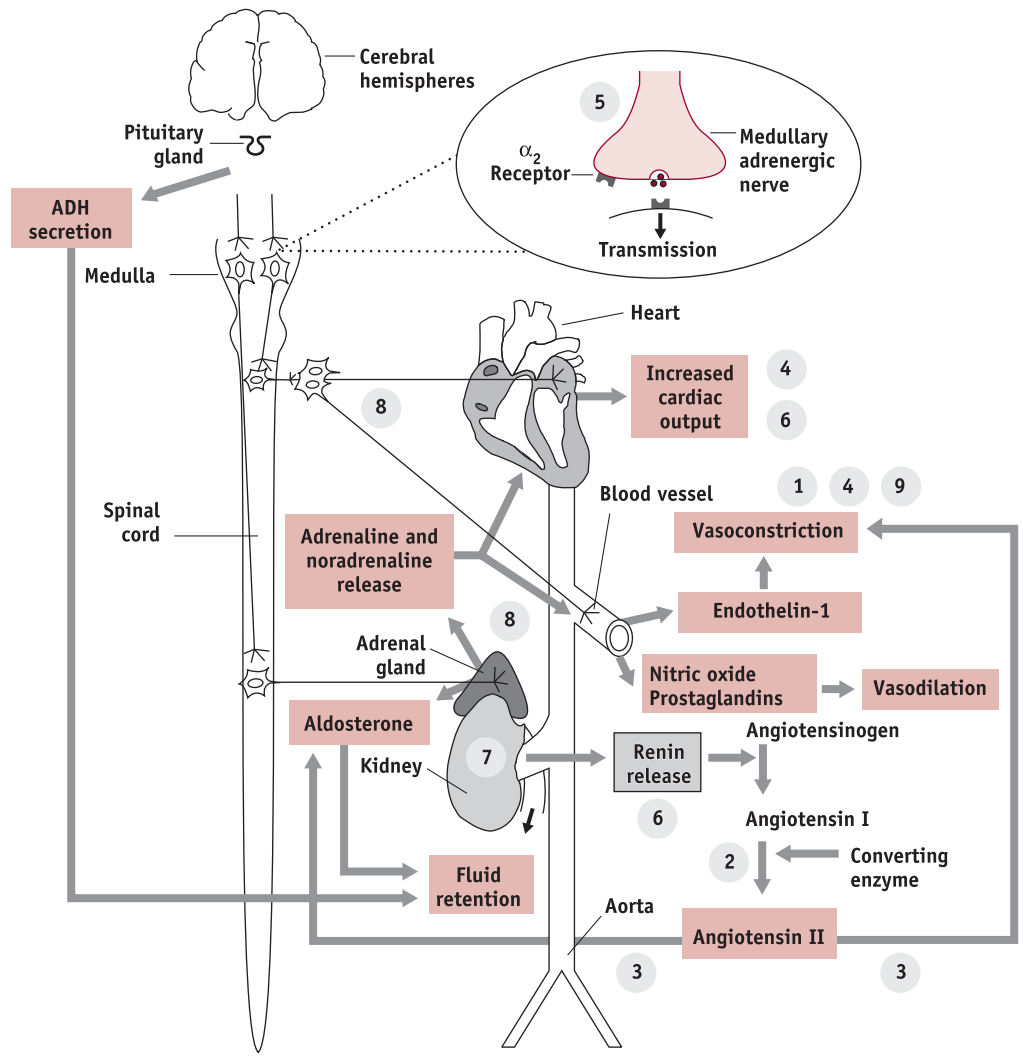
colleague has suggested that the major groups of first-line antihypertensive drugs can be arranged in order of the first five letters of the alphabet:

A is for ACE inhibitors, angiotensin II receptor antagonists and α antagonists.
B is for beta-blockers.
C is for calcium channel antagonists and drugs with combined actions.
D is for diuretics.
E is for endothelin receptor antagonists.

The sites of action of the various antihypertensive drug groups are illustrated in Figure 44.2.

FIGURE 44.2 SITES OF ACTION OF ANTIHYPERTENSIVE AGENTS

This figure shows where each of the major antihypertensive drug groups acts on the blood-pressure-control mechanisms to reduce hypertension.



ADH, antidiuretic hormone.

The antihypertensive actions and important adverse effects of each of these drug groups are discussed below. Other chapters give more detailed descriptions of the relevant drugs.

The latest National Institute for Health and Clinical Excellence (NICE) clinical guidelines for the treatment of hypertension have been funded by the National Collaborating Centre for Chronic Conditions working with the BHS and the Royal College of Physicians and can be found on the NICE website at www.nice.org.uk.

Angiotensin-converting enzyme inhibitors

■ MECHANISM OF ACTION

Drugs in this group act on the renin–angiotensin system by specifically preventing the conversion of angiotensin I into angiotensin II. As a result, blood pressure is lowered through a significant reduction in SVR. Moreover, because angiotensin II also stimulates the release of aldosterone, sodium and water retention (which could contribute to an elevation in blood pressure) are diminished.

ACE inhibitors inhibit the breakdown of the potent vasodilator peptide bradykinin, which makes a further contribution to the decrease in vascular resistance. This accounts for the effectiveness of ACE inhibitors in hypertensive patients who do not show elevated plasma renin levels. Bradykinin is believed to have a role as a chemical mediator in inflammation and allergy. It is an autacoid (see Chapter 28) that can induce pain, vasodilation and increased capillary permeability and stimulate the synthesis of prostaglandins.

The reduction of blood pressure by these agents is brought about without lessening cardiac output. This action makes ACE inhibitors the antihypertensive of choice in congestive cardiac failure, reducing the workload of the heart (lowering both pulmonary and systemic resistance) without affecting cardiac output. Indeed, clinical studies have shown that ACE inhibitor therapy improves survival in people with heart failure (see Chapter 48). There is also evidence that these drugs prevent, and possibly reverse, the extent of hypertrophy and fibrosis associated with cardiovascular disease. Following the publication of the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT), these drugs have become first line in the management of hypertension in patients under 55 years of age. **Captopril** is the prototype of this group. Some of these agents are prodrugs that, when absorbed, are converted rapidly into active ACE inhibitors. These are administered in preference to the active drugs because the latter are poorly absorbed from the gut. The prodrugs in this group include **cilazapril**, **enalapril**, **fosinopril**, **perindopril**, **quinapril**, **moexipril**, **ramipril** and **trandolapril**.

◆ COMMON ADVERSE EFFECTS

The adverse reactions associated with ACE inhibitors are related to the reduction of SVR. Hypotension, dizziness and headache are commonly observed. There is a chance of hyperkalaemia developing during therapy. As these drugs inhibit angiotensin II production, aldosterone secretion is also decreased. As aldosterone regulates potassium excretion, the elimination of potassium may be reduced. Renal stenosis is a contraindication of ACE inhibitor therapy. A summary of the desirable and undesirable effects of the ACE inhibitors is provided in Chapter 48.

The onset of a non-productive cough has been associated with ACE inhibitor therapy and is believed to be linked to the action of bradykinin. A prostaglandin may also have a role in causing this effect, but this is yet to be elucidated fully. The cough is often worse at night or when the patient lies down and, interestingly, is reported more often in women.

✚ CLINICAL CONSIDERATIONS

Non-steroidal anti-inflammatory drugs (NSAIDs) such as sulindac (see Chapter 40) and the asthma prophylactic cromoglycate (see Chapter 51) have been found to relieve the cough associated with ACE inhibitors.

As there is an increased risk of hyperkalaemia, serum potassium levels may need to be monitored closely during therapy. When starting treatment with ACE inhibitors, it is important to stop potassium supplements and potassium-sparing diuretics in order to avoid hyperkalaemia. Refer to the doctor if the patient shows signs of hyperkalaemia (confusion, nervousness, irregular heart beat, numbness and tingling of limbs and lips, muscle weakness).

Hypotension can occur with the first dose. Stop any diuretic for 24 hours before starting the ACE inhibitor. The first dose could be administered at night in order to avoid dizziness, lightheadedness and fainting. As these drugs are excreted mainly by the kidney, renal function and electrolyte levels are checked before therapy and then reviewed following 1–2 weeks of treatment.

Most drugs in this group, except for captopril, can be given once daily and maintain a good antihypertensive effect for 24 hours. Captopril and perindopril should be taken on an empty stomach.

Angiotensin receptor antagonists

The angiotensin receptor antagonists **losartan**, **irbesartan**, **candesartan**, **telmisartan**, **valsartan** and **eprosartan** are approved for use in the UK.

■ MECHANISM OF ACTION

The effects of these agents are similar to those of the ACE inhibitors in that they trigger a decrease in systemic vascular resistance and inhibit aldosterone release. Unlike the ACE inhibitors, however, the angiotensin receptor inhibitors do not inhibit the formation of angiotensin II; rather, they produce these effects by blocking the interaction of angiotensin II with specific angiotensin II receptors

referred to as angiotensin II subtype 1 (AT1), receptors. Candesartan is more potent than irbesartan and losartan. When compared with losartan, telmisartan produces a more prolonged antihypertensive action.

◆ COMMON ADVERSE EFFECTS

In contrast to the ACE inhibitors, the angiotensin receptor antagonists do not usually induce a cough or clinically significant hyperkalaemia. The drugs in this group appear to be tolerated well. Common adverse reactions include dizziness, headache, hypotension and gastrointestinal disturbances. As for the ACE inhibitors, treatment with angiotensin receptor antagonists is contraindicated in renal stenosis. The desirable and undesirable effects of the angiotensin receptor antagonists are shown in Figure 44.3.

✚ CLINICAL CONSIDERATIONS

The angiotensin receptor antagonists cause less cough than ACE inhibitors. They can be a useful alternative to ACE inhibitors for individuals who experience cough as a side effect. The angiotensin receptor antagonists may cause less hyperkalaemia than their ACE inhibitor counterparts, but they should not be administered with potassium or potassium-sparing diuretics.

Patients should be informed that the maximum antihypertensive effect occurs about 4–6 weeks following commencement of treatment.

These agents are administered once daily. Food may affect the absorption of eprosartan, but it does not alter the effectiveness of other drugs in this group.

Alpha antagonists

Prazosin and its derivatives, **doxazosin** and **terazosin**, are relatively specific α_1 antagonists. The non-selective α antagonists **phentolamine** and **phenoxybenzamine** are no longer used in the treatment of essential hypertension, but they may still be used in the management of hypertensive crisis.

■ MECHANISM OF ACTION

The α antagonists used in hypertension are designed to block α_1 receptors located on arterioles and venules. These receptors mediate the peripheral vasoconstrictive response. Therefore, blockade lowers systemic vascular resistance. The prazosin derivatives have longer half-lives, providing the advantage of once-daily dosing.

◆ COMMON ADVERSE EFFECTS

Common adverse effects include postural hypotension, nasal congestion, pupil constriction, fatigue, inhibition of ejaculation and diarrhoea. Prazosin is a short-acting drug that is likely to lead to postural hypotension. This problem is reduced by the use of longer-acting agents such as doxazosin and terazosin. The non-selective α antagonists produce more adverse effects than the specific α_1 antagonists. Figure 44.4 shows the desirable and undesirable effects of the α_1 antagonists.

✚ CLINICAL CONSIDERATIONS

First-dose hypotension is common with selective α_1 antagonists. This effect is more pronounced in older people, in patients with fluid depletion and in patients taking diuretics. To minimise this effect, a low starting dose should be administered at bedtime and titrated slowly at 2-week intervals. For patients on diuretics, the diuretic is withheld for a few days before commencing the α_1 antagonist. Advise the patient to rise slowly from a lying or sitting position to minimise the effect of postural hypotension.

Alpha-blockers are often used as first-line therapy for the control of hypertension if prostatic hypertrophy is also present. They relax smooth muscle in this condition and produce an increased urinary flow rate, so serving a dual function.

Beta-blockers

Despite the use of these drugs as antihypertensive agents for decades, the mechanism of action of beta-blockers in this context is unclear.

■ MECHANISM OF ACTION

The lowering of blood pressure takes 1–2 weeks to manifest and so cannot be accounted for simply by preventing sympathetically mediated cardio-acceleration. It has been suggested that an important effect that may contribute to a reduction of blood pressure is that renin release is mediated by β_1 receptors. Therefore, receptor blockade prevents angiotensin II formation and associated aldosterone secretion, resulting in a decrease in SVR. These drugs may also decrease sympathetic drive from the central nervous system (CNS).

◆ COMMON ADVERSE EFFECTS

Common adverse reactions of selective and non-selective beta-blockers include bradycardia, hypotension, cold extremities, vivid dreams and constipation (see Chapter 26).

✚ CLINICAL CONSIDERATIONS

Specificity is a problem with beta-blockers. Blockade of β_2 receptors causes bronchoconstriction, which can precipitate an asthma attack in susceptible individuals. Non-selective beta-blockers, such as **propranolol**, are not usually recommended in the treatment of hypertension.

Atenolol and **pindolol** are eliminated mainly by the renal route, although pindolol has also some elimination activity through the hepatic route. These agents may be preferred in patients with hepatic impairment. **Metoprolol** and **oxprenolol** are eliminated largely by the liver; therefore, these agents may be preferred in individuals with renal impairment.

FIGURE 44.3 FLOWCHART SHOWING THE EFFECTS OF THE ANGIOTENSIN RECEPTOR ANTAGONISTS

Desired therapeutic effect is shown in the darker shaded box.

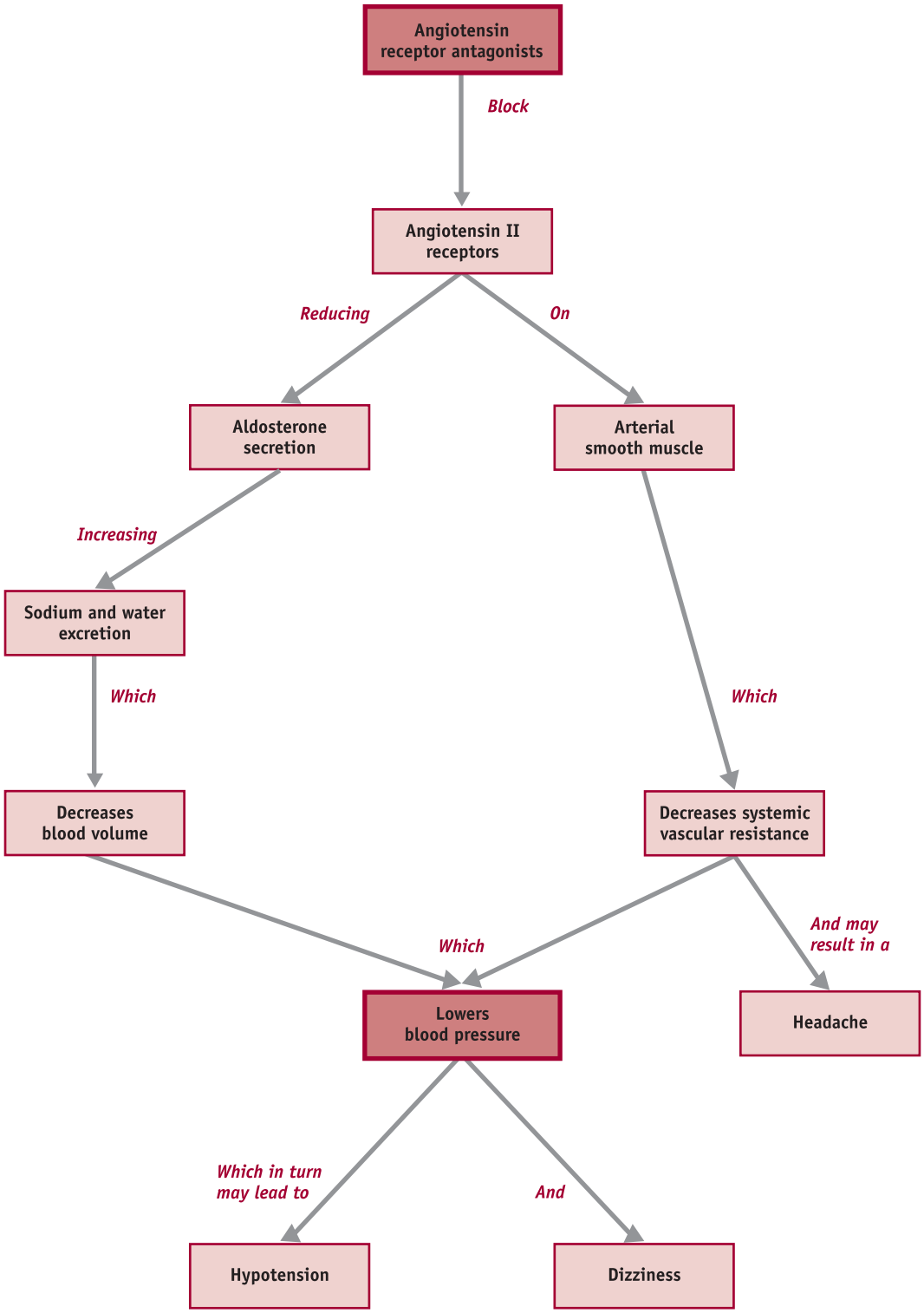
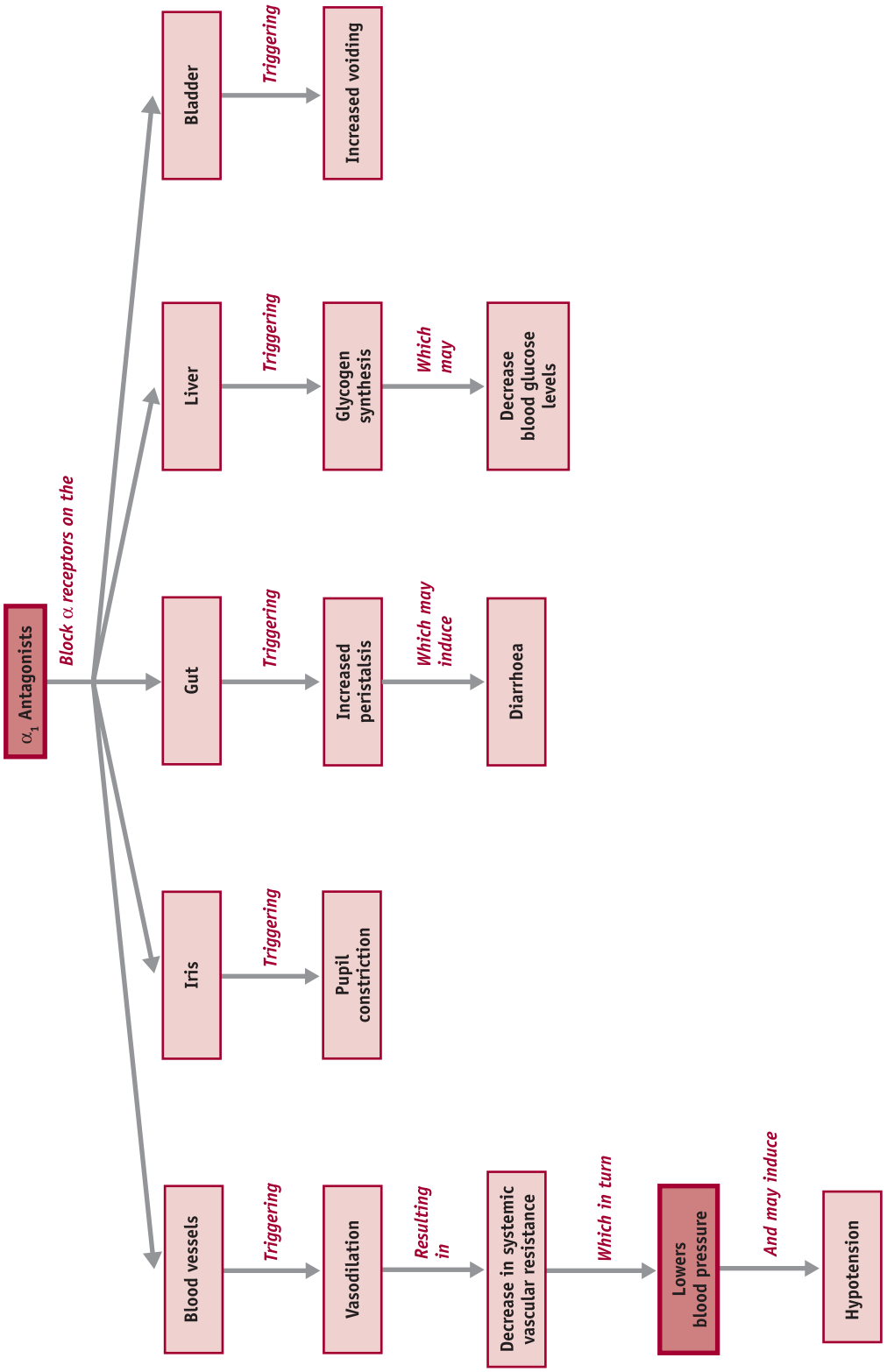


FIGURE 44.4 FLOWCHART SHOWING THE EFFECTS OF ALPHA-1 ANTAGONISTS

The desired therapeutic effect is shown in the darker shaded box.



Abrupt withdrawal may cause rebound hypertension. Therefore, reduce the dose gradually over 8–14 days.

As beta-blockers may cause insomnia and vivid dreams, the dose may be taken in the morning. A less lipid-soluble beta-blocker, such as atenolol, may also be used, as these are less likely to enter the brain.

Beta-blockers should not be used by patients with obstructive airways disease (asthma, bronchitis, emphysema), bradycardia, sick sinus syndrome, second- or third-degree heart block, cardiogenic or hypovolaemic shock, uncontrolled heart failure or severe hypotension. The use of beta-blockers should be avoided in patients with diabetes, as the drugs can mask or prolong insulin-induced or oral hypoglycaemic-induced hypoglycaemia.

Beta-blockers are not a preferred initial therapy for hypertension. Although they lower blood pressure, they have been less effective than comparator drugs in head-to-head trials at reducing major cardiovascular events, especially stroke. It must be noted that most studies have used atenolol as the beta-blocker and there is no certainty that these findings can be applied to other beta-blockers. The 2006 NICE guidelines state that beta-blockers may be considered in young people, especially those who cannot tolerate ACE-inhibitors or angiotensin receptor antagonists. They should also be considered in women of childbearing age and patients with evidence of increased sympathetic drive.

Calcium channel antagonists

These drugs have a role in the management of angina pectoris and cerebral ischaemia (see Chapter 45), selected cardiac dysrhythmias (see Chapter 48) and hypertension.

■ MECHANISM OF ACTION

Calcium channels regulate the influx of calcium across the membrane of muscle cells. They play particularly important roles in the heart and vascular smooth muscle. Calcium channel antagonists decrease the entry, and thus the availability, of calcium within the heart and blood vessels. Cardiac contractility, cardiac conduction and vascular tone can be affected.

The calcium channel antagonists are divided into three groups: the nifedipine-like agents (**nifedipine**, **felodipine**, **lercanidipine**, **amlodipine**), **verapamil** and **diltiazem**. The nifedipine-like agents are also known by the chemical grouping dihydropyridines. The primary difference between the three groups is their selectivity. The nifedipine-like agents are relatively selective for vascular muscle, diltiazem depresses heart and vascular muscle, and verapamil depresses cardiac and vascular muscle and atrioventricular (AV) node function.

◆ COMMON ADVERSE EFFECTS

Common adverse effects include hypotension, headache, facial flushing and rash. The depression of myocardial function can lead to bradycardia and other cardiac dysrhythmias such as AV block. The nifedipine-like agents cause less cardiac depression, and so these effects are less common. The calcium channel antagonists are not recommended in the long-term management of people with heart failure.

✚ CLINICAL CONSIDERATIONS

There is significant variability in the duration of action of the calcium channel antagonists. Nifedipine and felodipine have relatively short half-lives; their duration of action can be prolonged by administering controlled-release preparations, which require once-daily dosage. Amlodipine and lercanidipine have longer half-lives and can be administered once daily without the need for controlled-release preparations.

Calcium channel antagonists should be used with caution in second- and third-degree heart block, systolic dysfunction, congestive heart failure, unstable angina and recent acute myocardial infarction.

Calcium channel blockers or thiazide diuretics are the first choice for initial therapy in people over 55 years of age and black patients of any age.

Drugs with a combined action

■ MECHANISM OF ACTION

Labetalol and **celiprolol** are sympathetic depressants that non-selectively block all peripheral adrenoreceptors. The advantage is that the resulting reduction in blood pressure is produced at different sites of action (α and β receptors) and will be greater than at either site alone. The disadvantage is that the adverse reactions observed are the result of blocking both receptor types.

Another drug with combined action is **carvedilol**. This drug is a non-selective beta-blocker with α_1 antagonist activity that has been approved as supplementary therapy in the management of congestive heart failure (described fully in Chapter 48).

Beta-blockers induce a drop in SVR by suppressing the renin–angiotensin system. Alpha-1 antagonism triggers a further drop in SVR by direct vasodilation. As a consequence, blood pressure drops.

◆ COMMON ADVERSE EFFECTS

Common adverse reactions include hypotension, bradycardia and dizziness.

✚ CLINICAL CONSIDERATIONS

Labetalol produces greater α blockade than β blockade compared with carvedilol, which contributes to the postural hypotension associated with labetalol.

At cessation of treatment with these agents, dosage should be reduced slowly over 7–14 days because abrupt withdrawal can produce rebound hypertension. Patients

commencing treatment with carvedilol should be advised not to drive or operate machinery because of the risks of dizziness and fainting.

Diuretics

■ MECHANISM OF ACTION

Diuretics lower blood pressure acutely by reducing blood volume. This is achieved through increasing the amount of water excreted as urine. The problem associated with the use of diuretics is that this action may be excessive, resulting in dehydration, hypotension and electrolyte imbalances. (A detailed description of diuretics and their corresponding adverse effects is provided in Chapter 47.)

THIAZIDE DIURETICS

The thiazides and the thiazide-like diuretics are generally regarded as the diuretics of choice in the management of hypertension. The effects of this group of diuretics are more prolonged than those of the loop diuretics, the cost of therapy is low and, in combination with beta-blockers, they have been shown to reduce morbidity and mortality in people with chronic hypertension. Lowering of blood pressure occurs over a period of days and results from a gradual reduction in peripheral resistance. The precise mechanism of the antihypertensive action of the thiazides remains unclear, however. With continued use, urine output returns to normal and yet the antihypertensive action persists. Some researchers suggest that this effect may be related to continued sodium loss from the vascular smooth muscle, reducing vascular stiffness. Evidence has shown that lower doses of thiazide diuretics than previously recommended are just as effective in reducing blood pressure but result in fewer adverse reactions. Loop diuretics, such as **furosemide**, are useful in people with hypertension who have renal impairment.

POTASSIUM-SPARING DIURETICS

Potassium-sparing diuretics are also used in hypertension, but usually in combination with a thiazide diuretic. The reason for this is their tendency to induce hyperkalaemia when used alone. Potassium-sparing diuretics should not be used as first-line therapy in hypertension, but **spironalactone** (an aldosterone antagonist) may be useful in patients with resistant hypertension linked to hyperaldosteronism.

DIURETIC DRUGS WITH A MIXED ACTION

Indapamide is an antihypertensive with a mixed action. It produces a diuretic effect by inhibiting the reabsorption of sodium, water and chloride in the proximal convoluted tubule. It also reduces the responsiveness of peripheral vessels to endogenous vasoconstrictive substances such as noradrenaline and adrenaline. Indapamide reduces blood pressure at doses lower than those capable of inducing a diuresis. Increasing the dose produces diuresis but has no additional effect on blood pressure in the long term.

◆ COMMON ADVERSE EFFECTS

Common adverse effects of diuretics with a mixed action are similar to problems associated with diuretics in general and include dehydration, hypotension and electrolyte imbalances.

✚ CLINICAL CONSIDERATIONS

Some antihypertensive preparations are marketed that are combinations of a thiazide diuretic (such as **hydrochlorothiazide**) and another antihypertensive agent such as a beta-blocker, ACE inhibitor, angiotensin receptor antagonist or centrally acting sympathetic depressant. The rationale is that the preparation is a relatively safe and effective combination that produces a greater reduction in blood pressure than either agent alone.

Patients on diuretics need to be monitored for hypokalaemia, hyponatraemia and dehydration. If possible, diuretics are administered as a once-daily dose in the morning to prevent diuresis interfering with sleep. If a second dose is required, this is administered at midday or in the early afternoon.

Diuretics may cause hypokalaemia associated with weakness, dizziness and nausea. Advise the patient to eat foods with a high potassium content (see Chapter 49). A low-dose diuretic minimises potassium loss. Where possible, use potassium-sparing diuretics or potassium supplements.

Diuretics (except indapamide) can produce a dose-related hyperglycaemia. Use a low-dose thiazide or indapamide to avoid this effect.

Thiazide diuretics can cause photosensitivity due to the presence of a sulphonamide group in their chemical structure. Avoid use in patients with a sulphonamide sensitivity and advise patients to take precautions in the sun.

Potassium-sparing diuretics can produce hyperkalaemia when used in combination with potassium supplements, ACE inhibitors and angiotensin II receptor blockers.

HYPERTENSIVE EMERGENCIES AND SECOND-LINE HYPERTENSIVE THERAPIES

Peripheral vasodilators

These drugs are not considered first-line therapy in the management of essential hypertension. Rather, they are considered useful in the emergency management of hypertension.

■ MECHANISM OF ACTION

Peripheral vasodilators reduce total peripheral resistance by relaxing vascular smooth muscle. The manner in which

they produce vasodilation and the specific vascular site affected varies from drug to drug. This group includes arterial and arteriovenous vasodilators.

Hydralazine, **minoxidil**, **diazoxide** and **sodium nitroprusside** are vasodilator substances. All induce dilation of arterioles, the vessels controlling blood flow into body tissues, causing a lowering of SVR. Sodium nitroprusside is the only agent that dilates both arteries and veins; the other drugs affect only arterial vessels. As a consequence, sodium nitroprusside reduces not only peripheral resistance but also venous return. The latter effect diminishes cardiac output, producing a more profound effect on blood pressure than the other vasodilators. This makes sodium nitroprusside best suited to the emergency treatment of hypertension.

Glyceryl trinitrate can also be used as an antihypertensive; its action in angina therapy is discussed in Chapter 45. It is primarily a venodilator but it also affects arterial smooth muscle, reducing both venous return and peripheral resistance. Its use in this context is restricted mainly to hypertension associated with surgical and perioperative situations.

◆ COMMON ADVERSE EFFECTS

The main adverse effects associated with the use of all peripheral vasodilators are hypotension, headache (due to cerebral vasodilation), peripheral oedema (due to peripheral pooling) and allergic rash. Interestingly, a common side effect of minoxidil is increased body hair, which is not due to a drug-induced hormonal imbalance. The reason for this is not understood well, but normal distribution of body hair returns after cessation of treatment. This rather idiosyncratic effect makes minoxidil useful as a topical agent in the treatment of impending baldness (see Chapter 78).

✚ CLINICAL CONSIDERATIONS

Sodium nitroprusside and diazoxide can be administered only parenterally. Hydralazine and minoxidil are administered orally and are most suitable for effective long-term outpatient therapy.

Sodium nitroprusside is extremely light-sensitive and rapidly degrades to form cyanide and cyanogen; when this occurs, the solution develops a bluish tinge. The process of degradation cannot be prevented; it can be slowed, however, by covering the infusion system in aluminium foil and changing solutions every 4 hours.

These preparations are occasionally used intravenously to reduce blood pressure in hypertensive emergencies. When administered intravenously, great care must be taken to titrate the blood-pressure response. If a large drop in blood pressure occurs, this may lead to neurological complications such as stroke. Similarly, these medications are not stopped abruptly when used intravenously, as they may produce rebound hypertension.

Hydralazine can produce a lupus-like syndrome following prolonged treatment (more than 6 months). Antinuclear factor analysis is undertaken before and during treatment to detect this syndrome. Avoid using hydralazine in patients with systemic lupus erythematosus, severe tachycardia, high output heart failure and coronary artery disease.

As glyceryl trinitrate can adsorb on to some plastics, such as polyvinyl chloride (PVC), polyethylene administration sets are used.

The duration of treatment using sodium nitroprusside should not exceed 72 hours because of the possible accumulation of thiocyanate and subsequent cyanide toxicity.

As minoxidil causes hair growth, it is used rarely in women.

Other sympathetic nervous system depressants

The effects of the sympathetic nervous system can be attenuated in other ways. Rather than blocking peripheral α- or β-adrenergic receptors, the central medullary control centres and the adrenergic nerves can be targeted directly by drugs.

CENTRALLY ACTING AGENTS

Nowadays, this group of antihypertensive agents is not regarded as first-line therapy in hypertension. These drugs tend to be used in cases where the patient has not responded to other therapies.

■ MECHANISM OF ACTION

Centrally acting sympathetic depressants act by stimulating α_2 receptors located in the vasomotor centre of the medulla. These receptors are located presynaptically and are involved in inhibiting noradrenaline release from adrenergic nerve terminals (see Figure 44.2). Sympathetic outflow from the medulla is diminished and, as a result, either systemic vascular resistance or cardiac output decreases. The two agents in this group, **methyldopa** and **clonidine**, produce different effects – the former reduces SVR and the latter lowers blood pressure by affecting cardiac function. Therefore, it is likely that each drug acts on different medullary centres.

Methyldopa, an analogue of L-dopa, from which noradrenaline, adrenaline and dopamine are formed, is converted into the false transmitter methylnoradrenaline. Therefore, methyldopa is really a prodrug, whose metabolite produces the desired action. It still has a role in the treatment of hypertension in pregnancy. Clonidine acts directly as a partial α agonist. Even though both drugs are relatively selective drugs for α_2 receptors, stimulation of peripheral α_1 receptors is observed. This accounts for the initial transient elevation of blood pressure seen after intravenous administration of clonidine. Clonidine is used rarely due to its short duration of action and risk of withdrawal hypertension.

Moxonidine is a better tolerated drug that reduces sympathetic activity by acting as a central imidazoleine receptor antagonist and may be useful when thiazides, beta-blockers and calcium channel blockers are not appropriate or have failed to control blood pressure.

◆ COMMON ADVERSE EFFECTS

The major adverse reactions with both drugs are associated with CNS function. As central adrenergic receptors influence both mood and level of arousal, these drugs can produce mental depression, perceptual disorders, nightmares, sexual dysfunction and sedation. Clonidine stimulates the parasympathetic nervous system, which may result in dry mouth and constipation. Methyldopa treatment can induce too great a decrease in SVR, causing postural hypotension, dizziness, lightheadedness, oedema and impaired blood flow to the heart and brain. The central action of dopamine can be diminished during treatment with methyldopa, resulting in parkinsonian-like symptoms (tremor and rigidity) and increased prolactin secretion (inducing lactation in both men and women).

Individuals taking clonidine are advised not to cease therapy abruptly, because sudden withdrawal can result in a rebound hypertensive state, which may be severe.

✚ CLINICAL CONSIDERATIONS

The sedative effect of methyldopa can be potentiated by increasing the dose. Increases should, therefore, be reserved for the night-time dose.

Hepatitis and haemolytic anaemia may occur with methyldopa treatment. Because of the drug's possible effects on the hepatic and haematological systems, blood counts and liver function are monitored for the first 6–12 weeks of methyldopa therapy. If a patient on methyldopa therapy is also taking iron tablets, the two preparations should not be administered together. Iron can reduce the bioavailability of methyldopa and interfere with blood-pressure regulation.

As fluid retention can occur with methyldopa, a diuretic may also be necessary.

The withdrawal syndrome associated with the abrupt cessation of clonidine is characterised by a rapid rise in blood pressure, flushing, headache, sweating, agitation and tremor. A gradual reduction in clonidine dose needs to occur over days to weeks.

DRUGS THAT IMPAIR ADRENERGIC NERVE FUNCTION

■ MECHANISM OF ACTION

Guanethidine blocks adrenergic nerve transmission, preventing the release of transmitter. It lowers blood pressure by reducing both cardiac output and systemic vascular resistance. Today, this drug is rarely used in the management of hypertension, but it still has a role in the treatment of some forms of sympathetic nervous system dysfunction, such as reflex sympathetic dystrophy.

◆ COMMON ADVERSE EFFECTS

Guanethidine produces profound sympatholytic effects, which accounts for the severity of the observed side effects. Diarrhoea and increased gastric acid secretion can occur as a result of dominance of the parasympathetic division. This may be of concern in patients with peptic ulcers. Postural hypotension can also occur, but this is usually controlled by decreasing the dosage. Disturbances in male sexual function can occur and usually affect the sympathetically mediated process of ejaculation. Guanethidine induces similar side effects to those seen during methyldopa therapy as a result of central depletion of noradrenaline and dopamine. As a consequence, sedation, mental depression and parkinsonian-like symptoms may be seen.

APPROACHES TO ANTIHYPERTENSIVE THERAPY

When an individual is diagnosed hypertensive, the first approach is to facilitate a decrease in blood pressure through changes in lifestyle (e.g. reduce salt and alcohol consumption, promote exercise, cease smoking, restrict fat intake). If these measures fail to reduce blood pressure, then antihypertensive drug therapy is indicated.

The choice of drug depends on a number of factors relevant to the individual patient. Factors such as age, medical history, sex, severity of adverse effects and drug costs are considered. Table 44.2 shows the antihypertensive drug therapy indicated for various coexisting conditions and the antihypertensive drugs to avoid. The treatment of mild to moderate hypertension usually starts with one drug – a diuretic, an ACE inhibitor or a calcium channel antagonist. The NICE guidelines are stepped, and most patients eventually require more than one drug to control their blood pressure. Many patients in the UK are on monotherapy for hypertension, resulting in suboptimal blood-pressure control. If the first drug does not control blood pressure, a second drug should be added and then a third if necessary. Some patients may need a combination of four different drugs to control their hypertension, but at this stage the general practitioner should have sought expert advice. The guidelines issued by NICE are not intended to be restrictive, and the emphasis is on control of blood pressure successfully. The template used, and available on the website, allows use of all classes of antihypertensive drug.

When one drug is only partly successful in lowering blood pressure, it is preferable to try combinations of drugs rather than resorting to higher doses of the original drug. A stepwise approach to the addition of drugs is taken, and an interval of at least 4 weeks should be allowed, unless

TABLE 44.2 COEXISTING ILLNESS AND THE ANTIHYPERTENSIVE DRUGS

Coexisting condition	Antihypertensive therapy to consider	Antihypertensive therapy to avoid
Angina	ACE inhibitors, beta-blockers (not with intrinsic sympathomimetic activity), calcium channel blockers	
Asthma, bronchitis, emphysema	ACE inhibitors, calcium channel blockers	Beta-blockers
Constipation	ACE inhibitors, angiotensin II receptor antagonists	Calcium channel blockers (especially diltiazem, verapamil), high-dose diuretics
Depression	ACE inhibitors, angiotensin II receptor antagonists, calcium channel blockers, diuretics	Beta-blockers, centrally acting agents
Diabetes mellitus (type 1)	ACE inhibitors	Beta-blockers, high-dose diuretics
Erectile dysfunction		Beta-blockers, diuretics
Gout	ACE inhibitors, angiotensin II receptor antagonists, calcium channel blockers	Beta-blockers, diuretics
Heart block	ACE inhibitors	Beta-blockers, calcium channel blockers (except dihydropyridines)
Heart failure	ACE inhibitors, angiotensin II receptor antagonists, thiazide or loop diuretics, carvedilol, metoprolol	Beta-blockers (except carvedilol, metoprolol), non-dihydropyridine calcium channel blockers (verapamil, diltiazem)
Hyperlipidaemia	ACE inhibitors, angiotensin II receptor antagonists, α antagonists, calcium channel blockers	Beta-blockers, diuretics
Hyperthyroidism	Beta-blockers	
Lactation (breast feeding)	ACE inhibitors (captopril, enalapril), methyldopa, nifedipine	Angiotensin II receptor antagonists, clonidine, diuretics
Migraine	Beta-blockers (non-cardioselective), calcium channel blockers (non-dihydropyridines)	
Myocardial infarction	ACE inhibitors, beta-blockers (not with intrinsic sympathomimetic activity)	Calcium channel blockers
Osteoporosis	Thiazide diuretics	
Pregnancy	Methyldopa, hydralazine, prazosin, labetolol	ACE inhibitors, angiotensin II receptor antagonists
Renovascular hypertension	Beta-blockers, calcium channel blockers	ACE inhibitors, angiotensin II receptor antagonists
Peripheral vascular disease	ACE inhibitors, calcium channel blockers	Beta-blockers
Benign prostatic hypertrophy	Alpha antagonists	

ACE, angiotensin converting enzyme.

urgent lowering is necessary, to determine response. The NICE clinical guidelines in the UK recommend that if initial therapy was a calcium channel blocker or a thiazide diuretic and a second drug is required, then an ACE-inhibitor should be added. If an ACE inhibitor is the original drug, then a calcium channel blocker or a thiazide diuretic should be added. If three drugs are needed, then the combination of ACE inhibitor, calcium channel blocker and thiazide diuretic is recommended. Other antihypertensive drugs are used if a fourth drug is required; Examples are selective alpha-blockers and beta-blockers. Some common combinations are marketed as one preparation (see the drug summary table at the end of this chapter). Dosage regimens of antihypertensive drugs are calculated to provide control of blood pressure over a 24-hour period.

In severe hypertension, if the above combinations cannot control blood pressure adequately, then treatment with a direct-acting vasodilator, such as minoxidil, in conjunction with a beta-blocker and a diuretic is indicated.

The control of malignant hypertension is usually achieved by the use of a beta-blocker (labetolol or atenolol) or a long-acting calcium channel blocker (e.g. amlodipine). The diastolic blood pressure should be reduced to 100–110 mmHg within the first 24 hours and normalised over the next 2–3 days. Parenteral drugs are hardly ever necessary, but sodium prusside by infusion is the drug of choice if necessary.

CLINICAL MANAGEMENT

Antihypertensive drugs

Assessment

- Assess vital signs and compare with subsequent observations. Determine pulse rate, force and rhythm. Report diastolic blood pressure greater than 90 mmHg. Take lying, sitting and standing blood pressures, as several antihypertensive drugs cause postural hypotension. Check both arms for blood pressure.
- Assess for manifestations of hypertension, including headache, oedema (pitting oedema of legs), nocturia, lethargy, epistaxis and vision changes.
- Check serum electrolytes. Diuretics (especially the loop and thiazide types) can cause enhanced potassium excretion. Normal values for potassium are 3.5–5.0 mmol/l. Hypokalaemia is, therefore, a possibility and can lead to dysrhythmias, muscle weakness and diminished tendon reflexes.
- For a patient ordered captopril, assess for dehydration and whether the patient is taking a diuretic. These conditions may increase the incidence of first-dose hypotension and renal impairment.
- Before initiating treatment with angiotensin-converting enzyme (ACE) inhibitors, ensure that the patient has ceased taking potassium supplements and potassium-sparing diuretics.

Planning

- The patient's blood pressure will fall or will be within the normal diastolic and systolic range.
- Any oedema present in the extremities will decrease.
- Serum electrolyte levels will remain within normal levels.

Implementation

- Monitor vital signs, especially blood pressure and pulse. Compare vital signs with baseline values.
- For intravenous therapy, monitor the blood pressure every 5 minutes until stable, and then every 15–30 minutes. Keep the patient supine in bed with a buzzer close by and the cot sides up. Take an electrocardiogram (ECG). Intravenous drugs should be given through a volumetric infusion pump.
- Monitor serum electrolytes regularly, especially potassium levels. Sodium and water retention is common with alpha- and beta-blockers. Diuretics (particularly thiazide and loop diuretics) can cause electrolyte loss and body fluid imbalances.
- Monitor lung sounds for crackles. Many antihypertensive drugs, such as methyldopa, clonidine, prazosin and minoxidil, promote sodium and water retention.
- Weigh the patient daily at the same time each day.
- Monitor the extremities for peripheral oedema.
- Monitor urinary output. Maintain a fluid balance chart, documenting fluid input and output. Excessive urine output can lead to electrolyte imbalance and hypovolaemia.
- Supervise the patient when ambulating to guard against injury if the patient feels faint.
- Be aware that peripheral oedema induced by calcium antagonists does not require treatment with diuretics. Diuretics will not help the problem and will put the patient at risk of volume depletion.
- Beta-blockers may be used to treat the reflex tachycardia caused by calcium antagonists.

Patient teaching

- For patients on diuretics that tend to cause potassium loss, encourage an adequate intake of potassium from the diet. Good food sources of potassium include citrus fruits and juices, meat, fish, bananas, nuts and cereals.
- Instruct the patient that excessive sodium leads to fluid retention. The patient should, therefore, avoid foods that are high in sodium, including canned, frozen and dehydrated soup, processed cheese, salted biscuits, potato chips and pretzels, relishes and pickles, canned meat, salt-cured meat, seasoning and sauces, and added salt to food.
- Inform the patient about the importance of maintaining normal weight, not smoking, decreasing alcohol intake and having regular exercise. Stress-reducing activities such as relaxation are also beneficial.
- Advise the patient to check with the doctor and pharmacist before taking any over-the-counter preparations. These may contain salts of sodium, which may raise blood pressure.
- Caution the patient against driving a car and operating machinery if drowsiness occurs.
- Advise the patient that antihypertensive agents, such as vasodilators, angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor antagonists, may cause dizziness from postural hypotension. Suggest that the patient gets up from a lying or sitting position slowly in order to avoid dizziness (see Table 11.20 in Chapter 11 for additional measures that can be used for postural hypotension).
- Educate the patient and the family in taking the patient's blood pressure. This will promote self-care and determination of the effectiveness of therapy when at home.
- Instruct the patient that drug treatment for hypertension usually requires lifetime control.

Evaluation

- Evaluate the effectiveness of the antihypertensive drug by monitoring blood pressure.
- Evaluate the presence of adverse effects of the drug. The dose or drug regimen may need to be altered.

SUMMARY

- Hypertension is a vascular disease characterised by consistently elevated blood pressure recorded over a period of time.
- The main factors determining blood pressure are cardiac output and systemic vascular resistance (SVR). Blood pressure is regulated by an interaction between the nervous, humoral and renal systems.
- The major groups of antihypertensive drugs are the angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor antagonists, α-adrenergic antagonists, β-adrenergic blockers, combined α and β antagonists, calcium channel antagonists, diuretics, peripheral vasodilators, and centrally acting sympathetic nervous system depressants.
- Drugs that primarily lower SVR include ACE inhibitors, α antagonists and peripheral vasodilators.
- Diuretics lower blood pressure by lowering cardiac output.
- The beta-blockers, calcium channel antagonists, angiotension II antagonists, combined α and β antagonists and centrally acting sympathetic depressants lower both cardiac output and SVR.
- Postural hypotension is a common adverse effect of antihypertensive drugs. Abrupt withdrawal of treatment may lead to a rebound hypertension.

1. Define the three forms of hypertension.
2. What three factors determine blood pressure?
3. What are the major vasoactive substances that influence blood pressure control, and in which direction is the influence of each (i.e. raise or lower blood pressure)?
4. How do the effects of the angiotensin receptor antagonists differ from those of the angiotensin-converting enzyme (ACE) inhibitors?
5. Outline the non-pharmacological therapies used to control hypertension.

6 Name the factors that influence the choice of antihypertensive drug.

7 For essential hypertension, describe the drug approach used in restoring blood pressure to acceptable levels.

8 Eva Bernstein, aged 58 years, comments on how relieved she is now that her doctor has started her on the thiazide diuretic hydrochlorothiazide as part of her antihypertensive therapy: 'Now I won't have to worry about having food without salt. The water tablet will take care of it,' she explains. What would your response be to her? What other lifestyle issues will you explore with Ms Bernstein?

9 Paulo Guaniasis, a 65-year-old retired patient, is receiving the angiotensin-converting enzyme (ACE) inhibitor captopril for his hypertension. What patient education would you offer Mr Guaniasis?

10 Margaret Jenner is 72 years old. Her hypertension is being controlled using an antihypertensive preparation containing hydrochlorothiazide and amiloride. What is the rationale for using this particular combination? What observations would you monitor closely during the early stages of her therapy?

11 Kristina Alevano, a 66-year-old patient, has just commenced taking a β_1-antagonist as part of her antihypertensive programme. What observations would you make to evaluate the effectiveness of the treatment?

12 Milo Georgialis suffers from congestive cardiac failure and hypertension. Which group or groups of antihypertensive drugs would be suitable for treatment of Mr Georgialis's hypertension? Explain your answer.

13 A major adverse effect of the peripheral vasodilators is sodium and water retention. How would you assess this problem? What type of drug could be given to treat this problem?

14 Rob Tussin is a 47-year-old with moderate essential hypertension. His hypertension is controlled well using the combination therapy of the thiazide diuretic hydrochlorothiazide and the angiotensin II antagonist candesartan. What are the advantages of the angiotensin II antagonists over the angiotensin-converting enzyme (ACE) inhibitors? What adverse effects would you monitor at the start of Rob's treatment?

15 Joe Fernando, a 50-year-old office executive, comes to the community health centre to have his antihypertensive medications reviewed. You find his blood pressure is 150/95 mmHg. What non-pharmacological measures would you suggest to Mr Fernando to reduce his blood pressure?

44 DRUG SUMMARY TABLE: ANTIHYPERTENSIVE DRUGS

FAMILY NAME	GENERIC NAME	TRADE NAME(S)
Angiotensin-converting enzyme (ACE) inhibitors	Captopril	Capoten
	+ Hydrochlorothiazide	Co-zidocapt
		Capozide
	Cilazapril	Vascace
	Enalapril	Innovace
	+ Hydrochlorothiazide	Innozide
	Fosinopril	Staril
	Imidapril	Tanatril
	Lisinopril	Zestril
		Carace
	+ Hydrochlorothiazide	Carace plus
		Caralpha
		Lisicostad
		Zestoretic
	Moexipril	Perdix
	Perindopril	Coversyl
	+ Indapamide	Coversyl Plus

FAMILY NAME	GENERIC NAME	TRADE NAME(S)
	Quinapril	Accupro
	+ Hydrochlorothiazide	Accuretic
	Ramipril	Tritace
	+ Felodipine	Triapin
	Trandolapril	Gopten
		Odrik
	+ Verapamil	Tarka
Angiotensin receptor antagonists	Candesartan	Amias
	Eprosartan	Teveten
	Irbesartan	Aprovel
	+ Hydrochlorothiazide	CoAprovel
	Losartan	Cozaar
	+ Hydrochlorothiazide	Cozaar-Comp
	Olmesartan medoxomil	Olmetec
	Telmisartan	Micardis
	+ Hydrochlormethiazide	Micardis Plus
	Valsartan	Diovan
	+ Hydrochlorothiazide	Co-Diovan
Alpha antagonists	Doxazosin	Cardura
	Phenoxybenzamine	Dibenyline
	Phentolamine	Rogitine
	Prazosin	Hypovase
	Terazosin	Hytrin
Beta-blockers	Acebutolol	Sectral
	+ Hydrochlorothiazide	Secradex
	Atenolol	Tenormin
	+ Chlortalidone (diuretic)	Co-tenidone
		Tenoret 50
		Tenoretic
	+ Amiloride	Kalten
	+ Nifedipine	Beta-Adalat
		Tenif
	Bisoprolol	Cardicor
		Emcor
		Monocor
	Metoprolol	Betaloc
		Lopresor
	+ Hydrochlorothiazide	Co-Betaloc
	Nadolol	Corgard
	Oxprenolol	Trasicor
	+ Cyclopenthiazide (diuretic)	Trasidrex
	Pindolol	Visken
	+ Clopamide (diuretic)	Viskaldix
	Sotalol	Beta-Cardone
		Sotacor
Alpha and beta receptor blockers	Carvedilol	Eucardic
	Labetolol	Trandate
	Celiprolol	Celectol

FAMILY NAME	GENERIC NAME	TRADE NAME(S)
Calcium channel antagonists	Amlodipine	Istin
	Diltiazem	Tildiem
	Longer-acting	Adizem-SR
		Angitil SR
		Calcicard CR
		Dilcardia SR
		Dilzem XL
		Slozem
		Tildiam LA
		Viazem XL
		Zemtard
	Felodipine	Plendil
	Isradipine	Prescal
	Lacidipine	Motens
	Lercanidipine	Zanidip
	Nicardipine	Cardene
	Nifedipine	Adalat
	Long-acting	Adalat Retard
		Adipine XL
		Cardilate MR
		Coracten SR
		Fortipine LA
		Hypolar Retard
		Nifedipress
		Slofedipine
		Tensipine MR
	Nislodipine	Syscor MR
	Verapamil	Cordilox
		Securon
		Univer
		Verapress MR
		Vertab SR
Diuretics	Amiloride	
	Indapamide	Natrilix
	Bendroflumethiazide (bendrofluazide)	
	Chlortalidone (chlorthalidone)	Hygroton
	Cyclopenthiazide	Navidrex
	Spironolactone	Aldactone
Peripheral vasodilators	Diazoxide	Eudemine
	Glyceryl trinitrate (GTN)	
	Hydralazine	Apresoline
	Minoxidil	Loniten
	Sodium nitroprusside	
Centrally acting sympathetic depressants	Clonidine	Catapres
		Dixarit
	Methyldopa	Aldomet
Adrenergic nerve blockers	Guanethidine	Ismelin

DRUGS USED TO PROMOTE TISSUE PERFUSION

45

CHAPTER FORTY-FIVE

OBJECTIVES

After completing this chapter, the reader should be able to:

- **briefly outline the pathophysiology of angina pectoris;**
- **identify the major drug groups used in the treatment of selected conditions associated with poor perfusion of tissues, such as angina pectoris, cerebral ischaemia and erectile dysfunction;**
- **state the mechanisms of action of the major drug groups;**
- **demonstrate a knowledge of the adverse reactions associated with each drug group and how they derive from the mechanism of action.**

KEY TERMS

Adrenergic receptors
Angina pectoris
Calcium channels
Cerebral ischaemia
Erectile dysfunction
Nitric oxide
Phosphodiesterase
Second messengers

ANGINA PECTORIS

Angina pectoris literally means 'chest pain' and is associated with myocardial ischaemia. In angina pectoris, the lumen size of the coronary arteries is diminished greatly, due to either the build-up of atherosclerotic plaque (stable angina) or coronary vasospasm (variant or Prinzmetal angina). Unstable angina may be due to plaque rupture. As a result of these changes, the oxygen and nutrient supply is out of balance with the demand required by the heart muscle.

In the stable form of angina, chest pain is not experienced at rest because myocardial oxygen and supply remain in balance. When the workload of the myocardium increases during exertion, the higher demand cannot be met because of limited blood flow, which then causes ischaemia. In the variant form, angina attacks can occur any time, even at rest. The degree of vasospasm during the attack is so severe that not even resting oxygen demand can be supplied. Unstable angina is characterised by either a recent and severe onset or a sudden worsening of the condition.

Drug therapy for stable angina is directed towards restoring a balance between myocardial oxygen supply and demand (Figure 45.1). There are four main drug categories applicable: peripheral vasodilators, selective coronary vasodilators, β-adrenergic antagonists and calcium channel blockers. At a physiological level, these drugs reduce the availability of calcium ions to muscle cells. They achieve this by a variety of mechanisms: activation of a second-messenger system, blocking calcium entry, or hyperpolarisation of the cell membrane. Patients with unstable angina should be admitted to hospital where treatment is provided to prevent myocardial infarction.

Peripheral vasodilators

Peripheral vasodilators act on both the arterial and venous vasculatures to reduce the workload of the heart. By dilating arteries, the peripheral resistance that the ventricles must overcome to eject blood into the circulation (afterload) is significantly diminished. Venodilation results in peripheral

FIGURE 45.1 PATHOPHYSIOLOGY AND RATIONALE OF DRUG THERAPY OF AN ANGINA ATTACK

Diagrammatic representation of the pathophysiology underlying an acute angina attack. In a normal heart, a balance between myocardial oxygen (O_2) demand and supply is maintained (a). During an angina attack, the workload of the heart is such that the demand of the myocardium for O_2 far outweighs the supply possible. As a result, the myocardium becomes ischaemic (b). The general approach in the drug management of angina is to try to increase the myocardial O_2 supply through O_2 therapy and vasodilating agents (1) and endeavour to reduce the workload of the heart, thereby reducing the O_2 demand (2).

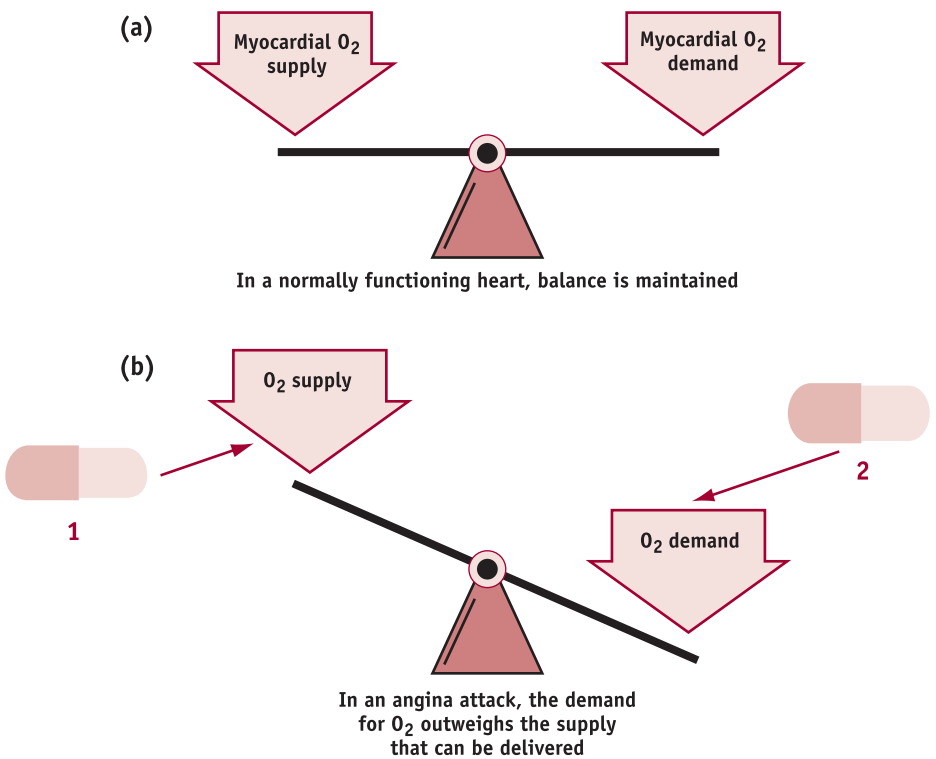
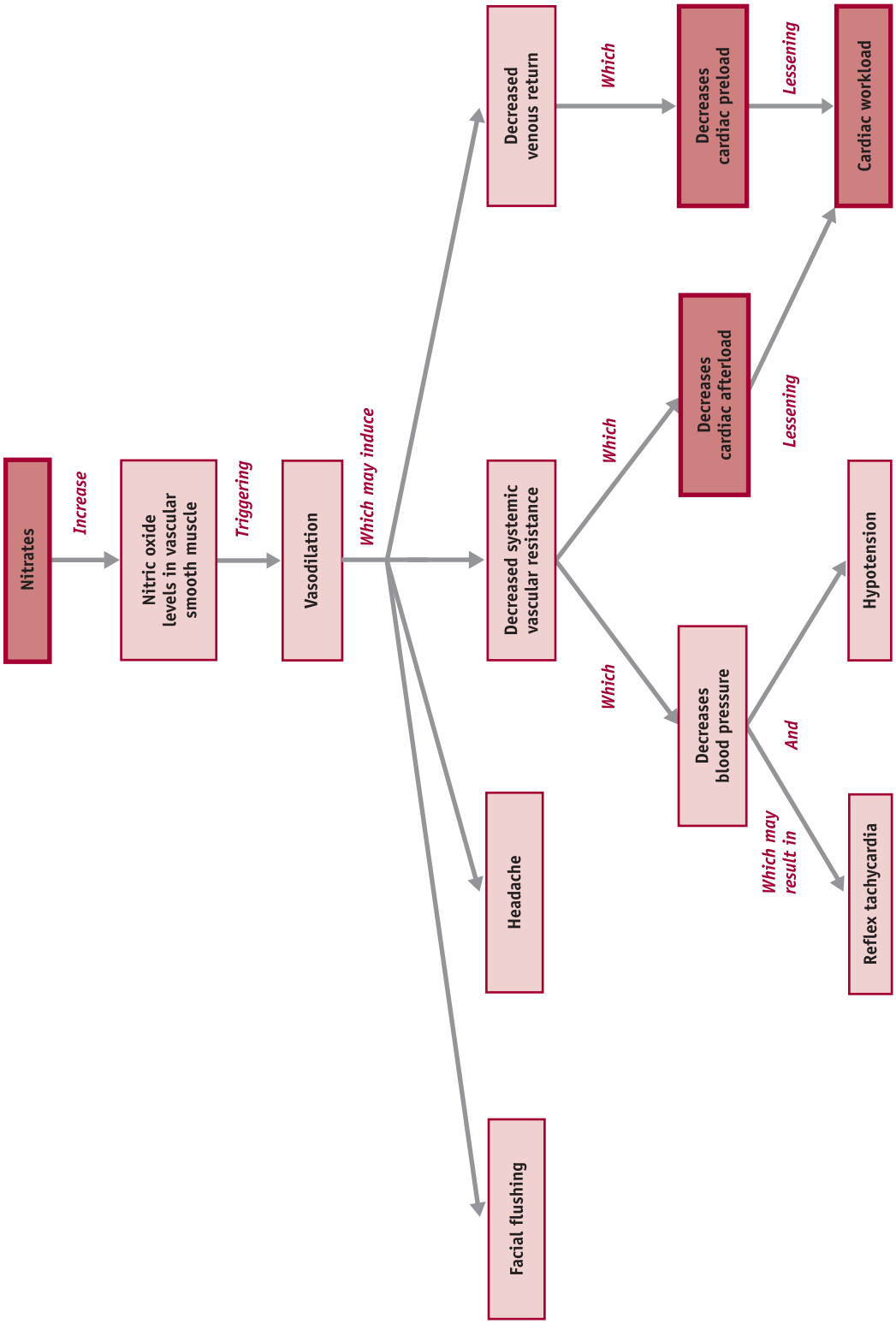


FIGURE 45.2 FLOWCHART SHOWING THE EFFECTS OF THE NITRATES

Desired therapeutic effects are shown in the darker shaded boxes.



pooling of blood, decreasing venous return and, in turn, ventricular filling (preload). Thus, less work is required to eject a lower ventricular volume. These drugs produce their effects by acting directly on the vascular smooth muscle, primarily that of veins, to cause relaxation.

The most important group of peripheral vasodilators is the organic nitrates: **glyceryl trinitrate** (nitroglycerine), **isosorbide dinitrate** and **isosorbide mononitrate**.

■ MECHANISM OF ACTION

Absorbed nitrates are taken up by the endothelial cells of the blood-vessel wall. They are converted into nitric oxide (NO) in the vascular muscle via a variety of mechanisms; for example, evidence suggests that denitration of glyceryl trinitrate by mitochondrial aldehyde dehydrogenase might be a clinically relevant mechanism. Nitric oxide increases the intracellular levels of the second messenger cyclic guanosine monophosphate (cGMP) (see Chapter 31), which in turn alters the availability of calcium ions within the muscle cell. As a result, blood vessels dilate. The vasodilating effect of the organic nitrates is more marked in venous capacitance vessels than in arterial vessels. The reduction in preload leads indirectly to a beneficial redistribution of coronary blood flow towards the endocardium. These drugs also dilate collateral coronary blood vessels, which leads to increased blood flow to ischaemic areas of the myocardium.

◆ COMMON ADVERSE EFFECTS

Common side effects associated with the vasodilators result from excessive vasodilation and include reflex tachycardia, hypotension, facial flushing, syncope and migraine-like headache, the latter due to cerebral vasodilation. Health-care professionals must be careful to avoid skin contact with glyceryl trinitrate paste when applying it to a patient as it can produce adverse effects in both patient and caregiver. Rashes have also been reported in patients during therapy.

Tolerance to the vasodilator effect of the nitrates occurs, and nitrate-induced production of reactive oxygen species may inhibit the ability of mitochondrial aldehyde dehydrogenase to produce NO. Fortunately, treatment tends to be intermittent, either in response to an acute attack or prophylactically before contact with a known trigger. In the case of transdermal administration, therapeutic activity is restored if treatment is withheld for a period of 8–12 hours in every 24 hours. This break in treatment allows replenishment of the sulfhydryl-dependent catalyst.

Figures 45.2 and 45.3 summarise the desirable and undesirable effects of the organic nitrates.

✚ CLINICAL CONSIDERATIONS

The nitrates are very lipid-soluble and are absorbed well through buccal and nasal mucosa and the skin. They produce their therapeutic effects rapidly but are also metabolised quickly. The nitrates are used to treat acute angina attacks and may also be used prophylactically before an activity expected to induce an attack. Glyceryl trinitrate is available as a sublingual tablet, a paste, a sticking plaster for transdermal absorption, a sublingual spray and an intradermal implant. One advantage of the sublingual spray over sublingual tablets is a longer shelf-life. The spray has a shelf-life of 5 years, whereas any unused tablets must be discarded a few weeks after breaking the seal on the container.

When using glyceryl trinitrate sublingual sprays, the patient should spray the preparation under the tongue or on to the buccal mucosa. Patches are applied to the trunk or upper arm on clean, dry, hairless skin. Patches are not suitable for treating an acute attack of angina. Sublingual tablets of glyceryl trinitrate and isosorbide dinitrate are placed under the tongue to relieve an angina attack.

Once angina symptoms have been relieved, the remaining part of the tablet may be removed from the mouth to prevent a headache developing.

Glyceryl trinitrate intravenous infusions are used in critical care environments to treat unstable angina and to reduce blood pressure. In these environments, the infusions are delivered in polyethylene administration sets to avoid adsorption on to plastic.

FIGURE 45.3 EFFECTS OF ORGANIC NITRATES

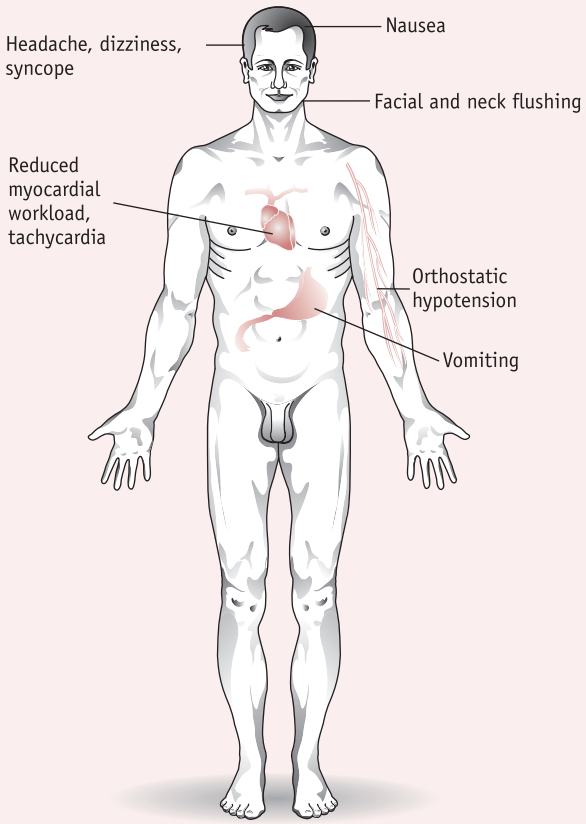
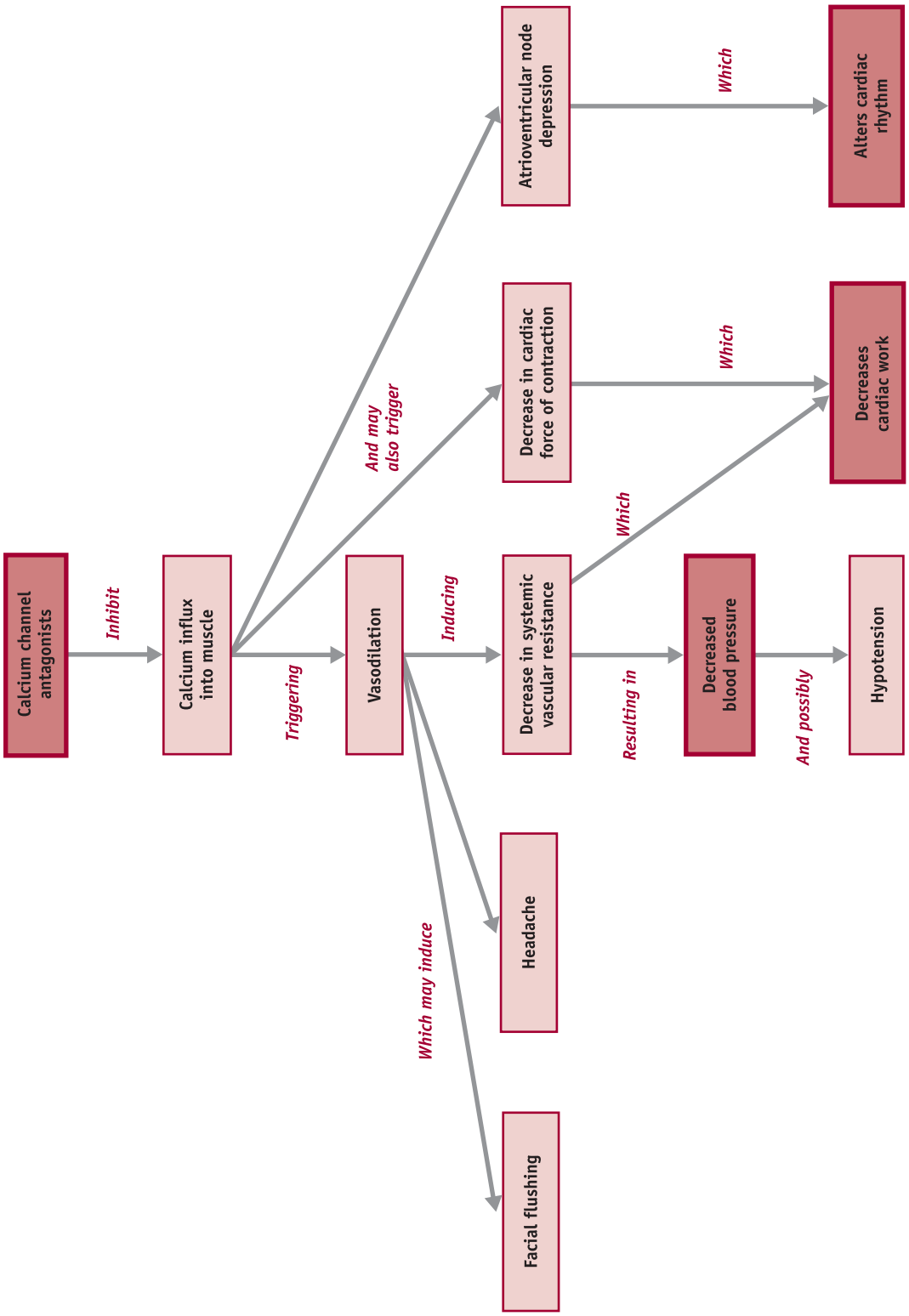


FIGURE 45.4 FLOWCHART SHOWING THE EFFECTS OF CALCIUM CHANNEL ANTAGONISTS

Desired therapeutic effects shown in the darker shaded boxes.



Isosorbide mononitrate tablets are available in a controlled-release form, which are taken at the time of the day when angina is most problematic.

Beta-blockers

Beta-blockers are used prophylactically to reduce the severity and frequency of acute angina attacks and to decrease the requirements for glyceryl trinitrate.

■ MECHANISM OF ACTION

Beta-blockers reduce cardiac workload by reducing both heart rate and force of contraction and improve exercise tolerance and relieve symptoms in patients with stable angina. Beta-blockade prevents sympathetic stimulation of the heart. Beta-1 antagonists are relatively cardioselective and produce fewer side effects than the non-selective agents.

◆ COMMON ADVERSE EFFECTS

Common adverse effects include bradycardia, dizziness, gastrointestinal disturbances and atrioventricular (AV) block. Cessation of therapy should occur slowly over a period of 8–14 days in order to avoid an exacerbation of angina.

Calcium channel blockers

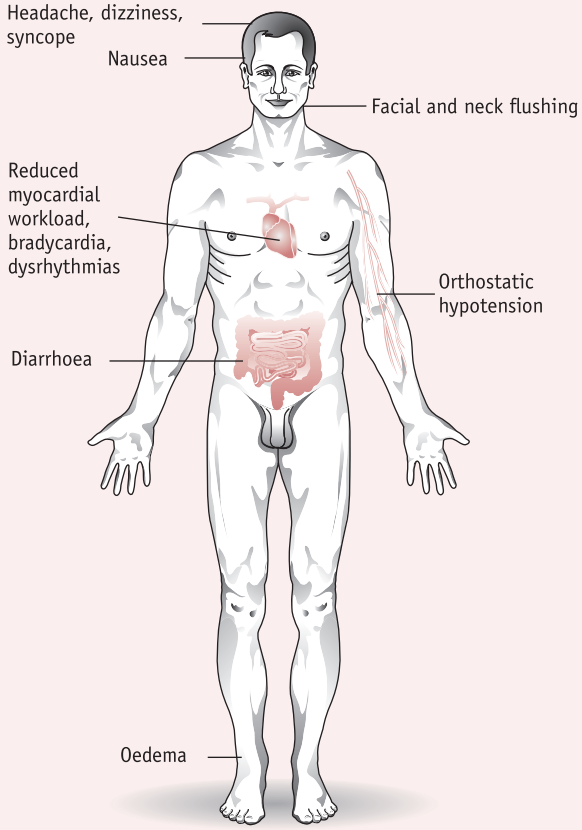
The indications for calcium channel blocking agents are angina pectoris and hypertension. Calcium channel blockers used in the treatment of angina are **amlodipine**, **felodipine**, **nicardipine**, **nifedipine**, **nisoldipine**, **diltiazem** and **verapamil**. Those calcium channel antagonists used as antihypertensives are listed in Chapter 44. Like the beta-blockers, the calcium channel blockers are used to reduce the severity and frequency of angina attacks.

■ MECHANISM OF ACTION

During depolarisation, calcium channel blockers inhibit the movement of calcium ions via calcium channels into vascular and cardiac muscle. Calcium ions are necessary for contraction of muscle; without them, muscle tone is diminished. As a result, blood vessels dilate, particularly coronary arteries in spasm, and the force of contraction of the heart is reduced. Both effects have great therapeutic value because the work of the heart and the resistance against which it labours are decreased significantly. The ultimate outcome is a fall in myocardial oxygen demand and a rise in blood flow to the heart muscle.

Interestingly, although the calcium channel blockers are grouped together because of the similarities in their action, structurally they are quite different. As a consequence of their structural differences, they tend to bind to different sites of the calcium channel and to different subtypes of calcium channel. This produces a degree of selectivity as to the types of calcium channels influenced and, in turn, the types of muscle affected. For example, nifedipine seems to be slightly more selective for the calcium channels of vascular smooth muscle than for those of the myocardium, causing less cardiac depression than the other calcium channel blockers.

FIGURE 45.5 EFFECTS OF CALCIUM CHANNEL BLOCKERS



◆ COMMON ADVERSE EFFECTS

The adverse reactions that accompany the use of calcium channel antagonists are similar to those observed during peripheral vasodilator therapy and include hypotension, headache, facial flushing and rash. The most serious side effect is cardiac depression resulting from extreme inhibition of myocardial calcium influx. This can lead to bradycardia, AV blockade and even cardiac arrest.

Figures 45.4 and 45.5 summarise the desirable and undesirable effects of the calcium channel blockers.

✚ CLINICAL CONSIDERATIONS

Calcium channel antagonists should be used with caution in combination with beta-blockers, as both drug groups induce negative chronotropic and inotropic effects. Treatment with calcium channel antagonists should not be withdrawn abruptly, as this may exacerbate angina. Verapamil and diltiazem should be avoided in heart failure.

Nifedipine and felodipine, which have relatively short half-lives, are available as controlled-release preparations

to prolong their duration of action and enable once-daily dosing. Amlodipine, which has a relatively long half-life, can be given as a once-daily dose without the need to administer a controlled-release preparation.

Peripheral oedema associated with these medications does not need to be treated with diuretics, which may put the patient at risk of volume depletion.

Potassium channel openers

Nicorandil is a derivative of the nitrates. It also has a novel action as a potassium channel opener or potassium channel activator, however. Nicorandil has become available as an antianginal agent and is used as both a monotherapy and as an addition to other antianginal therapy.

■ MECHANISM OF ACTION

As a nitrate derivative, nicorandil directly relaxes vascular smooth muscle, particularly that of the veins. In opening potassium channels in the muscle membrane, it allows an efflux of potassium. This hyperpolarises the membrane and, in turn, prevents calcium channels from opening. The unavailability of intracellular calcium produces arterial vasodilation.

◆ COMMON ADVERSE EFFECTS

Common adverse effects include headache, facial flushing, nausea, vomiting, dizziness and weakness. The headache tends to improve as therapy continues. Clinical studies suggest that tolerance is not a problem. Nicorandil is contraindicated in patients with cardiogenic shock, left ventricular failure and hypotension.

✚ CLINICAL CONSIDERATIONS

Headaches occur commonly following initiation of nicorandil therapy. This adverse effect can be alleviated by starting at a low dose and increasing gradually if required.

CEREBRAL ISCHAEMIA

Cerebral ischaemia occurs when the blood flow to brain tissue is decreased. The consequences of this state are injury to nerve cells and, ultimately, if blood flow cannot quickly be re-established, infarction. Cerebral ischaemia can arise from a meningeal haemorrhage associated with head injury (i.e. subarachnoid or epidural haemorrhage) or stroke. Stroke can result from an obstruction to the cerebral vasculature by a thrombus or embolism, or from a cerebral haemorrhage. The drug treatment of these conditions is not particularly successful. The principal aims of therapy are to re-establish blood flow in ischaemic tissue and to prevent neurons from sustaining permanent damage. The best results have been associated with fibrinolytic and thrombolytic agents. These drugs are described in Chapter 46 and are not discussed here. They have become important in the acute management of stroke and myocardial infarction.

NIMODIPINE

Calcium channel blockers are also used as agents to prevent and treat neurological deficits associated with cerebral ischaemia following a subarachnoid haemorrhage.

■ MECHANISM OF ACTION

Nimodipine is a calcium channel blocker that, due to its structural differences from the other members of this group, is relatively selective for cerebral blood vessels. It may also prevent calcium overload in neurons. Nimodipine has been shown to increase cerebral blood flow, particularly to damaged areas of the brain and to areas with restricted circulation. It readily crosses the blood–brain barrier to interact with cerebral blood vessels.

◆ COMMON ADVERSE EFFECTS

The adverse reactions that accompany the use of nimodipine are similar to those observed during therapy with other calcium channel antagonists. Common adverse effects include hypotension, headache, rash, nausea, abnormal liver tests and cardiac dysrhythmias.

✚ CLINICAL CONSIDERATIONS

Nimodipine is available in oral and intravenous formulations. It is highly lipid-soluble, is absorbed from the oral route rapidly and is relatively unaffected by the presence of food in the gut.

When administering nimodipine by intravenous infusion, polyvinyl chloride (PVC) giving sets should not be used because of adsorption of the active substance on to plastic. Polyethylene sets should be used instead. If commenced early after onset of cerebrovascular symptoms, nimodipine is of benefit.

ERECTILE DYSFUNCTION

Penile erection results from engorgement of the spongy tissue via the mechanism of arterial vasodilation. Impotence is a failure to produce or maintain a satisfactory erection and may arise from psychogenic, vascular, neurogenic or endocrine dysfunction. One of the causes of impotence involves impairment of blood flow through the penis during sexual stimulation. Impotence is a common complication associated with radical prostatectomy, spinal-cord injury and diabetes mellitus. For a significant number of men with this kind of impotence, erectile function can be restored by improving penile tissue perfusion. A number of drugs – **alprostadil**, **apomorphine**, **sildenafil**, **tadalafil** and **vardenafil** – are used to correct erectile dysfunction. Sildenafil and related drugs have captured the attention and

the imagination of the developing world, and it has become fashionable to try these drugs. People without impotence have asked their general practitioner for sildenafil or bought it over the Internet in response to claims that their sexual performance will be enhanced, and the drug has managed to corner a lucrative market in a relatively short time.

Phosphodiesterase type 5 inhibitors

Increased perfusion of the penis involves the release of nitric oxide in the spongy tissue. As described earlier, nitric oxide production leads to elevated intracellular levels of cGMP, which, in turn, alters the availability of calcium within vascular smooth muscle.

■ MECHANISM OF ACTION

Sildenafil, tadalafil and vardenafil inhibit phosphodiesterase type 5 (PD5), which is found in the corpus cavernosum. Tadalafil is more selective than sildenafil for PD5. Nitric oxide is released in the spongy tissue of the penis (the corpora cavernosa and corpus spongiosum) during sexual stimulation. The drugs prevent the breakdown of cGMP, maintaining the relaxation of penile vascular smooth muscle. These drugs do not cause the release of nitric oxide or mimic its action.

◆ COMMON ADVERSE EFFECTS

Common adverse effects include headache, flushing, dyspepsia and hypotension. Sildenafil can induce altered visual acuity, which manifests as a coloured tinge or blurred vision and is due to the inhibition of phosphodiesterase enzyme type 6, located primarily in the eye.

A number of deaths have been reported in the relatively short period since sildenafil's international release in 1998. These deaths have been associated mostly with cardiovascular changes. In people taking nitrates, an interaction associated with nitric oxide production can lead to a severe drop in blood pressure; therefore, nitrate therapy is considered a contraindication when taking these drugs.

✚ CLINICAL CONSIDERATIONS

The major advantage of these drugs over alprostadil is simply a matter of convenience: they are available as oral preparations. Sildenafil has a half-life of 3–5 hours and reaches peak blood levels within 2 hours of administration. In order to achieve the maximal therapeutic benefit, it is recommended that administration takes place 1 hour before intercourse.

Tadalafil has a mean half-life of 17.5 hours and reaches peak blood levels within 2 hours of administration. The major advantages of tadalafil over sildenafil are that the former appears to produce its effects more rapidly (within 16 minutes of ingestion) and has a longer duration of action. Unlike sildenafil, administration of tadalafil with food does not appear to impair oral absorption. Vardenafil is absorbed rapidly and produces its effects within 15–25 minutes. It is subject to significant first-pass effects, and the rate of absorption is slowed with a high fat meal. The half-life is around 4–5 hours.

Sildenafil may cause visual disturbances, and all of these drugs can induce dizziness. Patients should be advised that if these adverse effects occur, they are not to drive or operate machinery.

Other drugs used in the treatment of erectile dysfunction

ALPROSTADIL

Alprostadil is prostaglandin E_1 (see Chapter 30 for general actions and functions of prostaglandins) and is used in erectile dysfunction. It can also be used as palliative therapy to maintain a patent (open) ductus arteriosus in neonates with congenital heart defects. The ductus arteriosus is a fetal blood vessel connecting the aorta and pulmonary trunk, allowing relatively oxygenated blood to bypass the fetal lungs on its way to the systemic circulation.

■ MECHANISM OF ACTION

Alprostadil directly relaxes the smooth muscle of the spongy tissue of the penis (the corpora cavernosa and corpus spongiosum) and dilates the cavernosal arteries. As a result, the spaces in the spongy tissue enlarge and blood flow into the penis is increased. Penile erection occurs within minutes of administration; its duration is dose-dependent. In the ductus arteriosus, alprostadil is believed to relax the vascular smooth muscle.

◆ COMMON ADVERSE EFFECTS

The most common adverse effect is a painful penis, but this is not usually a barrier to continued use of the drug. Haematoma has been reported in association with intracavernosal injection. Priapism has been known to occur, but less so with the intraurethral pellet; patients who maintain an erection for more than 4 hours should be instructed to seek medical help.

In neonates with congenital heart problems, the most common adverse effects are apnoea, flushing, bradycardia, fever, seizures and hypotension.

✚ CLINICAL CONSIDERATIONS

As a naturally occurring prostaglandin, alprostadil is metabolised rapidly. It has a half-life of around 1 minute. Therefore, it must be administered locally to be effective. Until recently, the drug has been available only via injection directly into the corpus cavernosum of the penis, a technique that initially needs careful, supervised training. The needle used is not larger than 27-gauge. The injection is not painful, but the idea is unpleasant to many patients.

Alprostadil is available for intracavernosal injection as a frozen solution that must thaw to room temperature before

use. The manufacturer advises that one should not attempt to defrost the solution in hot water or in a microwave, in order to prevent inactivation of the drug and possible tissue burns.

In 1999, a new formulation of alprostadil became available as a pellet inserted into the urethra. The instructions for administration are complex and the user must urinate before inserting the pellet. The drug is absorbed quickly and acts faster than sildenafil, however. The main advantage of sildenafil over alprostadil is simply a matter of convenience, as the former is available as an oral preparation. Nevertheless, for men in whom sildenafil, tadalafil and vardenafil are contraindicated or ineffective, the intraurethral pellet may be considered. When using the pellet, a condom must be worn during intercourse with a pregnant woman, as alprostadil induces uterine contractions.

APOMORPHINE

The antiparkinsonism agent apomorphine (see Chapter 36) is used in the management of erectile dysfunction.

■ MECHANISM OF ACTION

Apomorphine is a centrally acting dopamine agonist that is relatively selective for D_1 receptors. Unlike alprostadil and sildenafil, which act locally on the penis, apomorphine acts centrally on dopaminergic pathways influencing sexual activity. The use of apomorphine for this purpose arises from the observation that increased sexual desire occurs in people with Parkinson's disease who receive treatment with apomorphine or other dopamine agonists. Apomorphine is particularly useful for impotent men where the problem is of a psychological nature, for example performance anxiety or depression.

◆ COMMON ADVERSE EFFECTS

Common adverse effects include nausea, hypotension, headache, dizziness, drowsiness, flushing and sweating. Apomorphine is contraindicated in severe unstable angina, recent myocardial infarction, severe heart failure and severe hypotension.

✚ CLINICAL CONSIDERATIONS

Apomorphine is administered as a sublingual tablet 20 minutes before sexual activity. Nausea is minimised when the dose is low. Apomorphine can be absorbed rapidly, in this case via the sublingual route.

Apomorphine interacts with centrally acting dopamine agonists and antagonists. Caution is advised when used in combination with antihypertensive agents and organic nitrates.

General clinical considerations of drugs used to treat erectile dysfunction

Men who do not have potency problems should be discouraged from using these drugs because they have a greater risk of priapism (prolonged erection). The ideal dose of these preparations should produce an erection that lasts no longer than 1 hour. Due to the potential for adverse effects with these medications, regular medical reviews are required.

Some conditions predispose individuals to priapism, including sickle cell anaemia, myeloma and leukaemia. These medications are contraindicated in such patients.

If an erection lasts more than 2 hours, individuals are advised to take oral pseudoephedrine. Emergency treatment is essential if an erection lasts longer than 4 hours, and involves aspiration of 20–50 ml blood from the corpus cavernosum.

CLINICAL MANAGEMENT

Drugs used to promote tissue perfusion

Assessment

- Assess the chest pain associated with angina attacks, such as the onset, duration, location, nature, intensity, and precipitation from cold, stress, a heavy meal and exertion.
- An electrocardiogram (ECG) is performed to determine changes to cardiac trace and the area of heart muscle affected.
- Assess vital signs so that baseline pulse and blood pressure can be compared with subsequent observations.
- For beta-blockers, assess the patient's history for congestive cardiac failure, heart block, asthma, diabetes, liver and renal disease. Contact the doctor if any of these conditions is present.
- For calcium channel blockers, assess the patient for congestive cardiac failure, severe hypotension and cardiogenic shock. Notify the doctor if any of these conditions is present.
- Use of sildenafil, tadalafil, vardenafil and alprostadil is contraindicated in male patients on nitrates.

Planning

- The patient will be free from neurological deficits after administration of nimodipine.
- The patient will have normal blood pressure if administered medication for hypertension.
- The patient with chest pain, after administration of medication, will be free from anginal pain.

- For the patient administered sildenafil, tadalafil, vardenafil or alprostadil, the aim will be to achieve normal erectile function.
- Male patients should be assessed for cardiovascular risk before being prescribed sildenafil, tadalafil, vardenafil or alprostadil. Treatment should be avoided in severe heart disease, hypotension, recent stroke or myocardial infarction, and known degenerative retinal disorders.
- The patient will not experience adverse effects from the drugs.

Implementation

- Monitor pulse and blood pressure. These drugs are prone to causing hypotension.
- Monitor chest pain following administration of the drug to determine effectiveness.
- Serum cardiac enzymes and electrolyte levels are also monitored.
- Monitor the electrocardiogram (ECG) to determine the effectiveness of drug therapy.
- Ensure the correct method is used when administering glyceryl trinitrate by the sublingual or transdermal route (see Tables 7.6 and 7.10 in Chapter 7 for further information).
- Ask the patient to lie down immediately after taking the medication for the first time. Check the vital signs while the patient is lying down and then when sitting up.

Patient teaching

General

- Encourage the patient to make lifestyle changes, such as losing weight, eating a balanced healthy diet, ceasing smoking and taking up regular exercise that has been approved by the doctor.

Nitrates

- Instruct the patient on the use of sublingual or transdermal preparations of glyceryl trinitrate (see Tables 7.6 and 7.10 in Chapter 7 for further information).
- Instruct the patient on the correct storage requirements for glyceryl trinitrate tablets. Once the bottle has been opened, the tablets are effective for 3 months. A tingling sensation indicates the tablets are still active. Hands should be kept dry, as moisture can cause deterioration. Other nitrate preparations should be kept in a cool, dry place.
- Explain to the patient that a glyceryl trinitrate tablet is used if chest pain occurs. When chest pain occurs, the patient should sit down, allow a tablet to dissolve under the tongue, wait 5 minutes and, if relief is not obtained, repeat the dose. Wait 5 minutes and, if needed, repeat the dose again for a maximum of three tablets. If pain continues, immediate medical help is necessary.
- Advise the patient that a headache is common when first taking nitrates. The patient should notify the doctor if the headache persists.
- Instruct the patient not to consume alcohol when taking nitrates, as this often worsens the adverse effects of hypotension, weakness and dizziness.

Beta-blockers

- Instruct the patient to call the doctor if dizziness or faintness occurs, as this may indicate hypotension.
- Advise the patient not to withdraw the medication abruptly, as this will result in rebound ischaemia, reflex tachycardia and pain.

Calcium channel blockers

- Advise the patient on the importance of taking these drugs as prescribed and the problems associated with abrupt withdrawal.
- Encourage the patient to have regular dental examinations and to exercise regular flossing and brushing practices.
- To administer nifedipine sublingually or intrabuccally, instruct the patient to chew the capsule to break it, and to guide the contents across to the cheek or under the tongue.
- Driving and using machinery are not advised during the early stages of verapamil therapy because the drug may cause lightheadedness and dizziness.
- Advise the patient to change position slowly in order to avoid dizziness (see Table 11.3 in Chapter 11 for further information).

Sildenafil, tadalafil and alprostadil

- Advise the patient that sildenafil and tadalafil may cause headache, flushing and low blood pressure.
- Advise the patient that alprostadil may cause a painful penis and a prolonged erection. Priapism and haematoma may also occur.

Evaluation

- Evaluate the effectiveness of the antianginal medication for relieving anginal chest pain.
- Evaluate the effectiveness of antihypertensive medication to lower blood pressure.
- Evaluate the effectiveness of sildenafil, tadalafil, vardenafil and alprostadil to produce normal erectile function.
- Determine the effectiveness of nimodipine in producing normal neurological function.
- Evaluate adverse effects such as hypotension, headache, dizziness and faintness. The dose or medication may need adjustment.

SUMMARY

- Conditions characterised by impaired blood flow include angina pectoris, cerebral ischaemia and impotence.
- In angina, the drug groups that restore a balance between myocardial oxygen supply and demand include the organic nitrates, beta-blockers, coronary vasodilators, potassium channel openers and calcium channel antagonists.
- In general, drugs that enhance tissue perfusion in the heart, brain and penis act by reducing the availability of calcium ions within the vascular smooth muscle cell.
- Prophylactic nitrate treatment is taken at the time of the day when angina is likely to be a problem, e.g. at night or in the morning.
- Ensure a nitrate-free period of about 12 hours daily when using nitrate patches.
- Counsel the patient to call an ambulance if angina symptoms are not relieved within 15 minutes of taking acute nitrate medication.
- Controlled-release preparations for short-acting calcium channel blockers, such as nifedipine and felodipine, will allow for better management of adverse effects such as dizziness and headache.
- To prevent priapism, men without potency problems should not be given drugs for erectile dysfunction.
- Consider the possibility that the patient has undiagnosed cardiovascular disease before administering drugs for erectile dysfunction.

1. Briefly outline the pathophysiology of the two types of angina pectoris and the aims of drug therapy.
2. Account for the facial flushing, headache and reflex tachycardia that may be observed after organic nitrate administration in angina therapy.
3. Compare the effects of each of the following drugs/drug groups on nitric oxide levels: potassium channel openers, organic nitrates and sildenafil.
4. Explain why nimodipine is the calcium channel blocker of choice in the treatment of cerebral ischaemia following a subarachnoid haemorrhage rather than another, such as verapamil.
5. Nimodipine may cause hypotension, bradycardia and flushing. Explain the pharmacological reasons underlying these adverse effects.
6. Explain why alprostadil must be injected locally and cannot be taken orally.
7. A 65-year-old patient is receiving nifedipine for the prophylactic treatment of angina. What education would you offer?
8. Neava Head, who has experienced a subarachnoid haemorrhage, is placed on a nimodipine infusion. She remains in a dark and quiet room. Ms Head complains to you of feeling nauseated. What measures can you implement to relieve her feeling of nausea? (Refer to Table 11.10 in Chapter 11 for futher information.)
9. Fred Jones is a 50-year-old man with diabetes mellitus. He has an erectile problem and would like to try sildenafil. What education do you offer Fred?
10. Jack McDuff is a 55-year-old man with stable angina. He has been using sublingual tablets of glyceryl trinitrate to manage his condition. In consultation with his doctor, he is changing formulations to the sublingual spray. What would you tell Jack regarding the difference between these two formulations of glyceryl trinitrate?

45 DRUG SUMMARY TABLE: DRUGS USED TO PROMOTE TISSUE PERFUSION

FAMILY NAME	GENERIC NAME	TRADE NAME(S)
Beta-blockers	Acebutolol	Sectral
	Atenolol	Tenormin
	+ Diuretic	Co-tenidone
		Kalten
		Tenoret 50
		Tenoretic
	+ Calcium channel blocker	Beta-Adelat
		Tenif
	Bisoprolol	Cardicor
		Emcor
	Carvedilol	Eucardic
	Celiprolol	Celectol
	Esmolol	Brevibloc
	Labetalol	Trandate2
	Metoprolol	Betaloc
		Lopresor
	+ Diuretic	Co-Betaloc
	Nadolol	Corgard
	Nebivolol	Nebilet
	Oxprenolol	Trasicor
	+ Diuretic	Trasidrex
	Pindolol	Visken
	+ Diuretic	Viscaldix
	Propranolol	Inderal
	Sotalol	Beta-Cardone
		Sotacor
Calcium channel blockers	Amlodipine	Istin
	Diltiazem	Tildiem
		Aldizem SR
		Aldizem XL
		Angitil SR
		Calcicard CR
		Dilcardia SR
		Dilzem SR
		Slozem
		Tildiem Retard
		Viazem XL
		Zemtard
	Felodipine	Plendil
	Isradipine	Prescal
	Lacidipine	Motens
	Lercandipine	Zanidip
	Nicardipine	Cardene
	Nifedipine	Adalat
		Adipine
		Cardilate MR
		Coracten SR
		Coracten XL

FAMILY NAME	GENERIC NAME	TRADE NAME(S)
		Fortipine LA 40
		Hypolar Retard 20
		Nifedipress MR
		Nifopress Retard
		Slofedipine
		Tensipine
	Nimodipine	Nimotop
	Nisoldipine	Syscor MR
	Verapamil	Cordilox
		Securon
		Univer
		Verapress MR
Coronary vasodilator	Dipyridamole	Persantin
Peripheral vasodilators	Glyceryl trinitrate	Coro-Nitro Pump Spray
		Glytrin Spray
		Nitrocine
		Nitronal
		Nitrolingual Pumpspray
		Nitromin
		Nitronal injection
	Transdermal preparations	Deponit
		Minitran
		Nitro-Dur
		Percutol
		Transiderm-Nitro
		Trintek
	Longer-acting	Suscard
		Sustac
	Isosorbide dinitrate	Angitak
		Cedocard Retard
		Isoket Retard
	Isosorbide mononitrate	Elantan
		Ismo
	Modified-release	Chemydur 60XL
		Elantan LA
		Imdur
		Isib 60XL
		Ismo Retard
		Isodur
		Isotard
		Modisal LA
		Monomax
		Monomil XL
		Monosorb XL 60
		Zemon
Phosphodiesterase inhibitors	Sildenafil	Viagra
	Tadalafil	Cialis
	Vardenafil	Levitra
Potassium channel openers	Nicorandil	Ikorel
Miscellaneous	Ivabradine	Procoralan

ANTICOAGULANTS, THROMBOLYTICS AND ANTIPLATELET DRUGS

46

CHAPTER FORTY-SIX

OBJECTIVES

KEY TERMS

Coagulation
Haemostasis
Embolism
Thrombosis
Activated partial thromboplastin time (APTT)
Internationalised normal ratio (INR)
Thrombolysis
Fibrinolysis

After completing this chapter, the reader should be able to:

- **outline the basic mechanisms of haemostasis;**
- **list the indications and use of anticoagulants;**
- **describe the dangers of oral anticoagulant therapy;**
- **explain the use of heparin as an anticoagulant;**
- **explain the use of antiplatelet drugs;**
- **explain the indications and uses of fibrinolytic agents;**
- **describe the dangers involved in the use of fibrinolytic agents.**

BLOOD COAGULATION IS OF THE UTMOST IMPORTANCE IN the protection of the body from undue blood loss. People with blood-clotting disorders, such as haemophilia, lead precarious lives that can be terminated abruptly by a minor injury, such as slight bruising. In a healthy person, such injuries would often pass unnoticed. Unfortunately, many people have problems with intravascular clots (thrombi) being formed. This can lead to blockage of the smaller blood vessels in the body and, consequently, tissue ischaemia. A common cause of this is venous stasis due to inactivity, such as can occur with prolonged bed rest.

Related to a thrombus is a blood embolus, which is a fragment of a blood clot that occludes a vessel. The clot may have been formed due to a procedure such as surgery (in which coagulation processes are obligatory). In this case, a fragment of a natural clot escapes into the circulation and blocks a major vessel, such as one of the pulmonary arteries, resulting in a pulmonary embolism. Note that not all emboli are blood clots; emboli can be derived from various materials such as amniotic fluid, fat and air.

A relatively common procedure today is percutaneous transluminal coronary angioplasty (PTCA), which is performed to clear or enlarge the lumen of blocked or partially blocked coronary vessels of atheromatous plaque (see Chapter 43). Unfortunately, this procedure can lead to intravascular clotting, which rather defeats the purpose of the procedure. During PTCA, the affected coronary artery is stretched; this stretching and the widening of the lumen dislodges the plaque, further opening up the vessel. This creates damaged intimal and medial layers, which can release platelet activators and lead to platelet aggregation and consequent thrombus formation. The use of antiplatelet drugs is thus of importance in this procedure.

ANTICOAGULANTS

In people prone to blood-clotting disorders, it is possible to use drugs that interfere with the normal blood-coagulation processes in order to prevent thrombus formation. The most serious problem related to this kind of therapy is overinhibition of the process, which leads to a bleeding disorder not unlike haemophilia, such that minor injuries can become major problems.

Blood clotting involves two processes: the process of platelets adhering to each other resulting in a platelet plug, and the process of the blood clot forming due to fibrin formation. Together, these procedures are very effective in stemming blood loss from injured tissues. The formation of fibrin is probably the most effective part of the coagulation process. Consequently, the treatment of acute and many chronic coagulation disorders is geared towards the partial inhibition of this process. Figure 46.1 shows the normal blood-coagulation process and the points at which the drugs used exert their effects. As can be seen, there are only two basic sites of action of the anticoagulant drugs in what is a complex series of reactions. This makes the pharmacodynamics relatively easy to understand.

HEPARIN

MECHANISM OF ACTION

Heparin is a polysaccharide that occurs naturally in the body, principally in the lungs, where its function is not known. Commercially available heparin is often made from the lungs of cattle. Heparin is a strongly ionic compound and, therefore, lipophobic, and so oral administration is not possible. As heparin is an effective anticoagulant, heparin in intramuscular injection can cause painful haematomata, so it is usual to inject it either subcutaneously for slow action or intravenously for fast action. Heparin acts by augmenting the function of the natural inhibitor of coagulation, antithrombin III. At high doses this augmentation leads to inactivation of almost all of the clotting factors, whereas at lower doses only factor Xa is inhibited. This reaction occurs quickly and makes the use of heparin very valuable in patients where immediate anticoagulation is needed, such as in pulmonary embolism and deep vein thromboses. In patients deemed to be prone to thrombotic episodes, heparin can be given prophylactically after surgery.

As heparin acts on preformed factors, it is also widely used as an in vitro anticoagulant. During thoracic surgery, in which extracorporeal circulation of the blood is required, heparin prevents coagulation of the blood in the heart–lung machine. Likewise, heparin is used in dialysis machines. It is useful as an anticoagulant to prevent blood clotting when plasma is needed for clinical chemistry analyses.

Heparin is available as salts, usually of calcium and sodium. (The lithium and strontium salts are sometimes used in vitro.) Heparin is usually measured in international units (IU) rather than milligrams. One international unit is the amount of heparin needed to prevent 1 ml of blood from clotting for 1 hour (1 mg is roughly 120 units). Heparin is now often referred to as being standard or unfractionated heparin to distinguish it from the low-molecular-weight heparins (LMWHs).

◆ COMMON ADVERSE EFFECTS

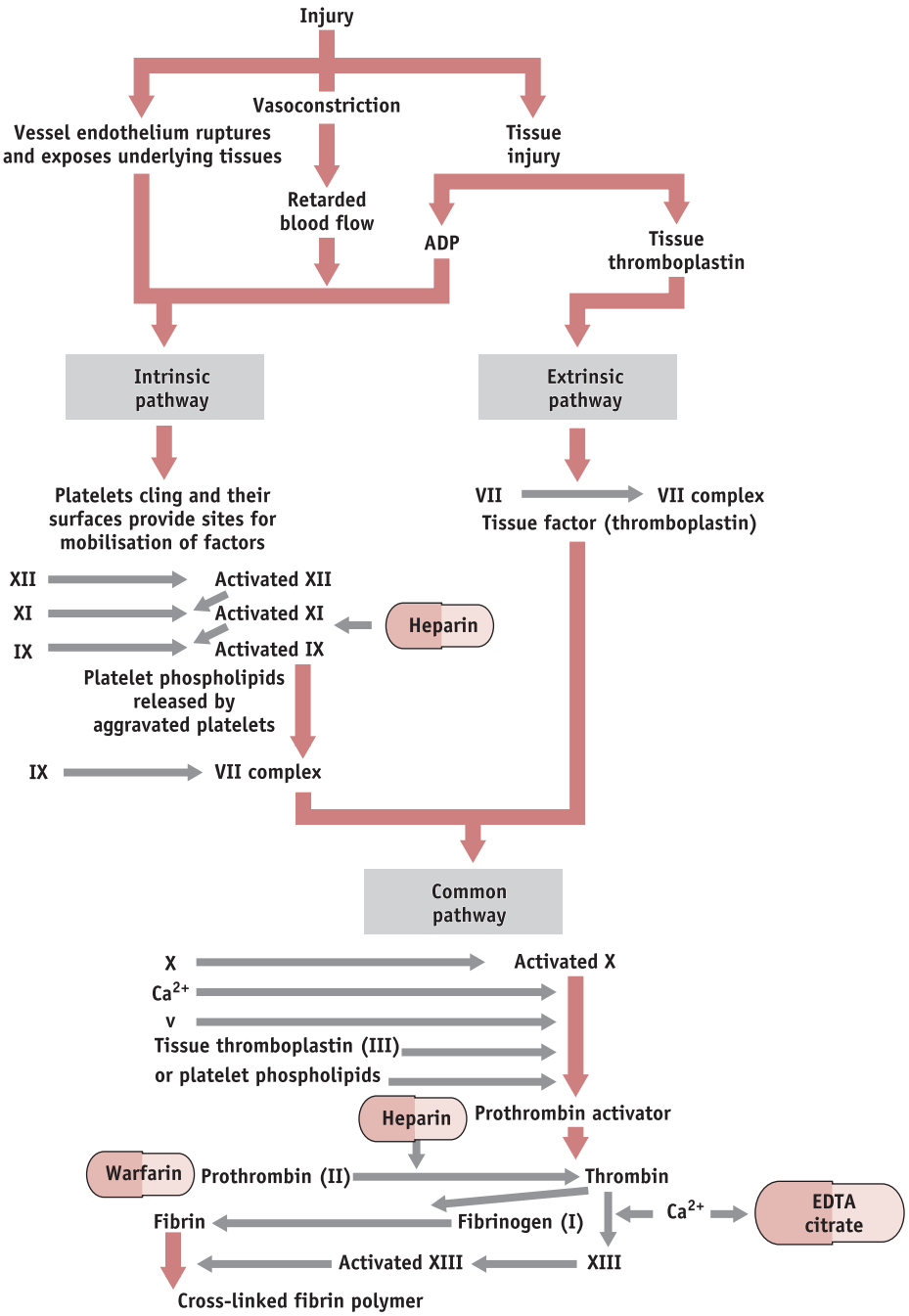
Heparin is fairly free of adverse effects, although osteoporosis, alopecia and thrombocytopenia are reported rarely. The main problem with the use of heparin, as with other anticoagulants, is bleeding. If dangerous bleeding occurs during heparin therapy, then the basic compound **protamine sulphate** (prepared from salmon sperm) is an effective antidote if given by slow intravenous injection; rapid injection can cause anaphylaxis. Protamine sulphate it must be given within 3 hours of the heparin injection.

✚ CLINICAL CONSIDERATIONS

After initiation of anticoagulant therapy with heparin, oral anticoagulants can be started immediately. The heparin needs to be continued for at least 5 days and until the international normalised ratio (INR) has been in the therapeutic range for two consecutive days, as warfarin takes this amount of time to fully exert its effects.

Heparin is a relatively crude preparation obtained from the lungs of oxen and the intestinal mucosa of oxen, pigs and sheep. Heparin prepared thus is of a high molecular weight; a problem associated with these high-molecular-weight heparins is thrombocytopenia. The more recently available LMWHs, such as **enoxaparin** and **dalteparin**, are more highly purified than the common heparins and reduce the risk of heparin-induced thrombocytopenia and thrombosis. LMWH compounds have relatively long half-lives, require less monitoring and are considered safer to use in pregnancy. They can be administered once daily and have the added advantage of greater bioavailability. In the UK, LMWHs have replaced unfractionated heparin (UFH) as the preferred option in many clinical situations,

FIGURE 46.1 NORMAL COAGULATION AND SITES OF ANTICOAGULANT ACTION



ADP, adenosine diphosphate; EDTA, ethylene diamine tetra-acetic acid.

including the prevention and treatment of venous thromboembolism and the treatment of acute coronary syndromes in most patients. For patients at high risk of bleeding, heparin is more suitable than LMWHs as its effects can be terminated rapidly by stopping the infusion.

In hip surgery, the LMWHs appear to be more effective in preventing thromboembolic episodes, but no explanation for this has been found. **Fondaparinux** (see below), a synthetic activated factor X inhibitor, is frequently used for the prevention of venothromboembolism in patients with hip fracture and patients undergoing hip and knee replacements.

When using unfractionated heparin, the activated partial thromboplastin time (APTT) is monitored regularly

throughout treatment. For LMWHs, monitoring using antifactor Xa is required only in patients who are at high risk of bleeding, including patients with multiple trauma or renal impairment. Advise the patient to report any signs of bleeding, including nose bleeds, black stools, unexplained bruising and bleeding gums. The use of heparinised saline to flush peripheral vascular cannulae should be avoided; this may lead to heparin-induced thrombocytopenia and is no more effective as a flush than normal saline. It is also important not to administer heparin by intramuscular injection, in order to avoid haematoma. Heparin is usually given by intravenous infusion, which requires hospitalisation. Alternatively, twice-daily dosing by subcutaneous injection may be administered. LMWHs are given by subcutaneous injection. As these preparations do not usually require monitoring, they can be used in the community.

HEPARIN-LIKE COMPOUNDS

The term 'heparinoid' refers loosely to a mixture of heparin and either natural and/or semisynthetic heparin-like substances, and is thus of no constant composition. These substances are commonly used in a cream form to treat semisuperficial clotting disorders, such as thrombophlebitis, haematomata (bruises) and contusions. Hyaluronidase (see Chapter 16) is sometimes incorporated in the mixture to enable faster penetration to the site of tissue damage, and there is some evidence that this may help in clot dissolution. Heparinoids are often used in sporting injuries and are available as over-the-counter preparations. They should not be used on bleeding surfaces. The only problem usually seen with heparinoids is slight reddening of the skin; most studies show a beneficial effect when used appropriately.

In combination with salicylic acid, heparinoids can be used where pain is also a problem. The preparation must be used on unbroken skin and rubbed in gently, and the area covered with a dry dressing.

Danaparoid is a heparinoid used for prophylaxis of deep-vein thrombosis in patients undergoing surgery. It is also used in patients who develop throbocytopenia with heparin.

ANTITHROMBIN III

Antithrombin III is a naturally occurring glycoprotein used in patients with genetically determined deficiencies of antithrombin III during procedures that could lead to thromboembolic disorders, such as childbirth. The drug is prepared from human plasma.

HIRUDINS

These are direct thrombin inhibitors. **Leirudin** is a recombinant hirudin licensed for anticoagulation in patients with immune heparin-induced thrombocytopenia. The dose is adjusted according to APTT.

Bivalirudin is a hirudin analogue and is a thrombin inhibitor licensed in the UK as an anticoagulant for patients undergoing percutaneous coronary intervention (PCI).

FONDAPARINUX

Fondaparinux is a synthetic inhibitor of clotting factor X. By inhibiting this factor, the clotting mechanism is slowed down or prevented. Fondaparinux is particularly useful in helping to prevent thromboemboli developing after orthopaedic surgery to the leg.

◆ COMMON ADVERSE EFFECTS

As well as an increased risk of haemorrhage, fondaparinux has a multitude of common adverse effects, including hypokalaemia, insomnia, confusion, dizziness, hypotension, nausea, constipation, vomiting, diarrhoea, dyspepsia, rash, pruritus, localised bullous eruptions, urinary retention, urinary tract infection, fever and oedema. This seems a long list, but this drug can and does save lives.

Oral anticoagulants

WARFARIN

Warfarin, the mainstay of long-term anticoagulant therapy, is one of the original drugs of the coumarin group. No real improvement was made with this type of drug since its introduction in the early 1940s until recently. The story of the discovery of the coumarins bears telling at this point. Early in the twentieth century, a farmer in the USA noted that when he was castrating young bulls, many bled to death. This was not an occurrence with which he was familiar. A veterinary surgeon involved in the investigation soon found that the cattle that had the bleeding problem had been eating a newly introduced fodder material, sweet clover. Following, years of research, the coumarin compounds were isolated from the clover, warfarin being one of the congeners. Many of the coumarins have pleasant smells and are used in perfumes.

■ MECHANISM OF ACTION

Warfarin is structurally similar to **vitamin K**, which is involved in the synthesis of prothrombin and factors II, VII, IX and X in the liver. In the process of acting as a coenzyme, vitamin K is reduced; before it can be reused, it must be oxidised back to its active form. This is represented simply by the following equation:

$$\text{Active vitamin K} \xrightarrow[\text{Epoxide reductase}]{} \text{Inactive vitamin K}$$

Warfarin inhibits epoxide reductase and thus depletes active vitamin K from the liver. Because of this mode of

action, warfarin takes several days to exert its clinical effect, as body vitamin K stores and coagulation factors have to become significantly depleted. As vitamin K itself is not interfered with by warfarin, excess of this vitamin in the diet can overcome the effect of warfarin and it is an efficient antidote to the drug. This slow onset of action is a disadvantage of warfarin, as patients with excessive coagulation problems need rapid treatment. Fortunately, heparin (above) has a rapid effect and is used together with warfarin in the initialisation of anticoagulant therapy.

Individual responses to warfarin therapy are varied. As the dose is critical, it is important to determine the effect of the drug in the individual patient. Until stabilisation occurs, the patient's clotting mechanisms must be assessed, usually by monitoring the prothrombin time, a standard coagulation test routinely performed in haematology laboratories. The INR is now the internationally recommended form of reporting prothrombin time when measuring warfarin. The INR is the ratio of the patient's clotting time to a standardised control clotting time. Normally, INR is around 1.0, but it is higher in patients receiving warfarin therapy (2.0–4.0). Warfarin is available in at least four dosage forms to allow for the variable doses that may be required in individuals.

◆ COMMON ADVERSE EFFECTS

In the correct individualised dosage, warfarin is almost devoid of adverse effects not related to its anticoagulant action; alopecia and priapism (sustained erection) are the only side effects of any consequence, but even these are rare. Adverse effects such as nausea and dizziness occur with similar frequency to those caused by placebo.

✚ CLINICAL CONSIDERATIONS

The pharmacological effect of warfarin must be monitored closely to prevent underactivity and overactivity. The effect required can be upset by many factors involving both food and drugs. Excessive vitamin K can affect the action of warfarin. In some countries vitamin supplements contain vitamin K and, if a patient on warfarin consumes such supplements, the effect of warfarin may be decreased. There has been at least one case of a patient on warfarin who ate enormous quantities of cabbage, which is high in vitamin K, and negated the effect of warfarin.

There are many interactions between warfarin and other drugs that can either increase or decrease the therapeutic activity of warfarin. In view of the very narrow range of plasma warfarin levels that must be maintained for normal therapeutic activity, it is critical that constancy is achieved. It is essential that patients on warfarin therapy do not take other drugs without obtaining expert advice. Health-care professionals involved with patients on warfarin should also be aware of the problems due to drug–drug interactions with warfarin. Tables 46.1 and 46.2 show some of the common drug–drug interactions with warfarin and their effects on its activity. These lists should not be considered exhaustive, but they serve to show the variety of ways in which the action of warfarin can be potentiated or inhibited. Health-care workers should be aware that drugs bought over the counter, including herbal remedies, can also interact with

TABLE 46.1 DRUGS THAT INCREASE WARFARIN ACTIVITY

Drug or drug group	Mechanism of action
Aspirin	Displacement from albumin and antiplatelet activity
Non-steroidal anti-inflammatory drugs	As for aspirin, but less antiplatelet activity
Phenylbutazone	Inhibition of metabolism
Amiodarone	Potentiation
Co-trimoxazole	Inhibition of metabolism
Metronidazole	Inhibition of metabolism
Nalidixic acid	Inhibition of metabolism
Tetracyclines	Inhibition of metabolism
Neomycin (oral)	Impairment of vitamin K absorption
Liquid paraffin	Impairment of vitamin K absorption
Monoamine oxidase inhibitors	Inhibition of metabolism
Propranolol	Inhibition of metabolism
Metoprolol	Inhibition of metabolism
Cimetidine	Inhibition of metabolism
Herbal medicines (e.g. garlic, ginger)	Inhibition of metabolism
High-dose vitamin E	Potentiation of effects
Fish oils	Affect platelet aggregation and clotting factors

TABLE 46.2 DRUGS THAT DECREASE WARFARIN ACTIVITY

Drug or drug group	Mechanism of action
Carbamazepine	Potent enzyme inducer
Phenytoin	Potent enzyme inducer
Phenobarbitone	Potent enzyme inducer
Rifampicin	Potent enzyme inducer
Oestrogens	Increase activity of clotting factors
Antacids	Decrease absorption
Cholestyramine	Decrease absorption
Colestipol	Decrease absorption

warfarin. The use of complementary and alternative medicines is on the increase and a recently completed survey in the UK found that 20 per cent of the general population had used such treatments within the previous year. Herbal medicines were the most popular, and there is often a misconception that such remedies are safe and do not interfere with any other form of medication.

Vitamin K serves as a useful antidote to warfarin in cases of haemorrhagic episodes. In cases of severe bleeding, parenteral treatment can be given. Any person involved with patients undergoing warfarin therapy should be aware of the potential for haemorrhage. Bleeding gums and signs of bruising should be reported to a clinician. Patients should be advised to wear a MedicAlert bracelet, use a soft toothbrush when cleaning their teeth and use electric rather than disposable razors.

Patients should be encouraged to take their warfarin tablets at the same time each day in order to ensure that a dose is never missed. A calendar or 'anticoagulant book' can be used to document each dose as it is taken. Regular blood tests for INR are required. As several preparations may interact with warfarin, patients are advised to notify their doctor or pharmacist if they intend to start or stop a particular medication. In particular, over-the-counter and herbal preparations can affect the bioavailability of warfarin. The patient must notify their doctor immediately if they develop signs of bleeding or bruising. Different brands of warfarin have been shown not to be bioequivalent; therefore, they should not be interchanged.

Phenindione is an indan-1,3-dione derivative that is similar in action to warfarin but has more side effects and occasionally causes allergic reactions. An unusual feature of phenindione is that it can cause a reddish discoloration of the urine, which may be confused with haematuria. The source of the colour can be determined easily by acidifying the urine with a dilute acid. The colour disappears if it is due to phenindione but not if it is due to blood.

ORAL DIRECT THROMBIN INHIBITORS

These drugs blocked the active site on the thrombin molecule independent of antithrombin and inactivated both circulating and fibrin-bound thrombin. Ximelagatran was the first new oral treatment for thrombosis in 60 years and the first oral direct thrombin inhibitor. It was a prodrug, rapidly absorbed and transformed into the active compound melagatran. The latter was available for administration subcutaneously. Ximelagatran had a rapid onset of action (within 30–60 minutes after ingestion) and reached its maximum concentration around 3–4 hours after administration. Most studies showed these drugs to be equivalent to standard (heparin and/or warfarin) for prophylaxis of venous thromboembolism, but there were problems with hepatotoxicity that prevented the drug being licensed in the UK. It was licensed in France, where liver function tests were monitored every month in patients prescribed the drug. In 2006 the company producing ximelagatran, Astrazenica, withdrew its application for marketing authorisation as part of a global withdrawal of medicines containing ximelagatran or melegatran. This was due to new safety data on severe liver injury. The long wait for a successful alternative oral anticoagulant to warfarin thus continues.

FIBRINOLYTIC DRUGS

A blood clot formed due to an injury is a temporary measure to protect the body from loss of fluids and entry of extraneous materials. The clot itself undergoes dissolution as the tissue repair takes place. This dissolution of the clot occurs slowly and involves the body's fibrinolytic system. The proenzyme plasminogen is present in blood and, when needed, can be converted into the enzyme plasmin, which degrades the fibrin present in a clot as well as other clotting factors. In the normal situation, this conversion takes place at the clot site due to the release of plasminogen activators from various cells, including macrophages.

Medicine has made use of this system to accelerate the dissolution of clots in cases of thrombosis and thus prevent ischaemia in blood-starved tissues. In the case of myocardial infarction, the use of fibrinolytic drugs (also referred to as thrombolytic therapy) can be life-saving. There are several ways in which the fibrinolytic system can be activated, all of which use enzymes. The four most commonly used are discussed below.

To be effective in cases of coronary vessel occlusion, thrombolytic therapy must be commenced within 12 hours of the occlusion (6 hours if tenecteplase is used), and the sooner the better. Paramedics administer these drugs in some parts of the UK.

Thrombolytic drugs are indicated following myocardial infarction in all patients where the potential benefits outweigh the risks. Benefit has been shown to be greatest where there are electrocardiogram (ECG) changes that include ST

elevation (especially an anterior myocardial infarction) and in patients with bundle branch block. Age is not a factor, as mortality is high in elderly patients and the reduction in mortality seen is just as high as in younger patients.

Early primary PCI may be an alternative to thrombolysis, but few NHS trusts at present have the capacity to provide it.

◆ COMMON ADVERSE EFFECTS

The most common complication with any thrombolytic drug is bleeding. This may be internal, involving intracranial and retroperitoneal sites, gastrointestinal tract, urinary tract and respiratory tract. Superficial bleeding may also occur, mainly at vascular puncture sites.

Cholesterol embolisation is a serious condition that can be lethal. It occurs rarely in patients receiving all types of thrombolytic agent.

Reperfusion arrhythmias may occur following thrombolysis and include sinus bradycardia, ventricular depolarisations and ventricular tachycardia. These can be managed with antiarrhythmic agents.

Allergic reactions are rare (anaphylaxis occurs in less than 0.1 per cent of patients treated) to all fibrinolytics except streptokinase.

STREPTOKINASE

■ MECHANISM OF ACTION

Streptokinase is the oldest thrombolytic agent and has been used since the early 1980s. It is an enzyme prepared from beta-haemolytic streptococci and is a potent plasminogen activator. Without directly enzymatically cleaving plasminogen into plasmin, it acts by binding to plasminogen. The streptokinase–plasminogen complex in turn acts on other molecules of plasminogen, converting them into plasmin molecules.

Streptokinase is administered intravenously as an intravenous infusion over 1 hour.

◆ COMMON ADVERSE EFFECTS

The process of plasminogen cleavage takes place generally throughout the bloodstream, releasing plasmin into the general circulation. This general increase in plasmin activity can cause degradation of clotting factors, leading to an increase in haemorrhagic episodes (as can occur during anticoagulant therapy, dealt with above). Furthermore, any recent clot formed due to normal coagulation activity, such as a hypodermic needle puncture wound, will be destroyed and could lead to uncontrolled haemorrhage. The main problem with streptokinase is that, being a protein of bacterial origin, it is antigenic; as most individuals have been exposed to beta-haemolytic streptococci, antibodies to the protein are commonly present in a patient's blood. This often necessitates a high dosage, owing to the destruction of some of the enzyme on administration.

Occasionally, a full-blown allergic response occurs, which needs urgent treatment. Such a response is more likely to occur if the enzyme has been administered to the patient in the previous 6 months, when antibody titres are likely to be high. Fever occurs in about a third of treated patients.

✚ CLINICAL CONSIDERATIONS

Heparin should be discontinued before commencing streptokinase. The APTT should be checked and should be less than twice the normal control before streptokinase treatment. Treatment is likely to be ineffective if given more than 4 days after a previous streptokinase course of therapy, due to the formation of antibodies and their prolonged persistence. An alternative thrombolytic agent should be used in these circumstances. Streptokinase is also available as Varidase™ for topical treatment to remove purulent accumulations in wounds, but antibodies may also appear following this use or following a severe streptococcal infection (e.g. rheumatic fever, glomerulonephritis).

Streptokinase is also licensed for the treatment of life-threatening venous thrombosis and pulmonary embolism where treatment needs to be commenced promptly.

ALTEPLASE

■ MECHANISM OF ACTION

Alteplase (rtPA) is tissue plasminogen activator of human origin made by recombinant DNA technology. The great advantage of this drug is that it is clot-specific. This means it activates only plasminogen within blood clots, thus minimising haemorrhagic episodes due to general plasminogen activation.

◆ COMMON ADVERSE EFFECTS

The main adverse effect is haemorrhagic events. Unlike streptokinase, rtPA can be given repeatedly with little fear of an anaphylactic reaction.

✚ CLINICAL CONSIDERATIONS

There is little evidence of reduced mortality with rtPA compared with streptokinase, but there is a lower incidence of adverse reactions to rtPA. Alteplase can be delivered in a standard or accelerated regimen. The accelerated regimen is used most commonly and is indicated up to 6 hours after symptom onset. An initial intravenous bolus injection is given, followed by two intravenous infusions. The first of these is given over 30 minutes and the second over 60 minutes. The standard regimen is used when the patient presents 6–12 hours after the onset of pain: This requires a bolus and five infusions over 3 hours.

It is usual to give concomitant aspirin and heparin to prevent further clotting.

Alteplase does not stimulate the production of antibodies and so can be used more than once. It is also licensed for use in pulmonary embolism and acute stroke, but treatment for the latter must commence within 3 hours of onset.

RETEPLASE AND TENECTEPLASE

These are the newest thrombolytic agents and have the advantages that they can be delivered in bolus doses and are not antigenic. They are forms of recombinant tissue plasminogen activator and are clot-specific. Heparin and aspirin are administered concomitantly.

Reteplase was introduced in 1997 in the UK and can be given up to 12 hours after symptom onset in two intravenous boluses, 30 minutes apart.

Tenecteplase was introduced in 2001 and is the drug used by many ambulance trusts, as it can be administered in one bolus dose according to body weight. The bolus is administered over 5–10 seconds but has to be administered within 6 hours of the onset of chest pain.

Tenecteplase is bioengineered tissue plasminogen activator produced by recombinant DNA technology using Chinese hamster ovaries. Amino-acid substitutions have led to a prolonged half-life, enhanced fibrin specificity and an increased resistance to plasminogen tissue inhibitor (PAI-1). The latter may interfere with clot dissolution. Mortality is similar to streptokinase.

HAEMOSTATIC AGENTS

■ MECHANISM OF ACTION

A consequence of thrombolytic therapy can be severe haemorrhage, which necessitates a reversal of the whole process. This can be accomplished by inhibiting fibrinolysis. There are three drugs commonly available for this – **aprotinin**, **tranexamic acid** and **etamsylate**. Aprotinin is a proteinase inhibitor prepared from bovine lung tissue, which inhibits plasmin. Tranexamic acid binds to fibrin strands and prevents the activation of plasminogen at these sites. Etamsylate reduces capillary bleeding in the presence of a normal platelet count; it does not work by fibrin stabilisation but probably corrects abnormal platelet adhesion. Tranexamic acid is licensed only for use in menorrhagia.

The use of aprotinin is mostly reserved for coronary artery bypass surgery and liver transplantation. Tranexamic acid can be used to prevent occurrence of haemorrhage after operations where large clot formation occurs, such as tonsillectomy, subarachnoid haemorrhage and uterine-cervical conisation.

◆ COMMON ADVERSE EFFECTS

Tranexamic acid is tolerated very well, with few adverse effects – nausea, diarrhoea and hypotension being noted only rarely. Tranexamic acid has been known in rare instances to alter the normal visual perception of colour. Aprotinin can result in anaphylactoid reactions in rare instances.

Other haemostatic agents are the clotting factors used to treat bleeding in haemophiliacs, and thrombin itself, which can be used to control bleeding in surgery when applied directly to the haemorrhaging surface.

✚ CLINICAL CONSIDERATIONS

Slow intravenous infusion of a haemostatic agent usually decreases the incidence of adverse effects, such as nausea and vomiting. Dosage should be titrated carefully against the clinical response.

ANTIPLATELET DRUGS

Fibrin formation is not the only factor involved in blood coagulation; the formation of the platelet plug is also important. In cases of tissue endothelial damage, collagen fibres become exposed. Platelets bind to these fibres, releasing various chemicals, including thromboxane, which is related to the prostaglandins. Thromboxane inhibits the enzyme adenylate cyclase, which is needed to make cyclic adenosine monophosphate (cAMP). cAMP inhibits platelet adhesiveness; it is destroyed by the enzyme phosphodiesterase.

Figure 46.2 shows a simplified scheme of events in the formation of platelet adhesiveness. It can be seen that any drug that alters the cAMP concentration will have an effect on platelet adhesiveness and aggregation. Most of the prostaglandin inhibitor drugs discussed in Chapter 40 have some antiplatelet activity, but none more so than **aspirin**, because of its non-competitive action.

ASPIRIN

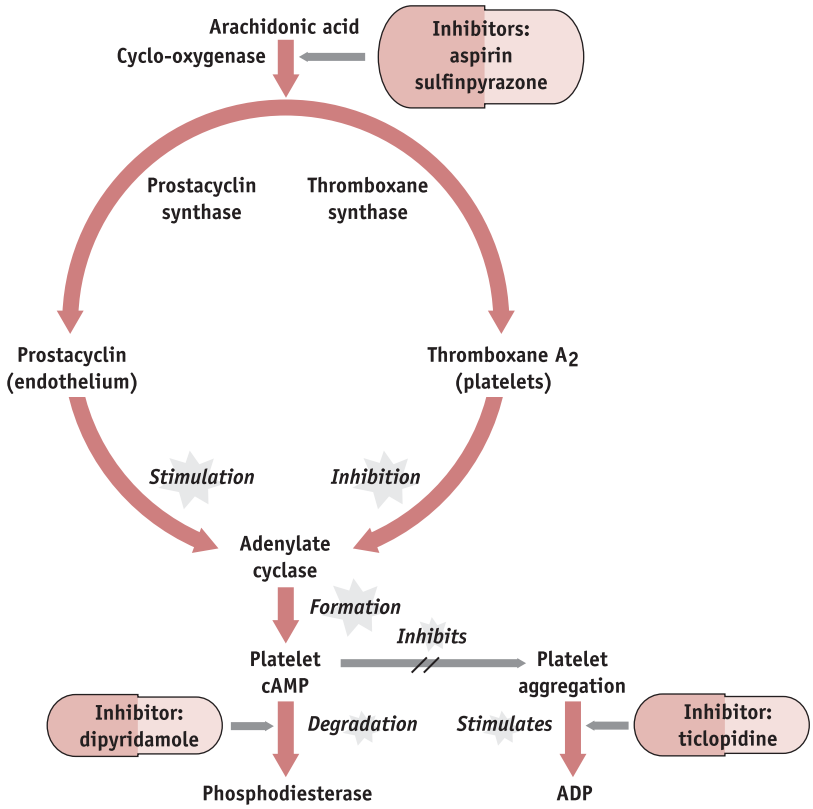
■ MECHANISM OF ACTION

Aspirin, or acetylsalicylic acid, is a member of the group of drugs known as salicylates, which have analgesic, antipyretic and anti-inflammatory properties (see Chapter 40). Aspirin is the only member of this group that has significant antiplatelet properties. The reason for this is the presence of an acetyl group. This acetyl group reacts chemically with the enzyme cyclo-oxygenase, which is needed in the synthesis of thromboxane. Aspirin is therefore a non-competitive inhibitor of this enzyme. Being a non-competitive inhibitor, it makes the enzyme completely inactive, rendering the platelets functionless for their lifespan (10–12 days).

◆ COMMON ADVERSE EFFECTS

The adverse effects of aspirin are discussed in Chapter 40. Due to the low dosage used in antiplatelet drug therapy,

FIGURE 46.2 PLATELET ADHESIVENESS AND DRUGS THAT IMPAIR THIS PROCESS



ADP, adenosine diphosphate; cAMP, cyclic adenosine monophosphate.

gastrointestinal problems and allergy are the most important to consider here.

✚ CLINICAL CONSIDERATIONS

Aspirin can be used as an adjunct in thrombolytic therapy and has been shown to be effective in reducing the incidence of death in cases of acute myocardial infarction and in patients with unstable angina. As aspirin is a non-competitive inhibitor of the enzyme, low dosage suffices. The exact dose required for treatment in thrombolytic therapy may be as low as 300 mg per day (compare with 600–900 mg for treating headaches and up to 5000 mg per day as an anti-inflammatory). In the prophylaxis of thrombotic episodes, 75 mg per day seems to reduce the incidence of thromboses. As an antiplatelet drug, for long-term use, aspirin is available as enteric-coated tablets, capsules and buffered tablets.

Aspirin is stopped 7 days before planned surgery and dental procedures in order to decrease the risk of bleeding. Dispersible tablets of aspirin are dissolved in water before consumption. Non-enteric-coated aspirin disintegrates rapidly on contact with moist air; these tablets should be removed from their packaging just before use.

DIPYRIDAMOLE

■ MECHANISM OF ACTION

Dipyridamole is a phosphodiesterase inhibitor that increases the concentration of cAMP in platelets and thus decreases platelet adhesiveness. It may potentiate the action of aspirin and the two drugs may be prescribed together.

◆ COMMON ADVERSE EFFECTS

The most commonly reported side effect is headache, which may be severe. Gastric upset, vomiting and nausea may occur, as may diarrhoea, myalgia, dizziness and facial flushing. In most cases, side effects reduce or disappear as treatment is continued.

✚ CLINICAL CONSIDERATIONS

In combination with warfarin, dipyridamole has been shown to reduce the incidence of thromboembolism in patients with prosthetic heart valves. Dipyridamole may be a useful alternative for patients who experience urticaria or asthma following the ingestion of aspirin, other salicylates and other non-steroidal anti-inflammatory drugs (NSAIDs).

GLYCOPROTEIN IIB/IIIA INHIBITORS: ABCIXIMAB

■ MECHANISM OF ACTION

This drug is rather different from most other drugs discussed in this chapter because it is related more to vaccines than to the conventional therapeutic substances used to treat most conditions. **Abciximab** belongs to an ever-growing group of substances known as monoclonal antibodies, which will probably become more and more common in the treatment of many diseases, especially cancer. In simple terms, a monoclonal antibody is an antibody prepared by the tissue culture of a cloned B-lymphocyte, which by definition produces only one type of antibody. (A textbook on immunology should be consulted for more information on monoclonal antibodies, as a detailed description of them is beyond the scope of this text.) Abciximab is prepared from a monoclonal antibody specific for certain glycoproteins on the surface of platelets that are intimately involved in platelet aggregation. When abciximab combines with these glycoproteins (i.e. abciximab's specific antigens), the platelets are inactivated and will not aggregate to form emboli. Abciximab is considerably more effective than other antiplatelet drugs, as it inhibits the aggregation mechanism rather than one or two of the stimuli that lead to platelet aggregation (as aspirin does, for example). Before the availability of abciximab, the use of aspirin and/or heparin to prevent ischaemic complications after percutaneous transluminal coronary angioplasty (PTCA) was not always successful. Abciximab has reversed this condition considerably in high-risk patients.

◆ COMMON ADVERSE EFFECTS

Abciximab is tolerated well by most patients. Its main adverse effect is an increase in haemorrhagic conditions due to thrombocytopenia. Hypersensitivity reactions are possible but extremely unlikely and have not yet been reported.

✚ CLINICAL CONSIDERATIONS

Abciximab is administered only by injection. It can be effectively combined with heparin or aspirin to prevent ischaemic cardiac complications. Repeat administration is not recommended, as human antichimeric antibodies develop in about 6 per cent of patients treated with abciximab. There is also the possibility of hypersensitivity reactions and reduced benefit following repeated treatments.

GLYCOPROTEIN IIB/IIIA INHIBITORS: EPTIFIBATIDE AND TIROFIBAN

Eptifibatide and tirofiban are newer drugs that have to be administered intravenously. They are licensed for use with heparin and aspirin to prevent early myocardial infarction in patients with unstable angina or non-ST-segment-elevation myocardial infarction. They should be used only by specialists. Only abciximab is licensed as an adjunct to percutaneous coronary intervention.

CLOPIDOGREL

■ MECHANISM OF ACTION

Clopidogrel is a prodrug and an analogue of ticlopidine (now withdrawn in the UK). It inhibits the aggregation of platelets by irreversibly inhibiting the binding of adenosine diphosphate (ADP) to its platelet receptor.

◆ COMMON ADVERSE EFFECTS

Ticlodipine was withdrawn because of the occurrence of neutropenia and thrombocytopenia. Clopidogrel's adverse-effects profile is less severe than that of ticlopidine, especially with regard to the occurrence of blood dyscrasias. Thrombocytopenia has been reported very rarely with clopidogrel. Clopidogrel partially inhibits the cytochrome P450 enzyme system in the liver (see Chapters 14 and 18), and therefore care is required with other drugs being administered simultaneously. Drug–drug interactions should be checked before administration of any drug, but even more so with cytochrome P450 inhibitors. Other adverse effects of clopidogrel are similar to those of aspirin but without the gastrointestinal effects. The concomitant administration of clopidogrel with warfarin is not recommended, since it may increase intensity of bleeding.

✚ CLINICAL CONSIDERATIONS

Clopidogrel may be a useful alternative for patients who experience urticaria or asthma following the ingestion of aspirin, other salicylates or other NSAIDs. Clopidogrel is combined with low-dose aspirin in acute coronary syndrome without ST elevation. The combination is given for at least 1 month but no more than 9–12 months, as long-term use increases the risk of bleeding.

TIROFIBAN

■ MECHANISM OF ACTION

When platelets become stimulated, certain receptors on their surface – glycoprotein IIb and IIIa receptors – are activated. These receptors bind to various macromolecules circulating in the blood, interlinking (i.e. forming cross-bridges) platelets with one another to produce the platelet aggregation, which results in the platelet plug. **Tirofiban** binds to these receptors in a similar manner to an antagonist and prevents cross-linking from occurring. Therefore, tirofiban is an antiplatelet drug with a completely different mechanism of action from the others. Tirofiban can be given only parenterally (intravenously) and is used mainly in combination with heparin to prevent myocardial infarction in unstable

angina. It is also under investigation for use in coronary angioplasty to prevent clotting at damaged vessel sites.

◆ COMMON ADVERSE EFFECTS

Bleeding, thrombocytopenia, nausea, fever, headache and rashes can occur with tirofiban.

✚ CLINICAL CONSIDERATIONS

Tirofiban may be administered together with heparin in the same intravenous line to treat unstable angina or non-Q-wave myocardial infarction. Dosage should be reduced by 50 per cent in moderate to severe renal impairment.

CLINICAL MANAGEMENT

Anticoagulants

Assessment

- Assess the patient for the presence of conditions usually contraindicated in anticoagulant use, including ulcerative lesions, haemorrhagic disease (e.g. haemophilia) and inflammatory disease of the gastrointestinal tract. Assess the patient for large open wounds, liver disease and renal conditions.
- Assess vital signs and compare with subsequent observations.
- Assess the patient for a history of problems with clots, bruising and bleeding.
- Take a baseline clotting profile. With parenteral anticoagulants, assess activated partial thromboplastin time (APTT) and platelet count.

Planning

- The patient's clotting profile will be carefully monitored and the prothrombin time (PT), international normalised ratio (INR) or activated partial thromboplastin time (APTT) will be about 1.25–2.50 times the control level.
- The patient will not experience the adverse effects of abnormal bleeding.
- The thromboembolic condition will be prevented.

Implementation

- Monitor vital signs for manifestations of haemorrhage, including rapid, feeble pulse and hypotension. Monitor level of consciousness. Bleeding may cause pale skin colour and weakness.
- Check the patient for bruising, ecchymosis, purpura and petechiae. Assess bleeding from the orifices, including nose bleeds and bleeding gums. Regularly assess injection, intravenous and wound sites for bleeding.
- Monitor urine and stools for the presence of blood.
- Perform regular clotting profiles. For patients receiving high-dose heparin (35–100 units/kg), the clotting profile is affected. For patients receiving low-dose heparin (e.g. 5000 units three times daily subcutaneously), the clotting profile is not affected. For patients on oral anticoagulants, monitor prothrombin time (PT), international normalised ratio (INR) and platelet count.
- Take care when handling the patient to avoid unnecessary bruising.
- Keep to hand antidotes for anticoagulants, such as protamine and vitamin K.
- Administer heparin subcutaneously or intravenously, and never intramuscularly. Due to the large number of blood vessels in the area, an intramuscular injection will be painful and a haematoma may result.
- Avoid administering intramuscular injections to patients on anticoagulants.
- The incidence of severe thrombocytopenia is much lower with danaparoid compared with other low-molecular-weight heparins and standard heparin. Danaparoid may be used as an alternative to standard heparin in heparin-induced thrombocytopenia, as cross-reactivity occurs in only about 10 per cent of individuals.
- In comparing low-molecular-weight heparins with standard heparin, the former are more effective in high-risk orthopaedic procedures and major general surgery. Low-molecular-weight heparins are therefore more appropriate in these situations.
- Low-molecular-weight heparins are administered once daily for the prevention of venous thromboembolism. Low-dose standard heparin is administered every 8–12 hours for the same condition.

Patient teaching

- Instruct the patient to report bleeding, such as petechiae, ecchymosis, purpura, blood in stools or urine, bloody nose, expectoration of blood, bleeding gums and unexplained bruising.
- Advise the patient to shave with an electric razor rather than a razor blade.
- All health-care professionals, including the patient's dentist and pharmacist, should be kept informed of anticoagulant use.
- Advise the patient not to walk barefoot.
- Advise the patient not to take over-the-counter preparations without checking with a doctor or pharmacist first. Usually, aspirin should not be taken with warfarin or heparin because aspirin intensifies the anticoagulant action and bleeding may occur.
- Instruct the patient not to consume alcohol, which could cause increased bleeding.
- Advise the patient on warfarin to maintain a consistent diet to stabilise the intake of vitamin K from food. Foods containing high amounts of vitamin K include leafy green vegetables, which, if consumed in large amounts, could reduce the anticoagulant effect.
- Teeth should be brushed with a soft bristle brush to prevent bleeding. Use of dental floss should be avoided.

Evaluation

- Evaluate the effectiveness of therapy in preventing the thromboembolic condition.
- Clotting profiles are within expected ranges for the patient taking the anticoagulant.
- The patient is free from adverse effects from the anticoagulant.

Thrombolytic drugs

Assessment

- Assess the patient for active, internal bleeding, recent cerebrovascular accident (CVA), cerebral neoplasm, anticoagulant therapy, recent surgery, severe hypertension, bacterial endocarditis and recent gastrointestinal bleeding. These conditions are contraindications to therapy.
- Assess vital signs and compare with subsequent observations.
- Assess blood profile, including haemoglobin, haematocrit, platelet count, activated partial thromboplastin time (APTT), prothrombin time (PT) and international normalised ratio (INR).
- Assess the patient for a history of problems with clots, bruising and bleeding.

Planning

- The blood clot will be dissolved and active bleeding will not occur.
- The patient will not experience the adverse effects of therapy.

Implementation

- Ensure that the patient is connected to a cardiac monitor during the administration of the drug.
- Monitor vital signs for manifestations of haemorrhage, including rapid, feeble pulse and hypotension. Monitor level of consciousness.
- Ensure that clotting profile, platelet count, haemoglobin and haematocrit are monitored regularly during therapy.
- Monitor for manifestations of an allergic response during therapy. An allergic response is more common with streptokinase than with other thrombolytics. Observe for anaphylaxis (e.g. dyspnoea, bronchospasm), urticaria, itching, flushing, nausea, headache and musculoskeletal pain. Use adrenaline, antihistamines and corticosteroids to treat the allergic response. Ensure that emergency equipment and personnel are available.
- Do not administer an intramuscular injection to patients receiving this therapy, as haematoma or bleeding may occur.
- Avoid performing arterial punctures on patients receiving thrombolytic therapy. If an arterial puncture is necessary, avoid the femoral artery and use the radial or brachial artery instead. Apply pressure to the site for at least 30 minutes following the puncture.
- If venepuncture is necessary, apply pressure to the site for at least 30 minutes following the procedure.
- Avoid inserting central venous catheters in patients receiving thrombolytic therapy.
- Monitor for the incidence of reperfusion dysrhythmias, which can occur as the blood clot dissolves. Antidysrhythmic treatment may be necessary.
- Avoid excessive and unnecessary handling of the patient, which may cause bruising or bleeding.

- Monitor for active bleeding for 24 hours after thrombolytic therapy has been completed.
- Avoid administering aspirin or non-steroidal anti-inflammatory drugs for pain.
- Ensure that the antidote for thrombolytic therapy – tranexamic acid – is available and close at hand.
- In the case of severe bleeding that is not controlled by local pressure, the thrombolytic infusion should be stopped. Administration of fibrinogen, platelets, coagulation factors, tranexamic acid and protamine (if heparin is used) should be considered.

Evaluation

- Evaluate the effectiveness of therapy in dissolving the clot without causing haemorrhage.
- Evaluate the presence of adverse effects and allergy.

Antiplatelet drugs

Assessment

- Assess the patient for a history of problems with clots, bruising and bleeding.
- Assess blood profiles, including haemoglobin, haematocrit and platelet count.

Planning

- The thromboembolic condition will be prevented.
- The patient will not experience the adverse effects associated with antiplatelet therapy.

Implementation

- Ensure that soluble aspirin is dissolved fully in water before administration.
- Administer medication with meals to prevent gastric irritation.
- For maximum benefit, abciximab must be administered in combination with aspirin and heparin.
- Where possible, aspirin should be stopped 7 days before surgery, including dental procedures.

Patient teaching

- Advise the patient to avoid taking over-the-counter medications, especially aspirin-containing products, without notifying the pharmacist and doctor.
- Instruct the patient to notify the doctor if the following manifestations of bleeding occur: bruising, bleeding gums, nose bleeds, or blood in stools or urine.
- Advise the patient to take clopidogrel or aspirin with meals to avoid gastric irritation.
- Advise the patient on clopidogrel to notify the doctor if fever, chills, sore throat or mouth ulcers develop. These are symptoms of neutropenia.
- Advise the patient on aspirin to mix dispersible tablets with water immediately before consumption.

Evaluation

- Evaluate the effectiveness of therapy in preventing the thromboembolic condition.
- Blood profiles are within expected ranges for the patient taking an antiplatelet drug.
- The patient is free from adverse effects from the antiplatelet drug.

SUMMARY

- Anticoagulants and antiplatelet drugs are used in thrombotic disorders.
- Fast-acting anticoagulants, such as heparin, are used in situations where intravascular clotting is a major problem.
- Slow-acting anticoagulants, such as warfarin, are used in long-term therapy for thrombotic disorders.
- Antiplatelet drugs are used in the long-term treatment of thrombotic disorders. Antiplatelet drugs can be used in the prophylaxis of intravascular clotting, in both the short and the long term.
- Fibrinolytic drugs are used in the emergency treatment of thromboses.
- Fibrinolytic agents are administered within 6–12 hours following the onset of chest pain in the management of acute myocardial infarction.

1. What are the antidotes to warfarin and heparin? How does each antidote work?
2. What observations should be made in patients taking warfarin?
3. What are the uses of tranexamic acid?
4. Why is the term 'fibrinolytic agent', when applied to drugs such as streptokinase, a misnomer?
5. Why is anaphylaxis a danger in the use of streptokinase?
6. State the advantages of recombinant plasminogen activators over streptokinase.
7. Explain the mechanism of action of the plasminogen activators.
8. Salicylic acid can be substituted for aspirin as an analgesic but not as an antiplatelet drug. Why?
9. Why should a patient on warfarin be told not to eat too much cabbage?
10. Lienhard Krug, a 45-year-old executive, is brought into the emergency department following an acute myocardial infarction. It is determined that Mr Krug has a past history of peptic ulcer treated with ranitidine. Mr Krug is given streptokinase intravenously. What is a major issue relating to the patient's safety? What assessment will be conducted regularly to monitor the effect of streptokinase?
11. As well as the international normalised ratio (INR), what forms of assessment will be conducted on a patient commenced on warfarin in hospital?
12. Leonora Alexandro, a 50-year-old patient, is discharged home with warfarin. What patient education would you provide before discharge?
13. Explain the problems associated with an intramuscular injection of heparin.
14. Marian Evian, a 56-year-old patient receiving a heparin infusion, has an activated partial thromboplastin time (APTT) of 120 seconds. As her nurse, what would you do?

46 DRUG SUMMARY TABLE: ANTICOAGULANTS, THROMBOLYTICS AND ANTIPLATELET DRUGS

FAMILY NAME	GENERIC NAME	TRADE NAME(S)
Antiplatelet drugs	Abciximab	ReoPro
	Aspirin	Angettes 75
		Caprin
		Nu-Seals Aspirin
	Clopidogrel	Plavix
	Dipyridamole	Persantin
	+ Persantin	Asasantin Retard
	Eptifibatide	Integrilin
	Tirofiban	Aggrastat
Parenteral anticoagulants	Bemiparin	Zibor
	Dalteparin	Fragmin
	Danaparoid	Orgaran
	Enoxaparin	Clexane
	Reviparin	Clivarine
	Tinzaparin	Innohep
	Heparin	Calciparine
		Monoparin
		Multiparin
	Antithrombin III	
	Fondaparinux	Arixtra
Topical anticoagulants	Heparinoid	Hirudoid
	+ Hyaluronidase	Lasonil
	+ Salicylic acid	Movelat Sportz
Heparin antagonist	Protamine sulphate	
Oral anticoagulants	Phenindione	
	Warfarin	
	Acenocoumarol	Sinthrome
Warfarin antagonist	Vitamin K	Konakion
Antifibrinolytics	Aprotinin	Trasylol
	Etamsylate	
	Tranexamic acid	Cyklokapron
Thrombolytic drugs (fibrinolytic drugs)	Streptokinase	Streptase
	Alteplase	Actilyse
	Reteplase	Rapilysin
	Tissue tenecteplase	Metalyse

DIURETICS AND OTHER RENAL DRUGS

47

CHAPTER FORTY-SEVEN

OBJECTIVES

After completing this chapter, the reader should be able to:

- **outline the normal physiology of the nephron;**
- **describe the sites and mechanisms of action of the various types of diuretic;**
- **list the high-efficacy diuretics, their uses and their adverse effects;**
- **describe the use of thiazides and related drugs;**
- **describe the use of potassium-sparing diuretics;**
- **outline the problems associated with the use of diuretics;**
- **describe the use of osmotic diuretics;**
- **describe the use of urinary alkalinisers and acidifiers;**
- **outline the treatment of diabetes insipidus.**

KEY TERMS

Antidiuresis
Diuresis
Hypertension
Hypokalaemia
Hyponatraemia
Oedema

DIURETICS ARE A GROUP OF DRUGS THAT PROMOTE WATER loss from the body into the urine. Urine formation takes place in the kidneys, and diuretics have their principal action at the level of the nephron. The action of some diuretics is not confined to their action on the kidneys, however, and they also act elsewhere in the body. This causes an amplification of their effects in certain conditions. Details of these effects are dealt with later in this chapter.

Diuretics are used principally to remove excess extracellular fluid from the body that can result in oedema of the tissues and hypertension. Diuretics are used so frequently in hypertension that they are (not always wrongly) termed antihypertensives.

In order to understand the actions of diuretics, it is important to have some knowledge of the basic processes that take place in the nephron. Figure 47.1 shows a nephron and the processes that occur in its various parts, with the emphasis on the areas where the various diuretics act.

Approximately 180 l of fluid are filtered from the glomeruli into the nephrons each day. The normal urine output is about 1.5 l per day, so only a slight interference with water reabsorption will produce a significant increase in urine output. For example, a 1 per cent decrease in water reabsorption will result in a doubling of urine output. Diuretics do not have to be very efficient in their action to produce a dramatic effect.

Note that dopamine (see Chapter 26) and the cardiac glycoside digoxin (see Chapter 48) increase blood flow in the glomerulus and therefore promote effective urine production. This secondary action of these drugs is useful in both shock and congestive heart failure, the respective indications for the drugs.

DIURETICS

Loop diuretics

■ MECHANISM OF ACTION

The drugs **furosemide**, **ethacrynic acid** and **bumetanide** act on the medullary part of the ascending limb of the loop (loop of Henle) of the nephron. They inhibit the reabsorption of chloride and sodium ions from the loop into the interstitial fluid. The result is that the interstitial fluid becomes relatively hypotonic. If a high concentration of ions is present here, water will flow from the adjacent collecting duct into the interstitial fluid and back into the bloodstream. Good control of water balance is achieved by alterations in the permeability of the collecting duct to water by the presence of antidiuretic hormone (ADH) from the posterior pituitary gland. This is one of the major control systems for water balance, and slight interference here will completely upset the normal function of the kidney and result in a variation in urine output. A hypotonic interstitial fluid will result in a diuresis.

As this system is one of the most important systems for water balance, the loop diuretics are of high efficacy. This must be borne in mind when treating patients, as the resulting diuresis makes visits to the toilet rather frequent. Because of this effectiveness, the loop diuretics are sometimes referred to as 'high-ceiling diuretics'. In high doses, furosemide and other loop diuretics can increase urine output very significantly, leading to severe hypovolaemia and death.

◆ COMMON ADVERSE EFFECTS

A major problem of the loop diuretics is electrolyte loss from the body. Potassium and sodium are the main ions affected. Potassium loss often leads to hypokalaemia, which can result in cardiac dysrhythmias and death. This is a problem in patients being treated with digoxin concurrently, which has an increased toxicity in cases of hypokalaemia. To counteract the occurrence of hypokalaemia, various measures can be taken, the most common being to use potassium chloride supplements, increase the intake of high potassium foods or use other drugs that promote potassium reabsorption from the nephron. Potassium supplements are irritant to the stomach and can be given as enteric-coated or effervescent tablets. High-potassium foods include bananas, leeks, fruit juices, nuts, sprouts, milk, meat and instant coffee. Potassium-sparing drugs are mentioned below.

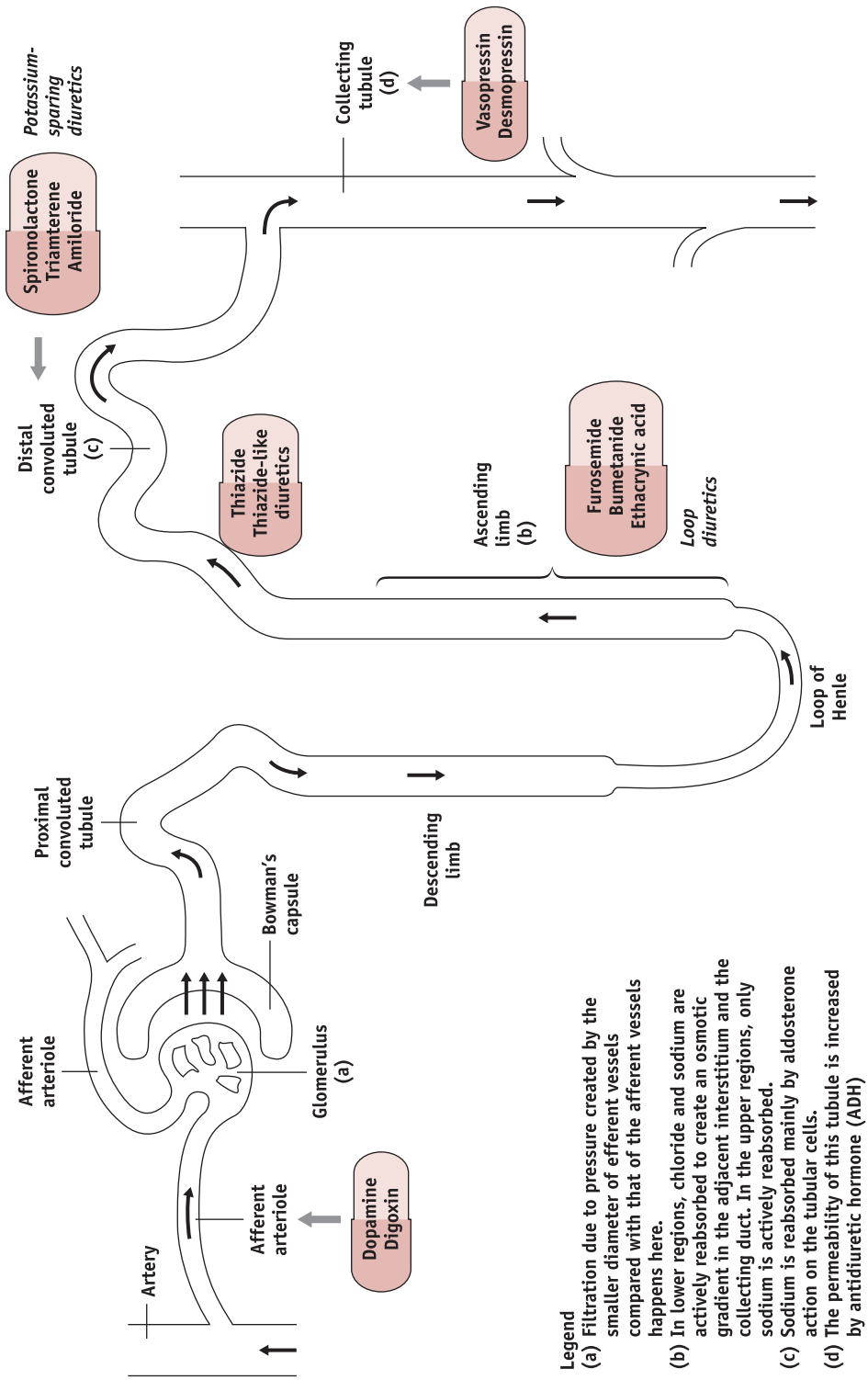
It has been noticed that confusion in elderly patients on loop diuretics is not always due to senility but may be a result of hyponatraemia. As potassium levels in the blood must be maintained in a narrow range for normality, blood sodium levels, which are not quite so critical, have tended to be ignored. More attention should be paid to blood sodium levels, however, especially in elderly patients. Other electrolyte changes can occur, especially with high doses of loop diuretics, and periodic assessment of blood calcium and magnesium levels is required. Uric acid levels may rise during loop diuretic therapy, which can be problematic for people with gout. In rare instances, hyperglycaemia may develop, and so individuals with diabetes mellitus should be monitored during therapy.

✚ CLINICAL CONSIDERATIONS

The loop diuretics are used in oedematous states and can be given intravenously for immediate action. They can be used in hypertension, but other diuretics are probably better in most cases of hypertension. In renal failure, loop diuretics can be effective in helping to normalise urine output. Routine administration of loop diuretics (and probably all diuretics) should be before late afternoon in order to avoid severe nocturnal diuresis.

It is important to monitor fluid and electrolyte status, especially at the commencement of therapy. Hypovolaemia occurs as a result of high doses of loop diuretics.

FIGURE 47.1 NEPHRON PHYSIOLOGY AND THE SITES OF ACTION OF RENAL DRUGS



Hypokalaemia resulting from the use of loop diuretics can be reduced by administering the drugs with an angiotension-converting enzyme (ACE) inhibitor, an angiotensin II receptor antagonist or a potassium supplement. Ototoxicity may occur with high doses of furosemide, which manifests as tinnitus, vertigo and deafness. To avoid ototoxicity, administer intravenous doses of furosemide no faster than 4 mg per minute.

Thiazide and thiazide-like diuretics

■ MECHANISM OF ACTION

This is a diverse group of drugs. Thiazides are a group of drugs that are chemically similar. The thiazide-like drugs are chemically dissimilar from the thiazides but have an identical mode of action. These drugs act on the cortical segment of the ascending loop and the distal convoluted tubule of the nephron and decrease sodium reabsorption. This results in a more concentrated fluid entering the collecting ducts and therefore decreases water reabsorption and results in diuresis. Thiazide and thiazide-like diuretics have an effect on the peripheral arterioles, which results in vasodilation. This, combined with their diuretic effect, makes them particularly suitable in hypertensive patients (see Chapter 44). This action of the drugs is not understood completely but may be due to an alteration in electrolyte concentration in vessel walls, lessening their response to pressor stimuli. Another advantage of this group of diuretics is that, in alkalosis, bicarbonate ions are excreted with the sodium ions; in acidosis, chloride ions follow the positive sodium ions. In both instances, this will help in the normalisation of the acid–base disturbance. In patients with normal acid–base balance, bicarbonate and chloride ions are excreted equally, with no resultant upset in acid–base balance.

◆ COMMON ADVERSE EFFECTS

As with the loop diuretics, potassium and sodium loss can result, and supplementation (as described above) is usually necessary.

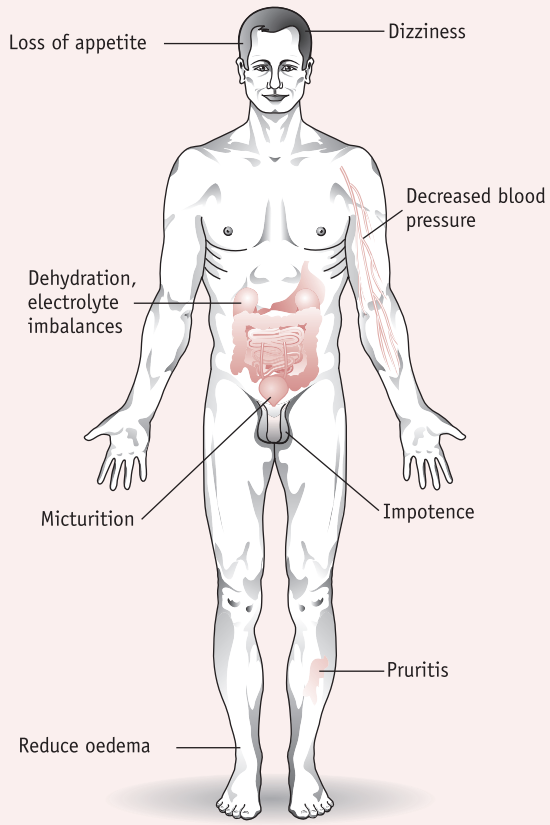
Thiazides occasionally cause a rise in blood uric acid levels, which can be problematic in patients predisposed to gout. Hyperglycaemia can also occur, which is potentially dangerous in diabetic patients.

Lactation can be suppressed by these drugs, and thiazides have been used for this purpose. Impotence may occur with these drugs in men; if this becomes problematic, a change to a calcium channel blocker or ACE inhibitor may be required. Sexuality should not be ignored, including in elderly patients.

Thiazide diuretics contain a sulphonamide group in their chemical structure. As such, they should not be used in patients with a known sensitivity to sulphonamides. Photosensitivity reactions may also occur, and it is recommended that the patient takes sun precautions during treatment. Low doses are used to reduce the incidence of metabolic adverse events, such as hyponatraemia and hypomagnesaemia.

The general adverse effects of the diuretics are detailed in Figure 47.2.

FIGURE 47.2 EFFECTS OF DIURETICS



✚ CLINICAL CONSIDERATIONS

Commonly used thiazide and thiazide-like diuretics are **bendroflumethiazide**, **indapamide**, **cyclopenthiazide** and **chlortalidone** (chlorthalidone). These drugs are still considered to be in the front line for the treatment of mild to moderate hypertension either on their own or combined with another antihypertensive, usually a beta-blocker. To give an example, in one trial, chlortalidone was sufficient as an antihypertensive agent on its own in 46 per cent of participants. Beta-blockers are generally less well tolerated in elderly patients because of the reduction in cardiac output during activity, which can lead to dyspnoea and fatigue.

Hypokalaemia can be avoided by administering the thiazide diuretic together with a potassium supplement or potassium-sparing diuretic when the serum potassium level drops below 3.5 mmol/l. Hypokalaemia is also less likely to occur if the thiazide diuretic is given with an ACE inhibitor or an angiotensin II receptor antagonist.

Potassium-sparing diuretics

■ MECHANISM OF ACTION

The advantage of this group of drugs is clear from their name, but unfortunately they are not very powerful as diuretics. Their main use is in the prevention of potassium loss due to the use of the diuretics mentioned above. To do this, the potassium-sparing diuretics are often given concurrently with loop or thiazide diuretics, sometimes together in one tablet.

There are two types of potassium-sparing diuretics – aldosterone antagonists and those independent of aldosterone.

The mode of action of the aldosterone antagonists (**spironolactone**, **eplerenone**) is to inhibit the action of aldosterone on the distal convoluted tubule of the nephron. Aldosterone is the sodium-retaining hormone secreted from the adrenal cortex. If it acts on the distal tubule, more sodium ions are retained by the body and water is conserved passively at the same time. When sodium is retained by the nephron at this site, potassium is lost. Therefore, if aldosterone is blocked, potassium is retained and sodium is lost along with a slight increase in diuresis. For every two molecules of potassium retained, three sodium molecules are lost. It is this phenomenon that induces diuresis, as more ions are lost than are retained. The effect of spironolactone as a diuretic is of value only when excessive production of aldosterone is involved in the genesis of oedema. Spironolactone has proved to be of tremendous value in the treatment of congestive heart failure (see Chapter 48).

The two other potassium-sparing diuretics, which work independently of aldosterone, are **amiloride** and **triamterene**. These act on the site of potassium–sodium exchange in the distal tubule, causing potassium retention and sodium loss.

◆ COMMON ADVERSE EFFECTS

Adverse effects that occur with this type of diuretic are related to their mode of action and include hyperkalaemia and hyponatraemia. It can be very dangerous to give potassium supplementation to patients on this type of diuretic, whether or not they are combined with the more efficacious diuretics. In men, spironolactone can produce gynaecomastia due to its oestrogenic effects.

✚ CLINICAL CONSIDERATIONS

Potassium-sparing diuretics are not usually required for patients who are on loop or thiazide diuretics. Instead, they are reserved for use if the serum potassium concentration drops below 3.5 mmol/l. Conversely, hyperkalaemia can occur if potassium-sparing diuretics are administered with ACE inhibitors, angiotensin II receptor antagonists or potassium supplements. Once-daily doses should be taken in the morning to prevent nocturnal diuresis.

Osmotic diuretics

■ MECHANISM OF ACTION

Osmotic diuretics work by interfering directly with osmosis. Any substance that enters the body in large enough quantities and is excreted via the kidneys will lead to water being kept in the renal tubules, and this results in water loss. This is due to the maintenance of a high osmotic pressure in the tubules. Substances that act as osmotic diuretics must conform to certain criteria. They must be relatively non-toxic, be excreted quickly and not be reabsorbed from the glomerular filtrate. They must, therefore, be very water-soluble, or hydrophilic. This makes such substances impossible to give by mouth, and so they must be given intravenously. If given by mouth, an osmotic laxative effect would most likely result (see Chapter 54).

Osmotic diuretics tend to remain in the blood and, by increasing the osmolarity of the blood, are useful in the treatment of oedematous states. These can occur in conditions such as glaucoma and elevation of intracranial pressure due to head injury. The fluid from oedematous states is extracellular and will, therefore, pass from these areas into the hypertonic blood, and then to the kidneys for removal.

◆ COMMON ADVERSE EFFECTS

Adverse effects include electrolyte imbalance and the potential for dehydration. This potential for dehydration is similar to that which would occur from the drinking of sea water.

Osmotic diuretics can result in hypervolaemia, which could be problematic in patients with cardiac failure.

✚ CLINICAL CONSIDERATIONS

The most commonly used osmotic agent is mannitol; other agents are used only infrequently. Mannitol crystallises at low temperatures due to the high concentration of solute compared with solvent. The solution can be redissolved by warming it in hot water and shaking. As mannitol produces severe osmotic diuresis, the unconscious or anaesthetised patient should have a urinary catheter inserted. Monitor for fluid and electrolyte changes by examining for signs of dehydration and checking electrolyte levels. Osmotic diuretics act quickly and are useful in emergency situations.

The commonly used osmotic diuretic is **mannitol**, a sugar alcohol derived from mannose. Glycerol, glucose and urea can also be used. Glucose is particularly useful in cerebral oedema associated with alcohol withdrawal, providing much-needed kilojoules simultaneously. Glucose must not be used in patients with diabetes mellitus if hyperglycaemia is present.

Carbonic anhydrase inhibitors

■ MECHANISM OF ACTION

Carbonic anhydrase is an enzyme that catalyses the conversion of carbon dioxide into bicarbonate ions and vice versa, according to the following equation:

$$CO_2 + H_2O \rightleftharpoons H_2CO_3 \rightleftharpoons H^+ + HCO_3^-$$

This reaction occurs in the kidney and other parts of the body. In the kidney, the reaction occurs mainly in the proximal tubule and, as it involves bicarbonate loss, is concerned with acid–base balance. The tubular cells are not very permeable to bicarbonate ions or carbonic acid but are very permeable to carbon dioxide. Under normal circumstances, carbonic anhydrase in the tubular cell converts the carbonic acid into carbon dioxide and water, which are promptly reabsorbed. If the enzyme is inhibited, there will be a net loss of bicarbonate from the body, with a consequent loss of water. The drug **acetazolamide** is a non-competitive inhibitor of this enzyme and has, on occasion, been used as a diuretic. The urine produced during acetazolamide therapy is alkaline, due to the excess bicarbonate ions (the hydrogen ions shown in the equation above are replaced with sodium ions). Alkaline urine is useful for dissolving renal calculi formed from acidic compounds such as the amino acid cysteine. Acetazolamide can be used to treat this type of disorder.

Carbonic anhydrase is involved in the production of aqueous humour and cerebrospinal fluid. This reaction occurs in the choroid plexus of the eye and the fourth ventricle in the brain, respectively. Inhibition of carbonic anhydrase results in a decrease of these fluids; acetazolamide or **dorzolamide** can be used to decrease the intraocular pressure that occurs in glaucoma (see Chapter 79) and occasionally in cases of increased intracranial pressure.

Acetazolamide is useful in both the treatment and prophylaxis of altitude sickness. At high altitudes (above 3000 m), hypoxia inevitably occurs in unacclimatised individuals. This leads to alkalosis (see a physiology textbook for more on gas exchange and the effect of pH on respiration); acetazolamide reverses the alkalosis by lowering the pH of the blood and helps to maintain arterial oxygen tension.

Carbonic anhydrase inhibitors can be used as a second line of attack in absence seizures of epilepsy and in the treatment of episodic ataxia. The mechanisms of action, however, are unknown.

◆ COMMON ADVERSE EFFECTS

Adverse reactions include Stevens–Johnson syndrome, hepatic necrosis, haematological reactions, paraesthesia, anorexia, polyuria, polydipsia, headache, flushing, drowsiness, fatigue, hypoglycaemia, hyperglycaemia, hepatic effects, blood dyscrasias, electrolyte imbalance and tinnitus.

✚ CLINICAL CONSIDERATIONS

When administering systemic carbonic anhydrase inhibitors, it is important to monitor fluid input and output and glucose and electrolyte levels. In particular, potassium, bicarbonate, calcium and chloride ion levels should be monitored carefully. The patient should be weighed regularly. Any rapid or excessive fluid loss may cause weight loss or hypotension. These drugs need to be administered with caution in patients with respiratory acidosis, emphysema and chronic respiratory disease, as diuresis can be diminished in the presence of acidotic conditions. If gastric irritation occurs, advise the patient to take the preparation with food.

URINARY ALKALINISERS

The use of substances to raise the pH of blood is mentioned above in the discussion about acetazolamide. This drug increases the excretion of bicarbonate ions. Another way to do this is to induce an alkalosis by giving excess sodium bicarbonate. This will result in a rise in the excretion of bicarbonate, with a concomitant rise in urinary pH. Citric and tartaric acid salts will do the same thing. Alkalinisation of urine is useful to relieve the painful dysuria in cystitis. Most of the pain in urinary tract infections is due to the high acidity of the urine burning the sensitive urethra. A bonus with urinary alkalinisers is that in *Escherichia coli* infections, the organism does not grow well at high pH values. Furthermore, some antibacterials, such as the sulphonamides, are more effective in alkaline conditions.

In cases of poisoning with acidic drugs such as **aspirin**, alkalinisation of the urine will increase the excretion of the drug. Aspirin ionises in basic conditions, and so that there will be less tubular reabsorption due to the lipophobic nature of the ions produced.

✚ CLINICAL CONSIDERATIONS

Alkalinisation is possible only if the creatinine clearance is at least 30 ml/minute. It may be necessary to check the patient's renal function before administration of a urinary alkaliniser. To determine the effectiveness of therapy and to avoid the risk of alkalosis, it is important to obtain blood pH, arterial blood levels of oxygen and carbon dioxide, and serum electrolyte levels. This is particularly important when alkalinisation is used to treat a severe condition. It is important to note that sodium bicarbonate is not used routinely for cardiac or respiratory arrest because it can lead to paradoxical acidosis from carbon dioxide production. Alkalinisation should be used with extreme caution in patients with heart failure, renal failure and other oedematous conditions.

URINARY ACIDIFIERS

Occasionally, in cases of overdose of basic drugs such as amphetamines and morphine, acidification of the urine with large doses of **ammonium chloride** or **ascorbic acid** is used to increase excretion of the drug from the body. Ammonium chloride can cause gastric irritation and nausea, and therefore the use of ascorbic acid is preferred. Ascorbic acid is sometimes used to acidify the urine in elderly patients with urinary catheters or urinary tract infections. The rationale is that bacteria are less likely to colonise the urinary tract if the conditions are acidic.

✚ CLINICAL CONSIDERATIONS

Careful monitoring of the blood pH is necessary during treatment to ensure it is maintained within the required levels. Urinary acidification should be used cautiously in patients with pulmonary insufficiency and cardiac oedema due to the propensity of the drugs to cause cardiac dysrhythmias and irregular respiration. With ammonium chloride, it is important to determine the carbon dioxide combining power and serum electrolyte levels before and during treatment in order to prevent the incidence of metabolic acidosis. Each gram of ammonium chloride reduces the carbon dioxide combining power by 1.1 per cent by volume. Ammonium chloride is not administered with milk or other alkaline fluids as they are incompatible. Regularly monitor respiratory rate, depth and rhythm in order to determine irregular respirations or periods of apnoea. These preparations should be used cautiously in individuals with pulmonary insufficiency or cardiac oedema. Oral preparations are taken after meals to reduce the incidence of gastric irritation.

ANTIDIURETICS

Diabetes insipidus results from failure of the posterior pituitary to produce antidiuretic hormone. Hypophysectomy will also cause this condition. Treatment is to replace the hormone by using either the natural hormone (**vasopressin**) or a similar semisynthetic polypeptide, such as **desmopressin**. This hormone can be given parenterally or by intranasal administration. When given by intramuscular injection, drug release can be slowed down by using the tannic acid salt of the hormone dissolved in arachis (peanut) oil. These compounds act on the collecting ducts, making them more permeable to water and thus increasing its reabsorption. A patient with diabetes insipidus can lose 20 l of urine per day and must drink similar amounts to prevent dehydration. These drugs let the patient lead a more normal life.

The hormones can have other effects on the body, namely stimulating smooth muscle. This action can be made use of to lessen the abdominal distension occurring after laparotomy. The drug should be given before surgery to be effective. An unusual use of ADH is in improving memory and learning capabilities. Some people claim that a squirt of ADH into the nostril before a studying session will enhance one's learning ability; this use cannot be advocated, however.

✚ CLINICAL CONSIDERATIONS

For diabetes insipidus, the largest dose of hormone is usually given at night to prevent nocturia and the smallest dose is administered during the day. Blood pressure is monitored to determine the effectiveness of medication treatment. Fluid intake is restricted when administering the hormone for renal function testing and nocturnal enuresis. Fluid intake, specific gravity of urine and fluid output are monitored, especially when the thirst response is not functioning adequately. This malfunction occurs in unconscious, sedated, postoperative patients and in patients with a craniopharyngioma or hypothalamic lesion. Patients should be advised to drink enough water to satisfy thirst. These preparations should be used with care in patients with coronary artery disease, hypertension and conditions involving fluid and electrolyte imbalances.

CLINICAL MANAGEMENT

Diuretics

Assessment

- Assess the patient for a history of renal failure, ascites, gout and diabetes. Caution should be exercised when administering diuretics to a patient with any of these conditions.
- Obtain baseline vital signs, especially blood pressure and pulse, as indications of body volume status. Initially, assess lying, sitting and standing blood pressures and compare measurements from both arms.
- Obtain a baseline value for body weight and compare with subsequent observations.
- Assess electrolyte levels such as potassium, sodium, calcium, magnesium and bicarbonate. Determine also blood glucose, uric acid, creatinine and urea levels.

Planning

- Pitting oedema in the extremities will resolve.
- The patient's hydration status will be maintained within acceptable levels.
- The patient's blood pressure will stabilise within normal limits.
- Laboratory levels will remain within normal limits.

Implementation

- Monitor vital signs, especially blood pressure and pulse.
- Monitor for manifestations of dehydration, including thirst, decreased skin turgor, dry mucous membranes, nausea, lightheadedness, weakness, increased pulse, oliguria, concentrated urine and decreased blood pressure.
- Monitor the patient's weight at the same time each day.
- Document the patient's fluid status on a fluid-balance chart to determine whether the patient achieves a positive, negative or even fluid balance.
- Monitor electrolyte levels regularly, especially for hypokalaemia. Manifestations of hypokalaemia include decreased or absent bowel sounds, muscle weakness, irregular pulse and confusion. Several diuretics are potassium-wasting. Note that dysrhythmias can occur with hypokalaemia and hyperkalaemia.
- Monitor dependent areas, such as the sacral area, feet and legs, for manifestations of pitting oedema.
- Monitor lung sounds on both sides of the chest for crackles.
- In patients taking osmotic diuretics, monitor for manifestations of circulatory overload, including weight gain, distended neck veins, crackles on lung auscultation, dyspnoea, agitation and dependent oedema.
- If the patient does not have a urinary catheter in situ, ensure that the last dose of diuretic is not administered late in the day in order to avoid overnight diuresis.
- Observe for changes in vision and hearing (thiazide and loop diuretics).
- Hypokalaemia from the use of a loop diuretic can be avoided by using a loop diuretic agent in combination with an angiotensin-converting enzyme (ACE) inhibitor or with an angiotensin II receptor antagonist.

Patient teaching

- If the patient has been switched from a potassium-wasting to a potassium-sparing diuretic, inform the patient about the need to stop taking the potassium supplement. The intake of potassium-rich foods should be limited.
- Instruct patients with diabetes to monitor their blood glucose levels carefully, as thiazide, loop and potassium-sparing diuretics can cause hyperglycaemia.
- Ensure that the patient has easy access to bathroom facilities.
- For patients taking carbonic anhydrase inhibitors, instruct them to avoid driving and operating heavy machinery if drowsiness or dizziness occurs.
- For patients on potassium-wasting diuretics, explain about the manifestations of hypokalaemia, such as muscle cramps and weakness, lethargy, anorexia, irregular pulse and confusion.
- For patients on potassium-sparing diuretics, explain about the manifestations of hyperkalaemia, such as thirst, dry mouth and drowsiness.
- Instruct the patient to monitor pulse if taking both a diuretic and digoxin. Bradycardia is a sign of digoxin toxicity. Caution the patient about the importance of maintaining normal potassium levels while on combination digoxin and diuretic therapy.
- Advise the patient to rise slowly from a sitting to standing position to prevent postural hypotension (see Table 11.20 in Chapter 11 for other measures used for postural hypotension).
- For patients on thiazide diuretics, loop diuretics or carbonic anhydrase inhibitors, advise that these drugs may cause photosensitivity (see Table 11.19 in Chapter 11 for further information on measures used to prevent photosensitivity reactions).
- Advise patients to avoid alcohol, which can enhance the hypotension caused by diuretics.

Evaluation

- Evaluate the effectiveness of the diuretic in reducing blood pressure, increasing urine output and reducing oedema.
- Evaluate whether electrolyte levels are maintained within a normal range.

SUMMARY

- Diuretics increase urine output and are used in oedematous conditions and in hypertension.
- Most diuretics act on the ascending limb of the loop of Henle or on the distal convoluted tubule.
- A common adverse effect of most diuretic therapies is hypokalaemia.
- Hypokalaemia can be controlled with a high-potassium diet, potassium supplements and concurrent use of a potassium-sparing diuretic.
- Diuretics that act on the distal tubule do not result in hypokalaemia and are termed potassium-sparing.
- Osmotic diuretics given parenterally can produce fast diuresis in emergency oedematous states.
- Antidiuretics promote water reabsorption and are used in diabetes insipidus.

1. List the main causes of oedema.
2. Why are potassium supplements often given during diuretic therapy? What alternatives are available to potassium therapy?
3. Why might a diabetic patient become hyperglycaemic when on thiazides?
4. Why should diuretics not normally be administered at night?
5. Why would mannitol be ineffective as a diuretic if given by mouth? What might be the consequences of oral mannitol?
6. What are the dangers associated with hyper- and hypokalaemia?
7. Why would alkalinisation of the urine help in aspirin poisoning?
8. Why do amphetamine addicts often mix the amphetamine with sodium bicarbonate?
9. Why is acetazolamide useful in the treatment of some forms of glaucoma?
10. Distinguish between the potency of the various diuretics.
11. Why is antidiuretic hormone (ADH) sometimes called vasopressin?
12. Try to explain the mechanism of action of acetazolamide in the treatment of altitude sickness.
13. A 64-year-old patient is receiving hydrochlorothiazide for congestive cardiac failure. What type of diuretic is hydrochlorothiazide? Explain the type of electrolyte imbalance that can occur with this diuretic.
14. Anna Graaf, a 50-year-old patient, is receiving furosemide as part of her antihypertensive programme. What type of diuretic is furosemide? Explain the type of electrolyte imbalance that can occur with this diuretic.
15. Reece Place, a 65-year-old patient diagnosed with renal calculi, is ordered acetazolamide. Explain how acetazolamide affects this condition.
16. Kim Dong-Jin, a 55-year-old patient, is ordered spironolactone as part of her antihypertensive regimen. What patient education would you offer her?
17. Gaye Edging, a 50-year-old patient, is newly diagnosed with hypertension. She also suffers from insulin-dependent diabetes. What form of diuretic is suitable for treatment of her hypertension?

47 DRUG SUMMARY TABLE: DIURETICS AND OTHER RENAL DRUGS

FAMILY NAME	GENERIC NAME	TRADE NAME(S)
Carbonic anhydrase inhibitors	Acetazolamide	Diamox
Loop diuretics	Bumetanide	Burinex
	+ Amiloride	Burinex A
	Furosemide (furosemide)	Lasix
	+ Amiloride	Frumil
		Aridil
Thiazides and thiazide-like diuretics	Bendroflumethiazide (bendrofluazide)	Aprinox
		Neo-Naclex
	Chlortalidone (chlorthalidone)	Hygroton
	Cyclopenthiazide	Navidrex
	+ Amiloride	Navispare
	Hydrochlorothiazide	
	+ Amiloride (co-amilozide)	Moduretic
		Amil-Co
	Indapamide	Nindaxa
		Natrilix
Osmotic diuretic	Mannitol	
Potassium-sparing diuretics	Amiloride	Amilamont
	Spironolactone	Aldactone
		Spirospare
Antidiuretics	Desmopressin	Nocutil
		DDAVP
		Octim
	Terlipressin	Glypressin
	Vasopressin	Pitressin
Potassium supplements	Potassium chloride	Kay-Cee-L
		Kloref
		Sando-K
		Slow-K

DRUGS USED TO TREAT CARDIAC INSUFFICIENCY

48

CHAPTER FORTY-EIGHT

KEY TERMS

Afterload
Automaticity
Cardiac action potential
Chronotropic effects
Dysrhythmia
Heart failure
Inotropic effects
Membrane ion channels
Preload
Refractory period
Vaughan Williams classification

OBJECTIVES

After completing this chapter, the reader should be able to:

- **briefly outline the pathophysiology of the cardiac conditions of heart failure and dysrhythmias;**
- **identify the major drug groups used in the treatment of these conditions;**
- **state the mechanisms of action of the major drug groups used to treat these conditions;**
- **demonstrate a knowledge of the adverse reactions associated with each drug group and how they derive from the mechanism of action.**

THE ORDERING OF CHAPTERS IN THIS SECTION REFLECTS a common progression in cardiovascular pathophysiology. Atherosclerosis (Chapter 43), hypertension (Chapter 44) and thrombus formation (Chapter 46) have been shown to contribute to the development of myocardial ischaemia (Chapter 45) and infarction. Moreover, myocardial infarction predisposes to dysrhythmias and heart failure.

In this chapter, the pathophysiology and drug treatments associated with heart failure and dysrhythmias are discussed. Both of these conditions are characterised by impairments in heart function. When the ventricles are implicated, a significant decrease in cardiac output would be expected.

HEART FAILURE

The prevalence of heart failure in the UK is around 8.3 per 1000 and is age-dependent. In people aged over 85 years, heart failure affects 125 per 1000 of the UK population. Heart failure is considered a major cause of admission to hospital medical wards. The prognosis for people diagnosed with chronic heart failure is poor, with a 60–70 per cent mortality rate within 5 years of diagnosis. A significant proportion of patients die suddenly. Common causes of heart failure are coronary disease, usually associated with a history of at least one myocardial infarction, hypertension and cardiomyopathy. In the UK, approximately half the cases of heart failure in men are in those with coronary artery disease and about half the cases in women are secondary to hypertension.

Underlying heart failure is an impairment of the pumping ability of the heart. The nature of the impairment is determined largely by the side of the heart involved. When the right side of the heart fails, blood accumulates in the venous circulation, causing organ congestion (liver, gastrointestinal tract, spleen) and peripheral tissue oedema. When the left side fails, blood accumulates in the pulmonary circulation, resulting in pulmonary congestion and fluid in the lungs. The ejection of blood from the left ventricle is impaired, so that cardiac output is diminished greatly, often to levels lower than the venous return to the right atrium. Indeed, a low cardiac output reduces blood pressure and decreases blood flow to all the major organs – the brain, the kidneys and the heart itself. As the blood flow to the kidneys decreases, urine production dwindles, culminating in fluid retention and more peripheral oedema.

The impairment of ventricular pumping ability, or contractility, not only affects cardiac output; it also results in a significant volume of blood remaining in the chamber after contraction. This volume increases the ventricular filling pressure and the ventricular wall stress. This stress is called preload.

Eventually, prolonged impairment of one side of the heart leads to the involvement of both sides, and the manifestations of left- and right-sided failure are combined. The failure of the heart to adequately pump the blood around the body leads to fluid retention and oedema, both systemically and in the lungs. This is termed congestive cardiac failure.

To compensate for the decreased cardiac output, the following measures are activated: The activity of the sympathetic nervous system is elevated and the renin–angiotensin–aldosterone system is activated. The change in activity of the sympathetic nervous system and the subsequent stimulation of the adrenal medulla to release noradrenaline and adrenaline result in increased heart rate and pronounced peripheral vasoconstriction in order to maintain blood pressure. The elevated blood levels of noradrenaline and adrenaline also increase the risk of cardiac dysrhythmia. The renin–angiotensin–aldosterone system is activated to correct the poor perfusion of the kidneys. The retention of salt and water is potentiated by the secretion of aldosterone, leading to further congestion and oedema.

In the long term, these compensatory mechanisms amplify rather than overcome the problem. The marked vasoconstriction increases the workload of the heart. It is now harder to push blood into the smaller-diameter vasculature than before because of increased resistance. The heart also works harder when the heart rate increases. The increase in workload (afterload) means that the myocardium requires more oxygen, but coronary blood flow is depressed due to the decrease in cardiac output. There is also a progressive reduction in the sensitivity of the arterial baroreceptor reflex to changes in blood pressure. This reflex is important in inhibiting sympathetic activation when blood pressure rises. As a consequence, sympathetic nervous system activity remains elevated in patients with heart failure, as do plasma renin levels.

Coupled with the increased ventricular filling pressure caused by poor ventricular emptying and the expansion of the intravascular volume, the ventricular chamber wall is subjected to increased stress. These stresses trigger myocardial remodelling. As a consequence, there is hypertrophy (increase in cell size) of the ventricular myocardium, dilation of the affected chamber (or chambers) and further reduction in contractility. An increased mass of cardiac muscle also places increased demands on oxygen consumption.

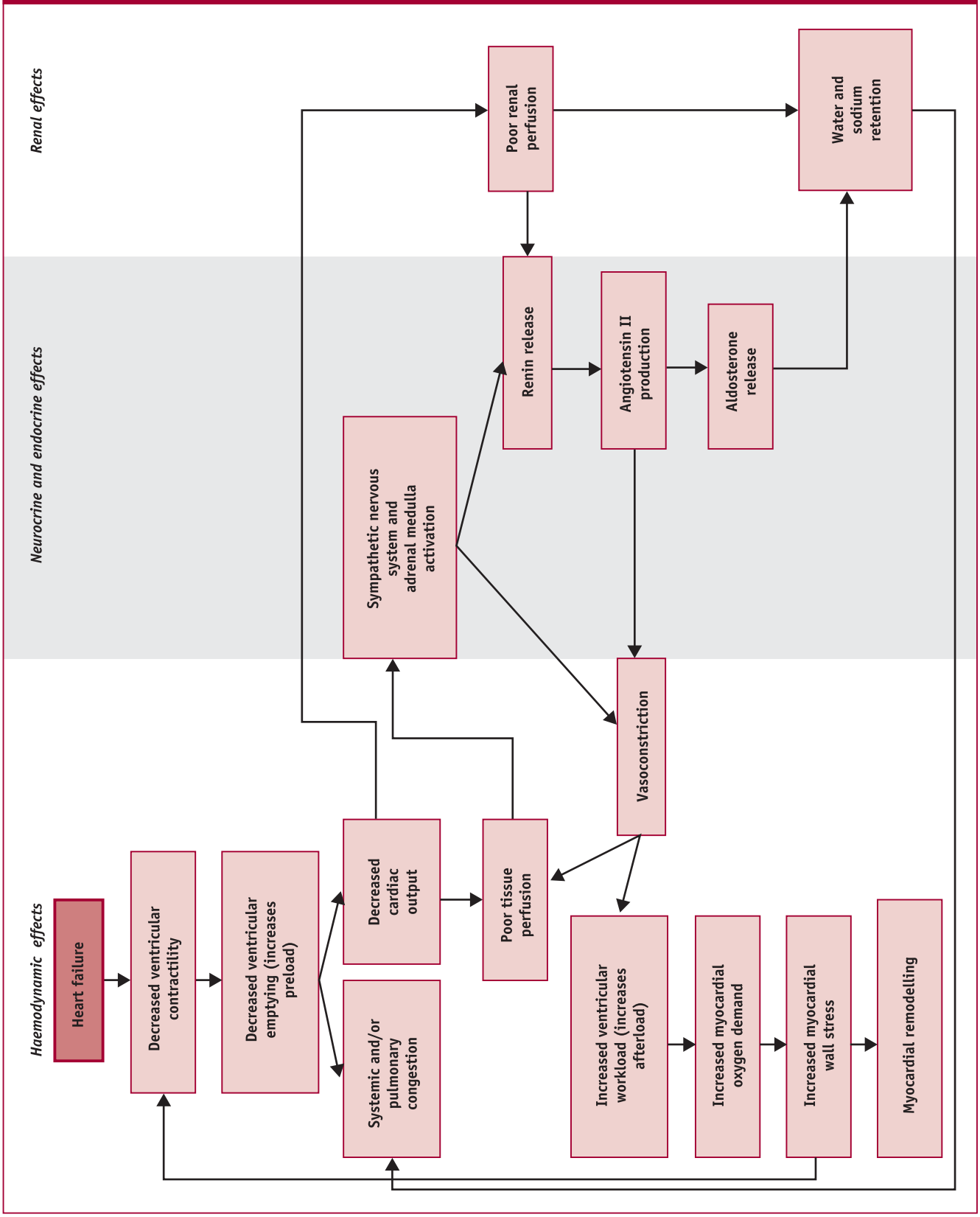
Thus, the compensatory mechanisms that, in the normal heart, act to increase cardiac output actually perpetuate and worsen the heart failure. The pathophysiology of heart failure is summarised in Figure 48.1.

DRUG THERAPIES IN HEART FAILURE

The aims of therapy in heart failure consist of treating the cause (if it can be resolved) and any other precipitating factors, enhancing ventricular function, and improving the person's quality of life and their survival.

The current recommendation is that people with heart failure should be treated using angiotensin-converting enzyme (ACE) inhibitors, diuretics, peripheral vasodilators and, in some cases, drugs that increase cardiac contractility (inotropic agents). There may also be a role for β-adrenergic blockers in the long-term management of this condition. The National Institute for Health and Clinical Excellence (NICE) has produced guidelines for the management of chronic heart failure in adults in primary and secondary care and these can be found on their website at www.nice.org.uk.

FIGURE 48.1 FLOWCHART SHOWING THE PATHOPHYSIOLOGY OF HEART FAILURE



Angiotensin-converting enzyme inhibitors

ACE inhibitors have become a mainstay of treatment in heart failure. This group of drugs has been shown to improve the manifestations of heart failure, reduce the progression of the condition, improve the person's quality of life and boost the survival rates of patients.

■ MECHANISM OF ACTION

These drugs act on the renin–angiotensin system and block the conversion of angiotensin I into the potent vasoconstrictor angiotensin II. The inhibition of angiotensin II leads to both arterial and venous dilation. Arterial dilation reduces afterload, while venous dilation decreases preload.

The angiotensin-mediated secretion of aldosterone is also inhibited. As a consequence, blood pressure drops, the excretion of sodium and water is enhanced and potassium is retained. Cardiac afterload is reduced, and aldosterone-mediated sodium and fluid retention are diminished. One of the major advantages of this group of drugs in heart failure is that they produce their effects without compromising cardiac function by reducing cardiac output or altering heart rate.

◆ COMMON ADVERSE EFFECTS

Common adverse effects include hypotension, an unproductive cough, hyperkalaemia, taste disturbances and progressive renal impairment. If the cough is troublesome, then an angiotensin II antagonist may be used instead of an ACE inhibitor (unlicensed use in heart failure). Angiotensin II antagonists do not inhibit the enzyme ACE, which is also involved in the metabolism of bradykinin. Accumulation of the latter is thought to be responsible for the cough. Angiotensin II inhibitors block the receptor for angiotensin II, thus still preventing its action. Figures 48.2 and 48.3 show the desired and unwanted effects of the ACE inhibitors.

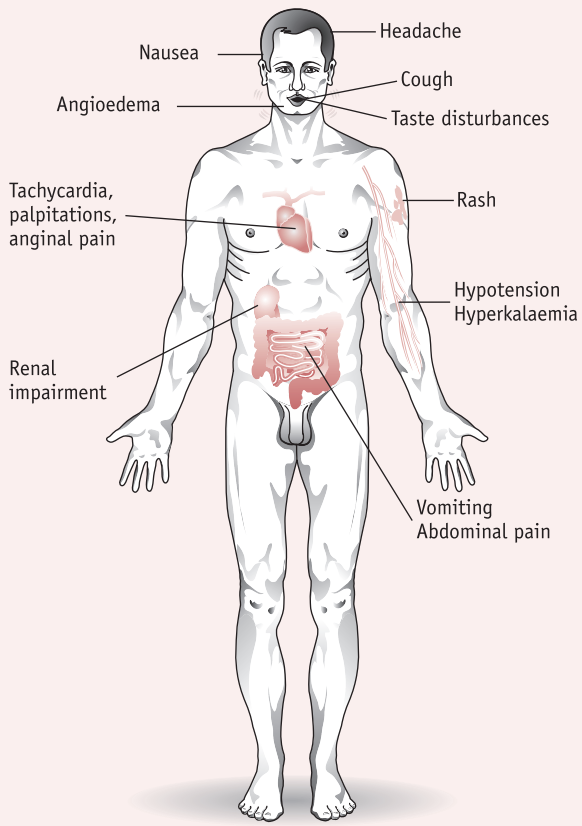
✚ CLINICAL CONSIDERATIONS

The ACE inhibitors can be given in combination with diuretics. A combination of a potassium-sparing diuretic or potassium supplements and an ACE inhibitor is not usually recommended because of the risk of hyperkalaemia. An exception is the use of **spironalactone** (see later).

Electrolyte and renal function should be examined before starting ACE inhibitor therapy and also during the course of treatment. Patients with renal impairment, which in some cases can be triggered by treatment with these drugs, are at increased risk of hyperkalaemia. Lower doses of ACE inhibitors should be administered to patients with renal impairment.

As the first dose of ACE inhibitors may cause severe hypotension, it is advisable to commence treatment with low doses, decrease doses of any diuretic a few days before commencing ACE inhibitor therapy, and avoid ACE inhibitors in patients with decompensated heart failure (e.g. pulmonary oedema).

FIGURE 48.2 EFFECTS OF ANGIOTENSIN-CONVERTING ENZYME INHIBITORS



Diuretics

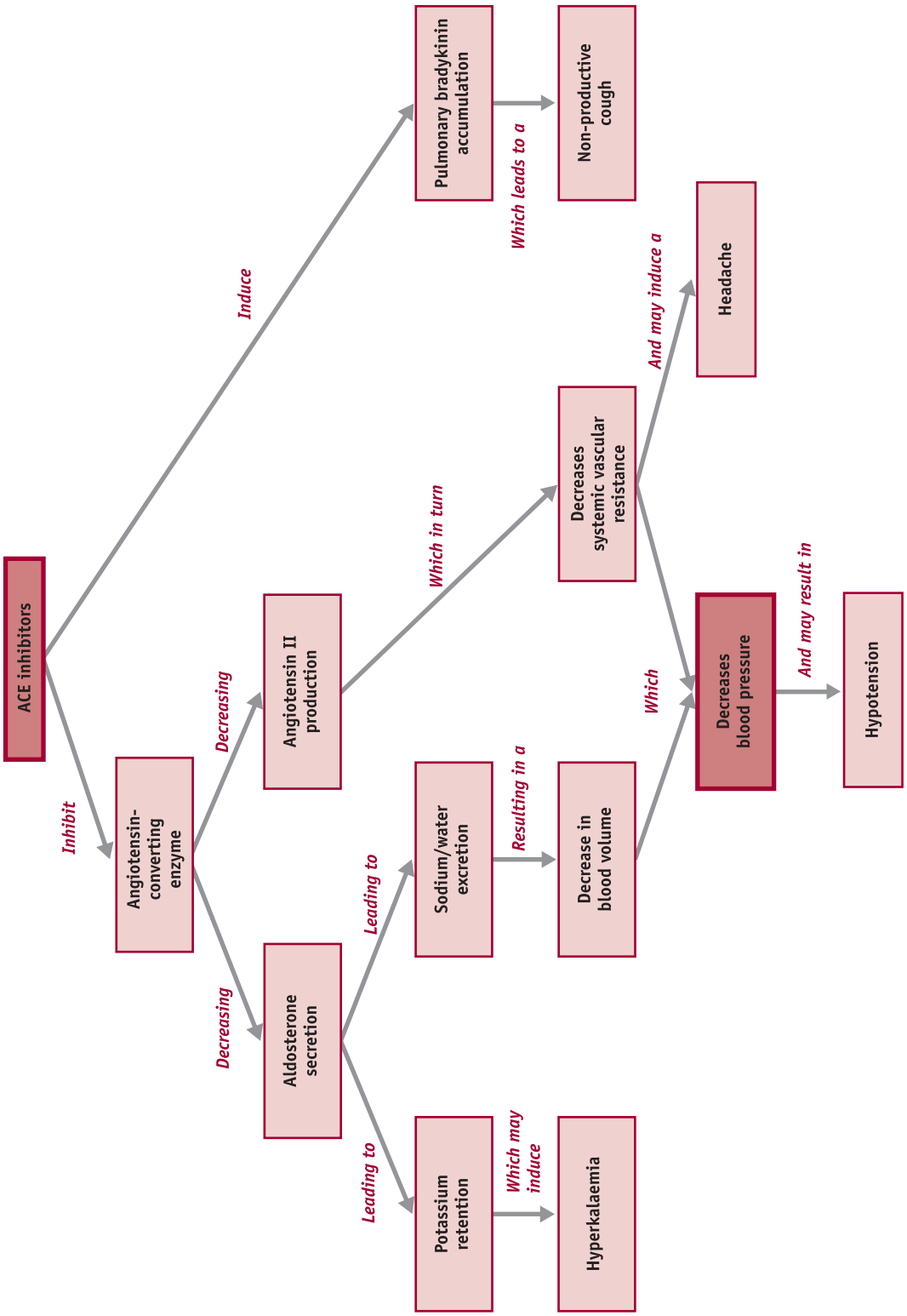
Diuretics are an important part of the management of heart failure. In heart failure, diuretics are used primarily to clear fluid overload and to sustain normal blood volume. Loop diuretics such as **furosemide** are potent but relatively short-acting diuretics used in the management of severe chronic heart failure. They are also useful in the treatment of acute heart failure. The thiazide diuretics are used in mild heart failure and produce a gentle and prolonged effect.

■ MECHANISM OF ACTION

The uses, actions, adverse reactions and issues related to clinical management of diuretics are detailed in Chapter 47. In general, diuretics act to inhibit the reabsorption of ions and water from the nephron to the blood. This leads to increased losses of fluid and electrolytes in urine and a reduction in retained fluid.

FIGURE 48.3 FLOWCHART SHOWING THE EFFECTS OF THE ANGIOTENSIN-CONVERTING ENZYME (ACE) INHIBITORS

Desired therapeutic effect shown in the darker shaded box.



◆ COMMON ADVERSE EFFECTS

Dehydration and electrolyte imbalances are commonly associated with diuretic therapy.

✚ CLINICAL CONSIDERATIONS

Diuretics are not used as monotherapy in chronic heart failure. There is evidence that in promoting a reduction in body fluid levels, they trigger compensatory neuroendocrine responses, such as further elevations in plasma renin levels. These responses are counterproductive in heart failure. Diuretics are now used in combination with ACE inhibitors.

When using diuretics, administer the minimum effective dose and monitor the response clinically and biochemically. Assess the fluid balance and electrolyte levels to prevent volume depletion and electrolyte imbalances. The use of a loop or thiazide diuretic with an ACE inhibitor reduces the incidence of hypokalaemia.

SPIRONOLACTONE

The aldosterone antagonist spironolactone in combination with an ACE inhibitor has proven to be quite beneficial in heart failure. Significant decreases in mortality and hospitalisation have been observed during therapy with spironolactone.

■ MECHANISM OF ACTION

The beneficial effect of spironolactone appears to be unrelated to its diuretic action. There is evidence that aldosterone may contribute to the pathophysiology of heart failure through losses of potassium and magnesium, by reducing the sensitivity of baroreceptors, altering myocardial responsiveness to noradrenaline and having a role in myocardial remodelling. Spironolactone may block some or all of these effects.

◆ COMMON ADVERSE EFFECTS

Hyperkalaemia and gynaecomastia (breast development in men) are common adverse effects of spironolactone.

✚ CLINICAL CONSIDERATIONS

The risk of hyperkalaemia with spironolactone, especially during concurrent use of an ACE inhibitor, necessitates monitoring of blood potassium levels.

Peripheral vasodilators

For people unable to take ACE inhibitors, a combination of the peripheral vasodilators **hydralazine** and **isosorbide dinitrate** (an organic nitrate) has been used. Clinical trials have shown that this combination increases survival in heart failure. The combination must be prescribed only by a specialist in this area.

■ MECHANISM OF ACTION

These drugs are discussed in detail in Chapters 44 and 45. The vasodilation produced by this drug combination decreases cardiac preload and afterload, thus reducing myocardial workload. Isosorbide dinitrate, as a relatively selective venodilator, produces a stronger effect on preload; in contrast, hydralazine produces a greater effect on afterload. In combination, there is synergistic interaction (see Chapter 15), such that there is potentiation of the vasodilator effect. In other words, the effect is more than simply additive.

A change in the force of contraction of the heart is called an inotropic effect. When the force of contraction is increased, this is a positive inotropic effect. There is evidence that hydralazine also has a positive inotropic effect on the heart muscle, increasing cardiac contractility. Hydralazine increases renal blood flow, making it useful for patients with renal impairment who cannot tolerate ACE inhibitors.

◆ COMMON ADVERSE EFFECTS

This drug combination may induce hypotension, flushing, headache and tachycardia.

✚ CLINICAL CONSIDERATIONS

Postural hypotension caused by these agents can be avoided by rising slowly and avoiding sudden changes in position. For patients taking hydralazine, check for signs of a lupus-like syndrome (e.g. sore throat, rash, fever, muscle and joint pain) (see Chapter 44).

Tolerance to nitrates can occur with continuous exposure; therefore, ensure a nitrate-free period of 8–12 hours each day.

OTHER VENODILATORS

In acute heart failure, the venodilating properties of **glyceryl trinitrate** and **morphine** are considered useful in the management of acute pulmonary oedema. The venodilation induced reduces pulmonary hypertension and assists in attentuating any oedema. (The characteristics of these drugs are covered in full in Chapters 45 and 39.) There is some controversy associated with the use of morphine in this context because of its potential to induce respiratory depression in patients with compromised respiratory function. Supporters of this therapy, however, suggest that further benefits flow on through a reduction in anxiety and apprehension as a function of judicial administration of morphine.

Inotropic agents

CARDIAC GLYCOSIDES

Historically, the main drugs used in the treatment of congestive cardiac failure were the cardiac glycosides. Their primacy in the treatment of heart failure has now been displaced by the ACE inhibitors, largely on the basis of

toxicity and clinical studies considering patient morbidity and survival. Today, the cardiac glycosides have been relegated to second-line therapy, used in combination with other agents in selected patients. They are especially useful where heart failure is associated with atrial fibrillation.

A number of plants contain cardiac glycosides. Digoxin is extracted from the leaves of the purple foxglove, *Digitalis purpurea*. The generic term 'digitalis' is often used to represent all cardiac glycosides used in the clinical setting.

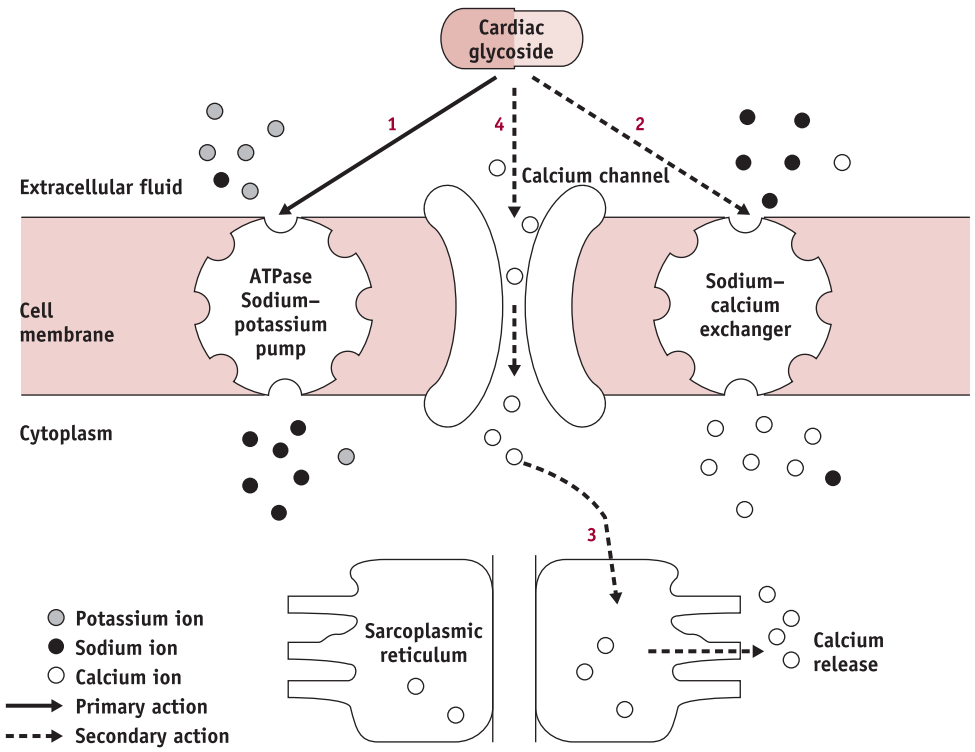
MECHANISM OF ACTION

Cardiac glycosides act by influencing the movement of ions into and out of the myocardial fibres and by altering the activity of the autonomic nervous system. The ions most affected by these drugs are calcium and sodium. The cardiac glycosides inhibit the enzyme associated with the sodium–potassium pump, ATPase. As a result of the increasing intracellular sodium ion concentration, exchange between sodium and calcium across the membrane is impaired, leading to a reduced removal of calcium ion from the cardiac muscle cell. Stores of calcium within the myocardium are released, and the membrane becomes more permeable to this ion during the cardiac action potential. As a result, intracellular calcium levels are elevated. Because calcium is necessary for normal muscle contraction, the elevated calcium levels result in a stronger force of contraction; that is, a positive inotropic effect (see Figure 48.4). A change in the force of contraction of the heart is called an inotropic effect. Since the force of contraction is stronger, this is a positive inotropic effect. Stronger myocardial contraction improves cardiac efficiency, boosting cardiac output.

The change in ion movements coupled with effects on the autonomic nervous system accounts for changes to the function of the heart's conduction system. The cardiac glycosides enhance parasympathetic stimulation of the heart and directly alter the responsiveness of the sinoatrial (SA) node. The outcome in terms of cardiac function is that the rate of impulse generation by the SA node is decreased.

FIGURE 48.4 NEUROPHYSIOLOGICAL ACTIONS OF THE CARDIAC GLYCOSIDES

The cardiac glycosides affect the movement of ions across the myocardial cell membrane and intracellular electrolyte levels (particularly sodium, potassium and calcium). (1) They inhibit the enzyme ATPase, which powers the sodium–potassium pump thereby increasing sodium accumulation within the myocardial cell (this is their principal direct action on heart muscle fibres). (2) The activity of the sodium–calcium exchanges moves out this excess sodium in exchange for calcium, thereby increasing intracellular calcium. (3) The increased intracellular levels of calcium may be stored and released on depolarisation of the cell. (4) They may increase opening of calcium channels during the cardiac action potential, further increasing available intracellular calcium. The net result of these effects is that the force of myocardial contraction is enhanced.



Any change in heart rate is known as a chronotropic effect; a decreased rate is a negative chronotropic effect. Such an effect is desirable because the excessive sympathetic stimulation characterising congestive heart failure causes a rapid irregular pulse. The conduction velocity through the atrioventricular (AV) node and ventricles decreases, as does the number of impulses transmitted through the former. This means that the interval between contraction of the atria and contraction of the ventricles lengthens. An increase in this interval allows more time for the ventricles to fill with blood. There is also experimental evidence that the cardiac glycosides alter arterial baroreceptor responsiveness to reduce sympathetic tone. This could represent a significant contribution to the efficacy of this drug group over and above the inotropic action.

In summary, the therapeutic effects of the cardiac glycosides – positive inotropy and negative chronotropy – are directed towards increasing the efficiency of the heart in order to improve cardiac output. Increased blood flow reduces tissue congestion and, in the kidneys, promotes urine formation. The latter effect alleviates oedema and is enhanced by concomitant diuretic therapy.

◆ COMMON ADVERSE EFFECTS

Just as the therapeutic effects of these drugs are produced by changing the heart's electrical activity, so too are the toxic effects. Through alterations in the activity of excitable myocardial cells, cardiac glycosides can induce many forms of dysrhythmia, including tachycardias, fibrillations, ectopic depolarisations and AV blockade. Moreover, cardiac glycosides stimulate the chemoreceptor trigger zone in the brain, which is linked to the medullary vomiting centre, to produce nausea and vomiting. Anorexia and diarrhoea are consequences of direct gastrointestinal irritation by these drugs. Disorientation, hallucinations and visual disturbances, including altered perception of colour, are central nervous system (CNS) effects reported in some cases of digitalis toxicity.

The effects on the movement of ions are not restricted to sodium and calcium alone – potassium and magnesium are also affected. The most important of these is the interaction with potassium. The cardiac glycosides and potassium compete for binding to the enzyme ATPase. Therefore, high levels of potassium reduce the effects of the glycosides, while low levels of potassium enhance the drug effects (see Figure 48.4). This is the basis of the concern regarding the use of digitalis in patients with hypokalaemia. The enzyme binding of the drug is enhanced greatly; so too are the effects. With such a narrow margin of safety, the toxic potential of the drug may be realised at plasma levels previously regarded as therapeutic.

✚ CLINICAL CONSIDERATIONS

The cardiac glycosides have a relatively narrow margin of safety and are potentially very toxic agents. Because of this, and individual differences in drug pharmacokinetics, it is necessary to assay plasma drug levels soon after treatment. This is to ensure that the drug is within therapeutic blood concentrations in order to minimise toxic reactions while providing the maximum therapeutic benefit.

Before administering the loading dose, obtain baseline observations for heart rate and rhythm, blood pressure, renal function and electrolyte (especially potassium) levels. Before administering a dose, note any decrease or irregularity in the pulse. Digoxin toxicity may occur in susceptible individuals, including older people and patients with electrolyte disturbances, hypothyroidism and hypoxia. The steady state for digoxin is reached after 5 days of therapy if renal function is normal. Blood levels for digoxin are taken immediately before or at least 6 hours after the dose is administered. The therapeutic range for digoxin is 1.0–2.6 nmol/l.

The pharmacokinetic properties of the cardiac glycosides have a significant effect on their administration. The half-life of digoxin is 40 hours. According to the laws of pharmacokinetics (see Chapter 14), it takes approximately five half-lives to reach a plateau in the plasma. With constant dosing of digoxin, this would take more than 1 week of therapy. If the therapeutic effects are required more quickly, then a dosing regimen of a large loading dose followed by smaller maintenance doses can be implemented. The pharmacokinetic profile of the cardiac glycosides also has implications for toxicity. The long half-life means that when toxic reactions occur, they persist for a long time. Therefore, supportive measures may have to be maintained for some time before the crisis has passed. The process of starting therapy and stabilising the patient at safe therapeutic levels is called digitisation.

DOPAMINE AGONISTS

The effects of **dopamine** and its derivative **dobutamine** are outlined in Chapter 26. Intravenous infusions of dobutamine can be used in the management of chronic cardiac failure.

■ MECHANISM OF ACTION

Dobutamine produces a positive inotropic effect by stimulating β_1 receptors on the myocardium, inducing a rise in cardiac output. Dobutamine is a direct-acting agent that induces very little change in heart rate unless it is administered at high doses. It also blocks noradrenaline reuptake, producing a prolonged stimulation of the myocardial receptor. A positive chronotropic effect may be therapeutically counterproductive as it increases the work, and therefore the oxygen demand, of an ailing heart. Dobutamine has β_2 agonist action and a mix of α_1 agonist and antagonist activity. It tends to produce a mild vasodilatory effect, which may result in a reduction in systemic vascular resistance. Interestingly, unlike dopamine, dobutamine has no dopamine receptor activity.

◆ COMMON ADVERSE EFFECTS

Common adverse reactions include an increase in heart rate and ventricular ectopic beats. Tolerance may develop during prolonged treatment.

✚ CLINICAL CONSIDERATIONS

When dobutamine is used in combination with a beta-blocker, its α agonist effects dominate; when used with an alpha-blocker, its β_2 agonist effects predominate.

INOTROPIC VASODILATORS

Milrinone is a phosphodiesterase inhibitor with both inotropic and vasodilator activity. It is used in short-term intravenous therapy in cases of severe congestive heart failure unresponsive to other therapies. For example, it may be used when tolerance to dobutamine therapy develops.

■ MECHANISM OF ACTION

Milrinone is a relatively selective phosphodiesterase inhibitor in vascular and cardiac muscle. Phosphodiesterases are a group of isoenzymes that degrade the intracellular messenger cyclic adenosine monophosphate (cAMP). The behaviour of many cells is regulated by cAMP, particularly in muscle and nervous tissue. cAMP acts as a second messenger in adrenergic receptor activation (see Chapter 26). Indeed, there are subtle chemical differences in the conformation of the phosphodiesterases in different cell types that afford therapeutic selectivity. As a consequence of phosphodiesterase inhibition, intracellular cAMP levels remain elevated. This particular action is not novel in clinical pharmacology, since the methylxanthine bronchodilators, which are well established in asthma management (see Chapter 51), are also phosphodiesterase inhibitors.

Milrinone selectively increases cAMP levels in vascular and cardiac muscle. This action results in arterial vasodilation and an increase in the force of myocardial contraction. The vasodilatory effect leads to improvements in peripheral tissue perfusion and a reduction in vascular resistance. The inotropic effect leads to an increase in cardiac output, which is desirable in patients with congestive heart failure.

◆ COMMON ADVERSE EFFECTS

Common adverse effects include dysrhythmias, hypotension, headache and chest pain.

✚ CLINICAL CONSIDERATIONS

During milrinone therapy, it is important to monitor cardiac rate and rhythm, arterial blood pressure, arterial blood gases, pulmonary artery pressure and urine output, and to titrate responses according to the response achieved with these parameters. Milrinone is not mixed with furosemide solution, as precipitation occurs. Similarly, milrinone is not compatible with solutions containing sodium bicarbonate.

Beta-blockers

It may seem strange that a group of drugs with negative inotropic properties can be therapeutically beneficial to someone with a major cardiac impairment. In long-term clinical studies, however, where therapy starts with low doses of beta-blockers and is increased gradually, researchers have found improvements in ventricle function, attenuation of the progression of the disease and a reduction in mortality.

It has been suggested that the beneficial effects of these drugs in heart failure may be related to a prolonged blockade of the harmful stimulatory effects of noradrenaline and adrenaline on the heart muscle, an antidysrhythmic action on the ventricles, and an antiremodelling action on the myocardium.

The beta-blockers used in the management of heart failure are **carvedilol**, **metoprolol** and **bisoprolol**.

BISOPROLOL AND METOPROLOL

Clinical trials have found that bisoprolol therapy reduces the rate of sudden death and pump failure in people with moderate to severe heart failure. It also improves the functional status of patients and reduces the number of hospitalisations required.

Metoprolol has been trialled in people with moderate to severe heart failure and is found to reduce the rate of sudden death and death from worsening heart failure.

■ MECHANISM OF ACTION

Bisoprolol is a relatively selective beta-1-blocker with negligible intrinsic sympathetic-stimulating or membrane-stabilising activity. Metoprolol is also selective for β_1 receptors, but not to the degree of bisoprolol, and retains some intrinsic sympathetic activity.

◆ COMMON ADVERSE EFFECTS

Common adverse reactions of these drugs include hypotension, bradycardia, headache, dizziness and gastrointestinal upset. Shortness of breath may be observed during metoprolol treatment.

✚ CLINICAL CONSIDERATIONS

Use beta-blockers cautiously in patients with diabetes and respiratory or hepatic disease and in older people. Monitor blood glucose levels closely in patients with diabetes because these agents mask signs of hypoglycaemia. These agents should not be stopped suddenly but should be reduced over a period of 1–2 weeks.

NICE recommends initiation of beta-blockers in patients with left systolic dysfunction after ACE inhibitor and diuretic therapy. Beta-blockade should be introduced in a ‘start low, go slow’ manner, with careful monitoring of heart rate, blood pressure and clinical status.

CARVEDILOL

Carvedilol is a novel beta-blocker approved for use in mild to moderate heart failure refractory to the standard therapies mentioned above.

■ MECHANISM OF ACTION

Carvedilol is a non-selective beta-blocker with α_1 antagonist activity. Blockade of the β receptors suppresses the renin–angiotensin–aldosterone system, leading to reductions in systemic vascular resistance (SVR) and aldosterone-mediated sodium and fluid retention. The α_1 antagonism induces direct vasodilation, which reduces cardiac preload and afterload. Further to this, the beta-blocking effect counteracts the reflex tachycardia triggered by the vasodilating response.

The literature on carvedilol suggests that other therapeutic benefits may arise from its antioxidant properties and its ability to inhibit neutrophil adhesion and the proliferation of smooth muscle.

◆ COMMON ADVERSE EFFECTS

Common adverse reactions are associated with adrenergic receptor blockade and include orthostatic hypotension, bradycardia, dizziness and syncope. Patients need to be monitored for any signs that their heart failure is worsening.

Figure 48.5 shows both the beneficial and adverse effects of carvedilol. Carvedilol is contraindicated in severe heart failure, bronchial asthma, liver failure and in second- or third-degree AV block. Interactions have been noted with digoxin, calcium channel antagonists and **insulin**.

✚ CLINICAL CONSIDERATIONS

Benefits from carvedilol therapy may take around 4 months to become apparent, and so compliance with treatment during this time is essential.

OPTIMISING HEART-FAILURE THERAPY

The NICE guidelines recommend that therapy for people with established heart failure should be commencement of treatment with an ACE inhibitor and to add a diuretic later. Beta-blockers should be initiated in patients with left ventricular systolic dysfunction, regardless of whether symptoms persist. The cardiac glycoside digoxin should be added after the ACE inhibitor, diuretic and beta-blocker if there is still worsening or severe heart failure. Digoxin is prescribed if atrial fibrillation is present with any degree of heart failure.

Figure 48.6 shows where the drugs used in heart failure disrupt the pathophysiological processes involved in this condition.

DYSRHYTHMIA

A dysrhythmia is an abnormality in the rhythm of the heart associated with impairment of the conduction system. Dysrhythmia is a more accurate term than arrhythmia, because ‘arrhythmia’ implies an absence of rhythm, as in cardiac arrest; however, the use of the term ‘arrhythmia’ to define all abnormal rhythms has crept into common medical language. The impairment in cardiac rhythm may manifest as an altered rate of impulse generation affecting only the atria (atrial or supraventricular dysrhythmia), only the ventricles (ventricular dysrhythmia) or the whole heart (originating in the sinoatrial [SA] node and known as sinus dysrhythmia). Faster rates of impulse generation are classified by degree, progressing from tachycardias (in an adult, between 100 and 150 beats/minute) to flutters (150–350 beats/minute), to fibrillations (more than 350 beats/minute). A slower rate is known as bradycardia (in a sedentary adult, less than 60 beats/minute).

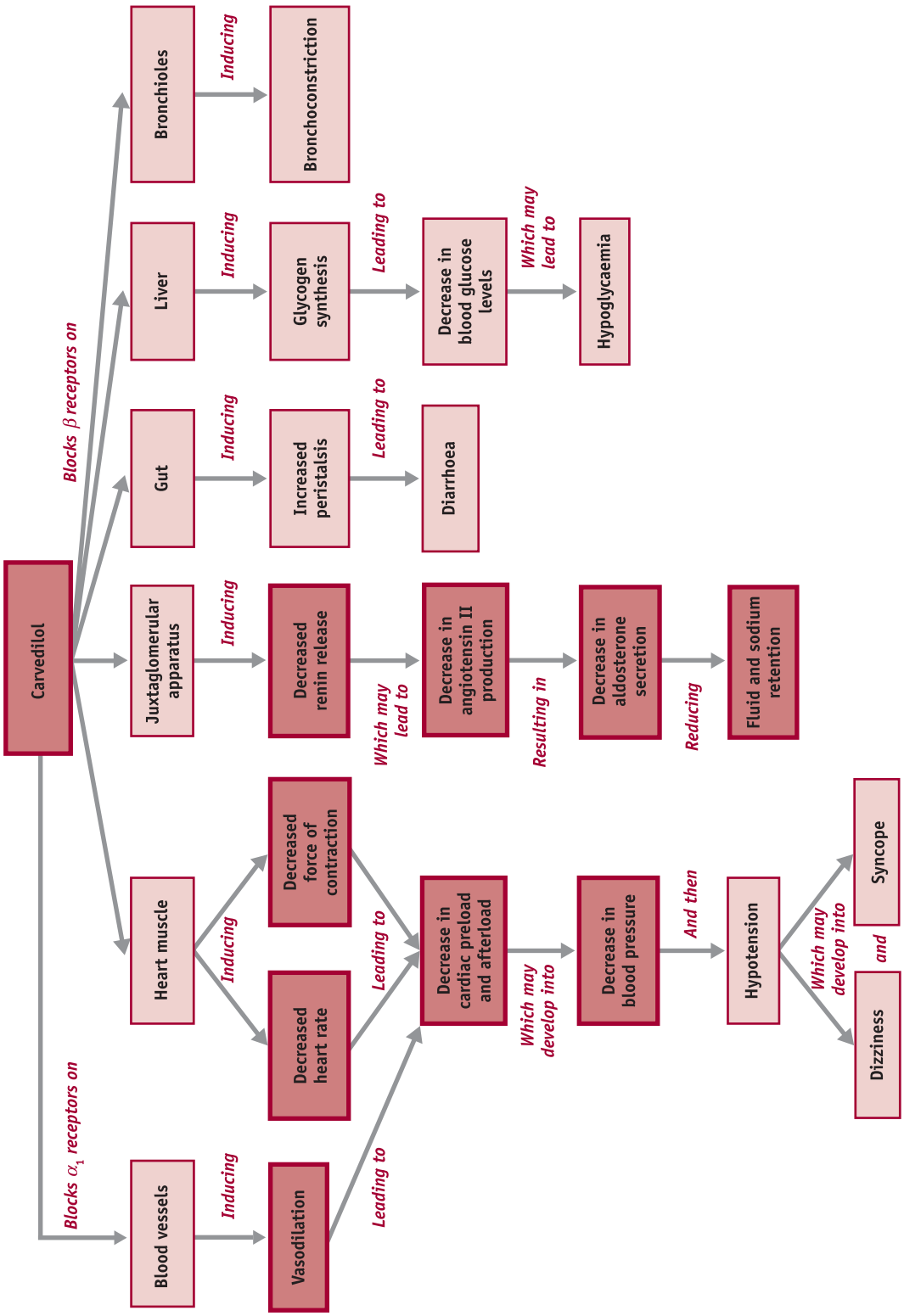
Cardiac muscle physiology

Impulse generation is an electrical event in all excitable tissues. In cardiac muscle, it principally involves the movement of sodium, potassium and calcium ions across the cell membrane. The ions move through specific channels in the cell membrane. A variety of stimuli, such as chemicals and changes in voltage, can open membrane channels. For the purposes of this discussion, we concentrate on voltage-gated channels (see Figures 48.7 and 48.8). These channels open and close in response to changes in membrane potential. It has been proposed that the sodium and calcium channels have two gates – an activation gate towards the outer margin of the channel and an inner inactivation gate. The potassium channels have only one gate (see Figure 48.7). It is not unreasonable to suggest that channels with two gates allow finer control of ion movements across the membrane than channels with only one gate. Indeed, you will see that the movements of sodium and calcium ions are highly regulated in order to achieve the desired electrical changes that characterise the action potential.

In the resting state, the activation gates of the sodium and calcium channels are closed, but the inactivation gate is open (see Figure 48.8a). At this time, the membrane is relatively permeable to potassium. In phase 0 of the action potential (rapid depolarisation), the sodium activation gate opens briefly (see Figure 48.8b), but within milliseconds the inactivation gate closes (see Figure 48.8c). These changes are sufficient for the permeability of the membrane to sodium locally to increase 100-fold. Sodium ions rush inwards and the membrane depolarises (see Figure 48.9). During this time, the membrane is relatively impermeable to potassium ions. As soon as the sodium influx commences, the sodium–potassium pump is activated

FIGURE 48.5 FLOWCHART SHOWING THE EFFECTS OF THE BETA-BLOCKER CARVEDILOL

Desired therapeutic effects shown in the darker shaded boxes.



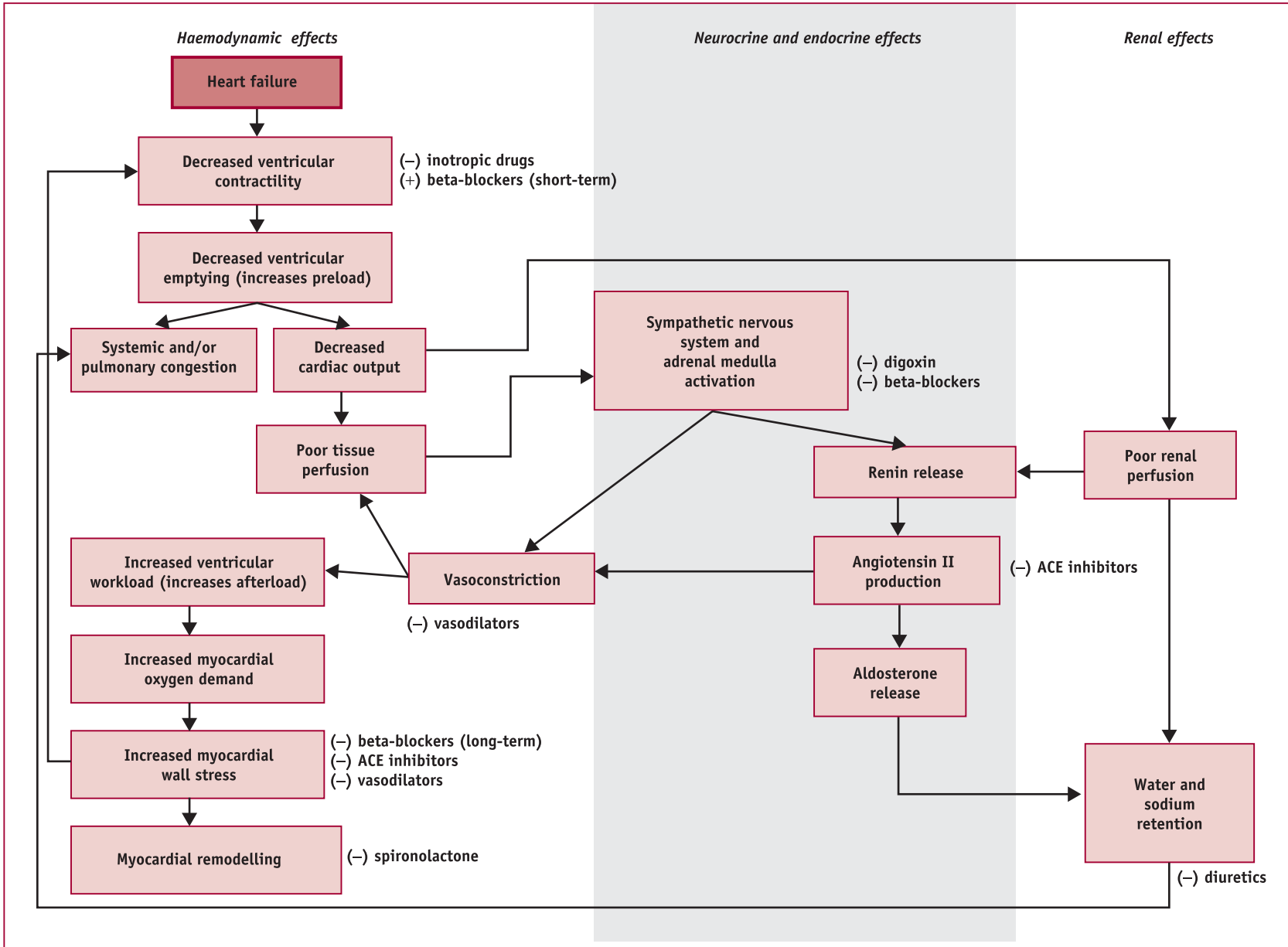
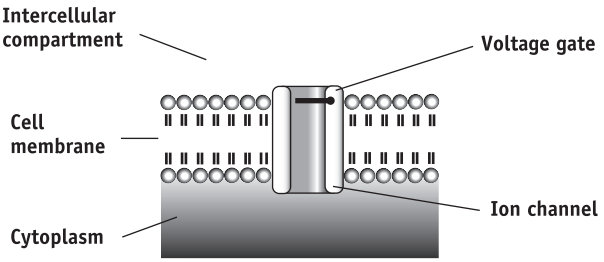


FIGURE 48.6 FLOWCHART SHOWING THE EFFECTS OF DRUGS ON THE PATHOPHYSIOLOGICAL PROCESS OF HEART FAILURE

ACE, angiotensin-converting enzyme.

FIGURE 48.7 VOLTAGE-GATED MEMBRANE CHANNELS WITH ONE GATE

This figure shows a section of nerve cell membrane with a typical voltage-gated ion channel, which opens and closes in response to changes in membrane potential. The figure shows a channel with only one gate associated with it. It represents a potassium channel.



to return the sodium to the extracellular fluid. When the sodium channels close and the influx of this ion ceases, there is a slight negative change in the membrane potential. This drop represents phase 1.

The calcium channels open in response to a higher membrane potential compared with the sodium channels. At this time, calcium ions move into the cytoplasm, thus maintaining depolarisation at around 0 mV. As a result of the calcium influx, the contraction of cardiac muscle fibres is sustained for about 200 times longer than for skeletal muscle fibres. This is known as phase 2, or the plateau phase.

During phase 2, the membrane permeability to potassium increases. Before the calcium channels close completely, the potassium channels are opening to allow potassium ions to diffuse out into the extracellular fluid. This represents phase 3, or the repolarisation phase. The efflux of positively charged potassium ions restores the membrane potential to its resting state of around −80 mV. During this phase, the inactivation gates of the sodium channels reopen in preparation for the next impulse. Once the action potential starts, the successive impulse is normally blocked until a point shortly after repolarisation is complete. This interval is known as the refractory period.

Cardiac muscle is the only type of muscle that has the ability to generate its own impulses without nervous stimulation. This property is known as automaticity and, in particular, affects the excitability of the following heart regions: the SA and AV nodes, Purkinje fibres and ventricular muscle. Following the repolarisation phase in these regions, the membrane begins to depolarise slowly, gradually reaching the threshold for fast depolarisation (−70 to −50 mV) and triggering a new action potential. This upward slope is known as phase 4. In nodal tissue depolarisation appears to be calcium-dependent, whereas in other regions of the heart it is sodium-dependent. Furthermore, the shape of the action potential varies across different regions of the heart. Figure 48.9 shows the form of the action potential in ventricular muscle; the inset shows the form of the action potential in the AV node. As you can see, it has no phase 1 or 2.

Pathophysiology of dysrhythmia

The pathophysiological mechanisms implicated in dysrhythmia include alterations in automaticity, conduction and refractoriness. These alterations can be induced by conditions such as myocardial hypoxia, ischaemia, inflammation and scarring and by electrolyte imbalances.

The dysrhythmias that respond best to drug therapy are the rapid rhythms, the tachydysrhythmias. In these

FIGURE 48.8 VOLTAGE-GATED MEMBRANE CHANNELS WITH TWO GATES

These figures show a channel with two gates: an activation gate and an inactivation gate. These figures represent either a sodium or calcium channel. (a) represents the resting state, where the activation gate is closed and the inactivation gate open. (b) shows both gates open, as they would be during depolarisation. Ions can move through the channel in accordance with their respective concentration gradients. In (c), the inactivation gate is closed but the activation gate is open. After repolarisation is complete, the gates return to their original configuration (a), ready to respond to the next stimulus.

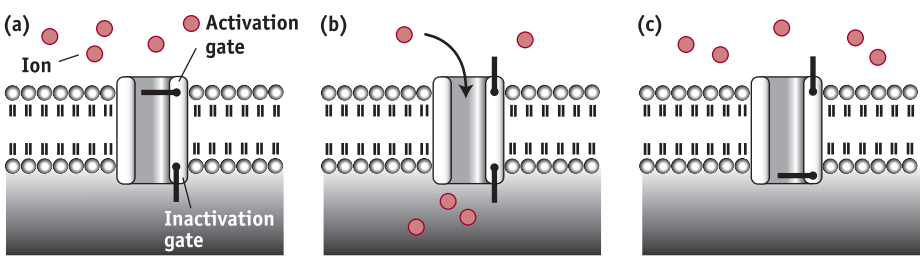
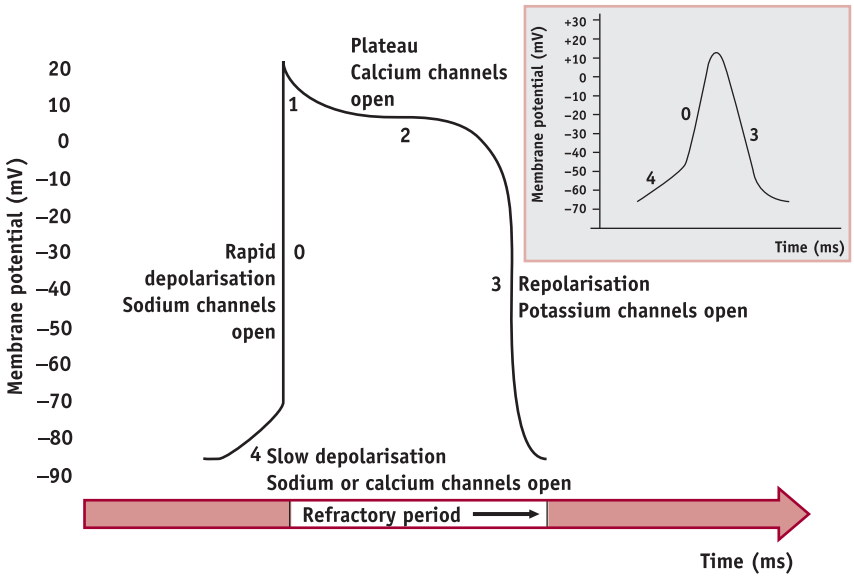


FIGURE 48.9 GENERALISED MYOCARDIAL ACTION POTENTIAL

The change in membrane potential of myocardial cells as an action potential passes over the tissue is represented here. When the membrane potential reaches its threshold for an action potential (around −70 mV), sodium channels open and sodium ions rush inwards. This triggers fast depolaristaion or phase 0. When the sodium channels close, there is a slight drop in membrane potential; this is called phase 1. Calcium channels then open and calcium ions move inwards, maintaining a steady depolarisation called the plateau, or phase 2. Potassium channels then open, causing an efflux of potassium into the intercellular fluid. During this stage, called repolarisation or phase 3, the inside of the membrane becomes negative, eventually re-establishing the resting membrane potential. In pacemaker cells, there is a slow influx of either sodium or calcium ions, which moves the membrane potential towards the threshold for the next action potential. This is called slow depolarisation, or phase 4. From phase 0 until midway through phase 3, the membrane remains unresponsive to stimuli. This is known as the refractory period.

The inset shows the form of the action potential in the atrioventricular (AV) node.



dysrhythmias, it is common for automaticity to be enhanced or refractoriness shortened. The drug therapies discussed below can correct these aberrations.

Other dysrhythmias involve impaired impulse transmission or the spontaneous generation of an impulse within non-nodal myocardial tissue. An example of the former is heart block, where transmission through the AV node is slowed or blocked. An example of the latter is an ectopic beat arising spontaneously within the non-nodular ventricular wall, such as a premature ventricular contraction, which affects the regularity of the heart beat.

This information sets the scene for an understanding of how the drugs used in the treatment of dysrhythmia act.

ANTIDYSRHYTHMIC AGENTS

In general terms, antidysrhythmic agents (or antiarrhythmic agents) act by impeding the movement of ions across the membrane of myocardial cells. This affects the characteristics of the cardiac action potential. Antidysrhythmic agents are best suited to the treatment of ectopic beats and increases in heart rate because they act to suppress and stabilise the excitable myocardial tissue. The means the various drug categories used to achieve this work by suppressing automaticity, by depressing the rate of depolarisation, by slowing impulse conduction through the tissue, by prolonging the action potential and by increasing the refractory period. Electrophysiologically, these effects can be achieved by blocking sodium, calcium and/or potassium channels associated with the myocardium. The net result is that the number of action potentials, and consequently the number of myocardial contractions in a given time interval, is reduced.

These drugs are not suitable for treating all forms of dysrhythmia and are actually contraindicated in some instances, such as heart block, where the transmission of impulses is impeded or totally blocked.

According to the accepted grouping proposed by Vaughan Williams, there are four classes (I–IV) of antidysrhythmic agent. This is not a perfect system, however, and the actions

TABLE 48.1 CLASSES OF ANTIDYSRHYTHMIC AGENTS AND THEIR APPLICATIONS

Drug	Class	Atrial dysrhythmias	Supraventricular dysrhythmias	Ventricular dysrhythmias	Trade name(s)
Disopyramide	IA		✔	✔	Rhythmodan
Procainamide	IA	✔		✔	Pronestyl
Quinidine	IA	✔	✔	✔	Kinidin Durules
Lidocaine	IB			✔	
Mexiletine	IB			✔	Mexitil
Phenytoin sodium	IB			✔	
Flecainide	IC		✔	✔	Tambocor
Propafenone	IC		✔	✔	Arythmol
Acebutolol	II	✔		✔	Sectral
Atenolol	II				Tenormin
Esmolol	II	✔	✔		Brevibloc
Metoprolol	II	✔	✔	✔	Betaloc Lopresor
Oxprenolol	II	✔	✔	✔	Trasicor
Pindolol	II	✔	✔	✔	Viskaldix
Propranolol	II	✔		✔	Inderal
Amiodarone	III	✔	✔	✔	Cordarone X
Sotalol	III		✔	✔	Beta-Cardone Sotacor
Verapamil	IV	✔	✔	✔	Cordilox Securon
Adenosine	N/A		✔		Adenocor
Digoxin	N/A	✔	✔		Lanoxin

of some antidysrhythmic drugs (e.g. **sotalol**, **amiodarone**) run across classes while those of others (e.g. **adenosine**, digoxin) do not fit into any of the classes. Today, many clinicians believe it is more useful to group these drugs according to the dysrhythmias they control. Bearing this in mind, the class approach is still a useful way of grouping these agents. Antidysrhythmic agents and their applications are listed in Table 48.1.

Class I antidysrhythmics

■ MECHANISM OF ACTION

Class I agents have local anaesthetic properties and act to stabilise excitable membranes. They inhibit the movement of sodium into the cell associated with depolarisation. The drugs in this class have high affinity for blocking sodium channels while they are in use. In electrophysiological terms, they have a higher affinity for channels in an activated or inactivated state (i.e. during depolarisation) and a lower affinity for channels in a resting state. This action makes them relatively selective to dysrhythmogenic cells rather than normal cardiac cells. They affect phase 4 of the action potential, decreasing automaticity. For some of the class I antidysrhythmics, phase 0 is affected, reducing the rate of depolarisation. They can be subdivided further according to whether they increase, decrease or have no effect on the duration of the action potential; they are then known as class IA, IB and IC agents, respectively.

CLASS IA AGENTS

Quinidine, **procainamide** and **disopyramide** are class IA agents used for atrial and ventricular dysrhythmias.

■ MECHANISM OF ACTION

Class IA agents primarily slow the rate of depolarisation (phase 0) and, in addition, prolong the duration of repolarisation (phase 3). In effect, they increase the duration of the action potential. In addition to their blockade of sodium channels, procainamide and quinidine also block potassium channels. The latter effect accounts for their action on phase 3.

◆ COMMON ADVERSE EFFECTS

All have a degree of antimuscarinic activity (greatest for disopyramide, lowest for procainamide), which can counteract the cardiac effects at lower doses. This activity may result in blurred vision, dry mouth and urinary retention. These

drugs depress vascular smooth muscle, which may result in a hypotensive state, especially if administered intravenously.

CLASS IB AGENTS

Lidocaine (lignocaine) is a class IB agent with little atrial activity. Therefore, its clinical use is limited to dysrhythmias of ventricular origin, usually associated with acute myocardial infarction or cardiac arrest. Interestingly, the antiseizure drug **phenytoin** is regarded as a class IB agent, but its use as an antidysrhythmic has been largely superseded.

■ MECHANISM OF ACTION

Lidocaine is considered quite specific to abnormal dysrhythmogenic cells rather than normal cardiac muscle fibres. In ischaemic cells, it affects phase 0, decreasing the rate of depolarisation.

◆ COMMON ADVERSE EFFECTS

Common adverse effects involve the central nervous system (CNS). At low doses, CNS depression (drowsiness, numbness) is observed; at higher doses, CNS stimulation (nervousness, tremor, convulsions) occurs.

✚ CLINICAL CONSIDERATIONS

Lidocaine is a relatively short-acting agent, with a half-life of 1 hour, and it must be administered parenterally, as it is subject to significant hepatic first-pass effects (see Chapter 14).

CLASS IC AGENTS

Flecainide and **propafenone** are class IC agents. They are used to treat supraventricular and ventricular dysrhythmias.

■ MECHANISM OF ACTION

Like lidocaine, flecainide affects phase 0, decreasing the rate of depolarisation, but it has little effect on phase 4. Propafenone's action is similar to that of quinidine; it also possesses some weak beta-blocking activity.

◆ COMMON ADVERSE EFFECTS

Dizziness, visual disturbances, nausea and headache are common adverse effects of flecainide. Of concern is that this drug can induce severe, life-threatening ventricular dysrhythmias in a significant proportion of patients. Common adverse reactions of propafenone include constipation and a metallic taste.

Class II antidysrhythmics

Class II agents are β-adrenergic antagonists, known otherwise as beta-blockers.

■ MECHANISM OF ACTION

Cardiac acceleration is mediated through stimulation of β_1 receptors on the surface of the myocardium. Blockade of these receptors leads to a decrease in responsiveness of the SA and AV nodes and a decrease in the speed of impulse conduction from atria to ventricles. The effective refractory period of these heart regions is increased. Pacemaker cells show depressed automaticity (phase 4) during drug therapy. A further action of some beta-blockers in this context is to stabilise the excitable membrane of the cardiac muscle fibre. Beta-blockers such as esmolol, however, have no intrinsic membrane-stabilising effect.

◆ COMMON ADVERSE EFFECTS

Common adverse reactions of beta-blockers are discussed in Chapter 26; they include bradycardia, hypotension and bronchospasm.

Class III antidysrhythmics

Amiodarone and **sotalol** belong in this class. Sotalol is used mainly in the treatment and prophylaxis of ventricular and supraventricular dysrhythmias. Amiodarone is effective against a variety of tachydysrhythmias.

■ MECHANISM OF ACTION

Class III agents act to prolong the duration of both the action potential and the refractory period. They achieve this action primarily by prolonging phase 3 of the action potential. They induce this effect to a much greater degree than do the class IA agents. It is thought that blockade of potassium channels underlies this effect. Amiodarone also blocks inactivated sodium channels. In addition to its effects on phase 3, sotalol has beta-blocking activity.

◆ COMMON ADVERSE EFFECTS

Sotalol's adverse effects are related to β-receptor blockade. Therapy with amiodarone requires close medical supervision because of the risk of pulmonary and CNS toxicity and the deposition of drug crystals into the eye and skin.

Class IV antidysrhythmics

Class IV agents are calcium channel blockers. **Verapamil** is used as an antidysrhythmic. The selectivity of **nifedipine** for vascular smooth muscle precludes its use as an antidysrhythmic agent.

■ MECHANISM OF ACTION

The main effect of these drugs is suppression of the activity of the SA and AV nodes. As a result, the rate of impulse generation is reduced and conduction from the atria to the ventricles is slowed. The latter effect is due to relatively specific action on the AV node. Phase 4 depolarisation of the AV node, dependent on calcium influx, is depressed by these drugs. These agents also increase the refractory period of the heart.

◆ COMMON ADVERSE EFFECTS

Adverse effects of these drugs include headache, flushing, tiredness, hypotension, peripheral oedema and palpitations.

Miscellaneous antidysrhythmics

ADENOSINE

Adenosine is an antidysrhythmic drug whose action is not described adequately by the classification system above.

■ MECHANISM OF ACTION

Adenosine activates specific adenosine receptors on the myocardium. It is thought that activation of this receptor enhances potassium efflux, causing hyperpolarisation of the membrane; it may also impede calcium influx. These effects are relatively specific to the AV node and result in a transient total AV conduction block. Adenosine is used for terminating paroxysmal supraventricular tachycardia (SVT) and as a diagnostic agent in identifying atrial dysrhythmias and wide complex tachycardias (WCT). If the dysrhythmia terminates after adenosine administration, then it is an SVT; if the dysrhythmia does not terminate, then it is atrial in origin or a WCT. In the latter instances, adenosine does no apparent harm to the patient.

◆ COMMON ADVERSE EFFECTS

Common adverse effects of adenosine include facial flushing, dyspnoea and chest tightening.

✚ CLINICAL CONSIDERATIONS

Adenosine is cleared from the body rapidly and efficiently after intravenous injection. It can be either taken up rapidly into cells or broken down by a degradative enzyme abundant within the vasculature. Its half-life is less than 10 seconds. As the active drug is short-lived within the body, it is generally tolerated well.

DIGITALIS

The cardiac glycoside digoxin can be useful in the management of atrial fibrillation, modulating the response of the ventricles to this state, and in the termination of re-entry involving the AV node.

■ MECHANISM OF ACTION

The cardiac glycosides trigger increased parasympathetic innervation of the heart. Electrophysiologically, calcium channels in the AV node are blocked and potassium channels in the atria are opened. In effect, the atria become hyperpolarised and impulse conduction through the AV node is impaired.

◆ COMMON ADVERSE EFFECTS

Nausea, altered colour perception and dysrhythmia are common adverse reactions. Of particular concern is that the dysrhythmic potential of these drugs is increased in hypoxia and in a variety of electrolyte imbalances (particularly hypokalaemia).

GENERAL CLINICAL CONSIDERATIONS OF ANTIDYSRHYTHMIC AGENTS

As many of the antidysrhythmic agents can provoke dysrhythmias, there is an increased reluctance to use these agents in non-urgent situations, such as atrial premature contractions and ventricular ectopic beats.

If possible, it is important to remove or treat the cause of the dysrhythmia. Possible causes may include myocardial infarction, electrolyte disturbance, thyroid disease, pneumonia and use of prodysrhythmic drugs, e.g. antidysrhythmics such as disopyramide, flecainide, quinidine, procainamide, sotalol and amiodarone; **fexofenadine**; tricyclic and tetracyclic antidepressants; anti-infective agents such as **clarithromycin** and **erythromycin**; **mefloquine** and **pentamidine**; and antipsychotic agents such as phenothiazines, **droperidol**, **haloperidol** and **pimozide**.

During antidysrhythmic therapy, haemodynamic and biochemical parameters, such as cardiac rate and rhythm, blood pressure, respiratory rate and rhythm, urine output, conscious state and electrolyte levels, are monitored regularly. If dizziness, loss of consciousness or hypotension occurs, this is suggestive of a serious dysrhythmia.

CLINICAL MANAGEMENT

For the clinical management of patients on angiotensin-converting enzyme (ACE) inhibitors, beta-blockers, diuretics and peripheral vasodilators, see Chapters 44, 45 and 47.

Cardiac glycosides

Assessment

- Assess baseline vital signs and compare with subsequent observations. Compare apical and radial pulses. A deficit in the radial pulse can indicate irregularity in the heart rhythm. Report a pulse rate that has reduced by more than 25–30 beats/minute below the baseline value or is below 60 beats/minute.
- Assess baseline serum electrolyte levels.
- Assess the patient's body weight.
- Assess the patient for coronary occlusion, as cardiac glycosides are usually contraindicated in this condition.
- Use cardiac glycosides with caution in patients with renal impairment and potassium disturbances.

Planning

- The patient's condition of congestive cardiac failure, coronary artery disease or cardiogenic shock will improve.
- The patient will not experience the adverse effects associated with digitalis.

Implementation

- Check the pulse before administration of digitalis. Check with the doctor before administration if the pulse is less than 60 beats/minute and withhold the drug.
- Monitor fluid input and output. The patient may need to be placed on fluid restriction. Weigh the patient each day at the same time to assess body fluid status.
- Monitor for dependent oedema in the sacral area and feet/ankles. Through auscultation, listen for air entry into lungs. Compare both sides of the lungs. Crackles are indicative of lung oedema.
- Assess the electrocardiogram (ECG) and chest X-ray periodically to determine the effect of digoxin on the condition.
- Monitor serum digoxin levels. The normal range for digoxin is 1–2.6 nmol/l. Digoxin has a low therapeutic index, such that the toxic effects occur close to the therapeutic range for the drug.
- Check serum potassium levels. Normal range is 3.5–5.0 mmol/l. Hypo- and hyperkalaemia should be treated before administering digoxin to prevent cardiac rhythm disturbances.
- Monitor for manifestations of digoxin toxicity. Acute signs of toxicity include nausea, vomiting, anorexia and diarrhoea. Chronic signs include bradycardia, dysrhythmias and visual disturbances.
- If serum potassium levels are not within normal limits before administration, notify the doctor and withhold the drug.
- Administer the drug with or following meals to reduce gastric irritation.

Patient teaching

- Inform the patient of the importance of taking the drug regularly and adhering to the correct dose.
- Instruct the patient on the adverse reactions attributed to these drugs and to notify the doctor immediately if they occur.
- The patient should be advised to avoid over-the-counter medications and antacids because of the potential for adverse drug reactions.
- Inform the patient to take the drug with meals to lessen gastric irritation.
- Teach the patient about the observations that may indicate digitalis toxicity.
- Instruct the patient on the importance of maintaining an adequate potassium level. Foods containing potassium include bananas, citrus fruits and juices, meat, fish, cereals and nuts.

Evaluation

- The patient undergoing digitalisation should demonstrate an improvement in condition, as shown by a regular, slower heart rhythm, decreased dyspnoea, fewer lung crackles, improved ability for activity, decreased productive cough, increased diuresis, weight loss and decreased peripheral oedema. Some of these effects will be achieved by the concomitant administration of a diuretic.
- Evaluate carefully for early manifestations of toxicity.

Antidysrhythmic drugs

Assessment

- Assess vital signs and electrocardiogram (ECG) for baseline observations and compare with subsequent observations. The patient is placed on a cardiac monitor if possible. For more serious dysrhythmias (e.g. generally ventricular dysrhythmias), the patient should be in a coronary care environment, where the cardiac rhythm can be monitored continuously. For less serious dysrhythmias (e.g. atrial dysrhythmias), the patient may be cared for in an acute care ward.
- Assess heart and lung sounds to obtain baseline parameters.
- Assess for the presence of chronic respiratory disease and congestive cardiac failure, as beta-blockers should be used with caution in patients with these conditions. Drugs in class IA may cause antimuscarinic effects and should be used with caution in patients with urinary retention and glaucoma.

Planning

- The patient will move from a potentially life-threatening rhythm to a less serious form or move to sinus rhythm if possible.

Implementation

- Carefully monitor the heart rate and blood pressure during administration. Generally, a change in heart rate is a desirable outcome of therapy, although a rate greater than 120 or less than 60 beats/minute should be avoided.
- During and after intravenous administration of antidysrhythmics, keep the patient supine until vital signs are stable. Ensure that emergency equipment and drugs are close by for a possible resuscitation attempt.
- Monitor serum electrolyte levels regularly. Electrolytes that tend to affect cardiac rhythm include potassium, magnesium and phosphate. Sodium can lead to retention of body fluid, which in turn increases the work of the heart.
- Assess for peripheral oedema in the feet and ankles and jugular venous distension. Monitor fluid input and output to determine fluid balance. Weigh the patient regularly.
- Monitor exercise tolerance with daily activities.

Patient teaching

- Educate the patient about the importance of non-pharmacological measures, such as weight reduction, balanced diet, stopping smoking, limiting caffeine intake, sodium restriction and use of potassium supplements.

Evaluation

- Evaluate whether the patient is in a stable cardiac rhythm, either sinus rhythm or a non-life-threatening dysrhythmia.
- Evaluate blood pressure and pulse after administration to determine effect of therapy.
- Evaluate the incidence of adverse effects, which may require changes to the dose or drug.

SUMMARY

- Heart failure is a disorder of the heart's pumping ability. As a result, cardiac output and tissue blood perfusion drop dramatically. The ventricles are unable to completely eject blood, and so tissue congestion and oedema develop. The ventricular wall stresses increase, leading to myocardial remodelling.
- The current management of this condition comprises angiotensin-converting enzyme (ACE) inhibitors, diuretics and, in some cases, inotropic agents. These agents have been shown to improve ventricular function, reduce mortality and improve the quality of life of patients with heart failure.
- For patients who are intolerant to ACE inhibitors, a combination of peripheral vasodilators can be effective. Beta-blockers may also have a role in the long-term management of the condition.
- For many of the drugs used in the management of heart failure, it is important to monitor renal function, blood pressure, fluid balance and plasma electrolyte levels.
- A dysrhythmia is an abnormal cardiac rhythm, the cause of which may include electrolyte disturbance, pneumonia, myocardial infarction, thyroid disease and cardiac surgery.

- The means by which the various drug categories used to correct dysrhythmias work are by suppressing automaticity, by depressing the rate of depolarisation, by slowing impulse conduction through the tissue, by prolonging the action potential and by increasing the refractory period.
- Electrophysiologically, these effects can be achieved by blocking sodium, calcium and/or potassium channels associated with the myocardium.
- A useful classification system for antidysrhythmic agents is the Vaughan Williams model. Class I agents have local anaesthetic properties and act primarily by blocking sodium channels. Class II agents are beta-blockers. Class III agents prolong the duration of the action potential and the refractory period. Class IV agents are calcium channel antagonists.
- During therapy, monitor haemodynamic and biochemical parameters such as cardiac rate and rhythm, blood pressure, respiratory rate and rhythm, urine output, conscious state and electrolyte levels.

1 For each of the following drug groups, indicate which cardiac condition(s) they may be used to treat:
(a) calcium channel antagonists;
(b) cardiac glycosides;
(c) beta-blockers.

2 Define the following terms:
(a) automaticity;
(b) chronotropic effects.

3 Describe the following agents in terms of their chronotropic and inotropic effects (hint: for each term, the drugs may have a positive effect, a negative effect or no effect):
(a) beta-blockers;
(b) cardiac glycosides;
(c) the dopamine agonist dobutamine;
(d) non-selective β agonists.

4 With which electrolyte imbalance can the cardiac glycoside digoxin have a therapeutic blood level and still exert toxicity? Why?

5 Account for the facial flushing, headache and reflex tachycardia that may be observed after the administration of an organic nitrate such as isosorbide dinitrate.

6 To which antidysrhythmic class do each of the following drugs/drug groups belong?
(a) calcium channel antagonists;
(b) beta-blockers;
(c) digitalis.

7 What evaluation would you make of a patient to determine the effectiveness of the angiotensin-converting enzyme (ACE) inhibitor captopril in treating your patient's congestive cardiac failure?

8 Voula Vousopoulos, a 75-year-old patient with congestive cardiac failure, is discharged from hospital with the following medication regimen: the angiotensin-converting enzyme (ACE) inhibitor enalapril, the loop diuretic furosemide and potassium chloride. What education would you offer Ms Vousopoulos in order to enable her to take her medications safely and accurately?

9 Maria Toraldo, a 65-year-old patient, is receiving nifedipine for the prophylactic treatment of angina. What patient education would you offer Ms Toraldo?

10 What evaluation would you make of a patient to determine the effectiveness of an antidysrhythmic agent?

48 DRUG SUMMARY TABLE: DRUGS USED TO TREAT CARDIAC INSUFFICIENCY

FAMILY NAME	GENERIC NAME	TRADE NAME(S)
ACE inhibitors	Captopril	Capoten
	Cilazapril	Vascace
	Enalapril	Innovace
	+ Hydrochlorothiazide	Innozide
	Fosinopril	Staril
	Lisinopril	Carace
		Zestril
	+ Hydrochlorothiazide	Carace Plus
		Caralpha
		Lisicostad
		Zestoretic
	Perindopril	Coversyl
	+ Indapamide	Coversyl Plus
	Quinapril	Accupro
	+ Hydrochlorothiazide	Accuretic
	Ramipril	Tritace
	Trandolapril	Gopten
		Odrik
Beta-blockers	Bisoprolol	Cardicor
		Emcor
		Monocor
	Carvedilol	Eucardic
	Metoprolol	Betaloc
		Lopresor
Cardiac glycosides	Digoxin	Lanoxin
Diuretics		
Loop diuretics	Bumetanide	Burinex
	Furosemide (frusemide)	Lasix
	+ Amiloride	Frumil
Potassium-sparing diuretics	Amiloride	
	+ Hydrochlorothiazide (co-amilozide)	
	+ Furosemide	Co-amilofruse
	+ Bumetanide	Burinex A
	Spironolactone	Aldactone
	+ Hydroflumethiazide	Co-flumactone
	+ Furosemide	Lasilactone
Thiazide and thiazide-like diuretics	Bendroflumethiazide (bendrofluazide)	
	Chlortalidone (chlorthalidone)	Hygroton
	Cyclopenthiazide	Navidrex
	Indapamide	Natrilix
Dopamine agonists	Dobutamine	
	Dopamine	
	Dopexamine	Dopacard
Peripheral vasodilators	Glyceryl trinitrate	Nitronal injection
	Hydralazine	Apresoline
	Isosorbide dinitrate	Isoket
	Morphine	
Inotropic vasodilator	Milrinone	Primacor

FLUID AND POTASSIUM IMBALANCES

49

CHAPTER FORTY-NINE

OBJECTIVES

After completing this chapter, the reader should be able to:

- **describe the differences in fluid composition at various stages of development and growth;**
- **explain the principles of fluid movement in the body;**
- **describe therapies applying to clinical situations that require restoration of fluid and potassium imbalance;**
- **explain the effects of fluid administration on body compartments;**
- **state the difference between crystalloid and colloid fluids;**
- **describe the composition and uses of different types of fluids used for fluid replacement therapies;**
- **describe the clinical manifestations and management of hypokalaemia and hyperkalaemia.**

KEY TERMS

Fluid balance
Potassium balance
Body composition
Osmolarity
Crystalloid solution
Colloid solution

THIS CHAPTER DEALS WITH FLUID AND POTASSIUM imbalances, identifying the causes and describing treatments used to rectify these imbalances. Understanding what happens at a physiological level provides the backbone for rational forms of treatment for these conditions.

FLUIDS

Although we tend to focus on the state of organs to determine the health of an individual, fluids also play an important part in body function. The term 'body fluid' refers to the body water and its dissolved substances, such as electrolytes.

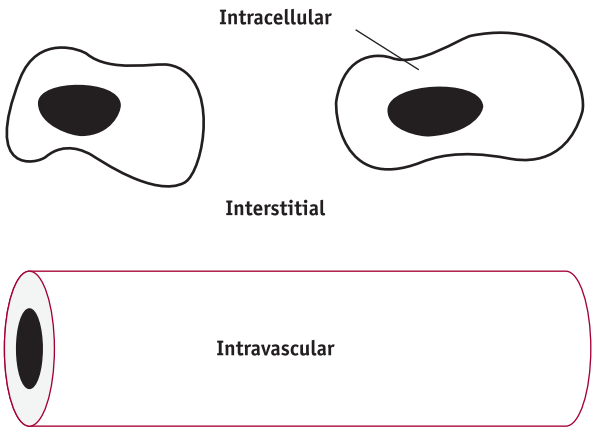
Body composition and fluid

Fluids make up the bulk of the body's weight. The percentage varies between individuals and depends mainly on the amount of fat present and age. As fat does not contain fluid, slim individuals have a greater proportion of body fluid than heavy individuals. Increasing age also tends to decrease the fluid proportion. In the adult male, body fluid makes up about 60 per cent of the body weight. In the adult female, fluid comprises 55 per cent of the body weight. The extra body fat present in women creates the lesser proportion of body fluid compared with men.

The premature infant's body contains about 85 per cent fluid, while the full-term newborn infant's body contains about 70 per cent fluid. Infants have proportionally more fluid in the extracellular compartment than adults. Compared with the adult, who has less than 20 per cent fluid in the extracellular compartment, the infant has 40 per cent fluid in this compartment. As the infant grows, the proportion of extracellular fluid to intracellular fluid falls. This loss of extracellular fluid is due to an increasing rate of growth of muscle compared with collagen, and the development of cellular tissue. By the end of the infant's first year, body fluid makes up about 67 per cent of weight. After the second year, body fluid constitutes about 65 per cent of bodyweight. By the time adolescence is reached, the proportion of body fluid is similar to that of an adult. Table 49.1 indicates the differences in fluid and fat composition at various stages of development.

Body compartments are separated by selectively permeable membranes. About half of the body fluid is located in cells, and this is termed intracellular fluid. The remaining fluid is called extracellular fluid and includes the fluids associated with dense connective tissue, bone, cerebrospinal fluid, urine and other secretions.

FIGURE 49.1 DISTRIBUTION OF BODY COMPARTMENTS



Regardless of the body area, movement of fluid occurs between three main compartments – the intracellular, interstitial and intravascular compartments. When the body is in a fluid balance, it contains a specific amount of fluid in the various compartments according to need. Figure 49.1 is a schematic representation of these compartments.

Fluid distribution

The movement of fluid between the different compartments is a dynamic and constantly changing process. In a healthy individual, the composition of fluid in each compartment remains stable in spite of this constant movement. This condition of maintaining fluid balance is known as homeostasis, whereby the body's internal environment remains stable and in equilibrium. Fluid balance, or equilibrium, involves a complex interplay between the nervous, endocrine and renal systems. Chapter 44 provides a discussion of the interplay between these systems in their effort to control fluid balance. Chapter 58 describes the

TABLE 49.1 DISTRIBUTION OF BODY FLUIDS AND FAT AT DIFFERENT AGES

	Total body water (% weight)	Extracellular fluid (% weight)	Intracellular fluid (% weight)	Fat (% weight)
Premature baby	85	50	35	1
Full-term neonate	70	40	30	15
Infant (6 months)	70	35	35	15
Child	65	25	40	15
Young adult	60	15	45	20
Elderly person	45	10	35	10

TABLE 49.2 DEFINITIONS OF PRESSURES EXISTING AT THE CAPILLARY LEVEL

Pressure	Definition
Capillary hydrostatic pressure (CHP)	Pressure created by the outward force exerted by fluid contained within the capillary; occurs because of blood volume, mechanical pressure created by heart contraction, and resistance of blood vessels
Interstitial fluid hydrostatic pressure (IFHP)	Pressure of interstitial fluid against capillary wall; tends to move fluid out of the capillary
Capillary osmotic pressure (COP)	Inward force that draws fluid from interstitial space into the capillary; due to the presence of large amounts of plasma proteins, which cannot pass through the capillary membranes
Interstitial fluid osmotic pressure (IFOP)	Tends to move fluid out of the capillary; due to small amounts of proteins in the interstitial fluid

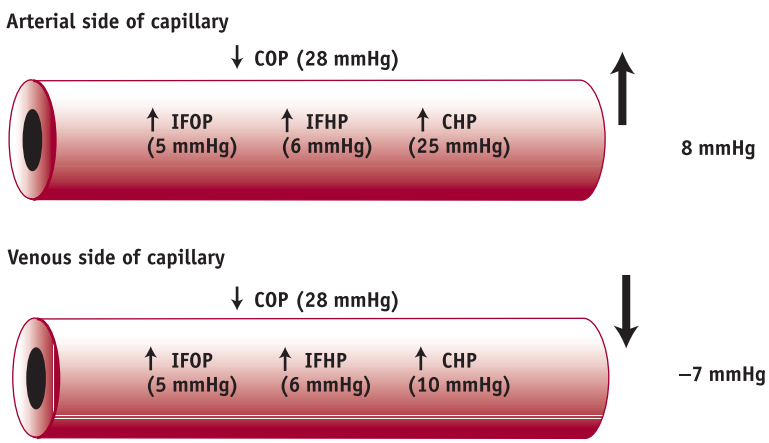
effect of mineralocorticoids in creating sodium and water retention. This chapter focuses specifically on the osmotic influences of fluid movement. It is, however, important to keep in mind the interplay of hormones, neuronal activity and chemical factors in the control of fluid and electrolyte movement.

Movement of fluid between the interstitial and intravascular compartments occurs at the capillary level, where the membrane separating the compartments is quite thin. This movement of fluid is governed by four pressures: capillary hydrostatic pressure, interstitial fluid hydrostatic pressure, capillary osmotic pressure, and interstitial fluid osmotic pressure. Their definitions are given in Table 49.2. Movement of fluid occurs along the entire length of the capillary. Figure 49.2 shows fluid movement across the arterial and venous ends of the capillary. The net direction of movement of the fluid is termed the effective filtration pressure. This is calculated using the following formula:

$$P_{(effective)} = [\text{Capillary hydrostatic pressure} + \text{interstitial fluid hydrostatic pressure} + \text{interstitial fluid osmotic pressure}] - \text{capillary osmotic pressure}$$

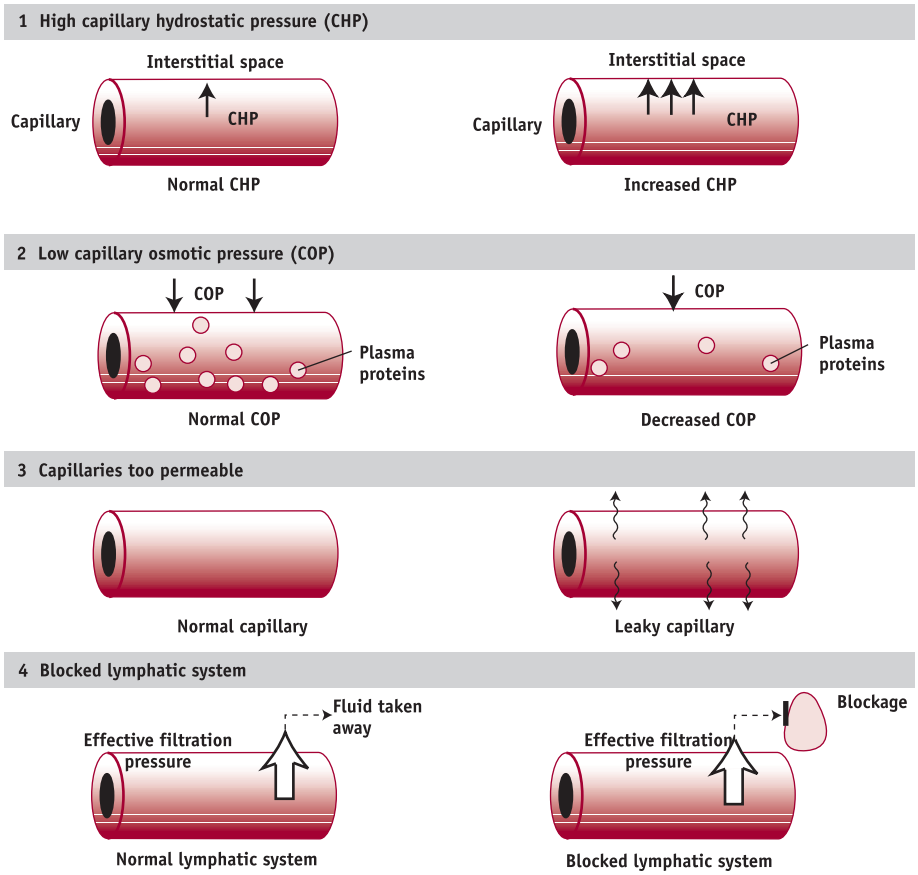
FIGURE 49.2 MOVEMENT OF FLUID ACROSS THE CAPILLARY

At the arterial end, fluid moves (is filtered) out of the capillary into the interstitial space. Its role is to deliver oxygen and nutrients to the cells. At the venous end, fluid moves (is reabsorbed) into the capillary from the interstitial space. Its role here is to move waste products away from the cells. Not all fluid filtered at the arterial end is reabsorbed at the venous end. The excess fluid (8 – 7 = 1 mmHg) and any proteins that escape are returned by the lymphatic system to the cardiovascular system.



CHP, capillary hydrostatic pressure; COP, capillary osmotic pressure; IFHP, interstitial fluid hydrostatic pressure; IFOP, interstitial fluid osmotic pressure.

FIGURE 49.3 SCHEMATIC REPRESENTATION OF CHANGES IN FLUID PRESSURE THAT LEAD TO OEDEMA



As shown in Figure 49.2, the effect of all four pressures is to move fluid out of the capillary at the arterial end and move fluid into the capillary at the venous end. Not all fluid filtered at the arterial end is reabsorbed at the venous end. The excess fluid and any proteins that escape are collected by the lymphatic system and returned to the blood circulation.

OEDEMA CAUSED BY ALTERATIONS IN FLUID DISTRIBUTION

Developing an understanding of the fluid dynamics facilitates an appreciation of the clinical situations that can arise following changes in fluid pressures. Four important changes in the pressures that regulate the movement of fluids may lead to a clinical situation known as oedema. Oedema is the abnormal increase in interstitial fluid leading to tissue swelling, which is visible to the eye. Figure 49.3 comprises schematic representations of the changes in pressure that lead to oedema.

VERY HIGH CAPILLARY HYDROSTATIC PRESSURE

A capillary hydrostatic pressure that is greater than normal means that a considerably greater proportion of fluid will be pushed out of the arterial end than is picked up at the venous end. This will lead to increased fluid in the interstitial space and blood pooling in the peripheries. This is the type of oedema that occurs in heart failure and renal failure and is due to inappropriate secretion of antidiuretic hormone (ADH).

LOW CAPILLARY OSMOTIC PRESSURE

This occurs when the plasma proteins in the capillaries are low. Less fluid tends to be drawn into the capillary than flows out. This is the type of oedema that occurs in liver disease (where the individual cannot make albumin), burns (where there is protein loss) and malnutrition (where a protein deficiency exists). Treatment for this type of oedema is by replacement with colloid fluids (discussed later in this chapter).

CAPILLARIES TOO PERMEABLE

If the capillary walls are too leaky, then plasma proteins can escape through the capillary pores into the interstitial space. This leads to lower capillary osmotic pressure and higher interstitial fluid osmotic pressure. This type of oedema

occurs in septic shock and burns. Treatment for this type of condition is usually by fluid replacement (discussed later in this chapter).

BLOCKED LYMPHATIC SYSTEM

In this situation, the fluid remains in the interstitial space and is not collected by the lymph. This type of oedema occurs in metastatic involvement of lymph nodes. Treatment of this type of condition is usually by radiotherapy or chemotherapy (see Chapter 76). Depending on the type of oedema, the condition is treated with fluids or medications.

EFFECT OF THE OSMOLARITY OF FLUIDS INTRODUCED TO THE BODY

Movement of fluid is a constantly changing process, which is under the influence of the nervous, renal and endocrine systems. These systems also affect electrolyte movement. In addition to these systems, water movement is affected by the process of osmosis. Osmosis is the principal way in which water moves in and out of body compartments. More specifically, osmosis involves the movement of water through a selectively permeable membrane from an area of high water concentration to an area of lower water concentration, until equilibrium is reached. The term 'concentration' refers to the ratio between dissolved particles (solutes) and dissolving fluid (solvent). Hence, osmosis is the movement of water (solvent) from an area with fewer solute particles, across a selectively permeable membrane, into an area with more solute particles. In addition to body fluids moving around the different compartments, when fluids are introduced into the body these also move around the compartments, depending on their osmolarity. Fluids can be classified as isotonic, hypotonic or hypertonic.

An isotonic solution is one in which the osmotic pressure is the same as that of the body's plasma. Osmotic pressure is the force under which water moves through a selectively permeable membrane from an area of higher water concentration to an area of lower water concentration. The plasma's osmotic pressure, or osmolarity, is the solute concentration per volume of solution, or milliosmoles (mosm) per litre. The osmolality is the solute concentration per weight of solvent, or milliosmoles per kilogram of solvent. In clinical practice, the difference between osmolarity and osmolality is slight, and often the terms are used interchangeably. Normal plasma osmolarity is between 280 and 300 mosm/l. As the osmolarity of isotonic solutions is the same as that for plasma, there is no net movement of fluid when these solutions are introduced in the body. Examples of isotonic solutions include whole blood, **Hartmann's solution** (compound sodium lactate), **4% glucose with 0.18% normal saline**, **5% glucose** and **0.9% normal saline**. After the introduction of solutions with glucose into the intravascular compartment, there is rapid uptake of glucose into the cell; the glucose is then metabolised rapidly to carbon dioxide and water. In these quantities, there is insufficient glucose present to alter blood glucose levels.

A **hypotonic solution** is one in which the osmotic pressure of the solution is less than that of plasma. Hypotonic solutions will decrease the osmolarity of the intravascular compartment when added to the body and, therefore, will result in a water shift into cells to re-establish osmotic equilibrium. Examples include water, **0.45% normal saline** and **4% glucose**. Glucose solutions become hypotonic because of the rapid glucose uptake and metabolism of glucose to carbon dioxide and water.

The osmotic pressure of a hypertonic solution is more than that of plasma. Hypertonic solutions increase the osmolarity of the intravascular compartment when added to the body and, therefore, result in a water shift out of cells to re-establish osmotic equilibrium. Examples include **25% mannitol**, **10% glucose**, **5–10% glucose combined with 0.2–0.9% normal saline**, and **20% albumin**.

Figure 49.4 indicates the manner in which water moves after the introduction of an isotonic, hypotonic or hypertonic solution to the intravascular compartment of the body (e.g. by intravenous infusion). Hormonal responses such as renin/angiotensin, aldosterone, vasopressin and atrial naturetic factor (ANF) will also respond to volume and electrolyte changes to compensate for osmolar changes (see Chapter 44).

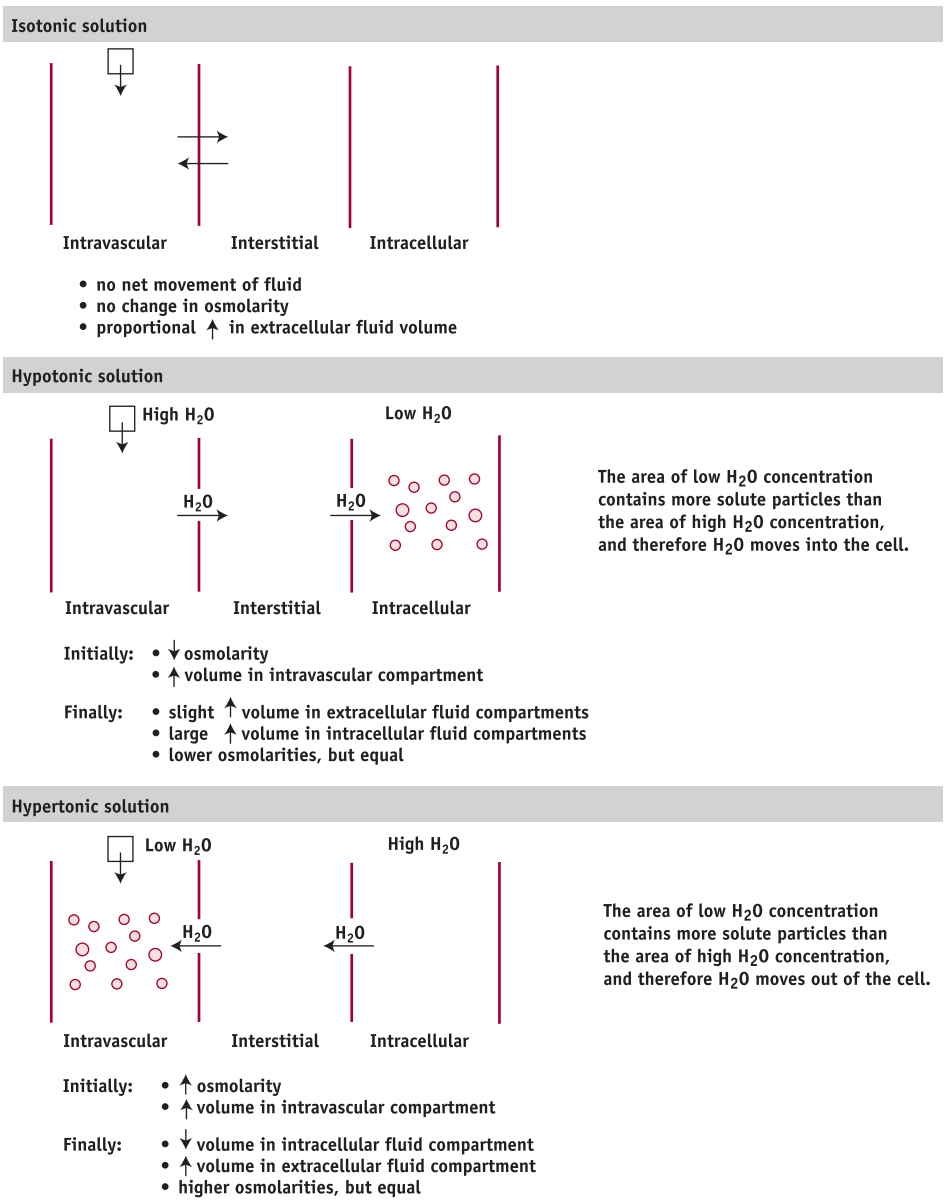
In the case of an isotonic solution, there is no change in osmolarity after its introduction to the intravascular compartment. There is, therefore, no net movement of water; there is, however, a proportional increase in the extracellular fluid volume.

When a hypotonic solution is added to the intravascular compartment, there is an initial decrease in osmolarity and an initial rise in the volume of the compartment. This causes the movement of water from an area of high water concentration to one of low water concentration until the osmolarities are equal. The net result is a slight rise in the extracellular volume, a large rise in the intracellular volume, and lower but equal osmolarities in all compartments.

Following the intravenous administration of a hypertonic solution, there is an initial rise in osmolarity and an increased volume in the intravascular compartment. This causes the movement of water from a high water concentration to a low water concentration until the osmolarities are equal. The net result is decreased volume in the intracellular fluid, increased volume in the extracellular fluid, and higher but equal osmolarities in all compartments.

Electrolytes that may be present in these solutions will move depending on their major area of location. For

FIGURE 49.4 EFFECTS OF ADDING DIFFERENT FLUIDS TO THE INTRAVASCULAR COMPARTMENT



example, potassium will mainly go into the cell and sodium will mainly stay outside the cell. Developing an understanding of where fluid goes enables an appreciation of the effects produced by fluid when administered to the body. This becomes more apparent when we focus on the types of fluids administered.

Indications for fluid administration

Fluids are used to replace those lost from the body. Fluid loss may be accompanied by loss of electrolytes and may involve different body compartments. The cause underlying fluid and electrolyte loss often determines the type of fluid administered. Table 49.3 indicates common clinical indications for fluid administration.

Aims of fluid therapy

Before we can examine the types of fluid available to treat various medical conditions, we need to state the aims of fluid therapy. There are four major aims of fluid therapy:

- to correct hypovolaemia or blood loss resulting from trauma and surgery;
- to restore an adequate intravascular volume (as opposed to the interstitial volume);

TABLE 49.3 CLINICAL INDICATIONS FOR FLUID THERAPY

Loss of extracellular fluid volume
- Sudden haemorrhage
- Prolonged vomiting
- Excessive diarrhoea
- Burns
- Inadequate intake of water in anorexia
- Patient to fast in preparation for, or following, medical procedure

Loss of proteins in intravascular compartment
- Malnutrition
- Liver disease

Movement of fluid to interstitial compartment
- Pancreatitis
- Peritonitis
- Ascites
- Burns
- Intestinal obstruction

Loss of electrolytes
- Diaphoresis (sweating)
- Diuresis

- to maintain an adequate oxygen-carrying capacity of the intravascular volume;
- to establish a haemodynamic stability, which is necessary for optimal tissue perfusion.

Crystalloid and colloid solutions

In addition to blood products, which are naturally occurring fluids, synthetic fluids are used, which are classified as either crystalloid or colloid solutions.

Crystalloid solutions contain low-molecular-weight particles such as ions. Examples include 0.9% normal saline, Hartmann's solution and 5% glucose. Glucose is not an electrolyte, but it is classified as a crystalloid. The advantage of crystalloids over colloid solutions is that the former distribute rapidly throughout the extracellular compartment and improve capillary perfusion by decreasing blood viscosity. Sodium-based fluids tend to remain in the extracellular compartment because of the distribution of the sodium ions. Their main disadvantage is that as they move freely between the intravascular and interstitial compartments, more fluid is needed to replace that lost from the plasma. More frequent administration is also required. Another disadvantage is that if large volumes of crystalloid solution are given, this can dilute the plasma proteins in the intravascular compartment, which lowers the capillary osmotic pressure. This means that less fluid is drawn into the capillary from the interstitial space, which leads to oedema.

Colloids are high-molecular-weight solutions. Their large particles create an increased capillary osmotic pressure, pulling water from the interstitial compartment into the intravascular compartment. Colloids are also called plasma expanders because of their ability to create a large pulling force in moving water from the interstitial compartment to the intravascular compartment. Examples include **albumin**, **dextran 40**, **dextran 70**, **succinylated gelatin** and **esterified starch**. Their advantage over crystalloid solutions is that less volume is needed for administration because colloids tend to remain in the intravascular compartment. Colloids are, however, fairly expensive. During rapid administration, colloid fluid in the intravascular compartment raises the capillary hydrostatic pressure, forcing water into the interstitial space and leading to oedema. If leaky capillaries are present, colloid solutions can move into the interstitial compartment, causing a decreased capillary osmotic pressure, also leading to oedema.

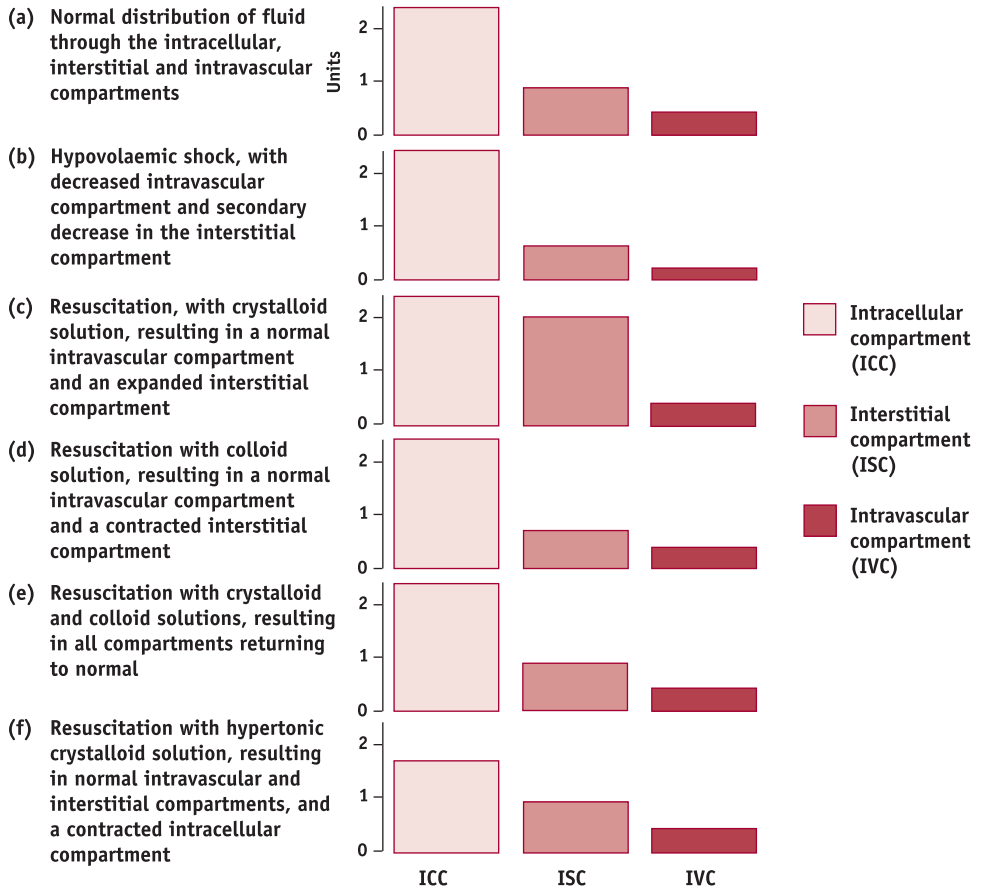
Controversy exists as to which type of solution should be given in particular situations. Generally, a combination of crystalloid and colloid therapy may be used in an emergency situation to restore fluid volume. At least twice the volume of this is required, however, to achieve the same effect as using colloid therapy alone. Once the patient's blood is grouped and cross-matched, red cell concentrate is used to return the haematocrit to at least 30 per cent. It is also important to note that adequate fluid resuscitation of the patient who sustains hypovolaemic shock involves the replacement of blood components. Generally, six units of platelets and six units of fresh frozen plasma can be administered for every six units of packed red cells if clotting studies are not available to guide blood replacement more accurately. Figure 49.5 indicates the effects of administering crystalloid, colloid and a combination of both fluids in the treatment of hypovolaemic shock. The resultant changes to the body compartments occur within 30 minutes of administration of the crystalloid or colloid fluids.

Tables 49.4, 49.5 and 49.6 provide information about blood products, colloid solutions and crystalloid solutions, respectively. Their composition and uses are indicated, with specific comments pertaining to particular solutions.

Techniques used to administer fluids

Fluids are administered intravenously through either a peripheral or central vein. If fluids are administered through a peripheral line and are to be used for re-establishing the blood volume, then a large-gauge needle is needed; a 14- or 16-gauge needle would be used in this case. A peripheral line is unsuitable for hypertonic solutions, as this leads to thrombophlebitis (inflammation and clot formation in the vein). All fluids, including hypertonic solutions, can be administered through a central vein.

FIGURE 49.5 EFFECTS OF CRYSTALLOID, COLLOID AND A COMBINATION OF BOTH FLUIDS IN THE TREATMENT OF HYPOVOLAEMIC SHOCK



POTASSIUM

Potassium is the major intracellular electrolyte of the human body. It is probably one of the most commonly supplemented electrolytes in clinical drug therapy. This electrolyte performs several important functions in the body. Potassium helps to maintain the fluid volume in cells. Normally, when potassium ions move out of the cell they are replaced by sodium and hydrogen ions, which move into the cell. This shift in ion movement assists in regulating blood pH. It also plays an important role in the function of nerve and muscle tissues. Along with other electrolytes, it is responsible for maintaining the osmotic pressure of the intracellular fluid compartment.

Potassium imbalances manifest as either a deficiency (hypokalaemia) or an excess (hyperkalaemia) and produce serious adverse reactions. It is important, therefore, to develop an understanding of the causes, clinical manifestations and treatment of these conditions.

Hypokalaemia

Hypokalaemia is defined as a serum potassium level below 3.5 mmol/l. This is a potentially life-threatening condition because the manifestations affect almost every body system. Causes of hypokalaemia are shown in Table 49.7.

Consistent with its role in the body, potassium deficiency can affect plasma pH and nerve and muscle function. Patients with hypokalaemia generally have a rapid, thready, weak pulse, postural hypotension, and peripheral pulses that are difficult to palpate. One of the most serious cardiac effects of hypokalaemia is the development of dysrhythmias. Respirations tend to be ineffective and shallow. Neuromuscular changes include anxiety, lethargy, confusion, muscle weakness and skeletal muscle paralysis. If the condition is severe enough, the patient may become comatose. Gastrointestinal changes include decreased or absent bowel sounds, nausea, vomiting, abdominal distension, paralytic ileus and constipation. Renal changes include decreased

TABLE 49.4 BLOOD PRODUCTS

Whole blood	**Composition** Red blood cells, white blood cells, plasma, platelets, clotting factors (except V and VIII), electrolytes (Na^+, K^+, Ca^{2+}, Cl^-), additive CPDA **Uses** Replaces blood volume Maintains haemoglobin level Increases oxygen-carrying capacity of blood **Comments** Needs typing and cross-matching Care required if patient requires massive transfusion Do not infuse cold
Red cell concentrate	**Composition** Red blood cells, 20% plasma, some white blood cells, platelets, CPDA additives **Uses** Increases haematocrit (proportion of red blood cells) Corrects red-blood-cell deficiency Increases oxygen-carrying capacity of blood **Comments** Needs typing and cross-matching Less volume loading needed than whole blood Contains less plasma protein and no clotting factors compared with whole blood
Fresh frozen plasma	**Composition** Plasma (with plasma proteins), factors VIII and IX, fibrinogen, electrolytes (Na^+, K^+, Ca^{2+}, Cl^-) **Uses** Restores plasma volume in hypovolaemic shock with increasing haematocrit Restores clotting factors **Comments** Administer promptly after thawing to prevent deterioration of factors
Platelets	**Composition** Platelets, lymphocytes, some plasma **Uses** Controls bleeding due to thrombocytopenia Maintains normal blood coagulability **Comments** Give as soon as possible: platelets viable for only 3 days Refrigeration decreases platelet viability

CPDA, citrate-phosphate-dextrose-adenine.

TABLE 49.5 COLLOID SOLUTIONS

Albumin (isotonic)	**Composition** 4–5% human albumin solution, 4–5 g/100 ml albumin **Uses** Hypoalbuminaemia from malnutrition, liver disease, severe sepsis, extensive surgery, e.g. cardiopulmonary bypass surgery Expands plasma volume, acute and sub-acute loss of plasma volume, burns, pancreatitis, trauma Plasma exchange **Comments** Administer no faster than 1 ml/min, otherwise could lead to histamine release and subsequent hypotension
Albumin (concentrated solution)	**Composition** 20–25% human albumin solution, 200–250 g/100 ml albumin **Uses** Hypovolaemia due to haemorrhage or plasma loss (burns, crush injuries, peritonitis, pancreatitis) Severe hypoproteinaemia associated with low plasma volume and generalised oedema Haemodialysis **Comments** Rapid infusion can stimulate histamine release, leading to hypotension Hypertonic solution
Succinylated gelatin (Gelofusine)	**Composition** Colloidal plasma volume substitute, high-molecular-weight gelatin complex, 4 g in 100 ml **Uses** To retain fluid in the intravascular space To treat hypovolaemia due to bleeding When haemodilution and extracorporeal circulation is required **Comments** May cause anaphylaxis in susceptible patients May cause fall in blood pressure and subsequent confusion
Esterified starch	**Composition** Starch composed of more than 90% amylopectin etherified with hydroxyethyl groups 6% in sodium chloride 0.9% Hetastarch has a higher degree of etherification than pentastarch **Uses** To retain fluid in the intravascular space To treat hypovolaemia

TABLE 49.6 CRYSTALLOID SOLUTIONS

Normal saline 0.9%	**Composition** Electrolytes (Na^+, Cl^-) **Uses** Replaces extracellular fluid **Comments** Does not stay in intravascular compartment long; diffuses throughout extracellular fluid, therefore useless for prolonged maintenance of blood pressure Potential for fluid retention and circulatory overload due to sodium content
Sodium lactate (Hartmann's solution, Ringer-lactate solution)	**Composition** Electrolytes (Na^+, K^+, Ca^{2+}, Cl^-, lactate) **Uses** Replaces extracellular fluid To buffer acidosis (lactate converts to bicarbonate in liver but process needs oxygen) **Comments** In shocked patient with lack of oxygen, conversion to bicarbonate cannot occur, therefore worsening acidosis Fluid retention and circulatory overload due to sodium content Electrolyte levels are 'fixed' in amount; patient may require greater or lesser amount
5% glucose (not a true crystalloid, as no electrolytes present)	**Composition** Glucose **Uses** To raise total body volume Provides small amount of kilojoules for energy **Comments** Distributes evenly in every body compartment (acts like free water) Dilution of plasma proteins and electrolytes due to rapid metabolism of glucose to water, causing movement of water to interstitial space
4% glucose and 0.18% normal saline	**Composition** Glucose, electrolytes (Na^+, Cl^-) **Uses** Maintains normal blood fluid volume Provides water, electrolytes and kilojoules **Comments** Distributes evenly between all fluid compartments
Mannitol 20%	**Composition** Mannitol (inert form of sugar mannose) **Uses** Treats cerebral oedema Glaucoma Increases renal drug excretion **Comments** Avoid use in renal failure and severe dehydration Hypertonic solution
Normal saline 0.45%	**Composition** Electrolytes (Na^+, Cl^-) **Uses** Treats hypernatraemia and severe intracellular dehydration Replaces water and sodium **Comments** May dilute plasma proteins and electrolytes Hypotonic solution

TABLE 49.7 CAUSES OF HYPOKALAEMIA

Inappropriate or excessive use of drugs
- Diuretics
- Corticosteroids
- Amphotericin
- Penicillins
- Gentamicin and other aminoglycosides
- Cardiac glycosides
- Laxatives
- β_2 agonists
- Vitamin B_{12} therapy

Body fluid loss
- Diarrhoea
- Vomiting
- Increased gastric-tube aspiration
- Wound drainage
- Excessive drainage from ostomies

Other causes
- Excessive amount of insulin in the blood
- Excessive diaphoresis
- Hypomagnesaemia
- Increased secretion of aldosterone
- Cushing's syndrome
- Inadequate intake of potassium
- Metabolic and respiratory alkalosis
- Hypocalcaemia
- Haemodilution
- Adrenal tumour

ability to concentrate urine, polyuria and a decreased specific gravity. Hypokalaemia may sensitise the heart to cardiac glycosides, which may increase the incidence of cardiac toxicity and dysrhythmias (see Chapter 48).

Hypokalaemia may also cause acid–base imbalances. In an attempt to maintain intracellular electrical balance, excess hydrogen ions tend to move from the serum into the cell, where their buffering action displaces potassium ions. This action then promotes movement of potassium ions from the cell into the serum. This movement of potassium and hydrogen ions leaves the serum alkalotic. In the kidney, aldosterone normally acts to retain sodium ions in exchange for potassium or hydrogen ions. In hypokalaemia, fewer potassium ions are available for exchange with sodium, and so more hydrogen ions are excreted, which increases the alkalosis. As a result, the patient with hypokalaemia tends to exhibit respiratory or metabolic alkalosis.

As noted in Table 49.7, respiratory or metabolic alkalosis can also cause hypokalaemia. In contrast to the situation where hypokalaemia causes manifestations of acid–base imbalances, the following may then occur: As hydrogen ions move out of the cell in an attempt to re-establish normal blood pH, potassium ions move into the cell. Thus, alkalosis can cause hypokalaemia. In alkalosis, the kidney also tends to retain hydrogen ions. The kidney therefore excretes potassium ions in exchange for sodium ions. This retention of hydrogen ions indicates the body's attempt to compensate for the alkalosis, but it contributes further to hypokalaemia.

Treatment for hypokalaemia depends on the severity of the condition. For mild hypokalaemia in a conscious patient, a high-potassium diet may be sufficient. Potassium is contained in foods such as nuts, vegetables and fruits. Table 49.8 indicates foods rich in potassium. If the patient is recommended to follow a potassium-rich diet, it is important to determine whether the patient is on a sodium-restricted diet, as some of these foods are also high in sodium.

In more severe cases of hypokalaemia, oral or parenteral forms of potassium supplementation are usually prescribed. Oral potassium preparations comprise effervescent tablets, soluble powders, elixirs and slow-release tablets. Effervescent tablets and powders are dissolved in water before administration. Preparations taken in a liquid form, such as dissolved effervescent tablets or powders and elixirs, are formulated so that they do not cause gastric ulceration or bleeding. Often, however, patients find their taste unpalatable; this unpleasant taste can be masked by adding the dissolved liquid to fruit juice. Slow-release tablets are designed to allow for gradual dissolution and release of potassium, therefore preventing gastric damage. With any potassium preparations, it is advisable to administer them with food in order to reduce gastric irritation.

TABLE 49.8 FOODS RICH IN POTASSIUM

- Citrus fruits and juices
- Bananas
- Apricots
- Grape, apple, pear, apricot and cranberry juices
- Tea and cola drinks
- Dried raisins
- Almonds
- Peanuts and peanut butter
- Pistachio nuts
- Wheatgerm
- Jerusalem artichokes
- Potatoes
- Spinach
- Kidney beans
- Mushrooms
- Lentils
- Salt substitutes

Slow-release tablets should be swallowed whole, without being chewed or crushed, to enable the slow process of dissolution to occur.

Parenteral potassium supplements are usually incorporated into intravenous infusions such as 5% glucose. A dilution of approximately 30–40 mmol of potassium in a 1-l bag of solution is recommended. Higher concentrations, such as 70–80 mmol/l, can be used in critical-care areas where potassium is often used to treat dysrhythmias. At low dilutions of potassium (up to 30 mmol in a 1-l bag of solution), there is less likely to be venous irritation. Infusions with low dilutions of potassium may be administered through a peripheral vein, generally without problems to the integrity of the vein. Sometimes potassium is ordered to be administered in the burette of an intravenous infusion. When potassium is given in this way, the patient may experience pain at the insertion site. **Lidocaine 1%** solution may be injected at the cannula site as a local anaesthetic to alleviate this transient pain.

The solution used for infusion should be normal saline, unless the use of normal saline is contraindicated. Using glucose as a vehicle for infusion may lower serum potassium levels, because glucose, in the presence of insulin, facilitates the movement of potassium into cells.

With higher concentrations of potassium (70–80 mmol/l), there is the danger that potassium will destroy the integrity of a peripheral vein. Often in this situation, a central vein such as the subclavian or jugular vein is used instead. Potassium is administered at an infusion rate of about 30–40 mmol/hour. In patients whose serum potassium level is above 2.5 mmol/l, the rate of infusion should not exceed 10 mmol/hour in a concentration of less than 30 mmol in a 1-l bag of fluid. The total dose should not exceed 200 mmol in a 24-hour period. In critically ill patients and in patients whose serum potassium level is less than 2.0 mmol/l, potassium may be infused at a rate up to 40 mmol/hour. The total dose in this instance should not exceed 400 mmol in a 24-hour period.

If an infusion rate higher than 40 mmol/hour is prescribed, this order should be rechecked with the doctor. When potassium needs to be administered at a high rate, it is preferable for the patient to receive cardiac monitoring. Potassium should never be administered as an intravenous bolus through the side arm of the intravenous line because of the danger of provoking hyperkalaemia and, as a result, cardiac arrest. Intravenous potassium should always be diluted and administered through a burette or infusion bag.

Hyperkalaemia

Hyperkalaemia is defined as a serum potassium level greater than 5.0 mmol/l. As with hypokalaemia, the imbalance may be life-threatening and the condition should be rectified quickly. Causes of hyperkalaemia are shown in Table 49.9.

TABLE 49.9 CAUSES OF HYPERKALAEMIA

- Excessive potassium intake
  - Potassium-containing foods and medications
  - Salt substitutes
  - Potassium chloride administration
  - Rapid administration of potassium-containing intravenous solution
  - Massive blood transfusion
- Decreased potassium excretion
  - Addison's disease
  - Renal failure
- Insulin deficiency
- Metabolic and respiratory acidosis
- Burns
- Rhabdomyolysis
- Aldosterone deficiency
- Drugs
  - Spironolactone
  - Triamterene
  - Amiloride
  - Indometacin
  - Captopril
  - Enalapril
  - Digoxin overdose
  - Beta-blockers
  - Suxamethonium
  - Heparin
  - Prostaglandin inhibitors
- Haemolysis
- Tumour lysis syndrome
- Haemoconcentration
- Trauma, crush injury

Many of the manifestations of hyperkalaemia are directly opposite to those of hypokalaemia. The functions of muscles and nerves and the regulation of plasma pH are altered in hyperkalaemia. Patients may exhibit a slow, irregular pulse and decreased blood pressure. Cardiac dysrhythmias may occur. Neuromuscular changes include muscle twitches, cramps and paraesthesiae. Gastrointestinal effects include hyperactive bowel sounds and diarrhoea. Respiratory failure occurs quite late, when skeletal muscle weakness also manifests. In extreme cases, hyperkalaemia can result in complete neuromuscular paralysis and cardiac or respiratory arrest.

In contrast to the metabolic and respiratory alkalosis arising from hypokalaemia, hyperkalaemia causes more potassium ions to move from the serum into the cell. To maintain intracellular electrical balance, hydrogen ions are displaced from the cell into the serum, producing acidosis. In the kidney, more potassium ions are exchanged for sodium, and so fewer hydrogen ions are excreted. This effect increases the acidosis. As a result, the hyperkalaemic patient tends to exhibit respiratory or metabolic acidosis. As well as hyperkalaemia causing acidosis, acid–base imbalances can lead to hyperkalaemia. In acidosis, excess hydrogen ions move from the serum into the cell, while potassium ions move from the cell into the serum. As a result, acidosis can result in hyperkalaemia. In the kidney, excess hydrogen ions are excreted rather than potassium ions in exchange for sodium ions. The body attempts to excrete hydrogen ions in order to normalise blood pH. As these excess hydrogen ions in the kidney block the secretion of potassium ions, hyperkalaemia results.

Treatment of hyperkalaemia involves the following forms of intervention:

- Intravenous glucose 10–20% infusion administered with 10–20 units of soluble insulin. The administration of insulin and glucose stimulates glycogen synthesis. This results in the cellular uptake of potassium. Insulin facilitates the movement of glucose into the cell, which subsequently converts to glycogen and carries potassium along with it.
- Intravenous sodium bicarbonate 50–100 mmol. Bicarbonate helps to correct acidosis of hyperkalaemia by encouraging the return of potassium from the serum into the cell. In exchange, hydrogen ions move from the cell into the serum.
- Intravenous calcium chloride 10% 5–10 ml. Calcium stimulates cardiac contractility to reverse the cardiac-depressive effect of potassium.
- Oral and rectal ion exchange resin (e.g. Resonium A™) 50 g. The ion exchange resin is a high-molecular-weight polymer that is not absorbed from the intestine. The cation with which the resin is loaded has a high affinity for potassium ions. As the resin binds to potassium ions, the potassium ions are excreted from the body when the resin is passed through the faeces.
- Peritoneal dialysis or haemodialysis. Dialysis facilitates the excretion of potassium.

Treatment of hyperkalaemia also involves immediately stopping all infusions containing potassium and maintaining a potassium-restricted diet. Whole blood or packed red blood cells should be administered only if absolutely necessary.

CLINICAL MANAGEMENT

Fluids

Assessment

- Assess the purpose of fluid therapy for the patient. The purpose will provide an indication of the type of fluid most suitable for administration.
- Assess the patient's observations, including blood pressure, pulse, respirations, temperature, conscious state, and skin appearance and turgor. These observations may alter depending on whether the patient is hypovolaemic, hypervolaemic or oedematous.
- Maintain a fluid-balance chart, documenting input, output and overall effect on balance.
- In severe hypovolaemic states, a urinary catheter will need to be inserted to accurately assess urinary output on a regular basis.
- Examine the patient's past history for renal, cardiovascular and liver disease, as some forms of replacement may be contraindicated or great care taken in their use. For example, saline solution is not administered routinely to a patient with cardiovascular disease.

Planning

- The patient will achieve a normal hydration status.
- Observations and laboratory results will be within an acceptable range.

Implementation

- Regularly monitor the patient's observations, including blood pressure, pulse, respirations, temperature, conscious state, and skin appearance and turgor.
- Maintain a fluid balance chart, documenting input, output and overall effect on balance. In cases of severe dehydration, monitor the patient's hourly urinary output from a urinary catheter.
- Monitor for complications of the intravenous route during administration. These complications include infiltration, thrombophlebitis, pain at the administration site, necrosis, pulmonary oedema, pyrogenic reactions and air emboli.

- Monitor laboratory results as required for a particular form of therapy. For blood products such as packed red blood cell concentrate and whole blood, haemoglobin, haematocrit and a full blood examination should be undertaken regularly.
- If the patient is receiving a blood transfusion, observe the patient closely for the first 50 ml of blood. Thereafter, assess observations at least every 30 minutes or as required by the institutional protocol. Assess also for rigours and shivering.
- For the patient with oedema, auscultate the chest for crackles. Monitor for dependent oedema in areas such as the sacrum, legs and feet.
- Certain fluids need to be administered on a separate intravenous line, including blood and colloid fluids.
- Calculate the drip rate (drops per minute) required for fluid administration and ensure that this rate is maintained to prevent problems with fluid overload or underload. Check the rate every 30 minutes to 1 hour.

Evaluation

- The patient will receive fluid therapy and maintain an adequate fluid balance.
- Evaluate laboratory results and patient observations. These should remain within normal limits.

SUMMARY

- For a full-term neonate total body water accounts for 70 per cent of the weight, while in a young adult total body water accounts for 60 per cent of the weight.
- Body compartments are separated by selectively permeable membranes.
- Movement of fluid occurs between three main compartments – the intracellular, interstitial and intravascular compartments.
- The process of maintaining fluid balance is known as homeostasis, whereby the body's internal environment remains stable and in equilibrium.
- Movement of fluid between the interstitial and intravascular compartments occurs at the capillary level, which is governed by four pressures: capillary hydrostatic, interstitial fluid hydrostatic, capillary osmotic and interstitial fluid osmotic pressures.
- Osmosis is the major way in which water moves into and out of body compartments.
- An isotonic solution is one in which the osmotic pressure is the same as that of the body's plasma.
- A hypotonic solution is one in which the osmotic pressure of the solution is less than that of plasma.
- The osmotic pressure of a hypertonic solution is greater than that of plasma.
- Crystalloid solutions contain low-molecular-weight particles such as ions.
- Colloids are high-molecular-weight solutions.
- Potassium is the major intracellular electrolyte of the human body.
- Potassium imbalances manifest as either a deficiency (hypokalaemia) or an excess (hyperkalaemia).

1. Explain the difference between colloid and crystalloid fluids.
2. With reference to what happens in the body compartments, explain why a colloid solution is preferable for a patient with a severe fluid volume deficit.
3. Molly Rattlers, a 70-year-old patient with dehydration, is ordered 1000 ml Gelofusine™ at 100 ml/hour intravenously. What observations would you make to evaluate the effectiveness of the infusion?
4. Why is it important to melt fresh frozen plasma (FFP) gradually when preparing it for administration?
5. Your patient, Barbara Loewenstein, is ordered 30 mmol potassium chloride intravenously. How would you administer this dose? Explain your reasoning. What observations would you make of Ms Loewenstein to determine whether she is hypokalaemic or hyperkalaemic?

ANTIANAEMIC DRUGS

50

CHAPTER FIFTY

OBJECTIVES

After completing this chapter, the reader should be able to:

- **define anaemia and identify the principal causes;**
- **describe the underlying pathophysiology associated with each form of anaemia responding to drug therapy;**
- **identify the various supplements used in nutritional anaemias, considerations relating to their administration and any common adverse effects;**
- **state the mechanism of action and the adverse reactions of the agents used in the treatments of anaemia associated with chronic renal failure and aplastic anaemia.**

KEY TERMS

Aplastic anaemia
Chronic renal failure
Folic acid
Hypochromic anaemia
Iron
Macrocytic anaemia
Microcytic anaemia
Nutritional anaemias
Vitamin B_{12}

ANAEMIA RESULTS FROM A DEFICIENCY OF NORMALLY functioning erythrocytes, due either to structural abnormalities or to low numbers of circulating red blood cells. As a consequence, the oxygen-carrying capacity of the blood is diminished and the function of body tissues may become compromised. Structural problems can arise as a result of a genetic disorder, as in sickle cell anaemia and thalassaemia, and as an outcome of nutritional deficiencies, for example pernicious anaemia and iron/folic acid deficiency anaemia. A fall in the number of circulating erythrocytes can occur as a consequence of haemorrhage or fluid influx into the cell, forcing the cell to rupture (haemolytic anaemia).

A reduction in blood-cell production will lead to a decrease in circulating erythrocytes. The kidneys produce the hormone erythropoietin, which stimulates erythrocyte production in response to alterations in tissue oxygen levels. In chronic renal failure, erythropoietin secretion is diminished, resulting in anaemia. Bone-marrow suppression leads to a reduction in the production of all blood cells (erythrocytes, leukocytes, platelets) and is termed aplastic anaemia. A number of drugs, especially cytotoxic agents, induce aplastic anaemia, as does exposure to certain chemicals and radiation.

Antianaemic agents are indicated in the treatment of anaemias that are the result of nutritional deficiencies, chronic renal failure and bone-marrow suppression. The most important nutrients involved in erythrocyte formation are vitamin B_{12}, folic acid and iron. The vitamins are essential for the DNA synthesis that precedes normal cell division (see Chapter 76 for a complete discussion on the cell cycle). Therefore, if vitamin B_{12} or folic acid becomes deficient, the mitotic processes are impaired. This has a profound effect on rapidly dividing cell populations, such as in bone marrow. Erythrocytes still form, but they are larger in size and extremely vulnerable to damage. This form of anaemia is known as megaloblastic or macrocytic, because of the change in erythrocyte appearance.

Iron is incorporated in the haemoglobin molecule as an essential component of the structure of haem, to which oxygen binds for transport to body cells. Without normal iron availability, the amount of haemoglobin per cell is reduced (hypochromic anaemia) and small erythrocytes form (microcytic anaemia). Iron deficiency anaemia is, therefore, one of the hypochromic microcytic anaemias.

THERAPY OF NUTRITIONAL ANAEMIAS

Folic acid deficiency anaemia

The treatment of this nutritional anaemia is directed towards restoring the normal levels of **folic acid**. Folic acid is available in an oral form. A derivative of tetrahydrofolic acid, **folinic acid**, is used as a substitute for folic acid when a patient is receiving treatment with drugs, such as **methotrexate** and **trimethoprim**, that antagonise folic acid. Folic acid antagonists prevent the conversion of folic acid to tetrahydrofolic acid, which is necessary for normal DNA synthesis. Folinic acid therapy bypasses this biosynthetic obstruction and allows normal blood-cell production.

✚ CLINICAL CONSIDERATIONS

Patients with small-bowel resection and intestinal malabsorption may need parenteral administration.

Folic acid preparations should be protected from light and heat and stored at room temperature. To prevent recurrence of anaemia, patients need to be taught the importance of proper nutrition and which foods contain folic acid; these include oranges, whole wheat, broccoli, brussels sprouts and liver.

With folic acid therapy, exclude vitamin B_{12} deficiency. High doses of folic acid will not prevent the associated neurological damage related to vitamin B_{12} anaemia.

For patients receiving folinic acid therapy, explain that it may cause urticaria and anaphylactoid reactions. It is important not to confuse folinic acid with folic acid. Folinic acid therapy is used to treat the overdose of folic acid antagonists, such as methotrexate and trimethoprim. Patients may need this difference explained to resolve any confusion.

Vitamin B_{12} deficiency anaemia

As described in Chapter 61, the cause of this form of anaemia is rarely related to an inadequate intake. It is more commonly associated with malabsorption of **vitamin B_{12}**. **Cyanocobalamin** and **hydroxocobalamin** are both pharmacologically inactive forms of vitamin B_{12} available for therapeutic use; they are converted into active forms after administration. Cyanocobalamin is available in oral and parenteral forms; hydroxocobalamin is available only in a parenteral form.

✚ CLINICAL CONSIDERATIONS

An important consideration when using the oral form is that its absorption from the gut is dependent on the presence of intrinsic factor, which is secreted by the stomach. In pernicious anaemia, the area of the stomach that produces intrinsic factor either is severely damaged or has been surgically removed. For these patients, vitamin B_{12} supplementation must be via a parenteral route. The oral form of vitamin B_{12} is avoided in states of malabsorption.

Vitamin B_{12} parenteral solutions are physically incompatible with a number of preparations, including glucose solutions, and alkaline and strongly acidic solutions. Vitamin B_{12} needs to be protected from light, and solutions should not be refrigerated or frozen. Large oral doses should be avoided because of its tendency to be lost through excretion.

Hydroxocobalamin is similar to cyanocobalamin except that the former produces a more sustained increase in serum vitamin B_{12} levels and has a longer duration of activity.

Causes of vitamin B_{12} deficiency need to be determined and include pernicious anaemia, total or partial gastrectomy, vegan diet, and ileal disease or resection. As high doses of vitamin B_{12} may cause hypokalaemia, monitor the serum potassium levels closely during the first 48 hours and administer a potassium supplement if necessary.

Iron deficiency anaemia

Elemental iron is available in a variety of forms, each containing variable amounts of the essential mineral. The form most efficiently absorbed from the gut is the ferrous ion. Salts of the ferrous ion (**ferrous sulphate**, **ferrous gluconate**, **ferrous fumarate**) are used as oral supplements. There is very little difference in absorption of iron from any of the ferrous salts and choice is usually dependent on the incidence of side effects and cost.

◆ COMMON ADVERSE EFFECTS

Common adverse reactions of oral iron therapy involve the gastrointestinal tract and include nausea, abdominal pain and cramping, diarrhoea and constipation.

✚ CLINICAL CONSIDERATIONS

If possible, oral solutions of iron should be consumed through a straw to prevent teeth discoloration. Gastric irritation may be reduced by starting at a low dose and by taking smaller doses more frequently. The adverse gastrointestinal effects can be reduced by administering the supplement with or immediately after meals. Although food may reduce the incidence of gastric adverse effects, it also reduces the bioavailability of iron. Milk and antacids should not be used, as they reduce iron absorption.

Gastric effects may be reduced by administering the preparation with orange juice. Vitamin C has been shown to enhance the absorption of iron from the gut.

Warn patients that iron preparations can turn the stools black. This effect is harmless, but it can mask melaena and may interfere with tests for occult blood. Constipation associated with iron preparations can be prevented by ensuring an adequate fluid intake and plenty of fruit in the diet.

Treatment is usually continued for about 3 months to ensure replenishment of iron stores.

Iron–carbohydrate complexes are used for parenteral therapy in patients unable to absorb or tolerate sufficient iron to overcome the deficiency by oral administration. The forms used are **iron dextran** and **iron sucrose**. The most common side effects of parenteral therapy are localised pain and tissue staining at the injection site. Anaphylactoid responses can occur following parenteral iron administration, and patients should receive a small test dose initially.

Supplements containing combinations of iron and folic acid are indicated for the prevention and treatment of nutritional anaemias in pregnancy. Combined supplements containing a number of vitamins (vitamin E and vitamins from the B group) involved in erythrocyte production are also available. Some preparations contain iron, but others do not. The *British National Formulary* (BNF) does not recommend compound iron preparations except iron and folic acid in pregnancy. One combined supplement contains vitamin B_6 (**pyridoxine**), necessary for the normal production of haemoglobin and red blood cells, and vitamin E (**α-tocopherol**), a deficiency of which gives rise to haemolytic anaemia.

Poisoning is sometimes observed with iron supplementation, but not so much in the user as in children following accidental ingestion. The body has no mechanism for dealing with iron overload, and toxicity is realised quickly. The first signs of poisoning are gastrointestinal distress (nausea, vomiting). Within a few hours, a state of metabolic acidosis develops, which leads to cardiovascular collapse. Iron has a tendency to leave the blood and accumulate within organs such as the skin, heart, liver and kidneys; severe organ damage develops and death can occur within 24 hours of ingestion. The management of iron poisoning is covered in Chapters 21 and 22. Gastric lavage is recommended within the first hour after ingestion, followed by the possible administration of the specific antidote **desferrioxamine**.

ANAEMIAS ASSOCIATED WITH DECREASED BLOOD-CELL PRODUCTION

ERYTHROPOIETIN

Erythropoietin is used in the management of anaemia associated with chronic renal failure and non-myeloid malignancies. The use of erythropoietin as a doping agent by athletes is addressed in Chapter 24.

■ MECHANISM OF ACTION

Erythropoietin is secreted by the kidneys in response to tissue oxygenation. It stimulates the differentiation of erythrocytes from bone-marrow stem cells. Erythropoietin is deficient in chronic renal failure; anaemic states secondary to chronic renal failure can be treated with supplements of erythropoietin. This drug is also indicated for anaemias associated with non-myeloid malignancies. Once treatment commences, it takes about 2 weeks for a rise in haemoglobin levels to manifest. Like many hormones manufactured for clinical use today, human erythropoietin is a product of recombinant technology. The human gene for erythropoietin has been inserted into a Chinese hamster ovary cell and a cell line developed from this. The peptide is then extracted from the cell culture for clinical use. The human recombinant forms of the peptide are referred to as **epoetin alfa** and **epoetin beta**; they are clinically indistinguishable. **Darbepoetin alfa** is a derivative with a longer half-life that may be administered less frequently. As these are peptide hormones, they cannot be administered orally.

◆ COMMON ADVERSE EFFECTS

Adverse reactions associated with this therapy are dose-related. They include hypertension, rash and flu-like symptoms.

✚ CLINICAL CONSIDERATIONS

The risk of hypertension, commonly caused by epoetin alfa and beta, can be reduced by aiming for a haemoglobin increase of around 10 g/l/month. In addition, hypertension can be treated during the early stages of treatment by using antihypertensive therapy, fluid removal and a decrease in the erythropoeitin dose. It is important to monitor urea, creatinine, phosphate and potassium concentrations during therapy as their blood levels may rise. Elevated concentrations can be treated through dietary changes, phosphate binders and changes in dialysis parameters.

ANABOLIC AGENTS

Relatively high doses of anabolic agents (discussed in Chapter 58), can be used in the treatment of aplastic anaemias. For example, **testosterone enantate** and the synthetic anabolic agent **nandrolone** have been used with some success. The use of these agents has been largely superseded by erythropoietin, however.

■ MECHANISM OF ACTION

The mechanism of action has not been elucidated fully but is believed to involve increased secretion of erythropoietin from the kidneys, increased iron clearance from plasma to blood-cell-forming tissues, and a stimulation of mitotic activity of bone-marrow cells.

◆ COMMON ADVERSE EFFECTS

Adverse effects associated with these drugs derive from the action of testosterone and include fluid retention, acne, hirsutism and deepening of the voice.

✚ CLINICAL CONSIDERATIONS

With anabolic agent therapy, the patient should be weighed routinely and encouraged to eat a diet high in kilojoules and protein, unless contraindicated. Liver function tests need to be monitored regularly as anabolic agents can cause reversible jaundice and cholestatic hepatitis. Intramuscular injections of anabolic agents should be injected deep into the gluteal muscle and injection sites should be rotated regularly. Small frequent meals are preferred with these drugs in order to prevent nausea.

CLINICAL MANAGEMENT

Antianaemic agents

Assessment

- Assess the patient for a history of poor nutritional intake, blood loss or lack of growth. Determine whether the patient is vegetarian or vegan.
- Obtain baseline data of vital signs, body weight and conscious state. Compare with subsequent observations.
- Laboratory blood tests should include haemoglobin, haematocrit, full blood examination and iron levels.
- Assess for neurological manifestations of anaemia, such as tingling fingers and toes.
- Assess for pallor, fatigue and lethargy, which are common manifestations of iron deficiency anaemia.
- For the patient ordered erythropoietin, assess for the incidence of hypertension, ischaemic vascular disease, history of seizures, and susceptibility to allergic reactions. Erythropoietin should be used with caution in these patients.

Planning

- If the source of the anaemia is dietary, the patient will establish nutritional eating patterns.
- If possible, and if the condition is not permanent, the patient will achieve normal laboratory blood test results.

Implementation

- Regularly monitor vital signs, body weight and conscious state.
- Regularly monitor laboratory blood tests for haemoglobin, haematocrit, full blood examination and iron levels to determine the effectiveness of therapy.
- Monitor the effect of therapy on the manifestations of anaemia.
- Parenteral administration of iron may cause anaphylaxis. A test dose of 25 mg is given first. Monitor the patient for vital signs, febrile reaction, myalgia, nausea, shivering, rash, headache and arthralgia. Wait 1 hour before administering the remaining dose. Ensure that emergency equipment is close at hand.
- For intramuscularly administered iron, use large muscle masses. Use the Z-track technique of administration.

- Vitamin B_{12} should be administered by the intramuscular route only.
- Allergic reactions can occur with folic acid, vitamin B_{12} and erythropoietin. Monitor vital signs and allergic reactions, such as rash, shivering and arthralgia.
- Iron status should be monitored regularly while the patient is receiving erythropoietin, on a monthly basis for the first 3 months and 3-monthly thereafter. All patients receiving erythropoietin will also require supplemental iron therapy.

Patient teaching

Iron therapy

- Although absorption occurs better when taken on an empty stomach, iron preparations commonly cause gastrointestinal irritation. If this happens, advise the patient to take the drug with meals. Note that iron absorption is reduced significantly by cereals, eggs, milk, tetracyclines and antacids.
- Recommend the patient to take iron tablets with orange juice, as vitamin C enhances iron absorption.
- Inform the patient that iron may turn the faeces a dark green or black. This change in colour is harmless.
- Advise patients on liquid iron preparations to sip the liquid through a straw to avoid staining the teeth. The liquid should be diluted with orange juice or water and the mouth should be rinsed out well with water after the dose is taken.
- Advise the patient on dietary sources of iron, including red meat, legumes, nuts, dried fruit, green and leafy vegetables, offal and whole grains.
- Some patients may experience diarrhoea while taking iron therapy, and others may experience constipation. Advise the patient on measures to take should these adverse effects occur (see Tables 11.4 and 11.15 in Chapter 11 for further information).

Vitamin B_{12} therapy

- Instruct the patient about pernicious anaemia and the reason why vitamin B_{12} therapy should be taken for life.
- Advise the patient on sources of vitamin B_{12} to be incorporated in the diet. These sources include animal protein, such as meat, milk, fish, shellfish, eggs and cheese.

Folic acid therapy

- Advise the patient on dietary sources of folic acid, including green and leafy vegetables, orange juice, liver, peanuts, legumes, whole grains and wheatgerm.

Evaluation

- During and following therapy, the manifestations of the anaemia will be controlled.
- Evaluate the patient's knowledge of dietary sources of the deficient substance causing anaemia, and the patient's adherence to this diet.

SUMMARY

- Anaemia results from a deficiency of normal functioning erythrocytes, due either to structural abnormalities or to low numbers of circulating red blood cells. As a consequence, the oxygen-carrying capacity of the blood is diminished and the function of body tissues may become compromised.
- Antianaemic agents are indicated in the treatment of anaemias that are the result of nutritional deficiencies (vitamin B_{12}, folic acid, iron), chronic renal failure and bone-marrow suppression.
- Supplementation of the deficient nutrients overcomes nutritional anemias. Where appropriate, educate the patient about food sources rich in folic acid, vitamin B_{12} and iron. In chronic renal failure and aplastic anaemia, erythropoietin (as epoetin alfa) or anabolic agents may be used.

1 Identify a megaloblastic anaemia and its treatment.

2 Identify a hypochromic microcytic anaemia and its treatment.

3 Identify which of the following agents is/are not usually administered orally:
(a) folic acid;
(b) iron dextran;
(c) hydroxocobalamin;
(d) folinic acid;
(e) ferrous sulphate.

4 Explain the role of anabolic steroids in the treatment of aplastic anaemias. Which organ's function must be monitored closely during this therapy?

5 Anabolic steroid treatment of this condition has been largely superseded by therapy with which other drug?

6 Svetlana Lutkina, an 85-year-old patient, takes ferrous sulphate for iron deficiency anaemia. She complains to you about nausea and abdominal discomfort. What comfort measures would you recommend? (See Table 11.10 in Chapter 11 for assistance.)

7 Intramuscular iron injections are administered by the Z-track technique to avoid leakage of iron into the subcutaneous tissue and skin. Leakage can lead to irritation and staining. Describe how to perform an intramuscular injection using the Z-track technique.

8 How would you evaluate the effectiveness of iron therapy for iron deficiency anaemia?

9 Nicole Jansen, 22 years of age, is 5 weeks pregnant with her first child. She is concerned about becoming anaemic during pregnancy but does not want to take iron supplements unless she has to. What advice can you give her about non-pharmacological means of managing this situation?

10 Oral iron formulations should not be administered with tetracycline antibiotics. Explain the mechanism underlying this interaction. (See Chapter 15 for assistance.)

11 Explain why a patient receiving phenytoin antiseizure therapy may need to take a folic acid supplement.

50 DRUG SUMMARY TABLE: ANTIANAEMIC DRUGS

FAMILY NAME	GENERIC NAME	TRADE NAME(S)
Iron supplements	Ferrous gluconate	
	Ferrous sulphate	Ironorm Drops
		Feospan
		Ferrograd
	Ferrous fumarate	Fersaday
		Fersamal
		Galfer
	Ferrous glycine sulphate	Plesmet
	Polysaccharide-iron complex	Niferex
	Sodium federate	Sytron
	Iron dextran	CosmoFer
	Iron sucrose	Venofer
Folic acid supplements	Folic acid	Folicare
		Lexpec
Vitamin B_{12} supplements	Cyanocobalamin	Cytamen
	Hydroxocobalamin	Neo-Cytamen
Combined supplements*	Ferrous sulphate + Folic acid + Ascorbic acid	Fefol
		Ferrograd Folic
		Ferrograd C
	Ferrous fumarate + Folic acid	Galfer FA
		Pregaday
Miscellaneous	Darbepoetin alfa	Aranesp
	Erythropoietin	
	Epoetin alfa	Eprex
	Epoetin beta	NeoRecormon
	Nandrolone	Deca-Durabolin
	Testosterone enantate	Nebido

* There are a number of multivitamin/mineral supplements available that contain iron but are not listed here.

DRUGS USED TO MAINTAIN GAS EXCHANGE

51

CHAPTER FIFTY-ONE

OBJECTIVES

KEY TERMS

Bronchial asthma
Chemical mediators
Chronic bronchitis
Cystic fibrosis
Emphysema
Obstructive airways disorders
Oxygen
Respiratory distress syndrome

After completing this chapter, the reader should be able to:

- **briefly describe the pathophysiology of obstructive airways disease;**
- **compare the underlying pathophysiology of extrinsic and intrinsic asthma;**
- **describe the mechanism of action, common adverse effects and contraindications of the bronchodilators, inhaled corticosteroids, asthma prophylactics, leukotriene receptor antagonists, oxygen, respiratory stimulants and surfactants.**

THE PRINCIPAL RATIONALE FOR THE USE OF DRUGS IN THE treatment of respiratory illness is to maintain the patency of the respiratory tract and ensure effective gas exchange between blood and tissues. Obstruction to airflow through the respiratory tract may be due to constriction of bronchioles, increased mucus production and oedema, either within the wall of the air passageways or accumulating within the respiratory tract lumen. Problems can arise at any level within the respiratory tract, from nasal cavity to alveoli, and have a variety of aetiologies, including infectious (e.g. viral, fungal, bacterial), immune (e.g. allergies, asthma) and inflammatory (e.g. bronchitis, asthma, emphysema).

In this chapter, the drugs used in the treatment of lower respiratory tract disease, primarily obstructive airways diseases, are discussed, including bronchodilators, inhaled corticosteroids, asthma prophylactics, leukotriene receptor antagonists, oxygen therapy, respiratory stimulants and surfactants. In Chapter 52, medications used in the treatment of a variety of respiratory conditions (e.g. colds, influenza, allergy) are discussed; these include decongestants, expectorants, antihistamines, antimuscarinics and analgesics.

PATHOPHYSIOLOGICAL ASPECTS OF RESPIRATORY ILLNESS

The conditions affecting the air passageways and air sacs throughout the lungs proper are infections and obstructive airways diseases. Obstructive airways diseases are characterised by restricted expiratory airflow. Bronchial asthma is a reversible condition caused by bronchospasm, mucus hypersecretion and oedema. Chronic obstructive airways disorders (COADs), also referred to as chronic obstructive pulmonary disease (COPD), are a group of respiratory diseases characterised by chronic and recurrent obstruction of the airways. The term is usually associated with chronic bronchitis and emphysema. Cystic fibrosis, an inheritable disorder affecting exocrine gland function, leads to abnormal secretions that obstruct the airways and pancreatic ducts. It shares many of the characteristics of the COADs. In this section, the discussion focuses on bronchial asthma, although many of the drugs used in this therapy are applicable to the management of the COADs.

The Lung and Asthma Information Agency (LAIA) claims that the prevalence of asthma in the UK in children is at least 15 per cent and in adults approximately 7 per cent. Data from the European Respiratory Health Survey suggests that in the UK, about one-quarter of adults between 20 and 44 years of age suffer from wheeze, with a prevalence of doctor-diagnosed asthma of around 7 per cent. The evidence suggests an increasing prevalence and severity of asthma in children, resulting in hospitalisation, exercise intolerance and sleep disturbances. There are over 600 asthma-related deaths in people under the age of 75 years in the UK each year.

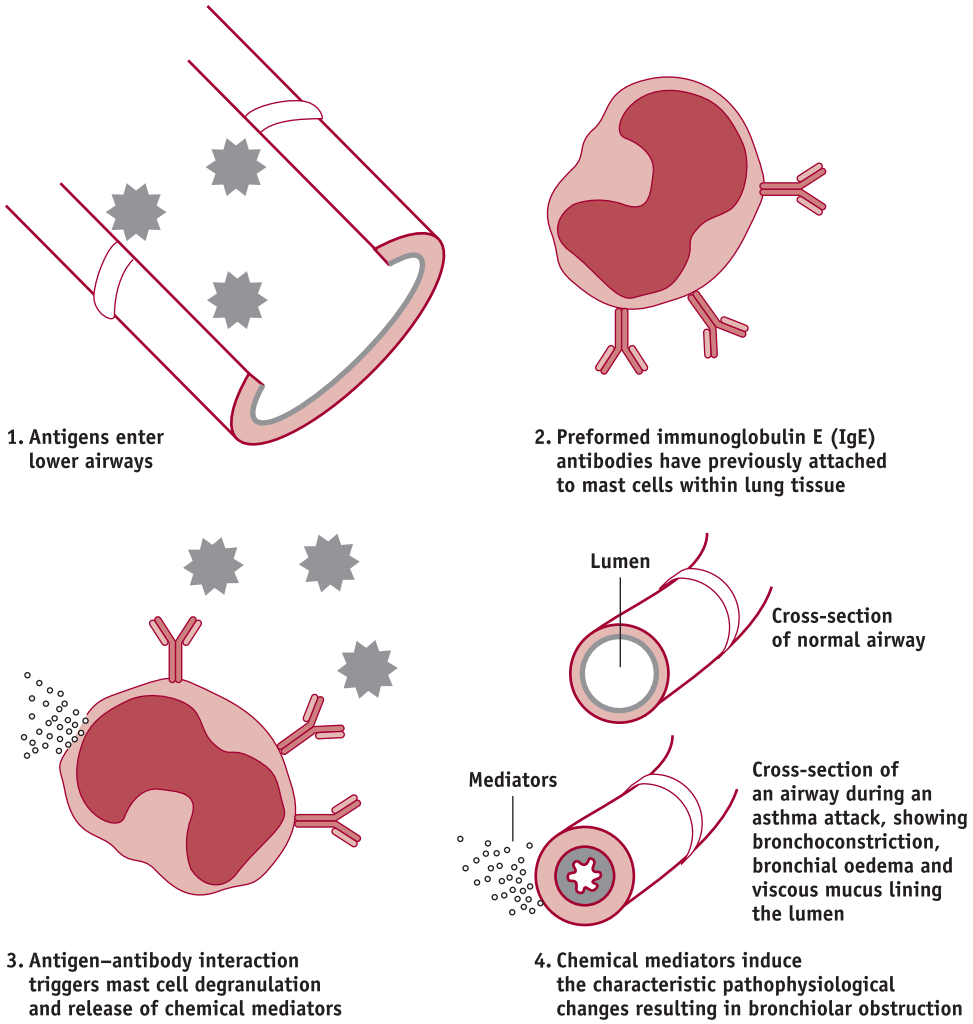
Bronchial asthma is characterised by a narrowing or complete obstruction of the air passageways leading to the alveoli. As a result, gaseous exchange is severely impaired. There are two forms of asthma: extrinsic and intrinsic. In extrinsic asthma, the aetiology is of an allergic nature. In an acute attack, the causative agent, an allergen (e.g. a pollen or grass), triggers the release of chemical mediators from lung tissue. The mediators, which include histamine, platelet activating factor (PAF) and the leukotrienes, induce vasodilation and increased permeability of pulmonary capillaries, viscous mucus production and severe constriction of bronchioles. The net effect of these pathophysiological changes is to narrow or totally obstruct the airways and lead to impaired gaseous exchange. The narrowed airways allow air to enter the alveoli but greatly impede the movement of air out of the lungs. The lungs become hyperinflated as the residual amount of air in the lungs between breaths increases. With repeated exposure to the causative agents, chronic inflammation develops, which leads to hyperreactivity of the airways.

This description does not really clarify the immune basis of this form of asthma, however. The tissues of the lungs are rich in mast cells, a tissue-bound form of the leukocyte subpopulation called basophils. Mast cells play a critical role in the development of respiratory conditions with an immune basis. The cytoplasm of these cells contains granules full of inflammatory mediators. When mast cell membranes rupture (a process known as mast cell degranulation), there is widespread release of chemical mediators, which results in bronchoconstriction, oedema and increased mucus production. The cause of degranulation is antibodies, providing the link to immunity. When an allergen enters the body for the first time, specific immunoglobulin E (IgE) antibodies are produced, which neutralise the foreign material. At the completion of this immune episode, excess IgE antibodies attach themselves to the cell membrane of mast cells. If the offending allergen enters the body again, it binds to the immunoglobulin, prompting the rupture of the mast cell membrane and the subsequent release of mediators (see Figure 51.1). Eosinophils, macrophages, T-lymphocytes and neutrophils also play a role in the pathophysiology of this form of asthma.

The intrinsic type of bronchial asthma is not triggered by allergens but is related more to an alteration in autonomic nervous system function. Intrinsic asthma is more common in people who develop the condition late in life. Intrinsic asthma is associated with an imbalance between sympathetic and parasympathetic stimulation of the bronchioles. Normally, sympathetic stimulation results in bronchodilation when we are stressed through activation of adrenergic β_2 receptors on bronchial smooth muscle. Parasympathetic stimulation elicits bronchoconstriction and increased mucus production while we are at rest through activation of the muscarinic receptors in bronchioles. In intrinsic asthma, the airways are considered hyperreactive, as the parasympathetic stimulation dominates (causing bronchoconstriction and viscous mucus production). Even though the aetiology is different, the pathophysiological changes that characterise intrinsic asthma result in a similar state to that observed during an attack of the extrinsic form. The types of stimuli that spark an acute attack are sudden changes in weather, infections and emotional states.

Chronic bronchitis, cystic fibrosis and emphysema are characterised by much the same kinds of pathophysiological changes: viscous mucus production, oedema and bronchoconstriction. In the genetic disorder cystic fibrosis, viscous mucus is produced, which obstructs the airways. Chronic bronchitis and emphysema are chronic inflammatory conditions brought about by exposure to environmental pollutants and cigarette smoke. During the development of these conditions, functional lung tissue is destroyed, leading to further impairment of gaseous exchange.

FIGURE 51.1 PATHOPHYSIOLOGY OF EXTRINSIC ASTHMA



RESPIRATORY PHARMACOLOGY

From the above discussion, it should be apparent that there are a number of drug classes that are useful in both preventing and alleviating the pathophysiological changes underlying respiratory illness.

Bronchodilators

Asthma is characterised by narrowed airways. One significant contribution to this pathophysiological change in airway diameter is bronchoconstriction. There are three groups of drugs that act to ameliorate this effect directly: β agonists, antimuscarinics and methylxanthines. In lay terms, bronchodilators are known as 'reliever' medications.

GENERAL MECHANISM OF ACTION

Each group triggers the same effect, bronchodilation, but by different means. The β agonists stimulate β-adrenergic receptors on bronchial smooth muscle. The antimuscarinic agents block muscarinic cholinergic receptors on bronchial smooth muscle. The methylxanthines elevate the levels of the intracellular messenger molecule cyclic adenosine monophosphate (cAMP), which modulates cellular activity. Because each drug group triggers the same response, these drugs can be used in combination to produce a greater effect than each used alone. This is an example of a synergistic drug interaction (see Chapter 15).

BETA AGONISTS

It is the β_2 receptor that mediates bronchodilation; β_1 receptors are associated with cardioacceleration. Because of the impairment of gaseous exchange that is a consequence of obstructive airways disease, cardiac stimulation is absolutely undesirable. Such effects may compromise heart function and lead to an anginal attack or myocardial

infarction. Therefore, the development and subsequent clinical use of specific β_2 agonists was necessary. Some residual heart stimulation is still observed following the administration of β_2 agonists, however. β_1 stimulation is more marked when these agents are given via a systemic route (oral or parenteral) rather than via inhalation.

Relatively selective β_2 agonists that are currently available include **salbutamol**, **formoterol** (eformotoral), **terbutaline**, **salmeterol** and **fenoterol**. **Bambuterol**, a prodrug of terbutaline, is also available in the UK. These agents are available in a variety of forms (inhalable, oral, injectable) depending on clinical need.

LONG-ACTING β_2 AGONISTS

Formoterol and salmeterol represent a new class of β_2 agonist because they are longer-acting agents. The bronchodilator effect may still be significant 12 hours after inhalation. Having said that, these drugs are not regarded as substitutes for the established β_2 agonists as therapy for the rapid reversal of an acute attack. Rather, they are recommended for the stabilisation of moderate persistent asthma and are regarded as adjunct therapy to the corticosteroids. In lay terms, they are known as 'symptom controller' medications. They do not replace the need for inhaled steroids and may actually mask growing airway inflammation that may lead to rapid lung deterioration and serious exacerbations of asthma. This means that patients using these drugs must also use an inhaled corticosteroid. The onset of action of formoterol appears to be faster than that of salmeterol (responses are observed within 3 minutes for the former compared with within 30 minutes for the latter).

SHORT-ACTING β_2 AGONISTS

Salbutamol is the most frequently used drug in this class. Inhaled salbutamol is effective within 5–15 minutes and has a 2–4-hour bronchodilator effect. It is used for the short-term relief of symptomatic asthma, but regular use does not provide any clinical benefit. When this inhaler is needed more than once daily, this suggests poorly controlled asthma and a corticosteroid inhaler should be considered.

◆ COMMON ADVERSE EFFECTS

The effects of the β_2 agonists are summarised in Figure 51.2. Common adverse reactions include fine muscle tremor, palpitations, peripheral vasodilation resulting in hypotension and headache (see Chapter 26 for a more detailed discussion). The only contraindications to be noted are hypersensitivity and hyperthyroidism. The drugs should be used with caution in patients with cardiovascular disease, arrhythmias, susceptibility to QT-interval prolongation and hypertension. The non-selective adrenergic agent ephedrine can also be used as a bronchodilator.

✚ CLINICAL CONSIDERATIONS

The patient should be advised to see their doctor if they are using their preparation in higher doses or more frequently than prescribed. For instance, if a short-acting β_2 agonist is required more than three or four times weekly, then a preventive anti-inflammatory preparation may also be considered.

It is important to note that severe hypokalaemia can occur with high doses of β_2 agonists. This effect may be aggravated by concomitant treatment with methylxanthines, corticosteroids and diuretics; it is also affected by hypoxia. Serum potassium levels are therefore monitored in cases of severe asthma.

ALPHA AND BETA AGONIST

EPHEDRINE

Ephedrine may be used in asthma management. It is less useful and less safe than the selective β_2 agonists because it is more likely to cause arrhythmias and other side effects. Its use should be avoided whenever possible. Ephedrine produces bronchodilation by activating β receptors and reduces oedema through pulmonary vasoconstriction via stimulation of α receptors. Adrenergic stimulation is achieved through a combination of direct and indirect activity (see Chapter 26).

ANTIMUSCARINIC AGENTS

■ MECHANISM OF ACTION

The synthetic atropine-like antimuscarinic agents **ipratropium** and **tiotropium** block muscarinic receptors associated with parasympathetic stimulation of the bronchial air passageways. Bronchodilation results and, in theory, viscous mucus secretion connected with obstructive airways disease is reduced. The onset of action is slower than that of the β_2 agonists (maximum effect in 30–60 minutes), but the duration of the effects tends to be more prolonged (3–6 hours). This is due to the slower absorption of ipratropium across biological membranes.

◆ COMMON ADVERSE EFFECTS

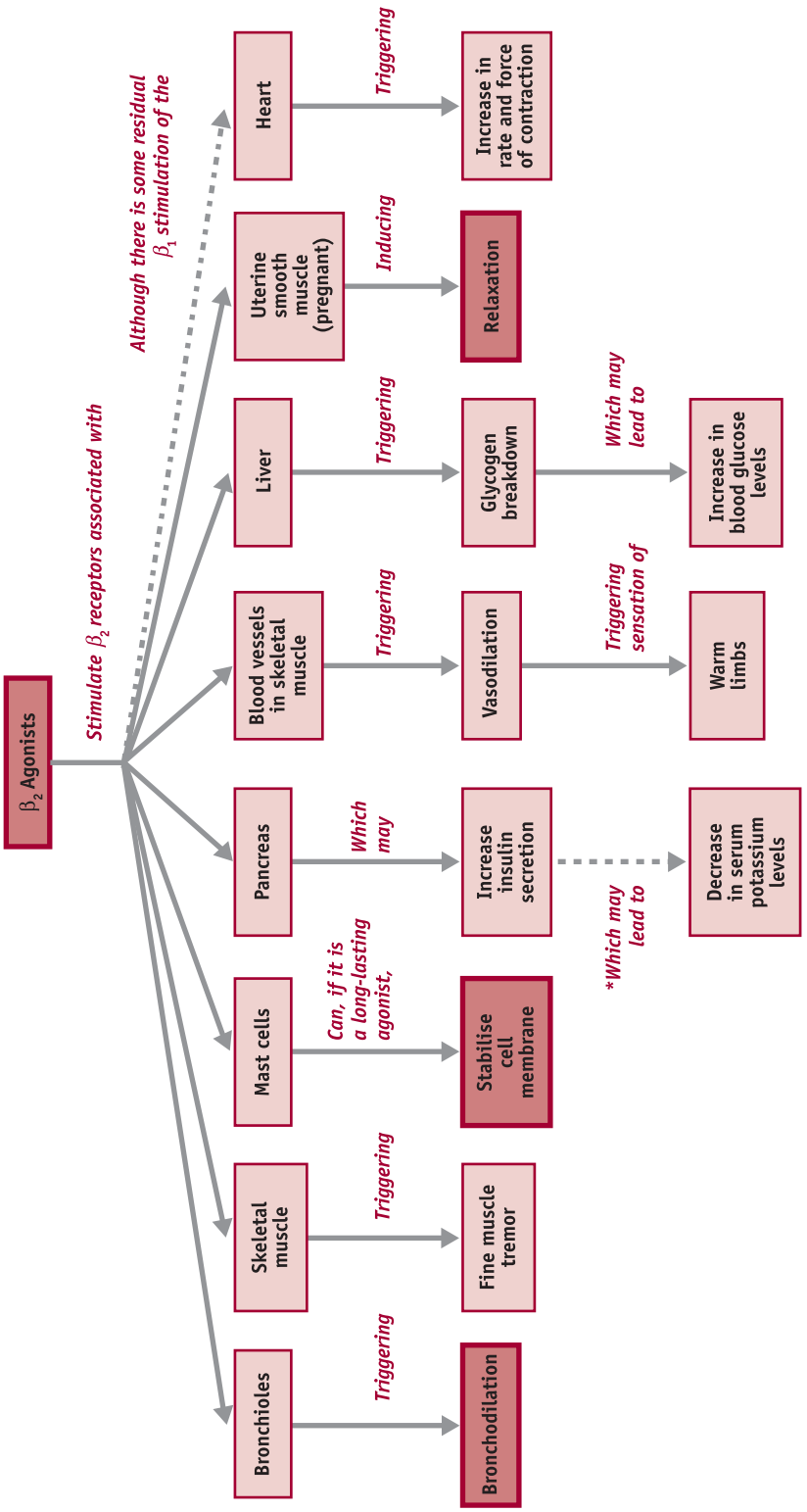
The effects of the antimuscarinic agents are summarised in Figure 51.3. Common adverse reactions associated with this treatment are of an antimuscarinic nature, such as dry mouth. Administering these drugs via the inhaled route greatly decreases systemic absorption. On occasion, however, urinary retention, pupil dilation and glaucoma have been reported after inhalation.

✚ CLINICAL CONSIDERATIONS

Clinical trials have indicated that tiotropium may be more effective than ipratropium in the long-term management of bronchospasm and dyspnoea related to COPD. Tiotropium

FIGURE 51.2 FLOWCHART SHOWING THE EFFECTS OF β_2 AGONISTS

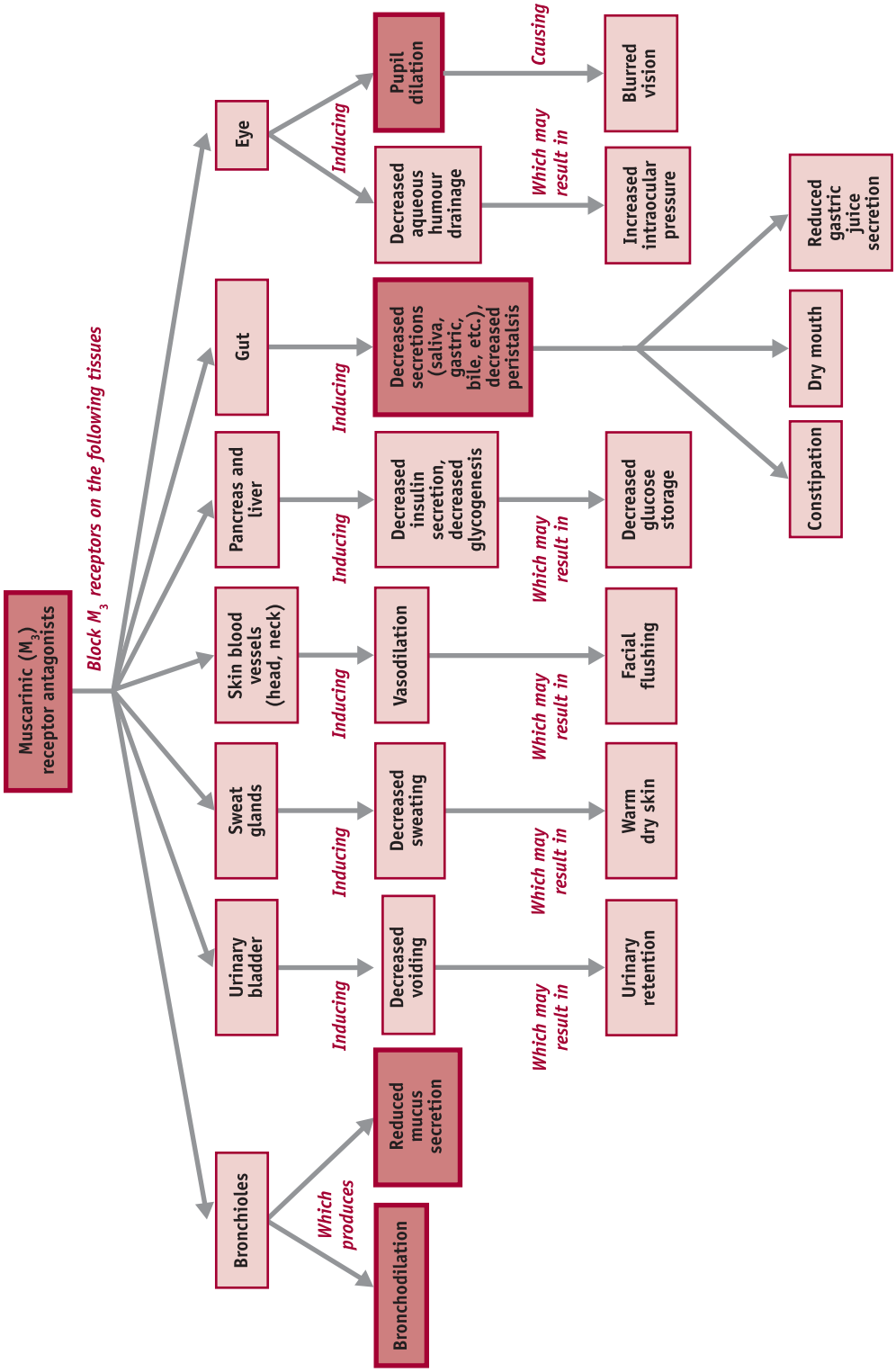
General therapeutic effects shown in the darker shaded boxes.



* More likely when systemic absorption is greater, e.g. after intravenous injection or frequent nebuliser use.

FIGURE 51.3 FLOWCHART SHOWING THE EFFECTS OF ANTIMUSCARINIC AGENTS

General therapeutic effects shown in the darker shaded boxes.



appears to be quite potent and has a significantly prolonged half-life of around 5 days compared with around 4 hours for ipratropium. Tiotropium is not suitable for the relief of acute bronchospasm.

Antimuscarinic bronchodilator therapy is used mainly when treatment with a β_2 agonist alone is inadequate. It is common for ipratropium to be administered concurrently with a β_2 agonist because the degree of bronchodilation produced is greater than that obtained using either agent alone. A mixture of ipratropium with a β_2 agonist is compatible within a nebulising solution. Combined inhalant preparations are also available. Administering the two bronchodilators in the same preparation simultaneously is convenient; the disadvantage, however, is that the range of potential adverse reactions is expanded because of the combined adrenergic and antimuscarinic actions.

Advise the patient to rinse their mouth following antimuscarinic therapy as preparations in this group commonly cause dry mouth.

When using nebuliser formulations, patients need to be warned not to get the solution near their eyes. If accidential spillage in the eye occurs, the eye area should be rinsed with copious amounts of water. Medical assistance should be sought if there are symptoms of eye pain, discomfort, blurred vision or changes in coloured vision.

METHYLXANTHINES

■ MECHANISM OF ACTION

The methylxanthines **theophylline** and **aminophylline** induce bronchodilation through a mechanism that bypasses the interaction with an extracellular receptor, either adrenergic or cholinergic. The intracellular chemical cAMP acts as a second messenger and is activated after an adrenergic receptor is stimulated by the sympathetic nervous system or agonist drugs (see Chapters 16 and 26). cAMP then catalyses a number of metabolic reactions within the cell, resulting in increased cellular activity. The higher the intracellular levels of cAMP, the higher the level of cell activity. The methylxanthines prevent the degradation of cAMP by phosphodiesterases, and the resultant increase in bronchial smooth-muscle cell activity leads to bronchodilation. In other words, the methylxanthines are phosphodiesterase inhibitors.

All clinical methylxanthines are essentially derivatives of theophylline, modified to enhance solubility. Aminophylline is a combination of theophylline and ethylenediamine. **Caffeine**, a constituent of many foods and beverages, is also a methylxanthine, but its bronchodilator action is very weak.

There is a lack of specificity in the action of the methylxanthines. Bronchial smooth-muscle cells are not the only body cells containing cAMP; other muscle cells and nerve cells also contain this substance, and in the presence of methylxanthines their activity also increases. Therefore, theophylline and aminophylline are general body stimulants, in the same way as caffeine, but with a narrower margin of safety at therapeutic levels. Furthermore, as any coffee-drinker knows, methylxanthines are weak diuretic agents; tolerance to this effect develops quickly.

◆ COMMON ADVERSE EFFECTS

The effects of the methylxanthines are summarised in Figure 51.4. The types of adverse reaction to expect relate mainly to nervous system overstimulation and include insomnia, anxiety, nervousness, epigastric distress, nausea, vomiting and tachycardia. The magnitude of these adverse effects is dose-related. More serious reactions include seizures and ventricular dysrhythmias.

✚ CLINICAL CONSIDERATIONS

Nowadays, theophylline and aminophylline are restricted to use in moderate to severe asthma where frequent bronchodilator therapy is required despite maximum doses of oral or inhaled corticosteroids. Usually, aminophylline injection is restricted to severe acute attacks of asthma, and only if no theophylline has been taken in the previous week. This is due to the long half-life and low therapeutic index of the methylxanthines.

Sustained-release forms of theophylline are not appropriate in the treatment of acute asthma attacks, but low-dose theophylline treatment may be useful as a preventive measure in children whose asthma is controlled poorly with moderate doses of inhaled corticosteroids. Theophylline should be used with caution in elderly people; the reductions in liver function and cardiac output associated with ageing (see Chapter 20) tend to produce more unpredictable effects during therapy, and elderly people appear more susceptible to the development of adverse effects.

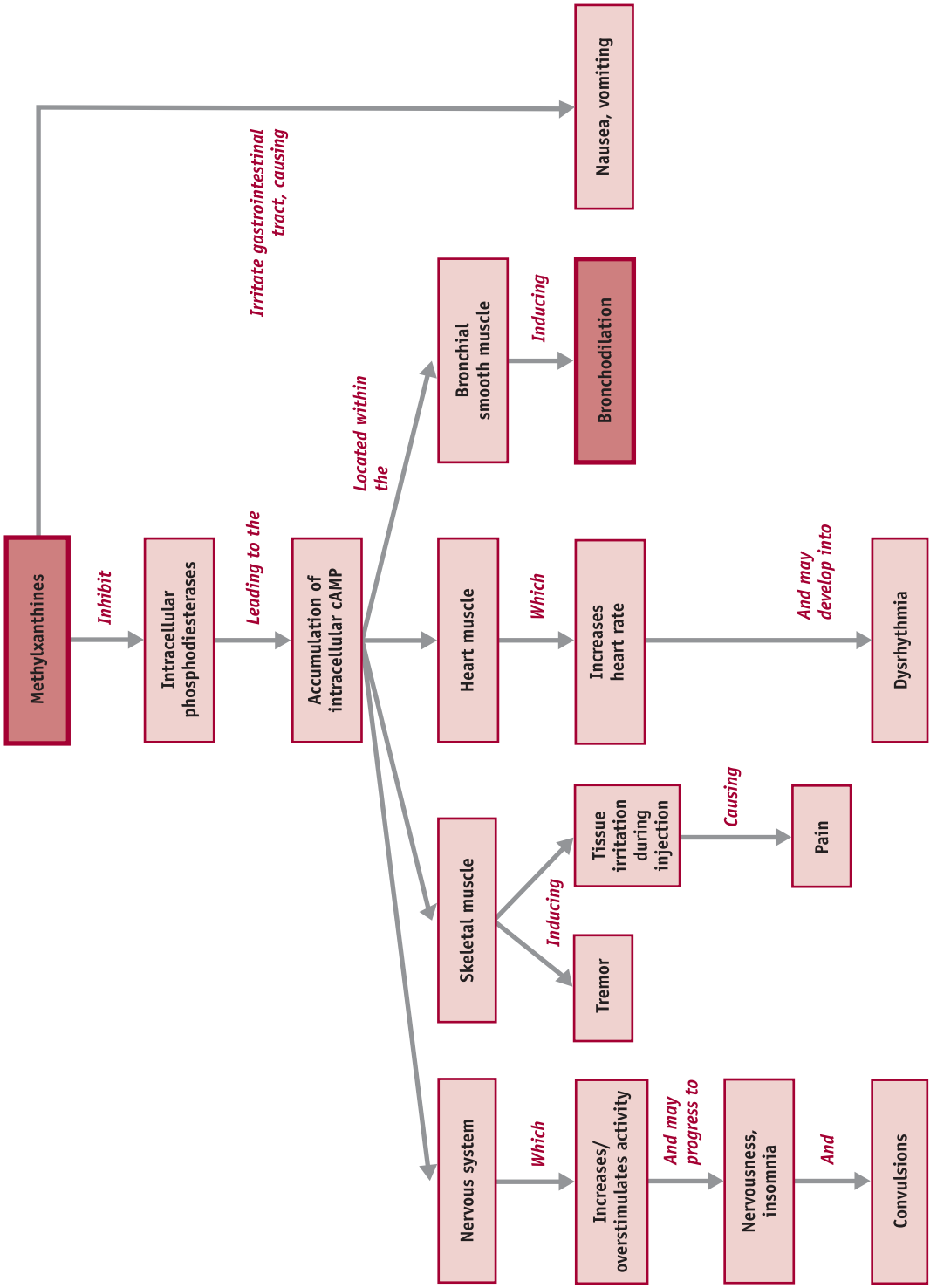
The narrow therapeutic index of the methylxanthines means that dosage needs to be carefully adjusted and controlled according to drug concentrations. Adverse effects can be reduced by using a low initial dose and by gradually increasing the dose at 3-day or longer intervals.

Inhaled corticosteroids

The corticosteroids are potent anti-inflammatory agents. There are a number of serious toxic reactions associated with systemic administration (see Chapter 58). Topical administration direct to the site of inflammation, in this case inhaled into the bronchial airways, greatly reduces the development of systemic adverse effects. Inhaled corticosteroids are very effective preventive agents that reduce clinical manifestations, airway inflammation and hyperresponsiveness. In lay terms, the inhaled corticosteroids belong in the ‘preventer’ class of medications.

FIGURE 51.4 FLOWCHART SHOWING THE EFFECTS OF METHYLXANTHINE BRONCHODILATORS

Desired therapeutic effects shown in the darker shaded box.



cAMP, cyclic adenosine monophosphate.

■ MECHANISM OF ACTION

The anti-inflammatory effects produced by these drugs are described in detail in Chapter 58, and so they will be mentioned only briefly here. The rupture of mast cells is inhibited, the synthesis of inflammatory mediators is diminished, new antibody production is halted, and the activity of immune cells (especially lymphocytes and macrophages) is suppressed. With the diminution of these effects, the magnitude of the dependent pathophysiological changes (oedema, mucus production, bronchoconstriction) is also lessened. The clinical effects of these drugs do not occur immediately after administration but take many hours to develop.

◆ COMMON ADVERSE EFFECTS

Common adverse reactions are the development of an opportunistic infection of *Candida albicans* in the pharynx, commonly known as thrush, and a hoarse voice. Thrush occurs as a result of a suppression of immune function of the pharyngeal mucosa by the corticosteroid, which adheres to its surface. The risk of this occurring is reduced if the patient gargles water after steroid inhalation and if a spacer is used.

There is some controversy associated with the use of inhaled corticosteroids and their effects on the growth of children. There is evidence that these agents suppress the hypothalamic–pituitary axis, especially at high doses and during prolonged therapy. Clinical studies have found short-term growth disturbances in children with mild asthma, but this effect was not sustained in the long term as the children reached normal adult height. Data are also emerging that these drugs may affect bone mineralisation and trigger adrenal suppression, resulting in a drug-induced Cushing's syndrome.

✚ CLINICAL CONSIDERATIONS

Although the corticosteroids are not bronchodilators, they do enhance the bronchodilator effect of β_2 agonists. Concomitant use with a bronchodilator should also enable the anti-inflammatory agent to penetrate the smaller airways, the site of inflammation, more deeply. For a patient with persistent asthma, regular use is required in order to achieve optimal therapeutic benefit. Inhaled corticosteroid treatment has been shown to improve the symptoms of asthma, increase lung function and decrease airway hyperreactivity. Inhaled corticosteroid therapy is useless in an acute asthma attack, however.

Three corticosteroids – **beclomethasone**, **budesonide** and **fluticasone** – are available as inhalants. Beclomethasone is the least potent of the inhaled corticosteroids, while fluticasone is the most potent. The bioavailability of these agents is poor, and they produce negligible systemic reactions. The therapeutic approach when using inhaled corticosteroids usually involves high daily doses to gain control of the condition, followed by progressive reductions in dose to the lowest possible level.

Inhaled corticosteroids should be considered if short-acting β_2 agonists are used more than three or four times weekly. The mouth should be rinsed after inhalation to prevent oropharyngeal candidiasis and systemic absorption. The eyes should be covered during nebulisation to prevent accidental spillage. Alternatively, a mouthpiece could be used instead of a mask during nebulisation to avoid increasing the systemic risk of glaucoma and cataract formation.

If control is achieved, the dose is stepped down by 25 per cent every 3 months under medical supervision. The dose of inhaled corticosteroid may be increased temporarily at times when asthma symptoms have deteriorated or when a respiratory tract infection is present.

Use of systemic corticosteroids in asthma

Systemic corticosteroid therapy may be used in the management of respiratory disorders such as asthma. These agents may be administered orally or intravenously and have a significant role to play in the management of acute asthma attacks. Clinical studies have found that systemic therapy reduces the severity and duration of an acute attack and prevents relapse. **Prednisolone** and **prednisone** are commonly used in oral therapy. The course of treatment is short, lasting either a few days or weeks, so as to achieve better control of the condition but avoid significant side effects. **Dexamethasone** and **hydrocortisone** are used as intravenous agents in the treatment of acute asthma attacks.

◆ COMMON ADVERSE EFFECTS

Common adverse effects include suppression of the hypothalamic–pituitary axis (as evidenced by a reduction in cortisol secretion), hyperglycaemia, hypokalaemia, fluid retention and increased susceptibility to infection. Adverse effects are uncommon, but patients should be monitored for the above reactions.

✚ CLINICAL CONSIDERATIONS

Inhaled corticosteroids are preferred to systemic corticosteroids because of the lower risk of adverse effects. Oral preparations are useful for acute exacerbations but, if possible, they should not be used for more than 2 weeks. If oral corticosteroids are used for this length of time, they can be stopped abruptly without tapering the dose. Long-term use of oral corticosteroids should be tapered gradually to prevent an adrenal crisis.

Prophylactic asthma preparations

CROMOGLYCATE AND NEDOCROMIL

Sodium cromoglycate and **nedocromil sodium** are topical prophylactic agents that can be used in asthma management. They belong in the 'preventer' group of

medications. These drugs are particularly effective in the management of asthma in children. They have been shown to reduce the frequency and severity of acute attacks.

■ MECHANISM OF ACTION

When inhaled, these drugs prevent the release of inflammatory mediators from sensitised mast cells; therefore, they reduce the incidence of acute asthma attacks. These drugs are useless as therapy in an acute attack, however, because the mast cells have already ruptured at that point. Evidence suggests that nedocromil sodium may be a more effective agent than sodium cromoglycate, but research findings have been inconsistent. Cromoglycate can also be used to prevent the non-productive cough adversely associated with angiotensin-converting enzyme (ACE) inhibitor therapy (see Chapters 44 and 48). This cough is believed to be associated with chemical mediator action, the most likely protagonists being bradykinin and a prostaglandin.

◆ COMMON ADVERSE EFFECTS

Sodium cromoglycate and nedocromil sodium are relatively non-toxic in most patients, with negligible systemic side effects. Common side effects are an unpleasant taste and respiratory tract irritation characterised by coughing. The greatest concern is hypersensitivity to the preparation; if this occurs, therapy should be abandoned.

KETOTIFEN

Another prophylactic agent is **ketotifen**. This is administered orally.

■ MECHANISM OF ACTION

Ketotifen acts to diminish the release of and responsiveness to the inflammatory mediators histamine, leukotrienes and PAF. All of these mediators contribute to the pathophysiological changes related to asthma, especially bronchodilation. Again, like sodium cromoglycate, ketotifen is of negligible use in an established asthma attack.

Ketotifen is also an effective antihistamine preparation, making it useful in the treatment of other allergic conditions, such as allergic rhinitis and urticaria.

◆ COMMON ADVERSE EFFECTS

As with other antihistamines, the adverse reactions associated with the use of ketotifen include sedation and antimuscarinic effects, such as dry mouth.

✚ CLINICAL CONSIDERATIONS

The above prophylactic asthma preparations can be introduced in the asthma therapy regimen to reduce the dosage of inhaled corticosteroids. As such, they are considered useful preventive preparations in young children because of the lower incidence of adverse effects. Adverse effects relating to cough and throat irritation can be reduced by rinsing the mouth and throat immediately following use.

LEUKOTRIENE RECEPTOR ANTAGONISTS

The leukotriene receptor antagonists are a novel group of antiasthma drugs. They are recommended for use in addition to other drugs in the management of asthma.

Leukotrienes are inflammatory mediators related closely to the prostaglandins and thromboxanes and belong in a group known as the eicosanoids (see Chapter 30). Like other eicosanoids, they are synthesised from arachidonic acid, which itself is formed from cell-membrane phospholipids. Leukotrienes cannot be stored within cells; they are produced in response to immune challenge. Three leukotrienes are associated with asthma (LTC_4, LTD_4, LTE_3) and are produced by inflammatory cells, particularly mast cells and eosinophils. The large and small airways bear specific receptors for these leukotrienes. They trigger smooth-muscle contraction, mucus secretion and airway-wall oedema. It has been shown that the leukotrienes are approximately 1000 times more potent than histamine in their ability to contract bronchial smooth muscle.

■ MECHANISM OF ACTION

The leukotriene receptor antagonists block the action of the leukotrienes in the airways, alleviating the inflammation and bronchoconstriction associated with asthma. The leukotriene receptor antagonists approved for use in the treatment and prevention of asthma in the UK are **zafirlukast** and **montelukast**. At this time their use is restricted to patients over 2 years of age. The literature suggests that the leukotriene receptor antagonists have little or no clinical benefit in an acute attack; thus, in practice, it would appear that their role in treatment is as preventive medication.

◆ COMMON ADVERSE EFFECTS

Common adverse reactions include headache and gastrointestinal upsets. Occasionally there have been elevations of liver enzymes, but this has not been significant.

✚ CLINICAL CONSIDERATIONS

In clinical studies comparing the inhaled corticosteroid beclomethasone with the leukotriene receptor antagonists, the latter were at least as effective as the corticosteroid. Montelukast has reportedly reduced the dose of β_2 agonist required by patients with asthma.

A gradual reduction in the dose of inhaled corticosteroids can be attempted under appropriate medical supervision.

Patients need to be reminded that these preparations are used to prevent an asthma attack rather than to relieve asthma symptoms. It is also important to note that these drugs should not be substituted abruptly for inhaled or oral corticosteroid therapy.

Rarely, a drug-induced hepatitis can develop. The patient must inform their doctor immediately if they have nausea, vomiting, loss of appetite, dark urine or jaundice.

APPROACHES TO ASTHMA THERAPY

In accordance with the National Asthma Campaign, the long-term aims in asthma management involve abolishing the symptoms, maintaining the best possible lung function, preventing the development of permanent lung impairment, reducing mortality resulting from acute attack, and avoiding unnecessary drug side effects. The person with asthma needs to identify and avoid triggers of an acute attack; common triggers include airborne allergens, fumes, air pollution, certain foods and respiratory infections. After an initial assessment, the patient must maintain regular contact with a skilled health-care professional for follow-up, support and education.

In terms of drug therapy for chronic asthma, inhalation is the preferred route of administration in order to deliver drugs to the desired site directly and to minimise systemic side effects. The first-line therapy is preventive, to stabilise and reduce the chronic inflammation of the airways using inhaled corticosteroids and/or asthma prophylactic agents. An inhaled β_2 agonist may be administered before exposure to a known trigger.

In an acute attack in an adult, a combination of bronchodilators is given via a nebuliser. A nebuliser allows deeper penetration of the drug aerosol into the bronchial tree. The dose and frequency of administration is determined by the severity of the attack. Peak-flow monitoring is used as a measurement of lung function. Oral or parenteral corticosteroids should also be given in an acute attack. The route of administration and, therefore, the choice of steroid used is often dictated by the severity of the attack. Oxygen therapy is required when the oxygen saturation of the blood falls to 93 per cent.

Care must be taken in the management of acute asthma in young children. Children can get very distressed during an asthma attack, leading to a difficulty in coordinating their breathing activity. For an acute asthma attack in a young child, it is important to correct the hypoxia using supplemental oxygen and to reverse the airway obstruction rapidly by the use of inhaled β_2 agonists and oral or parenteral corticosteroids. Peak-flow monitoring is not recommended for children as it is difficult to place a high degree of accuracy on the result. Acute management involves the administration of an inhaled β_2 agonist, such as salbutamol, by a metered-dose inhaler device or a metered-dose inhaler with a spacer device. A corticosteroid preparation may also be administered orally as a mixture or tablet, or parenterally by the intramuscular or intravenous route. Nebulisation is no longer used in paediatric emergency departments, as it has been shown to be less efficient, more difficult to administer, more expensive and less portable than metered-dose inhalers and spacer devices.

TABLE 51.1 SIGNS OF POOR ASTHMA CONTROL

The patient uses medication for symptomatic relief more than three times per week (not during times of illness or exercise)
The patient has symptoms of asthma on most days of the week, e.g. wheezing, coughing
The patient has early-morning or night-time symptoms at least once a week
The patient has frequent exacerbations of asthma (at least every 6 weeks)
The patient has poor levels of peak expiratory flow (less than 80 per cent of the patient's best score)
Attacks may occur infrequently, but they are life-threatening or severe, e.g. requiring emergency-department admission

Table 51.1 provides information on the signs of poor asthma control, while Table 51.2 indicates how to help patients achieve control with the use of their preparations and, therefore, improve adherence.

An important clinical consideration associated with some aerosols is that the same proprietary name may be

TABLE 51.2 HELPING THE PATIENT WITH ASTHMA TO ACHIEVE MEDICATION ADHERENCE

Ask the patient to demonstrate how to use their device, e.g. spacer, metered-dose inhaler, dry powder inhaler, nebuliser
Determine whether the patient knows when to administer particular medications
Determine whether the patient knows which medications to administer at particular times, i.e. prophylactically and during an asthma attack
Determine whether the patient knows how frequently to administer the medications
Counsel the patient about the medication regimen regularly
Check that the patient understands how the asthma medications work
Ensure that the patient attends an asthma review with a medical doctor at least annually

available in different formulations. If a patient is switched from the standard formulation to a 'forte' preparation, they must be cautioned about the number of times they should consecutively self-administer the drug. If the patient is used to three consecutive puffs with the standard formulation, then the same manoeuvre with a forte preparation may lead to overstimulation and the onset of stronger side effects. In this case, the number of consecutive puffs may need to be reduced to two. Aerosols that are available in forte formulations are listed in the drug summary table at the end of this chapter.

OXYGEN THERAPY

Oxygen is administered therapeutically to correct tissue hypoxia resulting from respiratory failure, anaemia, cardiovascular deficiencies and breathing air comprising low oxygen, e.g. at high altitudes. Oxygen can also be given as an antidote in carbon monoxide poisoning in order to displace carbon monoxide molecules bound to haemoglobin (see Chapter 21). Oxygen therapy is a medical order and has the potential for adverse reactions and toxicity; as such, it is regarded here as a drug. It can be administered as pure oxygen or mixed with air or other gases.

From respiratory physiology, you may know that the pO_2 of systemic arterial blood is normally around 12 kPa. Another way of saying this is that each 100 ml of systemic arterial blood contains 19.6 ml of oxygen. Hence, the oxygen content of systemic arterial blood is expressed as 19.6 vol%. Approximately 98 per cent of this oxygen (or 19.2 vol%) is bound to haemoglobin, while the remainder is dissolved within the plasma (0.4 vol%). When pure oxygen is administered, haemoglobin becomes completely saturated (20.1 vol%) and the component of oxygen dissolved in plasma rises to about 2.0 vol%. In effect, the systemic arterial pO_2 goes from about 12 kPa to 76 kPa – more than five times that of normal levels.

Pure oxygen can be administered continuously for only a short time (approximately 12 hours) before toxicity arises. An inflammatory response develops as a result of irritation to the air passageways, which subsequently leads to airway obstruction. If the alveoli that become obstructed contain only pure oxygen, then complete absorption of the gas follows, causing the air sacs to collapse, i.e. atelectasis.

Another important consideration in oxygen therapy is that patients with a long history of COAD adapt to lower systemic arterial pO_2 levels of around 7.3 kPa, and the stimulus to breathe changes from pCO_2 levels to low pO_2 levels; this is known as hypoxic drive. When oxygen therapy is indicated, the rate of administration should be altered to elevate arterial pO_2 levels back to around 7.3 kPa, not 12 kPa. The consequence of an arterial pO_2 level significantly higher than 7.3 kPa is that the stimulus to breathe is inhibited, resulting in apnoea.

Premature infants given oxygen therapy over a long period can develop retinal damage. This occurs because the therapy induces high concentrations of oxygen in the retina, which inhibits the development of its normal vasculature. When therapy ceases, the tissue becomes hypoxic, resulting in the proliferation of blood vessels, which can lead to retinal detachment.

Oxygen can also be administered at pressures greater than atmospheric, usually at two or three atmospheres; this is called *hyperbaric therapy*. At three atmospheres, the amount of dissolved oxygen carried in plasma rises to about 6 vol% (remember that haemoglobin is fully saturated), corresponding to a systemic arterial pO_2 of just under 266 kPa, nearly 20 times normal levels.

Oxygen can be used to treat tissue hypoxia associated with ischaemic disease and carbon monoxide poisoning, in the treatment of gangrene, and as an adjunct in the radiotherapy of tumours. In the latter case, hypoxic tumour cells that have outgrown their blood supply are resistant to radiation. A rise in pO_2 makes the cancerous cells more susceptible. With hyperbaric therapy, the potential for oxygen toxicity is enhanced, as is the risk of decompression sickness.

✚ CLINICAL CONSIDERATIONS

To avoid potential adverse effects of oxygen therapy, it is important that the dose delivered is titrated against oxygen saturation and oxygen blood levels. Oxygen saturation can be obtained readily by taking an oximeter reading; oxygen blood concentration can be obtained by arterial blood gas analysis.

RESPIRATORY STIMULANTS

Doxapram is a short-acting intravenously administered respiratory stimulant used occasionally in the UK for the treatment of COAD where there is acute hypercapnia.

■ MECHANISM OF ACTION

Primarily, doxapram acts by stimulating the respiratory centres in the medulla. With improved ventilation, more carbon dioxide is removed by the lungs.

◆ COMMON ADVERSE EFFECTS

As doxapram is a centrally acting stimulant, there is often a general increase in nervous system activity during therapy. Therefore, adverse effects derived from this stimulation include hyperactivity, disorientation, increased muscle tone (which may lead to spasms), dyspnoea, diarrhoea, chest tightness and palpitations.

An increase in blood pressure and tachycardia are commonly observed after administration. This is triggered indirectly through the release of noradrenaline from peripheral nerves.

✚ CLINICAL CONSIDERATIONS

Doxapram is used only in intensive care units, as the patient requires careful assessment of cardiac rate and rhythm, blood pressure and oxygen blood concentration.

SURFACTANTS

The walls of the alveoli are coated with a liquid film that assists the natural recoil of the lungs during expiration. The air sacs would collapse completely between breaths if it were not for the secretion of substances called surfactants. Surfactants act to reduce the surface tension of this film and thus keep the alveoli patent.

Surfactants are first secreted before we are born, but not until quite late in gestation. Some infants born prematurely experience a deficiency in surfactant levels, which leads to respiratory distress syndrome (RDS). In this condition, mechanical ventilation is necessary to keep the alveoli open between breaths; the mortality rate is high. An artificial surfactant, **colfosceril**, has been shown to improve lung function and reduce mortality in premature babies with RDS. Colfosceril is sprayed down the endotracheal tube of the premature neonate with RDS. A maximum of two doses, 12 hours apart, is recommended. The use of this drug is contraindicated in infants weighing less than 700 g because of the risk of pulmonary haemorrhage.

Another agent, **beractant**, is available for the treatment of RDS. This is an extract of bovine lung, with colfosceril and other phospholipids added to it. Its advantage is that it can also be used to prevent RDS; in order to be effective for this purpose, it must be given within minutes of birth. Like colfosceril, beractant must be administered into the trachea of the intubated infant.

✚ CLINICAL CONSIDERATIONS

Surfactants are administered only by experienced paediatric health-care professionals employed in neonatal intensive care units. As these drugs can cause bradycardia, decreased oxygen saturation and endotracheal tube obstruction during administration, it is important to regularly evaluate cardiac rate and rhythm, oxygen concentration and patency of the airway.

CLINICAL MANAGEMENT

Agents for the lower respiratory tract

Assessment

- Assess for manifestations of asthma, including shortness of breath, cough, feeling of tightness in the chest, dyspnoea, tachypnoea, expiratory wheeze, rapid and shallow respirations, fatigue, cyanosis, confusion and lethargy. Compare with subsequent observations.
- Check vital signs. Determine the amount and characteristics of bronchial secretions. Compare with subsequent observations.
- Auscultate breath sounds for the presence of wheeze. Auscultate the chest before and immediately after therapy.
- Determine peak-flow meter readings before and immediately after therapy.
- Determine arterial blood gas levels, which may indicate hypoxia or hypercapnia.
- Assess tolerance for activities and ability to perform activities.
- Assess precipitating factors for asthma, including pollens, moulds, dust, animal dander, viral infection, foods (nuts, shellfish, eggs), food additives (tartrazine, metabisulphites), medications (beta-blockers, aspirin), complementary therapies (echinacea, royal jelly), exercise, extremes in temperature, cigarette smoke, humidity, fumes and stress.

Planning

- The patient will achieve symptomatic relief of dyspnoea and wheezing.
- The patient will be aware of precipitating factors of the asthma and will endeavour to take measures to avoid these factors.

Implementation

- Monitor effect of the agent in treating the manifestations of asthma.
- Monitor vital signs and determine the amount and characteristics of bronchial secretions immediately after therapy.
- Provide for adequate hydration. Fluids lower the stickiness of bronchial secretions.
- Assess blood glucose levels in patients with diabetes, as bronchodilators can produce hyperglycaemia.
- Regularly monitor serum theophylline levels.
- Provide respiratory therapy by postural drainage and percussing. These techniques help to loosen and mobilise secretions.
- Ensure that the patient is sitting upright when taking nebulisation or inhalation therapy. This position aids the expansion of lungs and provides a greater surface area of lung tissue on which the therapy can act.

- As anxiety and fear can aggravate an asthma attack, adopt a calm and reassuring manner when caring for the patient.
- Administer oxygen therapy as required to treat hypoxia. Oxygen given at a high flow rate in severe acute asthma can achieve an inspired oxygen concentration of 40–60 per cent.
- Following methylxanthine therapy, monitor vital signs. As hypotension may occur, the patient should be supervised during ambulation.
- Intravenous aminophylline infusions should be administered through a volumetric pump at a rate no faster than 20 mg/minute. As aminophylline is incompatible with several drugs, a separate infusion line should be used.
- Antibacterial agents may be used for specific infections associated with an asthma attack. It is important not to confuse mucus and productive cough (both common manifestations of asthma) with an infection.
- Cromoglycate and nedocromil are especially recommended for children, given the possible adverse effects of corticosteroid medications.
- If oral corticosteroid medications are used for periods longer than 7–14 days, the dose should be tapered gradually and an inhaled corticosteroid added before reducing the oral dose.
- Spacer devices are particularly useful in young children and infants because they require less hand–breath coordination and are more efficient than metered-dose inhalers.
- Hypokalaemia may occur with high doses of β_2 agonists, which may be exacerbated by concomitant use of methylxanthines, corticosteroids, diuretics and hypoxia. It is, therefore, important to monitor the potassium concentration in situations of severe asthma.
- Pulmonary surfactants may cause transient bradycardia, decreased oxygen saturation and endotracheal (breathing) tube obstruction. As a result, they should be administered only by specialist medical and nursing staff in neonatal intensive care units.

Patient teaching

- Advise the patient on the correct use of inhalers, spacers or nebulisers, depending on what has been prescribed (see Tables 7.17 and 7.18 in Chapter 7 for further information).
- Advise the patient to follow the prescribed dosage levels, as overuse of the preparation may lead to tolerance and adverse effects. If the prescribed dose becomes ineffective, the patient should visit the doctor to obtain a review of medications.
- Teach the patient how to monitor the pulse rate after treatment. Tachycardia is an adverse effect of β_2 agonists.
- Instruct the patient to check with the pharmacist and doctor before taking over-the-counter preparations, as some medications may produce an additive effect on the prescribed drug regimen.
- Advise the patient to stop smoking.
- When bronchodilator and steroid inhalers are required to be administered together, instruct the patient to use the bronchodilator first, followed by the steroid inhaler.
- Inform the patient that inhaled short- or long-acting β_2 agonists, cromoglycate and nedocromil may be helpful in preventing exercise-induced asthma.

Methylxanthines

- Warn the patient to avoid driving and operating heavy machinery if dizziness and lightheadedness occurs.
- Advise the patient to limit the use of chocolate, coffee, tea and cola, as these food products contain caffeine, which may affect theophylline metabolism.
- If the patient is taking sustained-release preparations, instruct him or her to swallow the drug whole, without chewing. This method should control gastric irritation.
- Advise the patient to avoid smoking, as smoking can alter serum levels.

Anti-inflammatory drugs

- Teach the patient to gargle and rinse out the mouth after use to prevent oral candidiasis infections (see Table 11.7 in Chapter 11 for further information).
- Advise the patient on the importance of taking these drugs regularly, as ordered. They are helpful as prophylactic treatment but will not treat acute attacks of asthma.
- These drugs should not be discontinued abruptly, as a rebound asthma attack may occur.

Leukotriene receptor antagonists

- Explain to the patient that these agents are useful as preventive therapy. They are of little or no benefit in an acute attack.

Evaluation

- Evaluate the effectiveness of therapy in preventing and treating an asthma attack. The patient should report easier breathing, less fatigue, greater tolerance for activities and less shortness of breath. A post-peak-flow reading should improve on a pre-peak-flow reading. Patients need to be informed that measurements vary between meters, and so the same meter must be used. Patients also need to be aware that spirometers provide a more accurate evaluation of the effectiveness of asthma therapy compared with peak-flow readings.
- The patient should know which asthma-precipitating factors to avoid.
- The patient is able to demonstrate effective use of the particular method of administration, such as inhalation.
- Evaluate the incidence of adverse effects of treatment.

SUMMARY

- Obstructive airways diseases are characterised by restricted expiratory airflow. In this group, there are the chronic obstructive airways diseases (COADs), such as chronic bronchitis and emphysema, characterised by chronic and recurrent obstruction of the airways. Bronchial asthma is a reversible obstructive airways disease caused by bronchospasm, increased mucus production and oedema.
- Bronchodilators can act by stimulating β_2 receptors (β_2 agonists), blocking muscarinic receptors (antimuscarinic agents) or elevating intracellular cyclic adenosine monophosphate (cAMP) levels (methylxanthines) associated with bronchial smooth muscle.
- Corticosteroids are potent anti-inflammatory agents used to reduce the chronic inflammation underlying bronchial asthma. They may be administered by inhalation or systemically.
- Inhaled preparations are preferred because they cause fewer adverse effects and have a faster onset of action. Systemic preparations are used for acute severe asthma. The latter preparations are usually associated with a higher incidence of adverse effects.
- Prophylactic asthma preparations, such as nedocromil and cromoglycate, are not used for immediate relief of symptoms. They are useful as a preventive form of treatment in young children because of the decreased incidence of adverse effects.
- The goals of asthma management include abolishing symptoms, maintaining best possible lung function, preventing permanent lung impairment, reducing mortality and avoiding drug side effects.
- Oxygen therapy is used to correct tissue hypoxia. Pure oxygen therapy can cause an inflammatory response and subsequent airway obstruction. Premature infants given prolonged oxygen therapy may develop retinal damage.
- Monitor for appropriate oxygen levels by oximeter readings for oxygen saturation and arterial blood gas analysis for oxygen concentration levels and pH.
- Respiratory stimulants and surfactants can be administered only by experienced health-care professionals who work in critical care or neonatal intensive care units. Monitor regularly cardiac rate and rhythm, blood pressure and oxygen concentration.

1. State the three pathophysiological alterations associated with obstructive airways disease.
2. Describe the pathophysiology underlying the extrinsic form of asthma.
3. Compare and contrast the mechanisms of action of the various bronchodilator groups.
4. State the problems associated with oxygen therapy.
5. Compare and contrast the mechanisms of action of the following asthma prophylactics: ketotifen, nedocromil, sodium cromoglycate and the leukotriene receptor antagonists.
6. Jason Stolten, a 15-year-old patient with asthma, is using a beclomethasone inhaler. He develops an oral thrush infection, which causes him great discomfort. What comfort measures can you recommend for Jason? What should Jason do to prevent a further oral infection? (See Table 11.7 in Chapter 11 for assistance.)

7 Benjamin Habib, a 10-year-old patient, is newly diagnosed with asthma. What patient education would you provide him with regarding the use of an inhaler? (See Table 7.17 in Chapter 7 for assistance.)

8 Natasha Beck, 3 years old, has been admitted to the emergency department with a moderately severe asthma attack. How does the management of her attack differ from that of an adult admitted with a similar attack?

9 Yvonne Chow, aged 25 years, uses salbutamol and beclomethasone inhalers in conjunction with each other for asthma. Which inhaler should be used first? Why?

10 What observations would you make to evaluate the effectiveness of bronchodilator therapy?

11 When taking a patient's asthma history, what questions should the nurse ask?

12 Jacqui Renney, aged 30 years, has managed her asthma with a salbutamol inhaler since being diagnosed as a child. After evaluating the effectiveness of her treatment, you determine that she uses her inhaler almost every day. She is woken at night by coughing and tightness in the chest. What would you suggest about the effectiveness of her short-acting bronchodilator in controlling her asthma symptoms?

51 DRUG SUMMARY TABLE: DRUGS USED TO MAINTAIN GAS EXCHANGE

FAMILY NAME	GENERIC NAME	TRADE NAME(S)
Beta-2 agonists	Bambuterol	Bambec
	Formoterol (eformoterol)	Foradil
		Oxis turbohaler
	+ Budesonide	Symbicort
	Fenoterol	
	Orciprenaline	Alupent
	Salbutamol	Ventolin
		Ventmax
	Salmeterol	Serevent
	+ Fluticasone	Seretide
	Terbutaline	Bricanyl
Alpha and beta agonist	Ephedrine	
Antimuscarinic agents	Ipratropium	Atrovent
	Tiotropium	Spiriva
	+ Fenoterol	Duovent
	+ Salbutamol	Combivent
Methylxanthines	Aminophylline	
	Theophylline	Nuelin
		Slo-Phyllin

FAMILY NAME	GENERIC NAME	TRADE NAME(S)
Topical (inhaled) corticosteroids	Beclometasone	AeroBec Asmabec Beclazone Easi-Breathe Becodisks Beconase Becotide Qvar
	Budesonide + Formoterol	Pulmicort Symbicort
	Fluticasone + Salmeterol	Flixotide Seretide
	Mometasone furoate	Asmanex
Systemic corticosteroids	Betamethasone	Betnelan Betnesol
	Budesonide	Entocort
	Cortisone acetate	
	Deflazacort	Calcort
	Dexamethasone	
	Hydrocortisone	Solu-Cortef
	Methylprednisolone	Medrone Solu-Medrone Depo-Medrone
	Prednisolone	
	Triamcinolone	Kenalog
Respiratory stimulant	Doxapram	Dopram
Mucolytics	Carbocisteine	
	Mecyteine	Visclair
Asthma prophylactics	Ketotifen	Zaditen
	Nedocromil sodium	Tilade
	Sodium cromoglycate	Cromogen Easi-Breathe Intal
Leukotriene receptor antagonists	Montelukast	Singulair
	Zafirlukast	Accolate
Surfactants	Beractant	Survanta
	Poractant alfa	Curosurf

OVER-THE-COUNTER RESPIRATORY MEDICINES

52

CHAPTER FIFTY-TWO

KEY TERMS

Analgesics
Antihistamines
Antipyretics
Chemical mediators
Cough suppressants
Decongestants
Expectorants
Inflammation

OBJECTIVES

After completing this chapter, the reader should be able to:

- **describe the pathophysiology of upper respiratory tract illness;**
- **outline the mechanisms of action and common adverse reactions of drugs used to treat upper respiratory tract illnesses.**

IN CONDITIONS SUCH AS HAYFEVER, ALLERGIC RHINITIS AND upper respiratory tract (URT) infections, the causative agent precipitates a local inflammatory response, which primarily involves the mucosal and submucosal layers of the tract wall. Chemical mediators, such as histamine and prostaglandins, are released from mucosal and submucosal cells, which trigger vasodilation and increased permeability of local blood vessels, the first stage of inflammation (see Section VII). Histamine also stimulates the production of viscous mucus from mucosal cells. Such changes account for the runny nose and nasal congestion and contribute to the red, dry sore throat that characterise URT conditions.

RESPIRATORY PHARMACOLOGY

In this area of pharmacology, there is a plethora of over-the-counter (OTC) preparations marketed as remedies for colds, flu and allergy. These preparations contain a variety of drugs, each of which treats a particular manifestation of the condition. Combinations of an expectorant, decongestant, antihistamine, analgesic and cough suppressant are common. The products may even incorporate mixtures of miscellaneous agents, such as vitamins, plant extracts and volatile oils for symptomatic relief. There are also a range of alternative and natural therapies available for these conditions; some of these medicines are discussed in Chapter 65.

Generally, the community tends to self-manage the treatment of acute self-limiting respiratory illnesses at home. The beneficial effects of some substances, such as Irish moss extract and **vitamin C**, in the treatment of these conditions are yet to be proven. Importantly, a systematic review, published in the *British Medical Journal*, of OTC cough medicines (antitussives, expectorants, mucolytics, antihistamines and antihistamine–decongestant combinations) for acute cough in adults found little evidence for or against their effectiveness. The authors concluded that they could not recommend these preparations as first-line treatment and suggested that they could lead to unnecessary expense for the consumer.

It is beyond the scope of this text to address each preparation separately; instead, each drug category is examined to provide a broad picture of the market. The actions and major concerns associated with these drugs are considered.

Antitussive agents (cough suppressants)

Coughing is a reflex response to irritation of the bronchial mucosal layer such as that seen in inflammatory conditions. The cough reflex has an important role in clearing the lungs of excessive mucus and other secretions. Afferent fibres from the mucosa terminate in the medulla, where they synapse with efferent fibres to respiratory muscles.

■ MECHANISM OF ACTION

The action of cough suppressants is to interrupt the tussive reflex. The majority of these agents act centrally at the level of the medulla; some act peripherally, however, by impeding afferent transmission.

It is inappropriate to inhibit coughing altogether, as the accumulation of mucus in the lungs may lead to atelectasis (collapse of the lungs). The purpose of these agents is to reduce the frequency and severity of coughing when it is non-productive.

Narcotic agents and their derivatives are the most commonly used cough suppressants. **Codeine**, its derivatives **pholcodine** and **dihydrocodeine**, and the morphine derivative **dextromethorphan** act centrally. Dextromethorphan and pholcodine have little analgesic activity, whereas the others have both analgesic and antitussive actions.

◆ COMMON ADVERSE EFFECTS

Common adverse reactions of these drugs derive from their narcotic actions; they are potent emetics and often induce nausea and vomiting. Their central nervous system (CNS) depressant properties lead to drowsiness and sedation.

✚ CLINICAL CONSIDERATIONS

Cough suppressants are contraindicated in children under 2 years of age because of their CNS depressant effects. There is also little evidence that antitussive use in young children is very beneficial.

Patients need to be told that these products may make them drowsy and they should avoid driving and operating machinery. These preparations are contraindicated in patients with asthma or respiratory failure, as they adversely affect the respiratory drive.

Cough is a common feature of a viral URT infection. There is evidence to suggest that antitussive use does not help reduce the incidence of cough and that more conservative measures may be more effective, such as ensuring adequate fluid intake, maintaining a balanced diet and obtaining adequate sleep. It is important to note that antitussives should not be used in productive coughs.

Expectorants

■ MECHANISM OF ACTION

Expectorants are used to stimulate mucus secretion in dry irritated areas of the respiratory tract in individuals experiencing an annoying unproductive cough. These drugs may also act to reduce the viscosity of thick tenacious mucus, facilitating its movement out of the respiratory tract.

A number of plant derivatives are used as expectorants, including **liquorice** (*Glycyrrhiza glabra*) and extracts of **senega** and **squill**. They affect respiratory mucus production indirectly. Primarily, these drugs are irritants of the gastric mucosa and stimulate afferent fibres of the vagus nerve to the medulla. This in turn results in increased parasympathetic stimulation via efferent fibres of the vagus nerve back to the stomach. Vagal stimulation to the lungs increases, leading to elevated mucus production. These preparations are relatively safe to use in children, but not in infants.

Other expectorants produce their effects by stimulating the bronchial glands directly. OTC chest rubs contain mixtures of volatile oils, such as oil of turpentine, eucalyptus and pine, which are inhaled deep into the air passageways to activate mucosal glands. **Potassium iodide** and **ammonium salts** are often used as expectorants; as they are excreted by the bronchial mucosal glands, they stimulate mucus secretion.

Guaiphenesin and **guaiacol sulphonate** are expectorants that alter the structural characteristics of viscous mucus to make it flow more easily.

◆ COMMON ADVERSE EFFECTS

Expectorants are relatively free of adverse effects at the doses found in cold and flu remedies. Because some of them are gastric irritants, however, nausea and vomiting may occur. Other adverse effects include rash, diarrhoea, dizziness and headache.

✚ CLINICAL CONSIDERATIONS

The expectorant effects of these preparations can be promoted further by ensuring adequate fluid intake and performing regular coughing and deep-breathing. Their clinical efficacy has not been fully substantiated, and in some people it may involve little more than a placebo effect.

Mucolytic agents

BROMHEXINE AND ACETYLCYSTEINE

■ MECHANISM OF ACTION

Bromhexine and **acetylcysteine** are mucolytic drugs that are thought to alter the structure of viscous mucus. In so doing, they enhance the flow of mucus out of the respiratory tract.

◆ COMMON ADVERSE EFFECTS

No serious side effects have been reported during therapy with these agents. In some people, bromhexine causes mild gastrointestinal disturbances.

✚ CLINICAL CONSIDERATIONS

Acetylcysteine is available as an aerosol and is particularly valuable for therapy in cystic fibrosis, a condition characterised by excessive production of tenacious mucus within the lungs. It is also used as an antidote for paracetamol overdose (see Chapter 22).

DORNASE ALFA

Dornase alfa is a mucolytic agent used in the management of cystic fibrosis. The sputum of people with cystic fibrosis is thick and contains decaying inflammatory cells, particularly neutrophils. As the sputum accumulates, it can be difficult to clear, causing obstruction of the airways.

■ MECHANISM OF ACTION

Dornase alfa is recombinant human deoxynuclease. It is an enzyme that breaks down the DNA of the decaying neutrophils, making it easier to clear the sputum out of the lungs. Slight improvements in lung function and reductions in the frequency of respiratory infections have been reported in patients who have received treatment. The drug is administered via a nebuliser and, at the moment, is restricted to patients over 5 years old with a forced vital capacity greater than 40 per cent.

◆ COMMON ADVERSE EFFECTS

Common adverse reactions include pharyngitis and a hoarse voice.

✚ CLINICAL CONSIDERATIONS

The efficacy can be enhanced by ensuring the patient maintains an adequate fluid intake and performs regular coughing and deep-breathing.

Decongestants

Nasal congestion and a runny nose are associated primarily with the first stage of inflammation, vasodilation and increased capillary permeability.

■ MECHANISM OF ACTION

The most effective way of alleviating these symptoms is to induce vasoconstriction through stimulation of α receptors affiliated with the nasal vasculature. Therefore, decongestants are α agonists.

The α agonists used as decongestants include **oxymetazoline**, **pseudoephedrine**, **tramazoline** and **phenylephrine** and the longer-acting **xylometazoline**. **Ephedrine** can also be used as a decongestant, but it does not directly stimulate α receptors; it acts indirectly by causing the release of noradrenaline from the presynaptic terminal (see Chapter 26), which then stimulates α adrenoreceptors on the nasal vasculature.

◆ COMMON ADVERSE EFFECTS

A summary of the effects of α agonist drugs is provided in Figure 52.1. The adverse effects of these drugs derive from stimulating α receptors around the body; pupil dilation, constipation and hypertension are often observed (see Chapter 26).

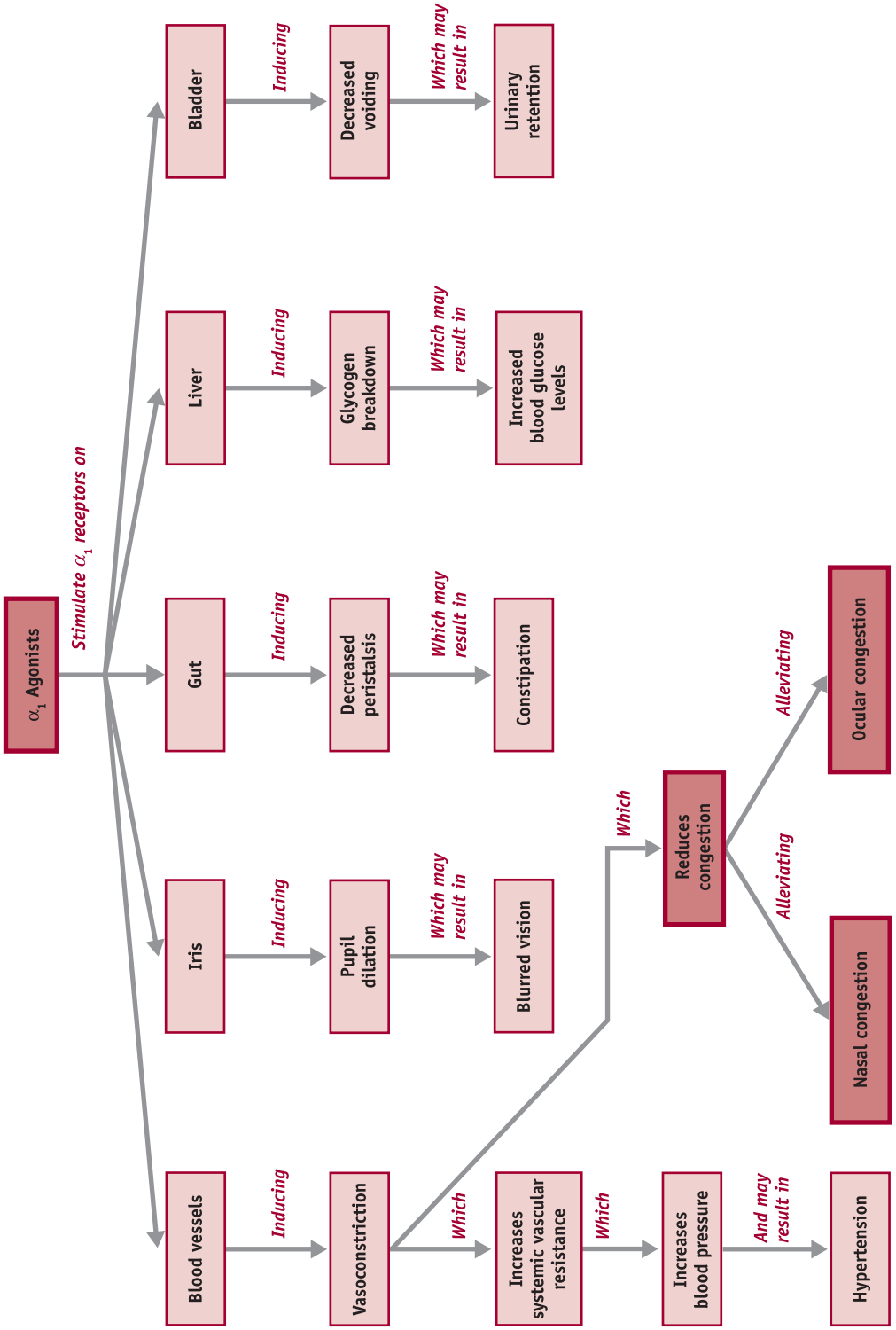
Pseudoephedrine, xylometazoline and ephedrine have CNS activity, which may lead to restlessness, insomnia, agitation and elevated mood.

✚ CLINICAL CONSIDERATIONS

Caution must be exercised when administering these drugs to patients with pre-existing cardiovascular conditions. Decongestants are contraindicated in patients taking non-selective monoamine oxidase inhibitors (MAOIs) for the treatment of depression, in order to avoid inducing a hypertensive crisis (see Chapter 35). A number of other antidepressant drugs can interact with nasal decongestants to potentiate pressor and other sympathetic-like responses. These drugs should be used in combination cautiously and include the tricyclic antidepressants and the monoamine

FIGURE 52.1 FLOWCHART SHOWING THE EFFECTS OF α_1 AGONISTS

Therapeutic effects shown in the darker shaded boxes.



oxidase A (MAO-A) inhibitor moclobemide. In order to minimise these side effects, topical application is preferred over systemic administration; many decongestants are now available as nasal sprays.

A problem associated with the use of these drugs as decongestants is that, with relatively prolonged usage of more than a few consecutive days, nasal congestion can re-emerge. The underlying reason for this is rebound vasodilation of the nasal vasculature mediated by pre-synaptic α_2 receptors. When α_2 receptors are activated, noradrenaline release from sympathetic postganglionic fibres is inhibited (see Chapter 26). This occurs because the α agonist action is not limited to α_1 receptors; that is, these decongestants are non-selective α agonists. Decongestants should be avoided in the evening as they can cause insomnia.

Another use of decongestants is in the treatment of red and sore eyes brought about through the congestion of blood vessels associated with the sclera (see Chapter 79).

Antimuscarinic agents

Mucus production in the respiratory tract is mediated by the activation of parasympathetic muscarinic receptors.

■ MECHANISM OF ACTION

Antimuscarinic agents block the muscarinic receptors, drying up excessive mucus. Preparations of alkaloids derived from the plants henbane (*Hyoscyamus niger*) and deadly nightshade (*Atropa belladonna*) are used in the management of URT conditions and contain the active constituents **atropine** (hyoscyamine) and **hyoscine** (scopolamine).

◆ COMMON ADVERSE EFFECTS

The side effects of such treatment include dry mouth, facial flushing, tachycardia, pupil dilation and constipation (see Chapter 27 for a more detailed discussion of the side effects of these agents).

✚ CLINICAL CONSIDERATIONS

Patients taking respiratory preparations containing antimuscarinic agents can reduce the adverse effects by rinsing their mouth with water following use, maintaining a high-fibre diet and avoiding strong light.

Antihistamines

Antihistamine preparations are used in the treatment of allergic skin conditions (see Chapter 78), as antiemetics (see Chapter 55) and as paediatric sedatives (see Chapter 34). In respiratory conditions of an allergic nature, antihistamine preparations are often regarded by the community as the first choice in providing relief. In reality, their usefulness is overrated and the side effects can be debilitating. There are a number of antihistamines available in OTC preparations. **Diphenhydramine**, **chlorpheniramine**, **dexchlorpheniramine**, **loratadine**, **promethazine**, **brompheniramine** and **triprolidine** are commonly found in OTC preparations.

■ MECHANISM OF ACTION

The rupture of mast cells and the release of chemical mediators, such as histamine, underlies many respiratory conditions. Antihistamines are ineffective in controlling the pathophysiological changes resulting from this event, however, because histamine is not the only mediator released from mast cells. Therefore, little symptomatic relief is provided by these drugs. More effective are the sympathomimetic drugs, which relax bronchial smooth muscle and reduce oedema. The fact that antihistamine agents reduce the excessive mucus secretion associated with allergic rhinitis is due to the secondary antimuscarinic action of these drugs (see above).

◆ COMMON ADVERSE EFFECTS

The most common side effect of these drugs is sedation. Uncoordination, lack of concentration and lassitude are also associated with these agents. Central and peripheral antimuscarinic effects may occur, such as blurred vision, constipation and urinary retention.

✚ CLINICAL CONSIDERATIONS

Users of these drugs must be cautioned against using machinery and driving during treatment. Newer antihistamines have been developed that induce less sedation or affect fewer people in this way; however, they are more expensive (see Chapter 29).

Analgesic and antipyretic agents

Many OTC cold and flu remedies contain an analgesic to reduce the discomfort associated with sinus congestion. Common agents include codeine, **aspirin**, salicylates and **paracetamol**. **Benzydamine** can be used topically in the oropharyngeal region.

■ MECHANISM OF ACTION

The mechanisms of the narcotic codeine and the non-narcotic analgesics are described in Chapters 39 and 40, respectively. The narcotics induce their effects by stimulating central opiate receptors. The non-narcotics inhibit the synthesis of prostaglandins. The advantage of using aspirin, salicylates and paracetamol is that these also act to reduce fever by this mechanism.

Benzydamine has analgesic, anti-inflammatory and antipyretic activity, like other non-steroidal anti-inflammatory drugs (NSAIDs). It is often used as a substitute for aspirin. Unlike aspirin and other NSAIDs, however, benzydamine is a basic drug rather than an acidic drug; as a consequence, it does not damage the gastric mucosa. Benzydamine also possesses some local anaesthetic properties.

◆ COMMON ADVERSE EFFECTS

Common adverse effects associated with the non-narcotics involve gastrointestinal disturbances. Common adverse effects of benzydamine include oral numbness and a stinging or burning sensation after administration.

✚ CLINICAL CONSIDERATIONS

It is important to note that preparations containing aspirin or another aspirin-like NSAID may cause gastric irritation. This effect can be reduced by administering the preparation with meals.

Preparations containing aspirin or salicylates should be avoided in children because of the potential to produce Reye's syndrome (see Chapter 40). The pharmaceutical companies market popular cold and flu preparations specifically for children, with paracetamol substituted for aspirin. The side effects of non-steroidal antipyretic analgesics such as aspirin include gastric irritation and bleeding disorders. The advantage of using preparations containing codeine is the antitussive action; however, the adverse reactions of using narcotic agents (e.g. constipation, nausea, vomiting) must be considered.

Benzydamine is available as an oral topical preparation for dental use and for an inflamed throat.

Miscellaneous agents

There are a variety of substances found in OTC preparations for use in respiratory conditions that do not fit into the above categories. Vitamin C is thought to stimulate immune processes. Indeed, such stimulation would be useful when in the grip of a relatively mild respiratory infection. The value of vitamin C in preparations such as these is yet to be proven, however.

Caffeine is a CNS stimulant incorporated in OTC preparations in order to overcome the generalised apathy associated with the common cold and other respiratory infections. At the doses used, side effects are minimal. Like the respiratory stimulant **doxapram** (see Chapter 51), caffeine stimulates the respiratory centres in the medulla and has been used to counteract the respiratory depression associated with alcohol intoxication.

Many cold and flu chest rubs contain **menthol** and **camphor**. When applied, these substances produce a localised vasodilation in the skin, which creates a comforting feeling of warmth. In conditions characterised by muscle and joint aching, such as influenza, these substances also provide some pain relief. They achieve this by irritating cutaneous sensory nerves, causing them to fire repeated messages towards the brain. In processing these competing sensations from the skin and the underlying muscles and joints, the brain is diverted from the perception of somatic pain in much the same way that vigorous scratching of the skin relieves a painful itch. Because one form of irritation counteracts another, that causes more discomfort, these chemical agents are termed counterirritants.

Demulcents are soothing agents incorporated in a number of OTC preparations, which reduce the discomfort associated with inflamed mucous membranes of the URT. Usually they are pectins or gums derived from plants, which form a coating over the inflamed area, reducing its exposure to irritation.

Antiseptics such as **cetylpyridinium chloride**, administered as a cream or lozenge, in addition to their ability to kill infecting microbes are useful in treating the dryness and irritation of the mucosal layer associated with nasopharyngeal infections.

CLINICAL MANAGEMENT

Over-the-counter respiratory medicines

Assessment

- Perform a respiratory assessment of the character and amount of any secretions. Also assess the lungs, nose, ears and throat.
- Assess baseline vital signs. An elevated temperature may indicate a viral infection. Compare with subsequent observations.
- Determine a history of environmental factors or irritants that could be aggravating the condition.
- For potassium iodide expectorant preparations, assess the patient for hyperkalaemia, hyperthyroidism and hypersensitivity to iodide, as these are contraindications.
- For decongestants, assess the patient for a history of hypertension, dysrhythmias and hyperthyroidism. The use of nasal decongestants can aggravate these conditions.
- For antihistamines, assess the patient for asthma, respiratory disease and liver disease, as use in these conditions is usually contraindicated. Take caution with use in narrow-angle glaucoma and prostatic hypertrophy.

Planning

- The patient will obtain relief from clinical manifestations, and a secondary bacterial infection will not occur.

Implementation

- Observe the colour of bronchial secretions. Yellow or green sputum is indicative of a bronchial infection and an antibiotic may be required.
- Monitor for relief of symptoms such as dry cough, nasal secretions and nasal congestion.

Patient teaching

- Advise the patient to maintain an adequate intake of fluids. Fluids decrease the stickiness of bronchial secretions and enable elimination of secretions by coughing.
- The patient's room can be kept moist with the use of a steam vaporiser, which will assist with liquefying bronchial secretions.
- Explain to the patient that a viral infection tends to be self-limiting and, therefore, should clear within 7–10 days. If there is no improvement in the condition during this time or if the condition worsens, the patient should see the doctor for further assessment and possible antibiotic therapy.
- Explain to the parent that a viral infection in a child tends to be self-limiting. If the condition does not improve within 5 days, or if the child displays signs of bacterial infection, such as a high temperature, coloured mucus, congestion of the chest or wheezing, then the parent should take the child to the doctor.

Cough suppressants and expectorants

- Teach the patient the difference between a cough suppressant and expectorant and explain the uses of each.
- Instruct the patient to avoid driving and operating heavy machinery if drowsiness occurs.
- Warn the patient that cough suppressants have the same potential for adverse effects as other narcotic agents, such as drowsiness and nausea.
- For preparations containing potassium iodide, ask the patient whether he or she has a history of allergy to iodine or shellfish before administration.
- Potassium iodide enteric-coated tablets should be swallowed whole, without crushing the tablet. Liquid iodide preparations are diluted with water, juice or milk before swallowing. The liquid is sipped through a straw to prevent tooth discoloration. Take iodide preparations with meals to avoid gastric irritation.

Nasal decongestants

- Instruct the patient not to take a decongestant at or near bedtime, as insomnia may occur. To prevent insomnia, the last dose should be taken around the time of the evening meal.
- Instruct the patient on the proper use of nasal sprays and drops (see Tables 7.7 and 7.8 in Chapter 7 for further information).
- Inform the patient that nasal decongestants should not be used for more than 5 days and to follow the recommended dosage schedule. Rebound congestion can occur with overuse.

Mucolytic agents

- Advise the patient to cough up the loosened secretions.

Antihistamines

- Advise the patient not to drive and operate heavy machinery during antihistamine use. Drowsiness is a common adverse effect of older antihistamines.

Analgesic and antipyretic agents

- Aspirin and other salicylate preparations should be avoided in children because of their potential to cause Reye's syndrome.
- Advise the adult patient to take aspirin rather than paracetamol for an inflamed and sore throat, as aspirin has both analgesic and anti-inflammatory actions.
- For the patient with a sore throat, recommend a soluble form of the preparation, as tablets and capsules may be difficult to swallow.

Evaluation

- Evaluate whether the patient's manifestations have been relieved without the onset of adverse effects.
- Determine whether the patient is afebrile and has adequate fluids and rest.

SUMMARY

- Antitussives, mucolytics, decongestants, expectorants, antimuscarinics, antihistamines, analgesics and antipyretics are used widely in the treatment of acute upper respiratory tract conditions.
- Most antitussives interrupt the cough reflex at the medullary levels, although some act on afferent transmission.
- Expectorants stimulate mucus secretion in dry, irritated areas of the respiratory tract. Mucolytic agents alter the structure of thick mucus, enhancing its flow out of the tract. Antimuscarinic agents also dry up excessive mucus.
- Decongestants relieve nasal congestion through vasconstriction. They are α-adrenoreceptor agonists.
- Antihistamines are used in the management of allergic respiratory conditions, but their usefulness is limited.
- Analgesics and antipyretics relieve fever and the discomfort associated with sinus congestion and sore throat.
- Avoid the use of antitussives in productive coughs and in children under 2 years of age because of the central nervous system depressant effects.
- Inform the patient that nasal decongestants should not be used for more than 5 days, in order to prevent rebound congestion.
- Aspirin must be avoided in children because of the possibility of inducing Reye's syndrome.
- Inform the patient that a number of these products could make them drowsy, so they should avoid driving and operating machinery if affected.
- Ensure the patient maintains an adequate fluid intake and performs regular coughing and deep-breathing.

1 Outline the underlying pathophysiology of upper respiratory tract illness.

2 State the mechanisms of action and common adverse effects of the following drug groups:
(a) antiseptics;
(b) mucolytic agents;
(c) narcotic cough suppressants;
(d) the expectorant potassium iodide;
(e) nasal decongestants.

3 What is the difference between an expectorant and a mucolytic agent?

4 What is the rationale for combining a variety of drugs in one over-the-counter preparation?

5 Can you think of any disadvantages of these combination over-the-counter preparations for colds, influenza and allergy?

6 Katrina Wenczel has a history of hypertension. What problems may occur following the use of a nasal decongestant?

7 What are some non-pharmacological measures available to a patient to liquefy and loosen bronchial secretions?

8 What patient education would you offer Molly Jones, who is keen to use a nasal decongestant spray for a blocked nose? Give rationales for your answer.

9 Jason Totter, a 3-year-old toddler, is very distressed by a head cold. On browsing through the shelves in the local pharmacy, his mother comes across a cough and cold preparation containing aspirin. Would you advise her to buy this preparation? Why?

10 Marcus Larkin is a 38-year-old being treated for major depression. He is currently receiving treatment with the tricyclic antidepressant clomipramine. At the moment, Marcus is suffering with hayfever and usually takes an over-the-counter preparation containing pseudoephedrine for relief of his symptoms. What advice would you give him?

11 Dolly Agneau, 25 years old, wishes to take an antihistamine for an allergic respiratory condition. What advice would you give her regarding these drugs?

12 What precautions would you advise for a patient who takes a cough formulation containing pholcodine?

CASE STUDY X.1 SA is a 57-year-old man with angina pectoris and moderate hypertension. He runs a small business with a staff of 30 people. His angina attacks are precipitated by overactivity and excitement. On at least two occasions, SA has had an angina attack at football matches when his team was narrowly beaten. When first diagnosed 5 years ago, the attacks were relieved easily with sublingual glyceryl trinitrate tablets. More recently, it has taken longer and more doses of the drug to relieve an attack.

SA describes himself as old-fashioned, a 'meat-and-two-vegetables' man. He enjoys nothing better than a barbecue at the weekend and beers with his mates. He is taking the beta-blocker metoprolol and the thiazide diuretic hydrochlorothiazide for his hypertension. He also requires an oral potassium supplement. His blood cholesterol level is moderately high and his HDL : LDL level is low. After failed attempts to modify his diet, SA's doctor has just started him on an HMG-CoA reductase inhibitor.

At the next football match, SA has a severe angina attack, where the pain is intense. It is not relieved by glyceryl trinitrate and SA thinks he is going to die. He is pale, grey, sweaty and dyspnoeic. He is taken to hospital by ambulance for treatment.

QUESTIONS

1. *What form of angina pectoris does SA have? Outline briefly its pathophysiology.*
2. *What is the mechanism of action of the organic nitrate glyceryl trinitrate?*
3. *State three common adverse effects of this treatment.*
4. *State SA's risk factors for hypertension.*
5. *What are the mechanisms of action of beta-blockers and the thiazides in hypertension?*
6. *What is the purpose of the potassium supplement? What is the normal range for a serum potassium level? What are the consequences of hypokalaemia?*
7. *Explain the clinical significance of the HDL : LDL ratio.*
8. *Describe the mechanism of action of the HMG-CoA reductase inhibitors.*
9. *State three common adverse effects of this treatment.*
10. *Is there any therapeutic benefit with regard to angina management from the use of the beta-blockers, thiazides or HMG-CoA reductase inhibitors? If so, in what way?*

CASE STUDY X.2 After SA arrives at the hospital, investigations confirm that he is suffering from an acute myocardial infarction. In the ambulance, a paramedic initiates oxygen therapy and administers morphine for pain relief and a low dose of aspirin. In hospital, SA receives an intravenous infusion of streptokinase and the antidysrhythmic amiodarone for ventricular tachycardia. Cardiac enzyme level tests indicate that the damage to the myocardium is extensive.

During his hospital stay, SA receives treatment with subcutaneous heparin and the beta-blocker atenolol. Acute heart failure develops, which requires treatment with the angiotensin-converting enzyme (ACE) inhibitor enalapril and the loop diuretic furosemide. The diuretic is for the treatment of SA's pulmonary oedema.

After a prolonged hospital stay, SA survives the myocardial infarction and is discharged. He goes on to develop chronic heart failure, which is managed with an ACE inhibitor, a diuretic and a peripheral vasodilator.

QUESTIONS

1. *What is the rationale for the use of thrombolytic drugs in acute myocardial infarction (AMI)? Are there any constraints regarding the timing of administration of these drugs in AMI?*
2. *Compare and contrast the mechanisms of action of the thrombolytic drugs streptokinase and aspirin.*
3. *What adverse reactions should be monitored during and after thrombolytic drug therapy?*
4. *Describe the mechanism of action of the antidysrhythmic agent amiodarone. To which Vaughan Williams antidysrhythmic drug class does it belong?*
5. *Compare and contrast the actions of heparin and streptokinase.*
6. *Outline the pathophysiology of heart failure.*
7. *Describe the mechanism of action of the angiotensin-converting enzyme (ACE) inhibitors and indicate why they are the drug of choice in heart failure.*
8. *Pulmonary oedema is caused by alterations in fluid distribution between pulmonary blood vessels and the lung tissue. Using fluid dynamics and changes in fluid pressure, explain the link between heart failure and pulmonary oedema.*
9. *Compare and contrast the actions of the loop and thiazide diuretics.*
10. *At what stages do the diuretics and the peripheral vasodilators interrupt the pathophysiology of heart failure?*

CASE STUDY X.3 BB, a 5-year-old boy with a history of chronic asthma, has been admitted to hospital suffering a moderately severe asthma attack. Over a period of time, his condition has been managed well using daily inhalation of the corticosteroid beclomethasone coupled with inhalation of the β_2 agonist salbutamol when required. His parents think that this particular attack was

brought on by a mild respiratory infection that has been affecting other members of the family.

Treatment begins with oxygen therapy and a dose of the β_2 agonist salbutamol via an inhaler and spacer. A dose of hydrocortisone is administered intramuscularly soon after. Inhaler treatment is repeated hourly. After 8 hours the acute attack is easing, and by 12 hours after admission BB is ready for discharge.

QUESTIONS

1 *Briefly outline the long-term aims of asthma management, the first-line therapy and the preferred treatment of an acute attack according to the National Asthma Campaign.*

2 *Explain why the mild respiratory infection would be considered a trigger for BB's asthma attack.*

3 *What is the rationale for the use of inhaled corticosteroids in the long-term management of BB's chronic asthma?*

4 *(a) What short-term adverse effects would you expect to see with inhaled corticosteroids?*
(b) What short-term adverse effects would you expect to see associated with inhaled β_2 agonists?

5 *What problem may be associated with the long-term use of inhaled corticosteroid therapy in young children?*

6 *Why has the health team managing BB's acute attack used an inhaler and spacer to administer the bronchodilator therapy rather than a nebuliser?*

7 *How does the systemic administration of the corticosteroid hydrocortisone assist in the recovery after an acute asthma attack?*

8 *What aspects of your patient's condition would you monitor during this combined therapy? Why?*

CASE STUDY X.4

Bert Bendower is a 54-year-old man with angina pectoris and type 2 diabetes mellitus. His angina has been controlled well using the calcium channel antagonist nifedipine and glyceryl trinitrate patches. In an acute attack, he takes a sublingual tablet of glyceryl trinitrate, which resolves the pain. His diabetes mellitus, which was diagnosed 12 years ago, is at present controlled well by dietary means and the biguanide metformin. Bert receives occasional visits from the district nursing service to assist with the management of his diabetes.

Last year, Bert was diagnosed impotent. At first he refused to mention the problem to his doctor, but with encouragement from his wife and the district nurse he eventually sought treatment. He was prescribed alprostadil pellets. Bert and his wife were pleased with the results but found the method of administration reduced the spontaneity of the sex. Bert had heard about sildenafil (Viagra™) in the newspaper and was keen to try it. His doctor was reluctant because Bert was taking glyceryl trinitrate. Bert was quite insistent and said that he was prepared to try a different therapy for his angina in order to get access to sildenafil. The glyceryl trinitrate was stopped and Bert was tried on a combination of nifedipine and the beta-blocker atenolol. After a trial period, he experienced no problems with his angina.

Bert appears to be satisfied with sildenafil. He found that it took longer than alprostadil to act and that he experienced facial flushing and, sometimes, a headache. He thought that it was worth persisting with because it was far more convenient to use.

QUESTIONS

1 *Briefly outline the pathophysiology of angina pectoris.*

2 *Compare and contrast the mechanisms of action of glyceryl trinitrate, calcium channel antagonists and beta-blockers with respect to controlling angina pectoris.*

3 *What is the property of glyceryl trinitrate that allows it to be effective as a patch?*

4 *Describe the mechanism of action of alprostadil in the treatment of erectile impotence.*

5 *Explain why alprostadil must be administered locally as an injection or urethral pellet rather than systemically.*

6 *Describe the mechanism of action of sildenafil.*

7 *Explain why glyceryl trinitrate is contraindicated when sildenafil is prescribed.*

8 *Would you expect alprostadil and sildenafil to be effective in the treatment of all forms of erectile impotence? Give your reasons.*

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WEB RESOURCES

ASCOT study www.ascotstudy.org

British Heart Foundation www.bhf.org.uk

British Hypertension Society www.bhsoc.org

Department of Health www.dh.gov.uk

National Institute of Health and Clinical Excellence www.nice.org.uk

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MODULATION OF GASTROINTESTINAL FUNCTION

An army marches on its stomach.

ATTRIBUTED TO NAPOLEON

Growth of the body depends on the consumption, absorption and metabolism of food. The gastrointestinal tract is involved in the first essential components of these processes. The gastrointestinal tract is subject to many disease conditions, some of which are very common. It is not surprising, therefore, that there are a multitude of drugs to treat these varying conditions. Due to the number of drugs available, it has been necessary to divide the gastrointestinal tract into two parts: the upper part, consisting mainly of the stomach (Chapter 53); and the lower part, from the duodenum to the anus (Chapter 54). Some problems of the gastrointestinal tract, specifically nausea and vomiting, are sometimes associated with the central nervous system; Chapter 55 deals with these problems.

XI

UPPER GASTROINTESTINAL TRACT DRUGS

53

CHAPTER FIFTY-THREE

OBJECTIVES

KEY TERMS

Peptic ulcer
Gastric ulcer
Duodenal ulcer
Gastritis
Gastro-oesophageal reflux disease (GORD)
Proton pump
Helicobacter pylori
Flatulence

After completing this chapter, the reader should be able to:

- **outline the aetiology of peptic ulcers;**
- **describe the use of histamine H_2-receptor antagonists in the treatment of peptic ulcers;**
- **describe the use of antacids in the treatment of peptic ulcers and in dyspepsia;**
- **describe the use of drugs that modify gastric mucus and/or acid production;**
- **list the problems involved in the use of antacids and antiulcerants.**

ONE OF THE MOST COMMON PROBLEMS INVOLVING THE stomach is excessive acidity and the regurgitation of stomach hydrochloric acid into the oesophagus. The stomach is well protected from its own acid and the proteinase pepsin, as it has a thick layer of protective mucus covering the mucosal cells. If this mucus layer is damaged and/or excess acid is produced, erosions can occur in the gastric mucosa, leading to a gastric ulcer. More commonly, the excess acid from the stomach enters the duodenum, where incomplete neutralisation occurs. The duodenal wall, which has less mucus than the stomach, is eroded and a duodenal ulcer results. These ulcers can eventually erode their way through the walls, causing a perforation and the leakage of unsterile material into the peritoneal cavity, leading to life-threatening peritonitis. Before an actual ulcer occurs, burning pain may be felt in the abdominal area, which can be relieved by neutralising the excess acid and/or inactivating the pepsin. When acid enters the oesophagus, a burning sensation is also felt in the region of the heart, hence the common name 'heartburn' for this condition. The cause can be due to the presence of a hiatus hernia, in which case the diaphragm is herniated where the oesophagus passes through it.

In severe cases, the stomach can pouch up through this break. With the contractions of the diaphragm during normal breathing, gastric contents can be squeezed back through the cardiac sphincter, causing the burning. This is called gastric reflux. Gastric reflux can have many other causes. Certain materials can lessen the tone of the oesophageal sphincter. Many foodstuffs can do this, such as fats, some fruit juices, tomatoes and chocolate. Strong alcoholic drinks, cigarette smoking, antimuscarinic drugs, diazepam, morphine and other narcotic drugs can also affect this pressure. Body posture may have an effect, such as lying on one's side, which causes an increase in intra-abdominal pressure. This condition is so common that many names have been given to the pain and discomfort that results. Apart from heartburn, other commonly used terms are 'indigestion' and 'dyspepsia'.

Continuous presence of acid in the lower oesophagus can lead to reflux oesophagitis and oesophageal damage. Treatment of this condition is mainly with antacids and associated drugs.

ANTACIDS

■ MECHANISM OF ACTION

The antacids are weak bases that combine readily with hydrochloric acid to neutralise it. This raises the pH of the stomach; above a pH of 4, pepsin is inactive.

Several bases are commonly used in antacid preparations. These are usually basic compounds of aluminium, magnesium, sodium, calcium and potassium. Of these, the most common are **aluminium hydroxide** and **magnesium carbonate**, usually in combination with each other. There is a good reason why these two are often combined – aluminium hydroxide can cause constipation, and magnesium compounds can act as osmotic laxatives. By combining them in the correct proportions, these effects are cancelled out. The antacid **hydrotalcite** is a complex of aluminium and magnesium hydroxides. In patients with hyperacidity problems and loose stools, aluminium hydroxide is available on its own, either as a suspension or as tablets. Aluminium hydroxide complexes with phosphates in the gut, promoting their excretion, and is useful in treating the hyperphosphataemia that can result from renal failure. Aluminium hydroxide can also be used to prevent the formation of phosphatic renal calculi.

Magnesium trisilicate is found in some antacids. When neutralised with hydrochloric acid, this produces a viscous jelly, which is said to coat and protect peptic ulcers, promoting their healing. When used alone, magnesium trisilicate is not a very effective antacid.

◆ COMMON ADVERSE EFFECTS

Aluminium binds to phosphates in the gut but, even in large doses, aluminium hydroxide rarely causes hypophosphataemia; however, this could be of concern in some patients with low phosphate intake or abnormal phosphate metabolism. Of slight concern is that aluminium has been implicated as a factor in the aetiology of Alzheimer's disease (see Chapter 36). It appears that aluminium is found in higher quantities in the defective neural tissue in this disease, and neural degeneration can occur in rats fed large amounts of aluminium ions. It is unlikely that aluminium per se is the causative agent in Alzheimer's disease, but it may be one of many factors that contribute to the disease processes. At the moment, there does not seem to be any reason for concern about the use of aluminium-containing antacids. Many people have been consuming enormous quantities of these antacids for many years without developing any neural degenerative diseases. A problem with aluminium-containing antacids is their ability to bind to other drugs given concurrently, and this may require adjusting the dosage schedule in order to allow the maximum interval between administration of the two agents and possibly higher doses of some drugs to obtain therapeutic effects. Two such examples are **warfarin** and **digoxin**. Aluminium and divalent ions combine readily with tetracyclines, completely inactivating them. Basic aluminium compounds inhibit the action of pepsin, and this contributes to their effectiveness.

No serious problems have been associated with magnesium apart from diarrhoea, any excess being excreted quickly by the kidneys. The use of magnesium salts in patients with renal disease may be problematic because of this. The liquid preparations are more effective than the tablets, but the tablets can be pocketed for use anywhere.

Calcium carbonate is used in several antacid preparations. Overuse of these antacids can lead to marginally high blood calcium levels. Although this is not enough to result in hypercalcaemia, these preparations can, over long periods of time, lead to calcification of soft tissues and the development of kidney stones.

Sodium bicarbonate (hydrogen carbonate), or baking soda, is a favourite of the older generation owing to its ready availability and short-term effectiveness. The release of carbon dioxide from sodium bicarbonate neutralisation causes eructation (belching), which some people seem to think is necessary to effect a cure. (There has been at least one case of a patient's stomach almost exploding due to massive release of carbon dioxide following consumption of too much bicarbonate-containing effervescent antacid.) The use of sodium bicarbonate as an antacid should be discouraged because of the potential of sodium to exacerbate pre-existing hypertension and because the absorption of excessive bicarbonate ions can cause alkalosis. The only legitimate use for sodium bicarbonate alone is in the

treatment of acidosis and to promote the excretion of acidic drugs, such as aspirin, following an overdose.

All antacids can lead to acid rebound, which is the production of more than normal amounts of acid after the effects of the antacids have worn off. This is more common with the calcium- and sodium-containing antacids.

✚ CLINICAL CONSIDERATIONS

Antacids react with a number of medications. Most interactions can be avoided by administering the antacid about 2 hours before or after other medications. For optimal antacid effect, antacids should be taken between meals and at bedtime; that is, about 1–3 hours following meals. Liquid preparations are usually more effective than solid preparations, but the former are less convenient. Ensure patients chew tablets thoroughly before swallowing to allow for complete and uniform distribution in the stomach before the contents enter the small intestine.

Alginates

The **alginates** are derived from seaweed. When alginates react with acids, they produce a viscous jelly that floats on aqueous solutions. This property gives the antacids that contain alginates the name 'raft antacids'. In theory, this 'raft' floats on top of the stomach and, being viscous, prevents gastric reflux. Proprietary preparations containing alginates include Algicon™, Gaviscon™, Peptac™ and Rennies Duo™. Most trials involving these antacids have shown them to be no better than the conventional types of antacid. In some body positions, the 'raft' floats in the cardia of the stomach, where prevention of gastric reflux is difficult.

ANTIFLATULENTS

Many problems associated with the gastrointestinal tract are due to gas formation from the fermentation of foodstuffs. Several litres of gas are produced every day, and most escapes unnoticed. The accumulation of gas, however, can cause pain and discomfort. Small bubbles do not escape easily from the gastrointestinal tract, but if the surface tension of the gastrointestinal fluids is lowered, these bubbles coalesce to form larger bubbles, which, in theory, are released from the tract, lessening the discomfort. Substances that do this are termed antiflatulents, defoaming agents and defrothicants.

Simeticone (or dimeticone), a silicone polymer (related to floor and furniture polishes), is the only commonly used antiflatulent. This substance is commonly included in antacid preparations, the premise being that hyperacidity and flatulence often go together. There are suggestions that simeticone may provide a protective coating to the gut wall, but this is doubtful. Simeticone is biologically fairly inert, and no problems are normally associated with it, except that it has been reported to lower the tone of the lower oesophageal sphincter, which could lead to gastric reflux.

Simeticone appears to be successful in treating the excessive gas production experienced by high-altitude pilots. Several preparations are available for paediatric use to relieve infant colic, particularly when given before food. There have been no adverse effects reported with simeticone.

Charcoal, in its activated form, has the capacity to adsorb gases (hence its use in gas masks, which act as protectors in cases of poisonous gases in war situations) and dissolved substances. Charcoal is used occasionally in cases of flatulence and to adsorb poisons (see Chapters 21 and 22), preventing their intestinal absorption. Its only problem is that it blackens the stools and is unpleasant to swallow.

✚ CLINICAL CONSIDERATIONS

For tablet preparations, advise the patient to chew the tablet thoroughly before swallowing. To aid the passage of flatus, it is important to change body position often and to ambulate regularly.

PEPTIC ULCERS

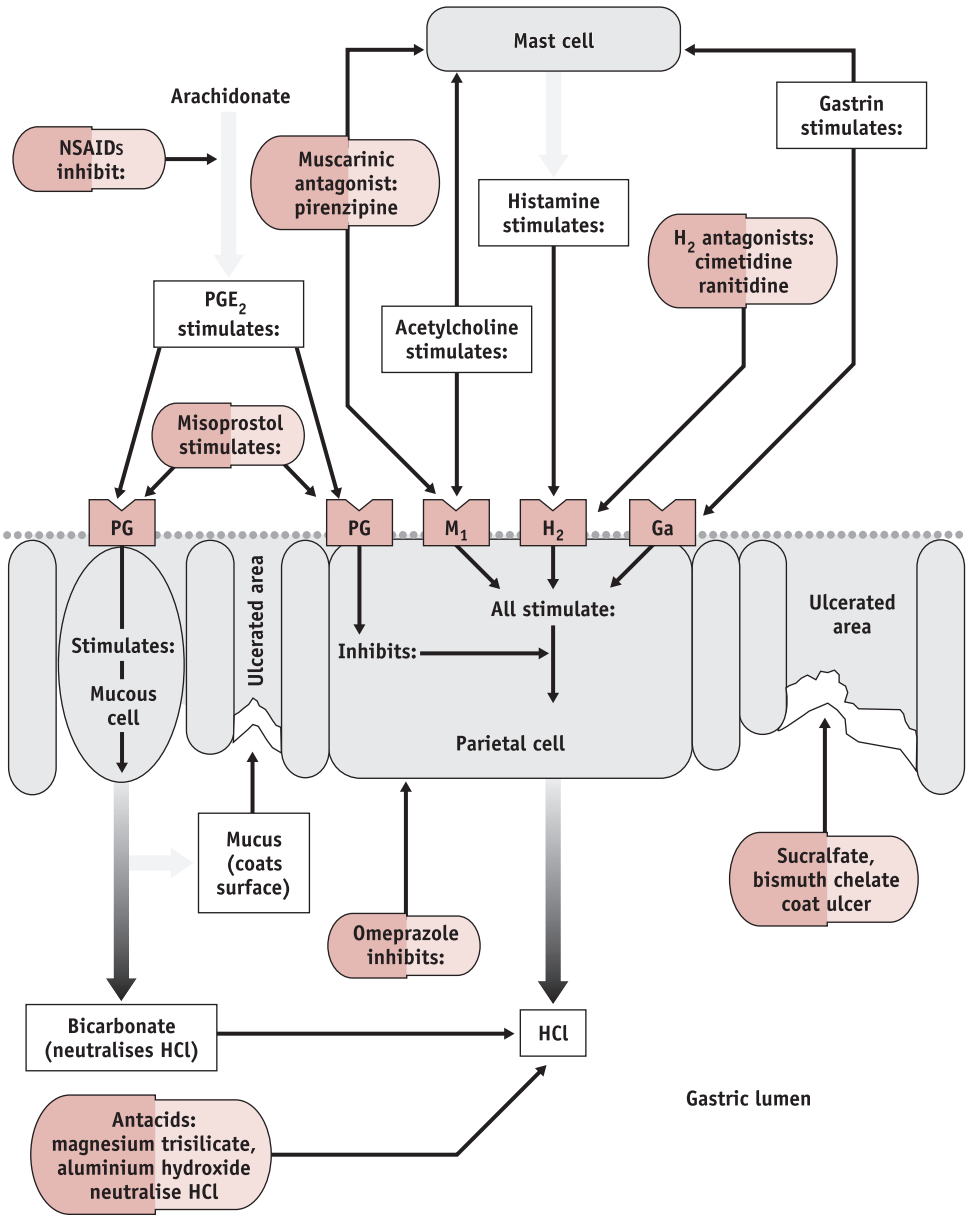
The problems associated with hyperacidity and excessive pepsin activity may eventually lead to the formation of a gastric or duodenal ulcer. Previously, antacids in enormous quantities taken for long periods were sometimes effective in curing such ulcers without surgical intervention. Today, several groups of drugs are available that have revolutionised the pharmacological treatment of ulcers and have more or less relegated surgery for this problem to history. In order to understand the action of these drugs, the physiology of acid and pepsin production needs reviewing.

There are three receptors in the stomach wall that need to be stimulated to cause the production of acid: H_2 histamine receptors, muscarinic cholinergic receptors and gastrin receptors. Figure 53.1 summarises the events leading up to acid production and shows where some of the antiulcer drugs work. Gastric ulcers are due mainly to a defect in mucus production, whereas duodenal ulcers are due mainly to an increase in acid production. This makes the treatment of each somewhat different.

In the early 1980s it was shown that about 70 per cent of cases of gastric ulcer and gastritis are due to the presence of the bacterium *Helicobacter pylori*. This major advance in the pathophysiology of peptic ulcers was first proposed by Barry Marshall, from Royal Perth Hospital, Western Australia, and for several years was greeted by most of the medical fraternity with a great deal of scepticism.

Acid inhibition combined with antibacterial treatment is extremely effective in the eradication of *H. pylori* and reinfection is not common. A 1-week triple-therapy

FIGURE 53.1 GASTRIC ACID PRODUCTION AND THE SITES OF ACTION OF ANTIULCERANT DRUGS



Ga, gastrin receptor; H_2, H_2-histamine receptor; M_1, M_1-muscarinic receptor; NSAID, non-steroidal anti-inflammatory drug; PG, prostaglandin receptor; PGE_2, prostaglandin E_2 receptor.

regimen composed of a proton pump inhibitor such as **omeprazole** together with **amoxicillin** and either **metronidazole** or **clarithromycin** eradicates *H. pylori* in over 90 per cent of cases. Resistance can occur to the antibiotics and is most common to clarithromycin and metronidazole. This resistance can develop during treatment. In the UK, a regimen containing amoxicillin and clarithromycin is recommended for initial therapy followed by treatment with amoxicillin and metronidazole if this first regimen fails. **Ranitidine** may be substituted for the proton pump inhibitor. Some manufacturers, in order to help with patient compliance during triple therapy, have introduced the three drugs packaged together. Quadruple therapy has also been advocated by some gastroenterologists in cases of resistance to triple therapy, but this should be used only in specialist settings. Two-week dual therapy with a proton pump inhibitor and one antibiotic is also licensed in the UK, but this is not recommended as it produces much lower rates of eradication of *H. pylori*.

✚ CLINICAL CONSIDERATIONS

It is important to emphasise to patients the need for compliance with combination antibiotic therapy. Eradication rates following therapy are usually about 90 per cent. Follow-up may be required, however, if ulcer bleeding or perforation occurs. The urea breath test is a non-invasive test used to establish the presence of *H. pylori* before commencement of treatment and to check for eradication 4 weeks after cessation of therapy. Endoscopy and biopsy, which are invasive tests, are used mainly for patients presenting with complications such as bleeding and for follow-up of gastric ulcer.

The other drugs used in ulcer treatment are grouped according to their mode of action.

Most other cases of peptic ulcers are caused by the therapeutic use of the non-steroidal anti-inflammatory drugs (NSAIDs). The treatment of these ulcers does not require an antibiotic; an H_2-receptor antagonist usually suffices in obtaining a cure but occasionally, in unresponsive cases, a proton pump inhibitor will be required. Thus, the aetiology of most cases of peptic ulcers can be attributed to these two factors with no mention of stress, which was thought for many years to be a major cause of peptic ulcers and was one of the factors causing the disbelief associated with Dr Marshall's research.

Histamine H_2-receptor antagonists

■ MECHANISM OF ACTION

As mentioned above and in Chapter 29, histamine is a potent agent, the release of which leads to acid production. The drugs termed antihistamines (H_1-receptor antagonists), which are used in the treatment of allergies, are of no use in antagonising the effect of histamine in the stomach. Acid secretion is stimulated by H_2-receptor activation. Antagonists to this receptor are effective in peptic ulcer therapy. Hence, the term H_2-receptor antagonist is used for drugs that do this.

The forerunner of the histamine H_2-receptor antagonists is **cimetidine**, which, following its release in the 1970s, was hailed as a wonder drug and quickly became a best-seller. There is no doubt that much of the accolade given to cimetidine was well deserved, as the need for surgery did decline; however, the incidence of perforations and other complications has not been reduced. The relapse rate is high after discontinuing the drug, so that maintenance therapy is often necessary.

◆ COMMON ADVERSE EFFECTS

The incidence of adverse effects of cimetidine is low, and because of this it is available in some countries without prescription. The most common side effects are muscular pain, headache and dizziness. Other effects are granulocytopenia, elevation of some liver enzymes and some mental aberrations. In high doses, as are used in Zollinger–Ellison syndrome (a rare gastrin-secreting tumour of the pancreas, commonly resulting in multiple ulcers), other effects are seen occasionally due to the antiandrogen effects of the drug. There may be a fall in libido and sperm count, and gynaecomastia may develop.

Of more concern is the ability of cimetidine to slow down the metabolism of many other drugs, resulting in an enhancement of their effects. Care must be taken with the use of cimetidine in combination with any other drug, and a check on interactions must be made before the concurrent administration of any other drug. An interesting use of cimetidine in many countries is to take it before drinking alcohol in order to prevent hangovers. Cimetidine inhibits an enzyme in the gastrointestinal tract that metabolises alcohol before it is absorbed. By preventing the intestinal metabolism of alcohol, the alcohol is absorbed at a faster rate and exerts its central effects more quickly; in theory this slows down the rate at which a drinker consumes alcohol. It is the congeners in many drinks that contribute to the hangover; as fewer of these congeners are ingested, there is less hangover. Cimetidine also prevents some of the gastritis associated with a hangover.

There are three other H_2-receptor antagonists: ranitidine, **nizatidine** and **famotidine**. These drugs are similar in most respects to cimetidine but have no antiandrogenic activity, and so they are preferred in the treatment of Zollinger–Ellison syndrome. Also they are less likely to block the metabolism of other drugs. In the UK and many other countries, many of the H_2-receptor antagonists no longer require a prescription for purchase and are recommended for the routine control of reflux oesophagitis. Anyone with an ulcer or severe or recurrent oesophagitis should, of course, seek medical advice.

Some proton pump inhibitors are available in combination with the antibiotics needed for eradication of *H. pylori*. The patient has to take only one capsule, instead of three different medications, which may increase compliance.

✚ CLINICAL CONSIDERATIONS

Patients can administer these preparations with or without meals, as food does not affect their absorption. The patient should be advised to avoid alcohol, smoking, aspirin products, **caffeine** and spicy food, as these may increase gastric acid secretion and worsen the disease. Cimetidine should be avoided because of its tendency to slow down the absorption of several drugs.

Proton pump inhibitors

■ MECHANISM OF ACTION

Several compounds have been investigated because of their ability to interfere directly with hydrochloric acid production. They are much more potent in inhibiting

hydrochloric acid production than the histamine H_2-receptor antagonists and have opened new doorways in the management of problems associated with hyperacidity. These drugs are termed proton pump inhibitors. The formation of hydrochloric acid depends on a supply of hydrogen ions (protons) being produced in the parietal cells; the proton pump inhibitors stop this from happening. Several of these compounds are available, omeprazole being the prototype. The others available in the UK are **esomeprazole**, **rabeprazole**, **lansoprazole** and **pantoprazole**. As a non-competitive inhibitor of the gastric (H^+/K^+) ATPase enzyme, these drugs have a relatively long duration of action in spite of their short half-lives. The drugs need an acidic environment in order to be active and therefore act on this enzyme only in the parietal cells of the stomach.

◆ COMMON ADVERSE EFFECTS

These drugs produce hypochlorhydria, which reflexively leads to an increase in gastrin production. The hypergastrinaemia so produced has led to hyperplasia of parietal cells and carcinoid tumours in rats fed on high doses for prolonged periods of time. Although these problems have not been observed in humans, until further long-term safety data are available, long-term treatment with omeprazole is contraindicated in peptic ulcer and ulcerative oesophagitis, as is the use of overly high doses.

The use of any compound that inhibits acid production in the stomach could be considered to be destroying one of the body's defence mechanisms against infection. Problems with gastrointestinal infections have not been noted with these drugs, but there have been instances of upper respiratory tract infections, including pneumonia. It is presumed that organisms from the stomach migrate to the trachea unhindered by acid. This is of particular concern in patients with a nasogastric tube, which afford an easier surface for the bacterial ascent. Not surprisingly, proton pump inhibitors are the worst offenders in causing this type of infection.

Side effects include gastrointestinal disturbances such as nausea, abdominal pain, flatulence, diarrhoea and constipation. Headache and dizziness may occur.

✚ CLINICAL CONSIDERATIONS

Omeprazole is particularly useful in the short-term management of reflux oesophagitis and in the treatment of duodenal ulcers not responsive to other drugs. There does not appear to be much difference between the proton pump inhibitors available, except that some reports have indicated that pantoprazole and lansoprazole provide relief from heartburn slightly faster (about 4 weeks) than with omeprazole, although endoscopic examination of the lower oesophagus showed similar rates of healing. Esomeprazole is one of the stereoisomers of omeprazole and dose for dose is more consistent in its action than omeprazole. There is no doubt, however, that the proton pump inhibitors are superior in action in cases of peptic ulcer and in oesophagitis to the H_2-receptor antagonists. The National Institute for Health and Clinical Excellence (NICE) has provided guidance on the use of these drugs for gastro-oesophageal reflux disease with severe symptoms and for NSAID-associated ulceration in patients who need to continue NSAID use.

It should be noted that proton pump inhibitors may mask the symptoms of gastric cancer. If 'alarm features' such as bleeding, dysphagia, recurrent vomiting and weight loss are present, it is necessary to rule out malignancy before treatment.

Proton pump inhibitor preparations tend to be enteric-coated tablets and capsules. These preparations should be swallowed whole and not crushed or chewed. Omeprazole and pantoprazole are available as injections. This formulation is used in severely ill patients where the oral route is not available.

Prostaglandins

As mentioned in Chapter 30, prostaglandins have a diverse variety of actions on the body. Table 53.1 shows the effects related to the stomach and associated structures.

All of the actions shown will tend to be antagonistic to ulcer formation in both the stomach and the duodenum. The prostaglandin analogue **misoprostol** is the most common. Although not as effective as the H_2-receptor antagonists, misoprostol has been effective in some cases where treatment with the former has not caused a response. Misoprostol can prevent NSAID-associated ulcers and is used in elderly and frail patients if NSAIDs cannot be discontinued.

◆ COMMON ADVERSE EFFECTS

Misoprostol causes diarrhoea in some patients, but this is usually mild and of short duration. The only other significant effect is on the uterus, where misoprostol can cause menorrhagia. The drug is contraindicated in pregnancy, as it can induce miscarriage.

TABLE 53.1 ACTIONS OF PROSTAGLANDINS ON SOME DIGESTIVE FUNCTIONS

Inhibition of gastric acid production
Inhibition of gastrin production
Inhibition of pepsinogen release
Stimulation of mucus secretion
Stimulation of bicarbonate secretion
Increase in mucosal blood flow

✚ CLINICAL CONSIDERATIONS

Misoprostol is not very effective in dealing with the pain of ulcers compared with other drugs. Smokers, heavy alcohol-drinkers and people on NSAIDs have a diminished prostaglandin activity in the stomach. Misoprostol, replacing the lack of endogenous prostaglandins, may be useful in treating ulcers in patients who will not cease such deleterious activities or who require NSAID therapy. In the UK, misoprostol is available combined with the NSAIDs **diclofenac** or **naproxen** for use in patients in whom NSAIDs alone are contraindicated due to gastrointestinal bleeding.

Misoprostol may induce premature labour by increasing uterine tone and contractility. Therefore, it should not be used in pregnancy. Gastrointestinal irritation can be reduced by administering the drug in divided doses with meals.

Chelates and complexes

SUCRALFATE

■ MECHANISM OF ACTION

Sucralfate is a complex of the sugar sucrose and an aluminium compound. (Do not confuse this compound with aluminium-containing antacids.) Sucralfate acts only in the presence of acid. It polymerises to form a thick paste-like substance, which adheres to the gastric mucosa, protecting it from the acid. Sucralfate should not be taken with antacids or with food, both of which lower overall gastric acidity. Studies have shown sucralfate to be very effective in healing duodenal ulcers with minimal side effects.

◆ COMMON ADVERSE EFFECTS

One significant side effect is constipation, as sucralfate is absorbed very poorly.

Sucralfate should be used with caution in seriously ill patients, especially those on enteric feeding or with delayed gastric emptying, following reports of bezoar formation (an insoluble mass formed within the stomach). Sucralfate is not recommended for use in premature infants. A French study in newborn infants who received sucralfate revealed that 73 per cent developed severe digestive problems and 36 per cent presented with an occlusive syndrome requiring medical treatment.

✚ CLINICAL CONSIDERATIONS

Advise the patient to take sucralfate on an empty stomach (1 hour before each meal and at bedtime). As sucralfate may cause constipation, ensure the patient consumes plenty of fibre and fluids and ambulates regularly.

BISMUTH CHELATE

Bismuth compounds have long been used in the treatment of ulcers and in some gastrointestinal infections. The simpler compounds have a potential to cause neurotoxicity, which has put them out of favour. **Tripotassium dicitratobismuthate** is a bismuth chelate that is effective in healing gastric and duodenal ulcers.

■ MECHANISM OF ACTION

Bismuth chelate has a low concentration of bismuth, but absorption has been reported. Encephalopathy has not been reported (this was a problem with older bismuth preparations). Like sucralfate, bismuth chelate forms a protective layer on the gastric and duodenal mucosa. Furthermore, the compound is bactericidal against *H. pylori*, which is very useful if this organism is involved in the aetiology of the disease. Ranitidine bismuth citrate is sometimes used with certain antibacterials for these purposes.

◆ COMMON ADVERSE EFFECTS

Blackening of the tongue and faeces can result. The latter should not be confused with melaena.

✚ CLINICAL CONSIDERATIONS

Bismuth chelate is available as tablets to be swallowed with half a glass of water 30 minutes before meals and one dose 2 hours after the evening meal.

Food or milk may bind with this drug and reduce its efficacy. A 4- to 8-week course is usually considered. If a further course is required for ulcer healing, the treatment may be repeated after a 4- to 8-week drug-free interval.

CLINICAL MANAGEMENT

Drugs used for peptic ulcers

Assessment

- Assess the patient's dietary intake, including alcohol, caffeine, spicy foods, and patterns of eating. Assess the patient's use of cigarettes.
- Assess the patient's baseline vital signs and level of consciousness. Compare with subsequent observations.
- Assess the patient's manifestations of a peptic ulcer, including the onset, duration and frequency of abdominal tenderness, cramps, indigestion, nausea and vomiting. Also determine the location of the pain.
- Assess the character and quantity of emesis and faeces, including the presence of occult blood.
- Administer antacids containing magnesium or calcium cautiously to elderly patients and patients with renal disease.

Planning

- The patient will not experience any abdominal pain after commencement of treatment.
- Any blood loss that has occurred will stop.
- The patient's ulcerated area will heal.

Implementation

- Monitor fluid balance by documenting fluid input and output.
- Monitor the drug's effects on the manifestations of the peptic ulcer.
- Appropriate laboratory monitoring includes haematocrit, haemoglobin, full blood examination and electrolyte levels.
- Avoid administering antacids with other oral drugs, as antacids can delay drug absorption. Ideally, antacids are given about 2 hours after other medications. An antacid should never be given with quinidine, digoxin or tetracycline, as the antacid binds to and inactivates these drugs.
- Administer H_2-receptor antagonists and antimuscarinics before meals to decrease food-induced acid secretion.
- Provide reduced doses of H_2-receptor antagonists to elderly patients, as such patients have reduced gastric acid, and in order to prevent metabolic alkalosis.
- The combination of two or more antimicrobial agents with a bismuth compound or proton pump inhibitor is considered the most successful regimen for combating *Helicobacter pylori*, the most important aetiological factor in peptic ulcer disease.
- At least two antibacterial agents should be used to reduce the problem of resistance and increase the chance of eradication.

Patient teaching

- Instruct the patient to report pain, coughing, vomiting of blood (haematemesis) and blood in faeces (melaena).
- Advise the patient to avoid foods that can aggravate ulcers, including caffeine-containing foods, alcohol and spices. Small, frequent meals are preferable to heavy, infrequent meals.
- Teach the patient relaxation techniques and other methods to decrease anxiety and stress.
- Indicate to the patient that compliance is essential for treatment to be successful. This may be difficult to accomplish, as many treatment regimens cause nausea, diarrhoea and altered taste sensation.

Antacids

- Remind the patient to chew antacid tablets and then to follow this with water. Antacid tablets should not be swallowed whole. With liquid antacids, a small amount of water is taken after the dose is consumed to ensure that the antacid dose is carried to the stomach.
- Advise the patient to take the antacid 1–3 hours after meals and at bedtime. Food slows down gastric emptying time, leading to increased gastric activity and secretions.
- Review with the patient their medications and try to work out a suitable plan that prevents the antacid from interfering with other medications. Instruct the patient to avoid taking antacids within 1–2 hours of other oral medications.
- Advise the patient to increase the fluid intake to about 3000 ml daily to prevent formation of kidney stones.
- Instruct patients with heart disease and those on a sodium-restricted diet to avoid antacids high in sodium content.
- Teach the patient to alternate an aluminium or calcium salt antacid with a magnesium salt antacid to prevent diarrhoea and constipation. If in doubt, the patient should notify the doctor.
- Remind the patient that an antacid should be used only for symptomatic relief.

Antimuscarinics

- Instruct the patient to increase fluids, fibre and mobility to prevent constipation.
- The doctor should be consulted if tachycardia or urinary retention occurs.

H_2-receptor antagonists

- Warn the patient to avoid smoking and drinking alcohol while taking an H_2-receptor antagonist, as these activities can impede the effectiveness of the drug.

Proton pump inhibitors

- Advise the patient that treatment with this group of drugs is for a short course of therapy only. Treatment is usually limited to about 4–8 weeks.

Prostaglandin analogues

- Query with female patients the possibility of pregnancy before administration of the first dose. Inform women of childbearing age that misoprostol can cause spontaneous abortion and that they should use adequate contraceptive cover. Misoprostol is also teratogenic in large doses. A more suitable alternative for childbearing women is ranitidine.
- Advise the patient that diarrhoea may occur with this drug but that this adverse effect usually disappears after the first month of therapy.

Sucralfate

- Ensure the patient takes sucralfate on an empty stomach to increase clinical efficacy.
- Advise the patient to avoid antacids within 30 minutes of sucralfate administration.

Bismuth compounds

- Advise the patient to take the preparation on an empty stomach.
- Indicate to the patient that bismuth may cause blackening of faeces and darkening of the teeth and tongue. These effects are not harmful.

Evaluation

- Evaluate the effectiveness of the medication to promote the healing of the ulcer without producing adverse effects.
- Evaluate the patients' ability to implement dietary and other changes in their lifestyle.

SUMMARY

- Antacids work by simple neutralisation of stomach acid.
- Antacids are very effective for quick and simple relief from hyperacidity symptoms.
- To avoid diarrhoea and constipation, aluminium and magnesium compounds are often present in the same antacid preparation.
- Peptic ulcers are most commonly caused by the use of non-steroidal anti-inflammatory drugs or the presence of a *Helicobacter pylori* infection.
- Antiflatulents reputedly disperse intestinal gases.
- H_2-receptor antagonists inhibit gastric acid production.
- Proton pump inhibitors non-competitively inhibit hydrogen ion production in the stomach.
- Prostaglandin analogues mimic stomach prostaglandins and inhibit acid production.
- Sucralfate protectively coats gastric-wall lesions and inhibits pepsin.
- Triple therapy involves the use of a combination of an H_2-receptor antagonist or proton pump inhibitor with two broad-spectrum antibiotics.
- *Helicobacter pylori* infections are best treated by triple therapy.

1. Discuss the aetiology of peptic ulcers.
2. Explain why proton pump inhibitors are the most effective drugs to use in hyperacidity problems.
3. Discuss the use of triple therapy in the treatment of some peptic ulcers.
4. What is the role of histamine in the production of gastric secretions?
5. What are the roles of prostaglandins in the production of gastric secretions?
6. Why would diphenhydramine, an H_1 antihistamine, be useless in the treatment of a peptic ulcer?
7. Antacids are relatively cheap and have been shown to heal peptic ulcers, but they are rarely used as the sole treatment for such ulcers. Why?
8. Why have gastrectomies and vagotomies been more or less relegated to the past as surgical procedures for peptic ulcers?
9. Why are magnesium and aluminium hydroxide often combined in antacid preparations?
10. What problems could arise from antacids containing calcium carbonate?
11. What problems could arise from antacids containing sodium bicarbonate?
12. What is Zollinger–Ellison syndrome, and why are H_2-receptor antagonists and proton pump inhibitors useful in its treatment?
13. Why is bismuth chelate therapy useful in the treatment of some types of gastritis?
14. Why should an antacid mixture and ranitidine not be taken at the same time?
15. Explain how ranitidine is advantageous over cimetidine as an H_2-receptor antagonist.
16. What non-pharmacological measures can you advise for alleviating manifestations of a peptic ulcer?
17. Rose Goldstein, a 40-year-old patient, is ordered bismuth chelate for gastritis. What patient education would you provide?
18. Jack Brown, a 56-year-old patient, has been prescribed a peptic ulcer treatment regimen consisting of omeprazole, metronidazole and amoxicillin. How would you advise Mr Brown on ways to prevent problems arising from altered taste, diarrhoea and nausea?

53 DRUG SUMMARY TABLE: UPPER GASTROINTESTINAL TRACT DRUGS

FAMILY NAME	GENERIC NAME	TRADE NAME(S)*
Antacids	Aluminium hydroxide + Magnesium compounds	Alu-Cap Aludrox Maalox Mucogel
	+ Magnesium compounds, calcium carbonate, sodium bicarbonate, alginates	Algicon Gastrocote
	+ Magnesium compounds, sodium bicarbonates, alginates	Gaviscon Peptac Rennie Duo Topal
	Calcium carbonate Sodium bicarbonate	Setlers
H_2-receptor antagonists	Cimetidine	Dyspamet Tagamet
	Famotidine	Pepcid
	Nizatidine	Axid
	Ranitidine	Zantac
	Ranitidine bismuth citrate	Pylorid
Proton pump inhibitors	Esomeprazole	Nexium
	Omeprazole	Losec
	Lansoprazole	Zoton
	Pantoprazole	Protium
	Rabeprazole	Pariet
Triple therapy	Lansoprazole, amoxicillin and clarithromycin	HeliClear
Prostaglandin analogues	Misoprostol + Diclofenac + Naproxen	Cytotec Arthrotec Napratec
	Bismuth chelate	De-Noltab
	Simeticone	Detinox Infacol
	Sucralfate	Antepsin

* Note that not all trade names for over-the-counter products available outside the National Health Service are given as there are so many in an ever-changing market; for example, some pharmacies have their own preparations.

LOWER GASTROINTESTINAL TRACT DRUGS

54

CHAPTER FIFTY-FOUR

OBJECTIVES

After completing this chapter, the reader should be able to:

- **outline the use of digestive enzymes in therapeutics;**
- **describe the mechanisms of action of bulk-forming, osmotic, surfactant and stimulant laxatives;**
- **explain the problems associated with laxative use;**
- **describe constipation and its management;**
- **list the common causes of diarrhoea;**
- **explain the conservative treatment of diarrhoea;**
- **describe the drug treatment of diarrhoea;**
- **list the problems associated with the drug treatment of diarrhoea;**
- **outline the management of ulcerative colitis and Crohn's disease;**
- **define the use of simeticone, peppermint and alginic acid in gastrointestinal disorders.**

KEY TERMS

Digestive enzymes
Laxatives
Constipation
Diarrhoea
Antidiarrhoeal agents
Ulcerative colitis
Crohn's disease
Irritable bowel syndrome
Gall-stone dissolution
Haemorrhoids

THIS CHAPTER COVERS THE PANCREATIC ENZYMES, LAXATIVE AGENTS AND antidiarrhoeals and drugs used in the treatment of irritable bowel syndrome, inflammatory bowel disease, gall-stone dissolution and haemorrhoids.

PANCREATIC ENZYMES

Deficiency of pancreatic enzymes can occur in pancreatitis, cystic fibrosis and obstruction of the pancreatic duct and after pancreatectomy. In such cases, digestion, especially that of fats, is impaired. This can result in deficiency of essential fatty acids and in steatorrhoea (fatty stools). Patients with these conditions require supplemental pancreatic enzymes to ensure a more normal digestion. The enzymes used are usually derived from pig pancreas. The impure preparation is called pancreatin, which contains a mixture of enzymes, including lipases, proteinases (proteases) and amylase. The main problem associated with these preparations is their inactivation by gastric acid. This can be overcome by using enteric-coated tablets or capsules containing enteric-coated microspheres. These preparations should be taken with every meal and snack. Other problems are rare, although allergy has been reported on occasion.

✚ CLINICAL CONSIDERATIONS

Enteric-coated tablets and capsules should be swallowed whole and not chewed or opened. Uncoated tablets and capsules may be more complicated to use, as they may require concurrent administration of H_2-receptor antagonists. Concurrent intake of hot liquid and food should be avoided, as heat can inactivate the sensitive enzymes.

LAXATIVES

Laxatives are occasionally termed aperients and purgatives. Not all can be termed purgatives, however, and this term is best reserved for the more potent laxatives.

Laxatives are among the most misused drugs. Many people misunderstand the meaning of the word 'constipation' and resort to the use of laxatives in cases of what could be termed 'perceived constipation'. Constipation has more to do with the ease of a bowel movement than with the frequency of bowel movements. If straining is necessary during a bowel movement, then the patient is more likely to be constipated than the patient who has weekly bowel movements made with no difficulty. There is some evidence that prolonged contact of bacterial and animal food breakdown products found in faecal material on the intestinal wall may lead to carcinoma, but this is not proven. Therefore, although having only one bowel movement per week may be inadvisable, normally laxatives are not needed in such people, and all that may be required is dietary change. This may call simply for an increase in liquid consumption: A common cause of constipation is dehydration due to inadequate liquid ingestion, especially in hot weather and in elderly people. Non-dietary constipation can be due to paralytic ileus (no peristaltic movements in the intestines), which can occur after abdominal surgery. When this occurs, laxatives must not be used, as the condition is self-limiting. Many drugs, particularly those with antimuscarinic activity, can slow down peristalsis and lead to constipation. Narcotic analgesics, as mentioned in Chapter 39, can stimulate mixing movements in the intestine, leading to more water absorption and, consequently, constipation. The use of these drugs often requires the concurrent use of laxatives to prevent prolonged constipation, which can result in impacted faeces (the faecal material losing most of its liquid content, producing rock-hard faeces that may need surgical removal).

The use of laxatives is contraindicated in many cases of gastrointestinal pathology. For example, administration of a drug that increases peristalsis can, in appendicitis, lead to rupture of the inflamed appendix, an extremely dangerous situation. As a general rule, laxatives should not be used to treat undiagnosed abdominal pain.

Laxatives can be grouped into several different categories depending on their mode of action. Table 54.1 shows details of the characteristics of different laxative categories.

Osmotic laxatives

IONIC OSMOTIC LAXATIVES

■ MECHANISM OF ACTION

These drugs usually act by a physical mechanism, as mentioned in Chapter 16. Many small molecules are not absorbed efficiently in the small or large intestine, thus creating a stronger than usual solution in the colon, where much water reabsorption takes place. The contents are hypertonic, causing water to be retained; if the osmotic pressure is great enough, this can pull water from the bowel's capillaries back into the bowel lumen. This results in a rise in pressure and volume in the colon and rectum, leading to stimulation of the defecation reflex. Many commonly used laxatives fall into this category. Magnesium and sulphate ions are like this and **magnesium sulphate** (Epsom salts, readily available in supermarkets) may be used as a laxative. This type of laxative, when taken by mouth on an empty stomach, can cause a bowel movement 3–4 hours

TABLE 54.1 CHARACTERISTICS OF LAXATIVE CATEGORIES

Laxative category	Examples	Onset of action (hours)	Use
Osmotic laxatives (hyperosmotic agents)	Glycerol, lactulose, sorbitol	24–72	First-line therapy for chronic constipation; second-line therapy for acute constipation and constipation induced by opioids
Osmotic laxatives (saline agents)	Magnesium salts, polyethylene glycol, sodium salts, phosphate enemas	0.5–3	Moderate to severe constipation; second-line therapy for chronic constipation caused by magnesium salts; bowel preparation
Stimulant laxatives	Bisacodyl, senna, dantron	6–12	Moderate to severe constipation; chronic use in spinal conditions; bowel preparation
Faecal softeners	Docusate, arachis oil enemas	24–72	Prevention of straining following rectal and perianal disease; limited use in acute and chronic constipation
Lubricants	Liquid paraffin	48–72	Acute constipation; prevention of straining following rectal surgery and perianal disease
Bulk-forming laxatives	Ispaghula husk, sterculia, methylcellulose	48–72	First-line therapy for acute and chronic constipation

after ingestion. Sodium salts (e.g. sodium sulphate) should be avoided, as they may cause sodium and water retention in susceptible patients. Another simple inorganic salt used as an osmotic laxative is **magnesium hydroxide**, which leads to rapid bowel evacuation.

◆ COMMON ADVERSE EFFECTS

The use of this type of laxative is contraindicated in patients with renal pathologies, as the ions may be absorbed and accumulate in the blood. Sodium-containing types should be avoided, especially in patients with hypertension.

CARBOHYDRATE OSMOTIC LAXATIVES

Some sugar derivatives are not absorbed well from the gut and can have a laxative effect. **Lactulose**, a derivative of lactose, is an example and is a commonly used laxative. Some of this compound is metabolised by the bacterial flora of the gut into various acidic compounds, which have a stimulant action on the bowel walls, increasing the laxative action of the drug. **Glycerol**, when given as a suppository, has both an osmotic effect and stimulant and softening properties. **Sorbitol**, used as an artificial sweetening agent in some low-calorie jams and chewing gums, is similar to lactulose in its action. As well as being available on its own as a laxative, sorbitol is included in some cough mixtures containing narcotic antitussives to prevent abuse.

◆ COMMON ADVERSE EFFECTS

Flatulence and abdominal discomfort can occur with lactulose. Overconsumption of sorbitol-containing products can lead to diarrhoea.

MISCELLANEOUS OSMOTIC LAXATIVES

Some osmotic laxatives are used to completely evacuate the bowels before gastrointestinal surgery and gastrointestinal X-ray procedures such as barium meal and enema radiography. These products may contain large amounts of polyethylene glycols (macrogols) and non-electrolytes in combination with equivalent amounts of normal electrolytes such as potassium, sodium and chloride ions. This solution is isotonic and promotes no net loss of electrolytes or of water but is very effective at cleansing the bowels. Usually 4 l of the solution is drunk over a period of 4 hours before an internal examination, such as colonoscopy, is made. The solution is consumed at a rate of about 1 l per hour until the stools contain no solid matter. Bowel-cleansing solutions such as Citramag™, Klean-Prep™ and Picolax™ are not treatments for constipation but are used to ensure the bowel is free from solid contents before a procedure or surgery. A standard irritant laxative such as **bisacodyl** may be given before the complete purging process begins to make certain that the colon and the rest of the gastrointestinal lumen is empty.

High concentrations of phosphates given orally or rectally are useful for rapid evacuation.

✚ CLINICAL CONSIDERATIONS

It is important that adequate water is consumed by patients using osmotic laxatives, as deaths from dehydration have occurred, albeit very rarely.

Osmotic laxatives are contraindicated in intestinal obstruction. Sorbitol is cheaper than lactulose but it is ineffective for hepatic encephalopathy. Oral lactulose is very sweet and not tolerated well; it is more palatable when mixed with fruit juice, water or milk. Serum sodium levels should be monitored following lactulose administration, especially when it is given in higher doses to treat hepatic encephalopathy. When using saline laxatives for procedure preparation, it is important not to eat for about 1–2 hours before commencing the preparation. Clear fluids are usually permitted during this time. Following administration of a saline preparation, diarrhoea can be expected to start occurring after about an hour. The patient should be advised to be near a toilet during this time.

Stimulant laxatives

■ MECHANISM OF ACTION

The stimulant laxatives are true purgatives, as they directly affect the walls of the small or large intestine and cause an increase in peristaltic movements, leading to defecation.

The mechanism of action of this group of drugs is varied. Postulated theories include interference with enzyme systems involved in ion transport, which increases the concentration of the intestinal fluid and leads to an osmotic effect. Some stimulant laxatives may directly prevent water reabsorption in the colon and may promote water excretion directly from the intestinal cells to the lumen. Others may simply irritate the smooth muscle of the intestinal wall or the mucosal cells, leading to a defecation reflex arc. Put in simple terms, the colonic or ileal sensory nerves tell the brain that irritation is happening, and the response is a sense of urgency to have a bowel movement (see Figure 54.1). Regardless of how the stimulant laxatives work, they are very effective.

◆ COMMON ADVERSE EFFECTS

A problem with the use of stimulant laxatives is rebound constipation, which can occur when laxatives are discontinued, especially after prolonged use. This could happen because the intestines adapt to being stimulated strongly; normal diet then does not cause enough stimulation, and the afferent messages from the intestine to the brain are ignored.

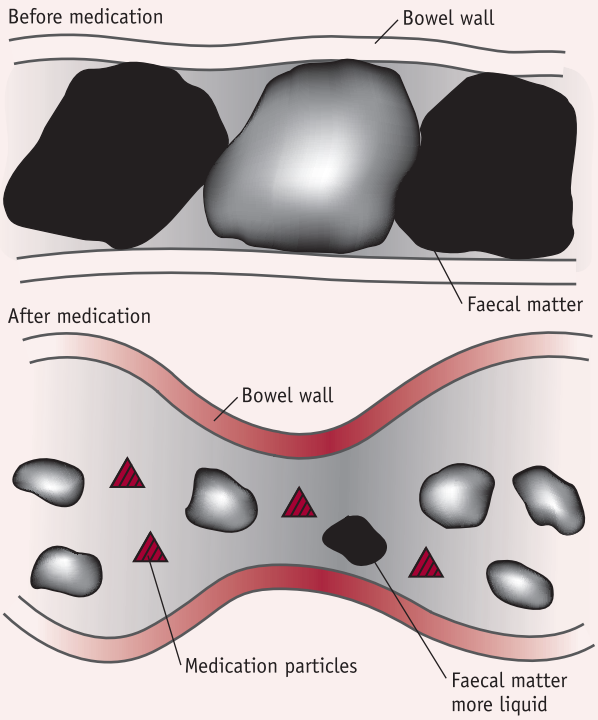
✚ CLINICAL CONSIDERATIONS

Stimulant laxatives are not recommended for use on a regular basis because this may lead to a dilated colon, with reduced peristalsis, and the need to increase the dose. These drugs are very suitable for intermittent use in constipation. Chronic use is acceptable in particular cases, including patients with spinal damage and neuromuscular disease. **Bisacodyl** tablets are swallowed whole and should not be crushed or chewed. To improve the palatability of **senna** granules, these can be mixed with water, milk or food.

Some of the more important stimulant laxatives and those with interesting properties are dealt with in some detail below.

FIGURE 54.1 PROPOSED MECHANISM OF ACTION OF STIMULANT LAXATIVES

Stimulant laxatives are thought to facilitate bowel movements by acting on nerve endings in the large intestinal wall. Following muscle contraction, faecal contents are propelled through the intestine, allowing less time for water absorption.



BISACODYL

Bisacodyl is a synthetic laxative related to phenolphthalein. In the majority of patients, bisacodyl does not cause any griping or any prolongation of its effects, as is found with phenolphthalein. As bisacodyl can cause gastric irritation, the oral preparation is in the form of enteric-coated tablets. Bisacodyl and a close relative, **sodium picosulfate**, are both prodrugs, being metabolised to the active form by colonic bacteria.

◆ COMMON ADVERSE EFFECTS

Irritation can occur in the rectum when bisacodyl is given as a suppository, especially after prolonged use, which is inadvisable. Occasionally, mild proctitis occurs, with considerable production of bloody mucus due to sloughing of the rectal mucosa. This is not a serious problem but could be very distressing and worrying to patients. A burning sensation on rectal insertion of bisacodyl is usual, and patients should be forewarned.

CASTOR OIL

Castor oil is a powerful stimulant laxative that is now obsolete for this purpose. It has an appalling taste. Its effect is mainly on the ileum rather than the colon, which is affected by other laxatives (6 m of small intestine compared with 1.5 m of large intestine). Castor oil in itself is not an irritant, hence its use in skin preparations such as zinc and castor oil ointment, but it must be metabolised to ricinoleic acid, a potent intestinal irritant. Ricinoleic acid can be absorbed and, as it also stimulates uterine smooth muscle, was previously used with some success to induce labour in pregnancy; this property of castor oil is still utilised in some countries.

SENNOSIDES

Sennosides are a group of plant products obtained from the pods of some species of *Cassia*. These pods are available in some pharmacies, and some older people brew them up to make a laxative tea. Sennosides can cause considerable griping, which may be distressing to some patients. Purified senna preparations, as found in **senna**, are reputed to cause less griping than impure preparations. Long-term use of senna can be detected easily during colonoscopy or sigmoidoscopy due to the brown-black pigmentation that it causes on the mucosa; this is termed 'melanosis coli', a presumed benign reversible condition.

OTHER AGENTS

Throughout the world there are numerous plant and other products that can have a laxative effect. You may be familiar with those in use in the UK, and there may be others you have heard about in use elsewhere.

Cascara is obtained from the buckthorn plant and is a powerful stimulant that should be no longer used.

These compounds and mixtures are popular with some people. There is probably little difference between them as long as they are used with care and for genuine constipation.

Faecal softeners

■ MECHANISM OF ACTION

These are sometimes known as emollients, surfactants and stool softeners. There are not many of these compounds in common use. One is **sodium dioctyl sulphosuccinate**, which is better known as **docusate**. This compound has detergent-like properties and seems to act mainly by holding water molecules in the faecal material, thus rendering them softer and easier to pass.

These compounds may also act on the intestinal wall to inhibit water absorption and promote water and electrolyte secretion, thus also having some stimulant properties.

As the main mechanism of action is the softening process (although docusate does also act as a gentle stimulant), these laxatives do not work quickly. Their effect usually takes several days to become apparent, and they are used to ease bowel movements rather than for a purging action.

◆ COMMON ADVERSE EFFECTS

Having detergent properties, these substances can affect the cell membranes of gastrointestinal mucosal cells, causing an increase in absorption of other drugs administered concurrently. This can increase the toxicity of the other drugs. Another concern is that docusate is absorbed, and it has been reported as being hepatotoxic. Some experts dispute the efficacy of this type of laxative, and the drugs are utilised less often nowadays. Prudent use of these drugs is therefore advisable. Dantron (danthron) is a stimulant laxative used in terminally ill patients. It has also been used in the care of elderly patients and in patients with conditions where straining must be avoided. Docusate has been shown to be carcinogenic in rodent studies, however and it is genotoxic, thus its use should now be restricted to terminally ill patients. Bile salts are physically and chemically related to these drugs.

✚ CLINICAL CONSIDERATIONS

These preparations are also known as detergent laxatives. Their effectiveness is improved if they are administered with plenty of fluid.

Lubricants

The lubricant laxatives are sometimes included in the faecal softeners group; however, their physical and chemical properties are dissimilar, and so they are separated into a different category here. The compounds usually included in this group are the mineral oils, namely **liquid paraffin**. Lubricant oils are very inert and their action is purely physical, with relatively little absorption occurring. Rather in the manner by which engine oil helps piston movement, liquid paraffin helps faecal movement. This explanation of liquid paraffin's action is considered somewhat naive by some, as the principal mode of action may be due to its coating the intestinal mucosa and, being hydrophobic, preventing water absorption. Being mixed with faecal material will also cause a stool-softening effect. The first explanation must be borne in mind, nevertheless, as one of the untoward effects: the problem of faecal

leakage through the anus due to a slippery rectum is due to this action. Patients must be made aware of this effect as it could prove embarrassing.

Chronic constipation is a relatively common problem in children and may be accompanied by faecal soiling and bowel accidents (encopresis). It is characterised by stool retention and a loss of sensation to defaecate. Children so affected require regular toileting programmes, dietary and activity changes, and long-term laxative therapy with liquid paraffin and senna for a period of 6 months or more to keep the rectum empty until sensation returns.

Liquid paraffin is the main ingredient of most bath and baby oils.

◆ COMMON ADVERSE EFFECTS

Being lipophilic, liquid paraffin can interfere with the absorption of fat-soluble vitamins, namely vitamins A, D, E and K.

Some liquid paraffin can be absorbed, particularly when abused or taken for long periods. It can accumulate in the intestinal mucosal cells and mesenteric lymph nodes, resulting in what are termed paraffinomata – polyp-like growths. These are not considered to be of much consequence. If the paraffin eventually finds its way into the general circulation or small amounts leak through the epiglottis when swallowed, accumulation in the lungs can occur, resulting in lipoid pneumonia. This is more likely to occur in the recumbent position, so patients should take liquid paraffin preparations at least half an hour before lying down. Long-term use has been linked to carcinomata of the gastrointestinal tract.

✚ CLINICAL CONSIDERATIONS

When used to alleviate the discomfort and pain of defecation after operations for haemorrhoids and anal fissures, liquid paraffin can delay the healing process.

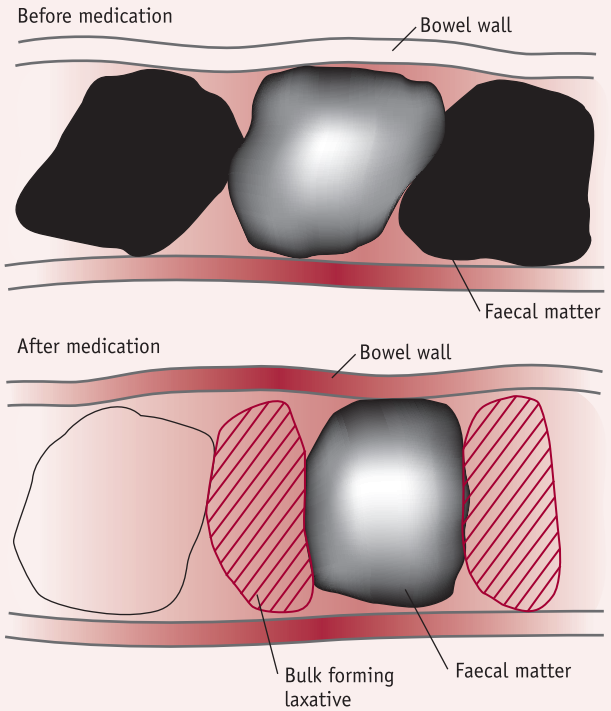
The chance of oil leakage can be reduced by titrating the dose by 5-ml aliquots in order to achieve one soft bowel motion daily or on alternate days. Administration should be avoided at bedtime in order to prevent lung aspiration.

Dietary fibre and bulk-forming laxatives

The proper function of the bowel is dependent on the presence of adequate amounts of liquid and dietary fibre. Dietary fibre consists of plant products such as cellulose, hemicelluloses and lignin, which are found in high quantities in the outer coating of seeds and grains. Many vegetables and fruits also contain high amounts of fibre. These substances are not digestible to any great extent by humans and therefore add bulk to the colonic contents, which stimulates forward-propulsive movements and the defecation reflex. These materials have an affinity for water, which in turn helps to prevent constipation (see Figure 54.2). Thus, the presence of adequate fibre in the diet should deem the use of laxatives, in the majority of cases, unnecessary. Fluid intake should be plentiful when a high-fibre diet is consumed. Apart from preventing constipation, a high-fibre diet may be preventive against some bowel cancers and diverticulosis. There is some evidence that a high-fibre diet can help lower blood cholesterol levels. In people who do not consume adequate fibrous fruits or vegetables, a bran supplement can be given, for example to be sprinkled over breakfast cereal.

FIGURE 54.2 PROPOSED MECHANISM OF ACTION OF BULK-FORMING LAXATIVES

A bulk-forming laxative is not absorbed as it passes through the gastrointestinal tract. The agent absorbs many times its own volume of water. This action increases the faecal bulk as it passes along the intestine.



A large number of commercial preparations of concentrated fibrous plant products are now available, many of which have a phenomenal capacity to absorb large amounts of water. It is not hard to visualise this if one takes a sachet of **ispaghula husk** (Fybogel™) and adds about 200 ml of water. After several minutes, the suspension sets into a fairly firm jelly.

Most of these preparations have no real generic name and are known by the botanical Latin name. As their names are sometimes real tongue-twisters, proprietary names are often used. Sometimes other laxatives and even antispasmodics are included in these preparations. Table 54.2

TABLE 54.2 COMMON BULK-FORMING LAXATIVES

Proprietary name	Botanical origin
Celevac	Methylcellulose
Fibrelief	*Plantago ovata* seeds (ispaghula)
Fybogel	*Plantago ovata* seeds (ispaghula)
Isogel	*Plantago ovata* seeds (ispaghula)
Ispagel	*Plantago ovata* seeds (ispaghula)
Normacol Plus	*Sterculia frangula* bark
Regulan	*Plantago ovata* seeds (ispaghula)
Resource Benefiber	Guar gum

lists some of the common bulk-forming laxatives commercially available.

◆ COMMON ADVERSE EFFECTS

If some of these preparations are taken with inadequate consumption of fluids, then constipation and even bowel blockage and impaction can occur. These drugs can be used with little consumption of fluids to treat diarrhoea. Some other problems associated with the use of bulk-forming laxatives are the prevention of calcium absorption, their binding to some drugs, flatulence and borborygmi (rumbling sounds caused by gas moving through the intestines).

✚ CLINICAL CONSIDERATIONS

It is important to ensure that adequate fluids are given with bulk-forming agents in order to allow for maximal benefit. The potassium content in these products and the need to consume a relatively large fluid volume may be a problem in patients with renal failure. Intestinal obstruction and colonic atony (impaction) are contraindications in the use of these preparations.

ANTIDIARRHOEALS

Diarrhoea is defined as an increase in volume, fluidity or frequency of bowel movements relative to the usual pattern for the particular individual. The causes of diarrhoea are numerous, and consequently the treatments are varied. In many instances, drug intervention is not required, for example in the case of infective gastroenteritis, where diarrhoea is a protective mechanism used by the body to flush out the offending pathogens; the use of drugs to slow down gastrointestinal motility in such circumstances would be inadvisable. Likewise, the use of antibiotics in bacterial infections of the gastrointestinal tract may kill the offending pathogens but also kill some normal bacterial flora, allowing opportunistic organisms to overgrow and cause subsequent diarrhoea or candidiasis. The World Health Organization (WHO) recommends that the first-line emergency treatment for diarrhoea be rehydration and electrolyte-replacement therapy (see below).

Under most circumstances, antibiotics are not used in the treatment of diarrhoea unless the cause of the infection is known and the diarrhoea requires the use of an antibiotic. These infections include the severe diarrhoeas produced by some *Salmonella*, *Shigella*, *Campylobacter* and *Clostridia* species. In most cases, the causative agent should be identified and antibiotic-sensitivity tests performed. There is one form of diarrhoea caused by infectious agents that, due to circumstances, is sometimes treated routinely or prophylactically with antibiotics – 'travellers' diarrhoea'; this has many names in different parts of the world; in the UK, the term 'Delhi belly' is often used. The infection is often caused by unfamiliar strains of *Escherichia coli* and can be avoided by following hygienic eating and drinking habits. Doxycycline and ciprofloxacin (see Chapter 68) are advocated by some but frowned on by others, both as a prophylactic measure and as treatment for travellers' diarrhoea. Symptomatic relief using peristaltic inhibitors can prolong the infection. The arguments against the use of these treatments are strong, but how many of us want to spend our holidays exploring public conveniences in strange lands?

Apart from the antibiotics, drugs used in the treatment of diarrhoea affect only the symptoms and not the underlying cause, which may be psychogenic or due to an inflammatory condition of the intestines. The treatment of each is quite different. The drugs used in the treatment of non-specific diarrhoea usually either slow down gastrointestinal motility or help to absorb the excessive fluids present in the colon. Antimuscarinic drugs (discussed in Chapter 27) can be used to treat the colicky pain caused by some diarrhoeas but have no effect on stool frequency or volume.

Infants often develop diarrhoea due to an infection with a rotavirus. Children at risk of this type of infection can be treated prophylactically with an active immunoglobulin (see Chapter 75) derived from cow colostrum.

Non-specific antidiarrhoeal drugs

OPIOIDS

■ MECHANISM OF ACTION

Most of the narcotic analgesics are stimulants of opioid receptors in the gastrointestinal tract. This stimulation increases the segmentation or mixing movements of the gut and simultaneously decreases the peristaltic movements. This in turn slows down forward movement and reabsorption, thus increasing the viscosity of the bowel contents and correcting the diarrhoea. The dose of narcotic needed is less than that needed for central analgesia, and so the potential for addiction is low, although there have been cases of this. **Codeine**, in syrup or tablet form, is commonly used, as is **morphine** combined with **kaolin** (see below). The synthetic opioid **diphenoxylate** is particularly useful as an antidiarrhoeal. As diphenoxylate is insoluble in water, it is not available in forms for parenteral administration and so has a low abuse potential. To further discourage abuse, it is combined with **atropine** in the preparation Lomotil™. If Lomotil is taken in a high enough dose to elicit the euphoric response to diphenoxylate, the antimuscarinic effects of the atropine will quickly counteract this euphoria.

Loperamide is a synthetic opioid related to pethidine (but note that pethidine itself has no effect on peristalsis). Loperamide cannot readily cross the blood–brain barrier, and so it has very low abuse potential.

◆ COMMON ADVERSE EFFECTS

The main adverse effect of these drugs is that there can be such a reversal in the movement of the bowels that constipation results. Loperamide has been associated with nausea, vomiting and abdominal cramping. Opioids should not be used in infants, as these drugs may produce respiratory depression; many deaths in developing countries have been caused by their misuse.

✚ CLINICAL CONSIDERATIONS

Opioid preparations are contraindicated in intestinal obstruction and should be avoided in children under the age of 6 years. In patients who have chronic diarrhoea, treatment with opioids should be considered a medical specialist's decision because of their possible abuse potential.

ADSORBENTS

■ MECHANISM OF ACTION

It used to be thought that certain substances, such as **bismuth salts**, kaolin and **pectin**, had the ability to adsorb bacterial toxins that might be implicated in causing diarrhoea. These preparations are still used in some parts of the world owing to their cheapness and, to a certain extent, their effectiveness. Bismuth salts are bactericidal, which is probably their mode of action (see the section on treatment of ulcers in Chapter 53). Kaolin and pectin work by increasing the viscosity of the gut contents, forming what could be called a sludge. These substances are usually minimally effective but can, on occasion, be very effective. Many preparations contain these substances, often in combination with opioids or antimuscarinics. Another adsorbent is **aluminium hydroxide** (found in many antacids – see Chapter 53).

Colestyramine (cholestyramine), discussed in Chapter 43, may be successful in the treatment of diarrhoea not responsive to other medications.

The use of some bulk-forming laxatives in the treatment of diarrhoea has already been considered.

◆ COMMON ADVERSE EFFECTS

Bismuth salts, if absorbed systemically, can be neurotoxic and should be avoided (note that **bismuth chelate** is relatively safe but no good for diarrhoea). Examine the label of antidiarrhoeal mixtures obtained overseas for the presence of bismuth compounds. Kaolin and pectin interfere with the absorption of other drugs.

✚ CLINICAL CONSIDERATIONS

Adsorbents should not be used in children and should be avoided in adults. They have been shown to be no more effective than having no treatment. Furthermore, they interfere with estimating the level of fluid and electrolyte loss, and they can bind to other drugs, such as antibacterials.

An important aspect of the treatment of diarrhoea is the replacement of electrolytes and fluid. In severe infections, such as cholera, intravenous fluids and electrolytes must be given, otherwise death occurs more from dehydration and electrolyte imbalance than from the infection itself. For less serious infections, oral supplementation is all that is necessary, especially in children. There are several proprietary flavoured electrolyte preparations containing both potassium and sodium ions that can be used for this purpose, such as Dioralyte™ and Rapolyte™.

DRUGS USED IN IRRITABLE BOWEL SYNDROME

Irritable bowel syndrome, which is often of unknown aetiology, is an extremely common and distressing condition. It is sometimes referred to as spastic colon and spastic colitis. Symptoms include lower abdominal pain, flatulence and loose stools. Diarrhoea may alternate with constipation.

Many drugs have been used in the treatment of irritable bowel syndrome, with varying success. These include anticholinergics, sedatives, bulk-forming laxatives and narcotic antidiarrhoeals, all of which are discussed elsewhere.

PEPPERMINT

■ MECHANISM OF ACTION

Peppermint oil is termed a carminative, which means that it causes relaxation of the sphincters. If the ileocaecal sphincter and internal anal sphincters are relaxed slightly, then the build-up of intestinal gases is prevented and, in theory, pain due to flatulence is avoided. The efficacy of peppermint oil in treating irritable bowel syndrome has been shown by some investigators to be no better than placebo. Other herbs such as **dill** and **aniseed** are reputable carminatives and are included in some commercial preparations to relieve wind and colic in babies.

◆ COMMON ADVERSE EFFECTS

Peppermint oil is enteric-coated, as relaxation of the cardiac oesophageal sphincter can lead to reflux oesophagitis if it is released in the stomach.

✚ CLINICAL CONSIDERATIONS

It is important not to allow enteric-coated peppermint oil capsules to be broken or chewed. Release of the oil into the mouth or oesophagus may cause local irritation. For best effect, these medications should be consumed on an empty stomach before food.

Antispasmodics

Antispasmodics are frequently used not only to control intestinal smooth-muscle spasm but also to control smooth-muscle spasms in other parts of the body, such as the uterus. Most antispasmodics are antimuscarinic drugs, which act on the muscarinic receptors of smooth muscle and inhibit contractions. These drugs are discussed in detail in Chapter 27. However, One antispasmodic, **mebeverine**, is used exclusively in the treatment of intestinal smooth-muscle spasms.

MEBEVERINE

Mebeverine, related to the antihypertensive **reserpine**, has a direct relaxing effect on intestinal smooth muscle. It appears to be quite effective in reducing colonic hypermotility and the associated pain without having the side effects of the antimuscarinics.

DRUGS USED IN INFLAMMATORY BOWEL DISEASE

Inflammatory bowel disease presents itself in two main forms – ulcerative colitis and Crohn's disease. Ulcerative colitis is an inflammatory condition of the rectum and colon, which in severe cases can lead to perforation of the colon due to abscesses eroding its walls. Crohn's disease can involve the whole intestine and is characterised by the formation of inflammatory nodules containing macrophages in the mucosal and submucosal layers. Both diseases can lead to chronic pain and abdominal discomfort of varying severity. Severe cases need surgical intervention. Two groups of drugs are used in the treatment of these conditions – the corticosteroids and the aminosalicylates. These drugs can be used alone or in conjunction with each other. (The corticosteroids as anti-inflammatory agents are dealt with in detail in Chapter 58.) The two most commonly used in both conditions are **prednisolone** as suppositories or retention enemas and **budesonide** as enteric-coated tablets used in Crohn's disease to induce remission; these tablets are designed to release the drug only in the ileum and colon, being enteric-coated and in a sustained-release formulation. Corticosteroids are not suitable for maintenance therapy because of their side effects.

Aminosalicylates such as **sulfasalazine** are extremely valuable in the maintenance of remission of ulcerative colitis, but they are less valuable in maintaining remission of Crohn's disease. The immunsosuppressant drug **azathioprine** may be given in resistant or frequently relapsing cases, although it is not licensed in the UK for this use. The antimetabolite **mercaptopurine** is occasionally given under close supervision, although again it is not licensed for this use. Methotrexate is tried in Crohn's disease if azathioprine or mercaptopurine cannot be used. In severe active Crohn's disease when other treatment has failed or is not tolerated, the National Institute on Health and Clinical Excellence (NICE) has recommended that **infliximab** may be prescribed by a gastroenterologist. This drug is a cytokine inhibitor and inhibits tumour necrosis factor (TNF).

SULFASALAZINE

■ MECHANISM OF ACTION

Sulfasalazine is an unusual drug. First, it can be classified as a prodrug, because it is not effective until metabolised in the intestine into two moieties, namely 5-aminosalicylic acid (5-ASA) and sulfapyridine. 5-ASA is the active molecule and sulfapyridine is responsible for most of the drug's adverse effects. A question arising from this is why do we combine these compounds rather than using only 5-ASA? The reason is quite simple: 5-ASA, if given alone, is absorbed fairly well and does not attain sufficiently high levels in the colon to be effective. The hydrolysis of sulfasalazine takes place in the colon, thus releasing the active drug where it is most needed.

Two molecules of 5-ASA have been linked to form **olsalazine**, and hydrolysis of this compound in the colon releases two molecules of 5-ASA. Mesalazine is 5-ASA and is used on its own, either as an enema or orally as capsules. Balsalazide is a prodrug of 5-ASA taken as capsules. These

drugs have advantages over sulfasalazine regarding the occurrence of sulphonamide-related side effects, but 5-ASA alone can still cause side effects, including blood disorders and lupoid phenomenon, also seen with sulfasalazine.

The mechanism of action of these drugs is the same as for all salicylates: 5-ASA is a prostaglandin inhibitor and was originally tried in cases of rheumatoid arthritis as an anti-inflammatory. It was noticed in clinical trials that patients with concurrent inflammatory bowel disease noted an improvement in this condition – another case of serendipity.

◆ COMMON ADVERSE EFFECTS

Sulfapyridine is absorbed and can cause some haematological disorders, including agranulocytosis. This warrants routine periodic blood counts during therapy.

The common adverse effects of 5-ASA are nausea and abdominal pain with watery diarrhoea. Sulfasalazine therapy can cause reversible male infertility by lowering sperm counts.

✚ CLINICAL CONSIDERATIONS

The newer 5-ASA derivatives, mesalazine, olsalazine and balsalazide, are more expensive than sulfasalazine but they are tolerated well. During sulfasalazine therapy, the patient should have urinalysis and a complete blood examination performed every 3–6 months. Before commencing sulfasalazine, the patient should be asked about allergic drug reactions to sulphonamides and salicylate drugs. Before commencing mesalazine, balsalazide or olsalazine, information should be sought from the patient about allergic drug reactions to salicylate drugs.

DRUGS USED IN GALL-STONE DISSOLUTION

Gallstones are found at autopsies in many gall bladders and are commonly asymptomatic; therefore, the presence of gall stones is not necessarily a medical or surgical problem.

If gall stones cause problems and they are cholesterol stones, cholecystectomy is not always the answer, as there are some compounds available that can help to dissolve the stones. With the use of laparoscopic cholecystectomy and endoscopic biliary techniques, however, there is less need for these drugs. In about 10 per cent of gall-stone disease, the stones contain calcium salts, which are unresponsive to pharmacological treatment.

URSODEOXYCHOLIC ACID

■ MECHANISM OF ACTION

Ursodeoxycholic acid is a naturally occurring bile acid, which, by an unknown mechanism, induces cholesterol-containing gall stones to dissolve. One proposed mechanism is that cholesterol secretion by the bile is decreased; the lower concentration of cholesterol in bile then allows the cholesterol in the gall stone to equilibrate with the bile. This may eventually cause the stone to disappear. It may take up to 2 years to occur, however, and this treatment is useful only if the stones are small, as a larger surface-to-volume ratio enhances dissolution.

◆ COMMON ADVERSE EFFECTS

This acid, being a naturally occurring bile salt, may be expected to be free from adverse effects. This is not the case, however, as diarrhoea can occur in almost half of all patients, particularly if the initial dose is too high. Of much greater concern is the drug's potential for hepatotoxicity, and it is recommended that periodic liver function tests be carried out in individuals being treated with the drug. Another problem is its cost and the length of treatment required. Ursodeoxycholic acid may have a further use in the treatment of some chronic liver diseases, including primary biliary cirrhosis and the hepatitides; research is still in progress regarding these uses. Liver tests improve in most patients, but the effect on overall mortality is uncertain.

✚ CLINICAL CONSIDERATIONS

Although ursodeoxycholic acid is generally tolerated well, it may cause nausea and vomiting. If these effects occur, they can be reduced by taking the preparation with food.

DRUGS USED IN THE TREATMENT OF HAEMORRHOIDS

Haemorrhoids, or piles, are varicose veins of the anal canal, which can be distressing to the sufferer. There is no pharmacological cure for this disorder, which is often self-limiting and, if not, may require surgical intervention. The use of faecal softeners can alleviate constipation, which may have caused the lesions in the first place, and lessen straining, which can worsen the condition. The only pharmacological treatment is in the relief of the associated pain, inflammation and/or pruritus. The rectal ointments and suppositories designed to treat haemorrhoids usually contain ingredients to treat these conditions.

Local anaesthetics (see Chapter 42) are included in most haemorrhoidal preparations to relieve the pain; **lidocaine** (lignocaine), **amethocaine**, **pramocaine** and **cinchocaine** are commonly used. Excessive use of these compounds on the anal mucosa can result in systemic effects due to absorption of the drug. Inflammation of the area may be exacerbated, especially in people who are allergic to local anaesthetics. Due to the anaesthetic action of the drug, this inflammation may go unnoticed until serious damage is done.

Corticosteroids in anal preparations help to suppress inflammation, itching and swelling. Excessive use can

lead to systemic effects. Commonly used agents are **hydrocortisone**, **prednisolone** and **fluocortolone**. Refer to Chapter 58 for problems associated with topical corticosteroids.

Vasoconstrictors such as **adrenaline**, **phenylephrine** and **ephedrine** are often included in haemorrhoid preparations, purportedly to lessen the venous swelling. It seems doubtful that their presence has any beneficial effect, however.

Another group of substances often included is astringent compounds. These include **tannic acid**, bismuth, **zinc** and **aluminium** compounds. In theory, they precipitate cell-surface proteins and thus eventually reduce swelling. Tannic acid and other astringents are found in **witch hazel** (*Hamamelis*) extract, which can be incorporated into baby wipes and used to cleanse and soothe the anal area after defecation. As discussed in the sections on antidiarrhoeals and on the treatment of peptic ulcers (see Chapter 53), bismuth can be neurotoxic if absorbed.

A non-pharmacological approach to haemorrhoid therapy is the use of a simple form of cryotherapy. This involves the insertion of a prefrozen implement into the rectum. The extreme cold is thought to relieve the symptoms and to cause shrinking of the dilated veins. This implement is called Anurex™ and is easily kept cold in a household freezer. The effectiveness of this appears good in many cases and may be superior to the use of medications.

Haemorrhoidal preparations containing local anaesthetics are also used to treat the pain of an anal fissure, but they will not cure this condition. An anal fissure is a tear in the mucosal lining of the anal mucosa, the pathology of which causes the sphincter muscle to constrict, thus cutting down on the blood supply, which ultimately prevents healing of the tear. **Glyceryl trinitrate** (see Chapter 45), when applied topically, relaxes the smooth muscle, improves the blood supply and allows healing to proceed without the need for painful surgery.

✚ CLINICAL CONSIDERATIONS

Patients should ensure they maintain a high-fibre diet with plenty of water to prevent straining and the pain associated with haemorrhoids. Topical anorectal preparations are only ever considered to be a short-term treatment of haemorrhoids. Patients need to be warned that local anaesthetics may cause sensitisation of the perianal skin and that corticosteroids may aggravate localised infection and cause skin atrophy.

CLINICAL MANAGEMENT

Laxatives

Assessment

- Obtain a history of constipation and possible causes, including insufficient fluid intake, diet deficient in fibre, immobility, concomitant use of medications such as narcotic analgesics and antimuscarinics, and recent surgery. Determine the frequency and consistency of bowel motions and general health status.
- Assess baseline vital signs and compare with subsequent observations.
- Auscultate for the presence of bowel sounds.
- Assess the patient's previous history of constipation and the patient's perception of the meaning of constipation.
- Assess renal function. Osmotic laxatives often contain sodium or magnesium and, in renal disease, excretion of these electrolytes may be impaired.
- Do not administer laxatives in cases of undiagnosed abdominal pain, nausea and vomiting, as an acute gastrointestinal disorder may be present.
- Determine fluid intake and output and the resultant fluid balance.

Planning

- The patient will achieve regular bowel motions with the assistance of the laxative. Laxatives should be considered only as a measure to promote regular defecation.
- The patient will focus on non-pharmacological measures that prevent constipation, including taking exercise, eating foods that are high in fibre and increasing fluid intake.

Implementation

- Monitor bowel sounds before administering any oral laxative. If bowel sounds are absent, withhold the drug and report to the doctor.
- Monitor fluid input and output. Be aware of manifestations of fluid and electrolyte imbalances that may occur with watery bowel motions.
- Monitor serum electrolytes for patients receiving osmotic laxatives.

Patient teaching

- Instruct the patient with constipation to increase fluid intake to at least 2500–3000 ml daily. To assist the patient to achieve this aim, be specific when suggesting what the patient drinks; for example, suggest the patient consumes a glass of water with every meal. Ensure that the patient does not have a medical condition requiring a fluid restriction, such as cardiovascular disease.
- Suggest the patient increases their fibre intake. Fibre is present in bran, whole cereals, fruits and vegetables.
- Teach the patient that a daily bowel action is not essential for normal gut function. Emphasise that bowel habits vary considerably among individuals.
- Advise the patient to avoid overuse of laxatives, as this can lead to dependence and fluid and electrolyte imbalance. Non-pharmacological measures are a more natural and effective means of control.
- For patients on magnesium sulphate or sodium sulphate laxatives, instruct them to chill the salt before drinking it to make it more palatable. Patients who are on a salt-restricted diet should avoid osmotic salt laxatives.
- For patients on stimulant laxatives, advise them to take the dose at bedtime to promote defecation in the morning. Enteric-coated tablets, such as bisacodyl, should be swallowed whole and not chewed. Bisacodyl must not be taken within 1 hour of milk or antacid consumption.
- Laxative suppositories must be kept in the fridge to make them firmer for easier insertion.
- As lactulose-containing laxatives contain high amounts of lactose and galactose, advise the patient with diabetes to monitor blood glucose levels carefully.
- Warn the patient on lactulose that abdominal cramps and flatulence are common adverse effects, which subside with continued use.
- With bulk-forming laxatives instruct the patient that the powder should be stirred into a glass of water. The patient should drink the mixture immediately while the powder is still suspended in the water. This should be followed by another glass of water. Advise the patient never to take the preparation dry, as it may cause oesophageal obstruction, and to avoid lying down for 1 hour after consumption in order to ensure passage to the gut.
- For patients on liquid paraffin, advise that the drug can interfere with the absorption of certain (fat-soluble) vitamins. It should not be used on a regular basis.
- Instruct patients on liquid paraffin not to consume it less than half an hour before bedtime, as it may cause aspiration.
- Advise patients on castor oil or phenolphthalein that urine may turn pink. This is a harmless effect.
- Children with chronic constipation require a plan involving regular toileting programmes, dietary and activity changes, and long-term laxative therapy for a period of 6 months or more.

Evaluation

- Evaluate the effectiveness of laxatives in promoting bowel action. Identify any potential for abuse with laxatives.
- Determine the effectiveness of non-pharmacological measures in treating constipation.

Antidiarrhoeals

Assessment

- Obtain a history from the patient of any viral and bacterial infections, recent international travel, recent antibiotic use, recent chemotherapy and food consumed, which may have contributed to diarrhoea.
- Assess the patient for a history of liver disease, ulcerative colitis and glaucoma. Many antidiarrhoeal drugs are contraindicated in these conditions.
- Assess vital signs and compare with subsequent observations.
- Determine the fluid balance by assessing input and output. Maintain a fluid balance chart as a record of body fluid loss. Assess for manifestations of dehydration, including dry mucous membranes, dry skin, decreased skin turgor and reduced urine output. Assess the patient's weight at the same time each day.
- Auscultate for bowel sounds. Hyperactive bowel sounds may indicate increased intestinal motility.
- Assess the frequency and consistency of bowel motions.
- Obtain a faecal specimen for microbiology and culture.
- For the patient with chronic, prolonged diarrhoea, determine serum electrolyte levels for electrolyte loss.

Planning

- The patient's bowel motions will be normal and diarrhoea will have ceased.
- The cause of the diarrhoea will be identified and treated.
- The patient's body fluid and electrolyte levels will be restored.

Implementation

- Antidiarrhoeal agents should not be used in children. Their use does not reduce fluid and electrolyte loss and may delay the removal of organisms.
- Acute diarrhoea in adults is usually self-limiting, and treatment with an antidiarrhoeal agent is usually unnecessary. Symptomatic control may help some adults, however.
- Monitor fluid balance carefully. Fluid replacement may be necessary.
- Monitor the effect of the antidiarrhoeal agent by determining the frequency and consistency of bowel motions.
- Monitor vital signs regularly. Dehydration may cause tachycardia and decreased blood pressure. Opiate and opiate-related drugs may cause respiratory depression and decreased blood pressure.
- If the microbiology and culture faecal specimen have indicated a cause for the diarrhoea, begin treatment for the causative agent.
- Limiting the patient's diet to clear fluids only may assist in reducing the diarrhoea.
- If the cause is related to a food intolerance, then refer the matter to the dietician. Food may need to be reintroduced selectively and gradually.
- Monitor serum electrolyte levels carefully. Replace electrolytes as required.

Patient teaching

- Encourage the patient to keep a record of bowel movements while on the medication to determine effectiveness and possible incidence of constipation.
- Advise the patient to ingest a clear-fluid diet for a few days, to avoid fruit juices and to maintain fluid intake at about 3000 ml each day.
- Advise the patient to avoid the use of alcohol, as it promotes diuresis.
- Advise the patient to avoid driving and operating heavy machinery if drowsiness occurs.
- If the diarrhoea persists for more than 5 days, the patient should see the doctor again.
- Teach the patient to keep the perianal region clean in order to avoid skin irritation.
- Inform the patient that diarrhoea affects the absorption of drugs, such as the oral contraceptive pill; females should use alternative means of contraception.
- Advise the patient that constipation can occur through overuse of antidiarrhoeals.

Evaluation

- Evaluate the effectiveness of the antidiarrhoeal agent in ceasing the diarrhoea without producing adverse effects.
- Evaluate the long-term use of opiates and opiate-related antidiarrhoeal drugs for possible dependence.

Drugs used in inflammatory bowel disease

Assessment

- Assess the patient on sulfasalazine and related drugs for liver, lung and kidney disease. These drugs can aggravate such conditions and are usually contra-indicated.
- Assess the patient with inflammatory bowel disease for manifestations of dehydration, including dry skin, dry mucous membranes and decreased skin turgor.
- Assess the patient for baseline vital signs and compare with subsequent observations.
- For the patient with inflammatory bowel disease, assess character and quantity of bowel motions.
- For the patient with inflammatory bowel disease, assess the fluid balance.
- Assess the fertility status of a male patient on sulfasalazine, as it often causes reversible male infertility.
- Before commencing sulfasalazine or related drugs, assess the patient for a history of allergic reactions to any sulphonamide and salicylate drugs.

Planning

- The patient's frequency of bowel motions will decrease following treatment with sulfasalazine or similar drugs.

Implementation

- Monitor the patient's vital signs. Dehydration arising from diarrhoea may cause tachycardia and decreased blood pressure.

- For the patient with inflammatory bowel disease, monitor the character and quantity of bowel motions during treatment.
- For the patient with inflammatory bowel disease, monitor fluid balance by documenting input and output. Aim to correct any negative fluid balance through adequate hydration.
- For the patient with gall stones, monitor the characteristics of the pain during treatment.
- Monitor for agranulocytosis and aplastic anaemia by undertaking full blood examinations every 3–6 months while the patient is on sulfasalazine or similar drugs.
- Monitor for manifestations of bone-marrow depression while the patient is on sulfasalazine and similar drugs. Symptoms include sore throat and fever.

Patient teaching

- Advise the patient on sulfasalazine or similar drugs to take the drug with food to avoid gastric irritation.
- Instruct the patient on sulfasalazine or similar drugs to drink plenty of fluids, to prevent dehydration either from inflammatory bowel disease or from the possibility of watery diarrhoea from these drugs.
- Advise the patient on ursodeoxycholic acid to consume plenty of fluids to assist in the dissolution of gall stones.
- Advise the patient on ursodeoxycholic acid to take the drug with food or milk, as the presence of bile and pancreatic juice in the intestine enhances dissolution.

Evaluation

- Evaluate the effectiveness of sulfasalazine and similar drugs by the decreased incidence of loose bowel motions.
- Evaluate the effectiveness of ursodeoxycholic acid to dissolve gall stones and alleviate manifestations of pain.

SUMMARY

- Constipation is having difficult or infrequent bowel movements, and has multiple causes.
- Laxatives exert their effect by variable mechanisms. They can stimulate the bowel, prevent water absorption from the colon, soften the faecal material and lubricate the bowel wall.
- Even though most laxatives work only in the intestine, adverse effects are common, especially with prolonged use.
- Gastrointestinal enzyme deficiencies can be treated with replacement therapy.
- Gall stones can sometimes be dissolved in situ, thus avoiding surgery.
- Topical anorectal preparations are only ever considered a short-term treatment of haemorrhoids.

1. Apart from the use of laxatives, what are some of the measures that can be used to help prevent constipation?
2. Describe how to obtain a complete bowel washout to enable an unobstructed view during colonoscopy.
3. Sorbitol is a poorly absorbed sugar alcohol sometimes used to sweeten diabetic jams and jellies. What would be a problem with eating too much of this sugar alcohol?
4. Which laxatives can affect the absorption of some vitamins, and why?
5. In what forms of constipation are laxatives contraindicated?
6. Why should diarrhoea resulting from pseudomembranous colitis not be treated with loperamide?
7. Why are paraffinomas so called?
8. Why should liquid paraffin not be taken less than half an hour before lying down?
8. What would be a major problem from diphenoxylate overdose?
10. Why is atropine included with diphenoxylate in the preparation Lomotil™?
11. Why can the so-called bulk-forming laxatives sometimes be used to treat diarrhoea?

54 DRUG SUMMARY TABLE: LOWER GASTROINTESTINAL TRACT DRUGS

FAMILY NAME	GENERIC NAME	TRADE NAME(S)
Laxatives	Bisacodyl	Dulco-lax
	Lactulose	Duphalac
		Lactugal
		Regulose
	Liquid paraffin	
	Macrogols	Movicol
		Movicol Paediatric Plain
	Magnesium hydroxide/citrate (milk of magnesia) + Liquid paraffin	Milpar
	Magnesium sulphate (Epsom salts)	
	Sennosides	Manevac
		Senokot
	Sodium dioctyl Sulphosuccinate (docusate)	Dioctyl
		Docusol
	Sodium picosulphate	Dulco-lax
		Picolax
Bile salt	Ursodeoxycholic acid	Destolit
		Urdox
		Ursofalk
		Ursogal
Antidiarrhoeals	Codeine	
	Diphenoxylate + Atropine	Lomotil
Electrolyte-replacement therapy		Dioralyte and Repalyte Preparations
	Loperamide	Imodium
Anti-inflammatories	Mesalazine	Asacol
		Ipocol
		Mesren
		Pentasa
		Salofalk
	Olsalazine	Dipentum
	Prednisolone	Predsol
	Sulfasalazine	Salazopyrin
	Pancreatic enzymes	Creon
		Nutrizym
		Pancrease
		Pancrex
Miscellaneous agents	Budesonide	Entocort
	Glyceryl trinitrate	Rectogesic
	Mebeverine	Colofac
	Peppermint	Colpermin
		Mintec

NAUSEA AND VOMITING

55

CHAPTER FIFTY-FIVE

OBJECTIVES

KEY TERMS

Chemoreceptor trigger zone
Dopamine receptors
Histamine receptors
Medullary vomiting centre
Morning sickness
Motion (travel) sickness
Serotonin receptors

After completing this chapter, the reader should be able to:

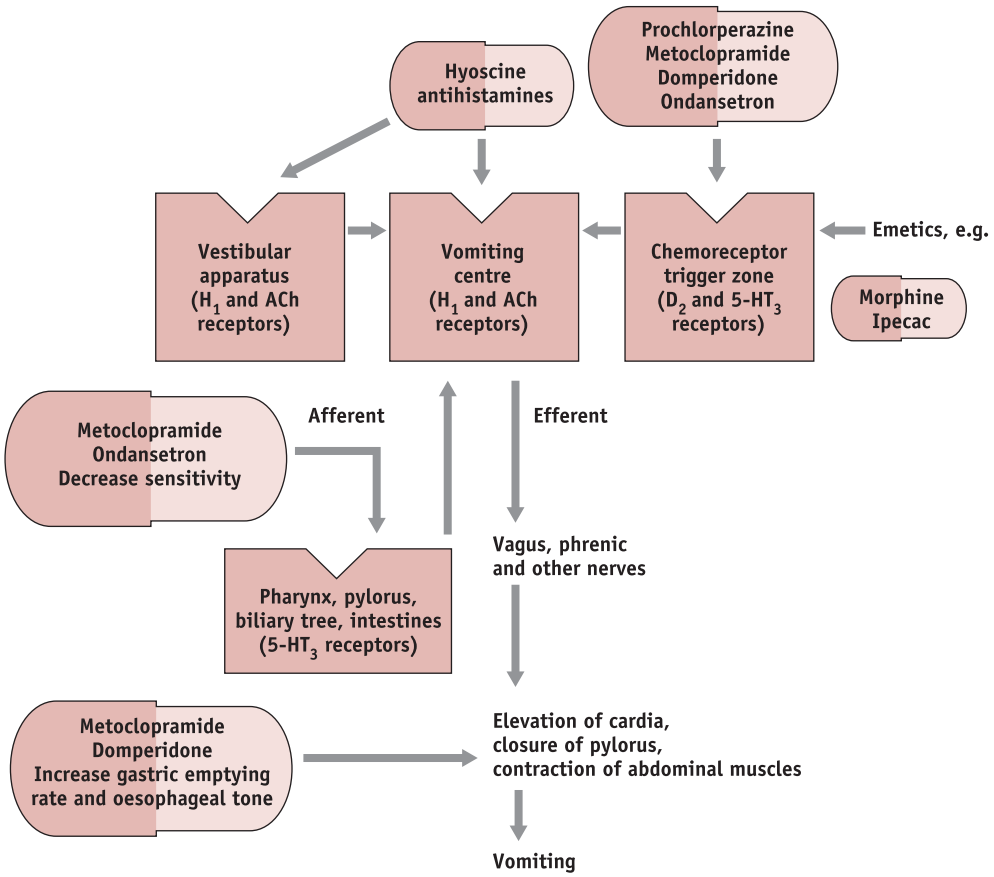
- **list the causes of nausea and vomiting;**
- **describe the use of phenothiazines and other dopamine antagonists in the treatment of nausea and vomiting;**
- **describe the use of antihistamines and antimuscarinics in the treatment and prevention of nausea and vomiting;**
- **describe the use of serotonin antagonists in the treatment of nausea and vomiting.**

NAUSEA AND VOMITING ARE INTIMATELY ASSOCIATED WITH each other but can be mutually exclusive. Most people have suffered at one time or another from nausea without being physically sick. Likewise, vomiting can be induced physically by stimulation of the oropharyngeal region (with one's fingers, for example) without necessarily causing nausea. In most cases, however, one can consider nausea to be a symptom and vomiting the result. The causes can be legion but, whatever the cause, the vomiting centre in the brain is involved. Mediation of this centre involves neurotransmitters and impulses from several regions of the body, as shown in Figure 55.1.

The treatment of these conditions depends on the causative factor. Drugs that affect the central pathways represented in Figure 55.1 are the antimuscarinics, antidopaminergics and antihistamines. Some drugs that affect gut motility can also be used if appropriate. The correct diagnosis of the cause of the nausea and vomiting is necessary for successful treatment.

To a certain extent, vomiting is a protective mechanism that can result from various noxious stimuli. Many of the worst cases of nausea and vomiting are due to the protective

FIGURE 55.1 PATHOPHYSIOLOGY OF VOMITING AND THE SITES AND MECHANISMS OF ACTION OF ANTIEMETIC DRUGS



ACh, muscarinic acetylcholine receptors; H_1, histamine receptors, subtype 1; D_2, Dopamine receptors, subtype 2; 5-HT_3, 5,hydroxytryptamine (serotonin) receptors, subtype 3.

Source: Developed from Grahame-Smith DG (1992) *Oxford Textbook of Clinical Pharmacology and Drug Therapy*, Oxford: Oxford University Press. Reproduced by permission.

function of the chemoreceptor trigger zone (CTZ) responding to therapeutic drugs. The body treats life-saving cytotoxic drugs as it might treat a dangerous poison, which is not surprising considering their action but is inconvenient and often very distressing for the patient. Note that the CTZ, which is situated near the vomiting centre in the medulla, is functionally not protected by the blood–brain barrier. This is a physiologically important protective mechanism, as noxious substances can be detected in the blood before reaching sensitive neural tissues. Note too that both mechanical and chemical stimuli to parts of the gastrointestinal tract can also initiate the nausea and vomiting reflex, again both mechanisms designed to protect the body. A mechanical obstruction can occur anywhere from the pharynx down to the colon. In the extreme case, faecal vomit can result from a colonic obstruction. Many drugs and poisons can chemically induce the vomiting reflex before any absorption has taken place, so this reflex is of great importance as a protective homeostatic function.

DRUGS USED TO TREAT NAUSEA AND VOMITING

In the treatment of vomiting, the use of suppositories is convenient and avoids the use of painful injections. In nausea, the cause is often known before the symptoms occur and can be prevented rather than cured in selected cases; this is true of motion sickness and drug-induced vomiting. In cases where nausea or vomiting is due to psychogenic factors, such as nauseating thoughts and sights, involving the cortical centres of the brain, then the use of the benzodiazepine sedatives is helpful.

Antimuscarinics

Antimuscarinic drugs are discussed in detail elsewhere (see Chapter 27), and so only a few pertinent comments are made here. The only antimuscarinic agent in common use as an antiemetic is **hyoscine**, which is available as Kwells™ and as the transdermal preparation Scopoderm TTS™. The only use of these drugs is in the prevention or treatment of motion sickness. Scopoderm, because of its slow delivery to the system, maintains high enough blood levels to affect the cholinergic receptors in the semicircular canals but not enough to cause other antimuscarinic effects in many patients. One patch delivers the drug to the body for up to 72 hours.

✚ CLINICAL CONSIDERATIONS

Hyoscine produces fewer adverse effects than other antimuscarinic drugs, such as **atropine**. Nevertheless, its use should be limited in children and adults should be advised that it can cause dry mouth, thirst, blurred vision, constipation, urinary retention and tachycardia.

Antihistamines

These drugs, like the antimuscarinics, are discussed in detail elsewhere (see Chapter 29), and so only a few points are made here. Any antihistamine can have antiemetic properties, although only a few antihistamines are used for this purpose. These drugs are effective in travel sickness due to their having inherent antimuscarinic activity in addition to their antihistamine effects. They can be used in many types of nausea, including Menière's disease and labyrinthitis (see Figure 55.1).

The older antihistamines such as **cinnarizine**, **cyclizine** and **promethazine** are among the principal drugs used for motion sickness. They are of similar efficacy but may differ in onset and duration of action and in the extent of side effects, such as drowsiness. If a sedative effect is desired, promethazine is useful, otherwise a slightly less sedating antihistamine such as cinnarizine or cyclizine may be preferred. Antiemetics are more effective for prophylaxis than for treatment and so should be given before a journey. They are slightly less effective than hyoscine but are tolerated better. Non-sedating antihistamines such as **terfenadine**, which penetrate poorly into the central nervous system (CNS), do not appear to be effective against motion sickness.

5-HT_3 antagonists such as domperidone and metoclopramide are not effective in motion sickness.

✚ CLINICAL CONSIDERATIONS

The main problem with antihistamine use is the concurrent drowsiness, which can be troublesome, especially for travellers. Antihistamines that cause drowsiness are contraindicated in drivers. Preparations available include **promethazine**.

Phenothiazines

These drugs are dealt with more fully in Chapter 33. They are dopamine antagonists and act centrally by blocking the CTZ. The only phenothiazine without appreciable antiemetic properties is **thioridazine**. In practice, only **prochlorperazine** is used commonly. These drugs are not of much use in the treatment of nausea due to motion sickness (except promethazine, which is an antihistamine phenothiazine).

◆ COMMON ADVERSE EFFECTS

As with other phenothiazines, extrapyramidal symptoms and oculogyric crises can occur in some patients.

✚ CLINICAL CONSIDERATIONS

Phenothiazines should be used with extreme caution in patients with impaired cardiovascular function, glaucoma, liver disease, seizure disorders and gastrointestinal obstruction. Because of the drug-induced photosensitivity, advise the patient to wear protective clothing when exposed to sunlight. Some phenothiazines are available as rectal suppositories. **Prochlorpromazine** is available as a buccal tablet to place between the upper lip and the gum.

Metoclopramide and domperidone

Metoclopramide and **domperidone** are related to the phenothiazines but have other effects on the aetiological factors involved in nausea and vomiting. Domperidone has the advantage over metoclopramide in that it does not cross the blood–brain barrier to any great extent, and so central effects such as an oculogyric crisis are not a problem. Domperidone, unlike metoclopramide, is effective in nausea of labyrinthine origin. As well as their effects on the CTZ, both of these drugs increase the rate of gastric emptying and decrease the sensitivity of receptors in the pharynx and upper gut to noxious stimuli.

✚ CLINICAL CONSIDERATIONS

As domperidone does not cross the blood–brain barrier, extrapyramidal side effects are rare. Extrapyramidal side effects are more likely to occur in patients younger than 20 years; in these individuals, domperidone may be a useful alternative to metoclopramide. If extrapyramidal side effects occur with metoclopramide, they are best treated with the antimuscarinic **benzatropine** (benztropine).

Setrons

Ondansetron, **dolasetron** (a prodrug), **granisetron**, **palonestetron** and **tropisetron** are serotonin antagonists that are highly selective for 5-HT_3 receptors found on the afferent fibres of the vagus nerve and in parts of the brain associated with the CTZ. Blocking these receptors helps to control chemically induced vomiting and nausea. These

drugs are particularly effective in controlling the vomiting associated with cytotoxic drugs used in the treatment of cancer.

◆ COMMON ADVERSE EFFECTS

Compared with the other potent antiemetics, setron therapy is free of extrapyramidal effects. The main adverse effects are mild – transient headaches, diarrhoea and constipation are most common, and some studies even show that the incidence of these effects is not much higher than that related with a placebo. Allergic reactions with these drugs are not common and have occurred only with parenteral administration.

✚ CLINICAL CONSIDERATIONS

These drugs are quite expensive, but their effectiveness is shortening the hospital stay of patients undergoing cancer chemotherapy. The drugs can be given orally or intravenously, preferably on an empty stomach.

In cases of intractable vomiting and nausea due to cytotoxic drug therapy, the corticosteroid hormones have sometimes proven to be successful. Their mechanism of action here is unknown. The combination of **dexamethasone** with ondansetron or tropisetron can be used with some success when all else fails.

Clinical efficacy for these agents is very similar. Compliance may be affected by their frequency of administration: dolasetron and tropisetron are given once daily, while ondansetron is given two or three times daily.

Intravenous injections of these agents are infused over a minimum of 5 minutes in order to prevent visual problems, such as blurred vision. As dolasetron can produce heart block and bradycardia, it should be avoided in individuals with cardiac disease.

NEW APPROACHES

Neurokinin-1 antagonists

The fact that substance P causes vomiting when injected intravenously and is found in the vomiting centre led to a belief that substance P antagonists could be useful antiemetics. **Aprepitant** is a substance P neurokinin-1 receptor antagonist licensed in the UK in 2003 for the prevention of nausea and vomiting associated with cisplatin-based cytotoxic chemotherapy. It is given with dexamethasone and a 5-HT_3 antagonist.

Cannabinoids

Nabilone is a synthetic cannabinoid that is antiemetic and may be used for nausea and vomiting in cancer chemotherapy that does not respond to other antiemetics. Cannabinoids decrease nausea and vomiting caused by substances that stimulate the CTZ. The antiemetic effects are antagonised by **naloxone**, suggesting that opioid receptors are involved. The unwanted effects of drowsiness and dizziness are common. Other side effects include postural hypotension and mood changes. Some patients may experience hallucinations.

NAUSEA AND VOMITING IN PREGNANCY

Nausea and vomiting in pregnancy (NVP) is very common in the first 3 months of pregnancy. Most cases of morning sickness are mild and do not require drug therapy. Some cases can be very severe, however, and can make for a miserable first trimester and occasionally for much longer. Hyperemesis gravidarum is a more serious condition that requires intravenous fluid and electrolyte replacement. As the first trimester shows an increase in teratogenetic effects from drug treatment, the selection of drugs for use in NVP is problematic. Pregnant women who refuse to take even well-proven safe drugs may still be treated successfully and safely with **ginger** (see Chapter 65) and/or **pyridoxine** (see Chapter 61). In severe cases, pyridoxine can be given intravenously. Some authorities claim that there is not enough literature on the use of ginger in NVP for it to be recommended unequivocally.

The *British National Formulary* (BNF) recommends that on rare occasions when vomiting is severe, short-term treatment with an antihistamine such as promethazine may be required. Prochlorperazine or metoclopramide are suggested as considerations for second-line treatment.

DRUGS USED TO INDUCE VOMITING

In cases of poisoning with non-corrosive agents, and assuming that incomplete absorption of the poison has taken place, induction of vomiting can be carried out. This is no longer recommended in the UK, however (see Chapter 21). The drug that used to be given to induce emesis is **emetine**, the active ingredient of **ipecacuanha**. Emetine induces vomiting by direct irritation to the upper gut and, on absorption, acts also on the CTZ. Emetine in low dosage is sometimes included in cough mixtures (expectorants) because of this action. Emetine stimulates the lower gut and can be used as a laxative in smaller doses than those used to induce vomiting.

CLINICAL MANAGEMENT

Drugs used in nausea and vomiting

Assessment

- Do not administer an antiemetic until the underlying cause for the vomiting or nausea is established. Possible causes include reaction to general anaesthesia or other medication, reaction to food, travel sickness, viral and bacterial infections, and intestinal obstruction.
- Check vital signs and compare with subsequent observations.
- Avoid the use of dopamine antagonists in patients under the age of 20 years as these agents are more likely to cause extrapyramidal adverse effects in young people than in older individuals.

Planning

- The patient will obtain relief from nausea or vomiting after implementation of the drug regimen and non-pharmacological measures.
- The patient's underlying cause for the nausea or vomiting will be determined and, if possible, corrected.

Implementation

- Monitor for manifestations of dehydration if vomiting is severe. These include dry mucous membranes, increased pulse, lowered blood pressure and reduced urine output.
- Auscultate bowel sounds for hypoactivity or hyperactivity.
- Monitor the quantity and character of any vomitus.
- Examine fluid balance by assessing fluid intake and output.
- If the patient is actively vomiting or has an intestinal condition, administer the antiemetic in parenteral or rectal form instead. Oral medication is also contraindicated after major abdominal surgery.
- Give antiemetics before the administration of chemotherapeutic agents.
- Provide mouth care after vomiting.
- Intravenous injections of serotonin antagonists should be administered over at least 5 minutes, as transient vision problems may occur if given more rapidly.

Patient teaching

- Advise the patient to avoid driving and operating heavy machinery while taking antiemetics, as drowsiness is a common problem with such drugs.
- Instruct the patient to avoid taking alcohol, as this intensifies the sedative effect of the antiemetic.
- Advise pregnant patients to avoid antiemetics in the first trimester. Non-pharmacological measures for nausea are safer and more appropriate. Such measures include eating small, frequent meals, nibbling on dry biscuits and being in a quiet environment. Parenteral pyridoxine (vitamin B_6) may also help in some cases.
- Suggest to the patient with travel sickness that antihistamines should be taken 30 minutes before travel. If the patient waits until nausea or vomiting occurs, the antihistamine will be ineffective.
- Teach the patient about non-pharmacological measures that may be effective in alleviating nausea and vomiting, including eating dry toast and dry biscuits and drinking flat carbonated drinks and weak tea.

Evaluation

- Evaluate the effectiveness of the antiemetic and non-pharmacological measures in alleviating nausea and vomiting without producing adverse effects.

SUMMARY

- Nausea and/or vomiting is often a protective response to remove potentially harmful substances from the body before further absorption takes place.
- The chemoreceptor trigger zone in the brain detects noxious substances in the blood and activates the vomiting centre in the medulla.
- Sometimes nausea and vomiting are non-productive, as in travel sickness.
- Drugs that suppress nausea and vomiting can act on the various body systems, including the gastrointestinal tract, semicircular canals in the ear and the vomiting centre and chemoreceptor trigger zone in the brain.
- Drugs used in the treatment of nausea and vomiting either act selectively or have multiple actions on dopamine, serotonin and histamine receptors, all of which can be involved in vomiting reflexes.
- Nausea and vomiting in pregnancy is a treatable condition.

1 What type of antiemetic would be best for use in a patient with terminal carcinoma who is on morphine?

2 What are the major adverse effects associated with phenothiazine use?

3 Why is domperidone sometimes preferred as a dopamine antagonist over prochlorperazine?

4 Why is it unwise for a car driver to take promethazine as a travel-sickness prophylactic?

5 Explain the three ways in which the vomiting centre can be stimulated.

6 Yavuz Olcay, a 60-year-old patient in your care, vomits after gastrointestinal surgery. You administer metoclopramide in an attempt to alleviate vomiting. What assessment would you undertake of Mr Olcay?

7 In a patient who is vomiting, what route of administration would you use for the antiemetic given?

8 Alberto Ripaldi, a 50-year-old patient, suffers from Menière's disease. Why is metoclopramide not the most suitable antiemetic to administer? Which antiemetic would you administer instead? (Menière's disease is a disorder of the labyrinth of the inner ear. Common manifestations of this disorder include progressive loss of hearing, headache, vertigo, tinnitus and a heightened sensitivity to loud sounds.)

9 What non-pharmacological measures would you provide for a patient suffering with nausea? (See Table 11.10 in Chapter 11 for assistance.)

10 Emma Doeline, aged 60 years, is about to take a trip from London to New York. As she is often affected by motion sickness, she buys an antihistamine preparation at the airport. How would you advise Ms Doeline to take the preparation?

55 DRUG SUMMARY TABLE: NAUSEA AND VOMITING

FAMILY NAME	GENERIC NAME	TRADE NAME(S)
Antimuscarinics	Hyoscine	Kwells Scopoderm TTS
Antihistamines	Cinnarazine	Stugeron
	Cyclizine	Valoid
	Meclozine	Sea-legs
	Promethazine	Avomine
Phenothiazines	Chlorpromazine	
	Domperidone	Motilium
	Metoclopramide	Maxolon
	Perphenazine	
	Prochlorperazine	Buccastem Stemetil
Serotonin antagonists (setrons)	Dolasetron	Anzemet
	Granisetron	Kytril
	Ondansetron	Zofran
	Palonostetron	Aloxi
	Tropisetron	Navoban

CASE STUDY XI.1

Mr JK was 50 years old and had for several years suffered progressively from joint pain, especially in his fingers. This pain was not incapacitating and he still had almost complete manual dexterity, but the pain was, at times, severe. His condition was diagnosed as rheumatoid arthritis and he was prescribed the non-steroidal anti-inflammatory drug (NSAID) ketoprofen, which he had been taking on and off for several years. Recently, he had begun to suffer from epigastric pain and his general practitioner replaced his ketoprofen capsules with the same drug in suppository form. This proved to be beneficial for several months. Recently, however, Mr JK suffered from a massive haematemesis with concomitant melaena. This necessitated emergency surgery, which resulted in a partial gastrectomy for a gastric ulcer.

After his surgery, Mr JK still needed pain relief, but his doctor was concerned about resorting to anti-inflammatories again and so prescribed ibuprofen and misoprostol. This did not cause epigastric pain but resulted in frequent episodes of diarrhoea. This was then controlled with an ispaghula preparation, and Mr JK is now leading a life relatively free of symptoms of his rheumatoid arthritis or epigastric pain.

QUESTIONS

1 *Why would suppositories be preferable to the capsules for Mr JK?*

2 *What caused Mr JK's gastric haemorrhage? What was the most probable reason?*

3 *Why would the combination of ibuprofen and misoprostol be prescribed?*

4 *Why would Mr JK get diarrhoea?*

5 *Why would ispaghula control diarrhoea?*

6 *What alternative therapy or therapies could have been prescribed?*

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WEB RESOURCES

How to prevent flatulence www.askmen.com/sports/health/38_mens_health.html

Medline Plus Constipation www.nlm.nih.gov/medlineplus/constipation.html

Medline Plus Nausea and Vomiting www.nlm.nih.gov/medlineplus/nauseaandvomiting.html

Oesophageal diseases www.pcsg.org.uk/html/dis_oesophagus.html

MODULATION OF BODY GROWTH, DEVELOPMENT AND METABOLISM

The farmer's daughter hath soft brown hair;
(Butter and eggs and a pound of cheese)

CHARLES STUART CALVERLEY – *BALLAD*

This section deals with how metabolism is controlled and influenced by chemical mediators. Hormones induce a wide range of effects in the body, including the regulation of the composition and volume of the internal environment. Hormones help the body cope with homeostatic imbalances and have a role in growth, development and reproduction. Many disorders are due to over- or undersecretion of hormones. The treatment of such disorders has evolved into a branch of medicine called endocrinology and led to the development of a vast armamentarium of drugs, including both naturally occurring and synthetic hormones. These drugs can either potentiate or inhibit normal hormonal action. Furthermore, these drugs can be used to alter the normal functioning of the human body for various purposes, such as the avoidance of pregnancy using chemical contraceptive measures. Hormones are secreted and released by endocrine glands and tissues. In this section, we examine the drug therapies associated with the hypothalamus and the pituitary (Chapter 56), the thyroid and the pancreas (Chapter 57) and the adrenal glands and the gonads (Chapter 58). The pathophysiology and treatment of metabolic imbalance underlying hyperuricaemia and gout are described in Chapter 59. Finally, the drug therapies associated with obesity are described in Chapter 60.

XII

DRUGS AND THE PITUITARY GLAND

56

CHAPTER FIFTY-SIX

KEY TERMS

Adrenocorticotrophic hormone
Antidiuretic hormone
Creutzfeldt–Jakob disease
Endocrine system
Hypothalamic-pituitary axis
Gonadotrophins
Growth hormone
Prolactin
Oxytocin
Recombinant DNA technology
Trophic hormones

OBJECTIVES

After completing this chapter, the reader should be able to:

- **identify the major endocrine glands;**
- **outline the physiological effects of the hormones produced by the pituitary gland;**
- **identify the endocrine agents that act on the pituitary gland;**
- **describe the actions and properties of the endocrine agents at this gland and, in general, the conditions they are used to treat.**

DRUGS THAT AFFECT ENDOCRINE FUNCTION CAN BE USED in a number of different situations. They may be used to correct an endocrine imbalance (deficiency or overabundance) in order to restore physiological homeostasis. It is rare that this therapy results in a 'cure' of the condition; rather, it often provides only symptomatic relief. Another use of these drugs is as a diagnostic tool to detect pathophysiological endocrine states.

Pharmacological preparations can be used to detect and treat disorders involving any of the following glands: pituitary, thyroid, adrenal cortex, pancreas, gonads. The effects of these drugs derive from the physiological actions of the endogenous hormones that they mimic (if they are agonists) or block (if they are antagonists).

The kinds of hormone produced by endocrine glands around the body can vary chemically. Some are peptides, some are steroids and others are biogenic amines. It is not the purpose of this book to dwell on the chemical structures of drugs; however, hormone chemistry has important implications for the way in which these drugs are administered in the clinical

setting. Peptide hormones, such as those derived from the pituitary and pancreas, cannot be administered orally because they are completely degraded by the proteolytic enzymes in the gut. Steroid hormones, such as those from the gonads and adrenal cortex, are more effective when injected. Synthetic forms of steroids, however, which are very effective when administered orally, are now available.

DRUGS AFFECTING THE PITUITARY GLAND

Table 56.1 lists the hormones produced by the anterior and posterior pituitary and their functions. As you can see, trophic hormones from the pituitary gland control the functions of the thyroid, adrenal cortex and gonads. Therefore, trophic hormones can be used to stimulate the activity of these dependent glands when endogenous stimulation is diagnosed as inadequate.

For the purposes of clarity, pituitary hormones with clinical applications are discussed according to their influence on gonadal and adrenal cortex function and how they are used in disorders of growth hormone and prolactin secretion. Figure 56.1 shows the pituitary hormones, their effects and the sites of action of drugs that affect pituitary function.

Trophic hormones affecting gonadal function

There are a number of drug groups used to alter gonadal function. In deficient states, these drugs can be used to supplement or stimulate gonadal function. In conditions characterised by excessive or inappropriate gonadal hormone responses, drugs can be used to treat the situation. The major drug groups discussed here include gonadotrophins (luteinising hormone (LH) and/or follicle-stimulating hormone (FSH)) extracted from human urine or synthesised using recombinant DNA techniques, and drugs that act as or stimulate gonadotrophin-releasing hormone (GnRH) from the hypothalamus.

EXTRACTED GONADOTROPHINS

Pituitary gonadotrophic hormones extracted from human urine may be used in selected cases of male and female infertility, delayed puberty and cryptorchism. The preparations used include **menotrophin** (human menopausal gonadotrophin), containing **luteinising hormone** and **follicle-stimulating hormone**, **human chorionic gonadotrophin** (hCG) (with LH-like activity), and **urofollitrophin**, consisting of FSH and hCG.

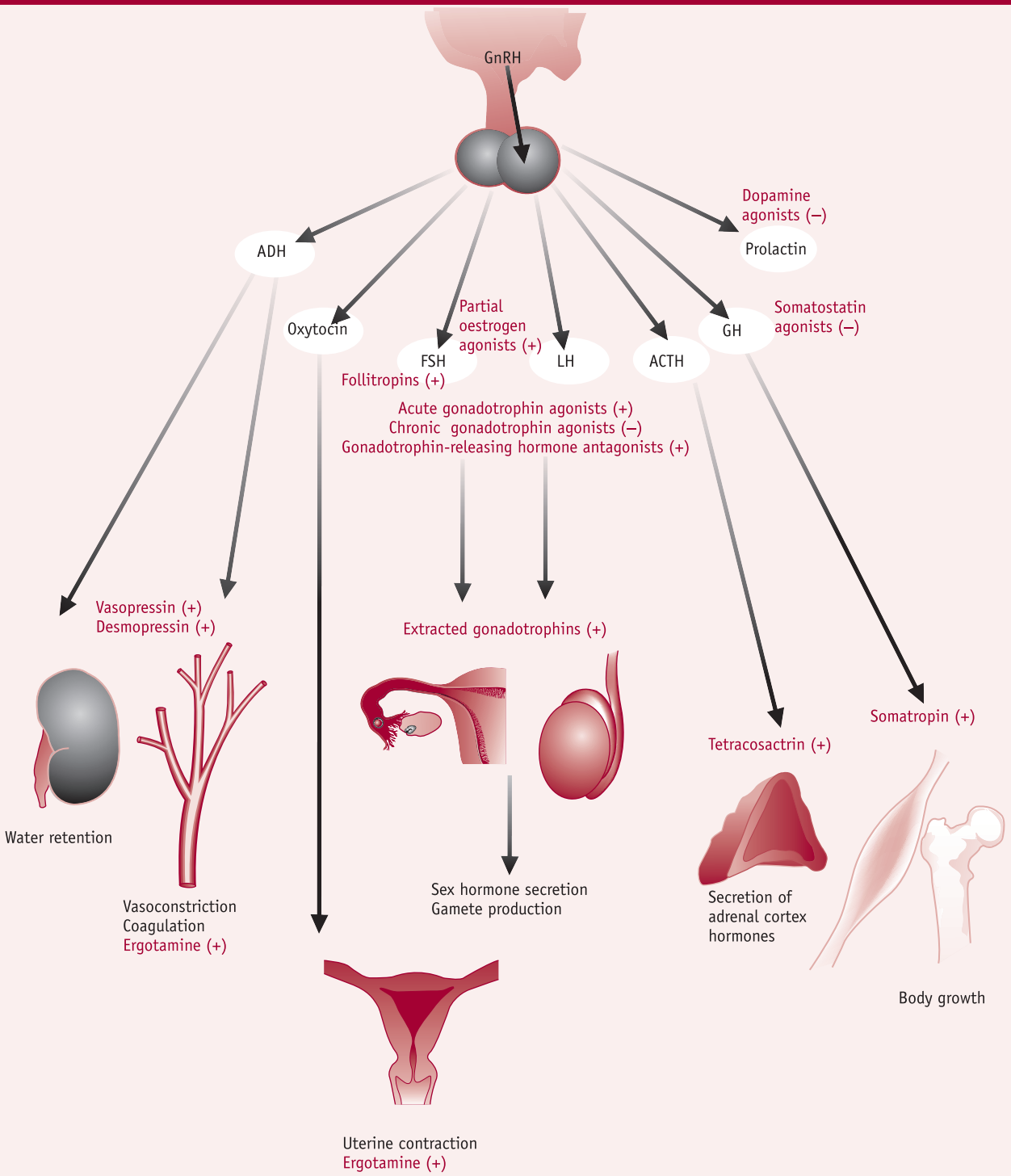
◆ COMMON ADVERSE EFFECTS

The side effects associated with these agents can involve the stimulation of excessive amounts of gonadal hormones, usually resulting in fluid retention and oedema. Ovarian

TABLE 56.1 PITUITARY HORMONES AND THEIR EFFECTS

Pituitary hormone	Effects
Anterior	
Adrenocorticotrophic hormone (ACTH)	Stimulates secretion of adrenocortical hormones
Follicle-stimulating hormone (FSH)	Stimulates maturation of ovarian follicle and oestrogen production in females; stimulates sperm production in males
Growth hormone (GH)	Stimulates body growth; promotes development of bone and muscle; mobilises fats
Luteinising hormone (LH)	Stimulates ovulation in females; promotes production of gonadal hormones (testosterone in males, oestrogen and progesterone in females)
Prolactin (PRL)	Promotes lactation; unknown role in males; may play a role in caretaking behaviour
Thyroid-stimulating hormone (TSH)	Stimulates secretion of thyroid hormones
Posterior	
Antidiuretic hormone (ADH)	Water retention within kidneys
Oxytocin (OT)	Stimulates ejection of breast milk; initiates labour; stimulates contraction of myometrium; may be needed for clitoral and penile erections and orgasm in both sexes; may facilitate trust

FIGURE 56.1 EFFECTS OF PITUITARY HORMONES AND SITES OF ACTION OF DRUGS AFFECTING PITUITARY FUNCTION



ACTH, adrenocorticotrophic hormone; ADH, antidiuretic hormone; FSH, follicle-stimulating hormone; GH, growth hormone; GnRH, gonadotrophin-releasing hormone; LH, luteinising hormone.

hypersecretion may lead to the development of large cysts, which are prone to rupture, resulting in a medical emergency. Because the hormones are derived from human rather than animal sources, allergic reactions can occur and take the form of a mild rash.

✚ CLINICAL CONSIDERATIONS

Use of these drugs is restricted to medical specialists in assisted-reproduction techniques. Specific care should be taken in administering these medications to individuals with asthma, epilepsy and cardiovascular and renal disorders, as there is a risk of androgen-induced fluid retention.

Use in prepubertal boys may lead to the premature closure of the epiphyses. If these agents are used for female infertility, close monitoring of follicular development and oestrogen secretion is required, together with meticulous titration of dosage in order to prevent the ovarian hyperstimulation syndrome. This syndrome is a rare, severe, life-threatening condition associated with the development of large ovarian cysts. These cysts can lead to rupture, ascites, pleural effusion, thromboembolic disorders and death.

GONADOTROPHIN-RELEASING HORMONES

Another approach is to use drugs that act directly on the hypothalamic-pituitary axis to stimulate the secretion of endogenous gonadotrophins. This approach has both diagnostic and therapeutic usefulness. **Goserelin**, **leuprorelin, buserelin**, **nafarelin** and **triptorelin** are available in the UK (note the common suffix '-relin' associated with these generic names).

■ MECHANISM OF ACTION

These drugs are analogues of GnRH (also known as LH-releasing hormone) and stimulate the secretion of LH and FSH. With repeated or chronic use, however, these agents suppress the secretion of pituitary gonadotrophins and, consequently, inhibit the function of the gonads.

Nafarelin is used clinically in endometriosis therapy to suppress the growth of ectopic endometrial tissue. It is convenient to use because it is available as a metered-dose nasal spray. Buserelin is used in the management of endometriosis and to induce ovulation in women receiving fertility treatment. Goserelin, triptorelin and leuprorelin are used in the management of prostate cancer. Goserelin is also used in the management of early and advanced breast cancer.

◆ COMMON ADVERSE EFFECTS

Adverse effects of this therapy are associated with gonadal stimulation or inhibition. Stimulatory effects include gonadal hyperstimulation syndrome (ovarian cysts, worsening of endometriosis). Inhibitory effects include menopausal symptoms in women (hot flushes, sweating, mood swings, vaginal dryness), altered libido, headache and nausea. Treatment is contraindicated in women who are pregnant, trying to get pregnant or breast feeding.

In men, hot flushes, changes in blood pressure, sweating, chills and impotence may be noted.

✚ CLINICAL CONSIDERATIONS

Occasionally, ovarian hyperstimulation syndrome may occur when a GnRH analogue is combined with FSH in reproductive technology. Symptoms of the syndrome in this situation are usually mild, with slight abdominal pain and ovarian enlargement. For use in infertility, it is important to titrate the dose according to follicular development and oestrogen secretion so that ovarian hyperstimulation is prevented.

In patients who do not have a cancerous condition, use of these preparations is not recommended for more than 6 months, and repeat courses are not recommended because of the risk of decreased bone mass.

When used in women of childbearing age, the first injection is usually given at menstruation or in the mid-luteal phase to exclude pregnancy. Use of these drugs during pregnancy is contraindicated. During in vitro fertilisation, treatment is stopped at least 3 days before fertilised embryos are placed in the uterine cavity. At this time, it is important to take care when dilating the cervix because of the increased risk of a cervical tear.

Patients should be advised regarding the appropriate use of a nasal spray for the administration of nafarelin (see Table 7.8 in Chapter 7).

PARTIAL OESTROGEN AGONISTS

A novel way of stimulating gonadotrophin release can be achieved using the partial oestrogen agonist **clomifene** (clomiphene). This is used in the treatment of ovulatory failure. **Tamoxifen** is an anti-oestrogen used for the same purpose. Chorionic gonadotrophin is sometimes used as an adjunct.

■ MECHANISM OF ACTION

Clomifene is an anti-oestrogenic substance with some affinity for oestrogen receptors. By occupying the receptors, the drug blocks endogenous oestrogen access. Clomifene stimulates gonadotrophin release by preventing the feedback inhibition of the hypothalamic-pituitary axis by oestrogen. Tamoxifen works by occupying oestrogen receptors in the hypothalamus and thus interfering with feedback mechanisms.

◆ COMMON ADVERSE EFFECTS

The side effects are dose-related and are linked to excessive levels of oestrogen, e.g. hot flushes, abdominal discomfort and breast soreness.

✚ CLINICAL CONSIDERATIONS

Before starting treatment with clomifene, liver function is checked. If visual blurring occurs, treatment is stopped. Ovarian hyperstimulation may occur in women with polycystic ovary disease, particularly if pregnancy occurs during the cycle when clomifene is given. Pregnancy rates are very poor in severe polycystic ovary disease.

RECOMBINANT FOLLICLE-STIMULATING HORMONE (FOLLITROPIN)

A form of human FSH has become available using recombinant DNA technology. This drug is called **follitropin** and is available only in an injectable formulation for subcutaneous or intramuscular injection.

■ MECHANISM OF ACTION

There are two subtypes of follitropin available: **follitropin alfa** and **follitropin beta**. Follitropin alfa is used to stimulate ovarian function and can be used alone or in combination with other fertility drugs. Follitropin beta can also be used for this purpose and is used to activate spermatogenesis in males with hypogonadotrophic hypogonadism.

◆ COMMON ADVERSE EFFECTS

Common adverse reactions include headache, rash, gastrointestinal upset, hyperstimulation of the ovaries and bloating. There are a number of contraindications, including ovarian cysts/enlargement, tumours of the pituitary or sex-hormone-dependent tissues, abnormal vaginal or uterine bleeding, and pregnancy.

✚ CLINICAL CONSIDERATIONS

Careful titration of the dose is required to prevent the occurrence of ovarian hyperstimulation syndrome.

GONADOTROPHIN-RELEASING HORMONE ANTAGONISTS

Cetrorelix and **ganirelix** are GnRH antagonists used to prevent premature ovulation associated with assisted reproduction.

■ MECHANISM OF ACTION

The GnRH antagonists bind to receptors for GnRH in the pituitary gland, preventing gonadotrophin (LH and FSH) release. The inhibition of gonadotrophin release is dose-dependent and immediate and does not induce initial stimulation. Clinical trials have shown that these drugs produce suppression of gonadotrophin secretion comparable to that of the GnRH analogues.

◆ COMMON ADVERSE EFFECTS

Common adverse effects include local reactions at the subcutaneous injection site (e.g. redness, itching, swelling) and systemic effects, such as nausea and headache. Ovarian hyperstimulation may occur.

✚ CLINICAL CONSIDERATIONS

For cetrorelix, the favoured subcutaneous injection site is the lower abdominal wall; for ganirelix, it is the upper leg. The injection site for ganirelix should be rotated to minimise the incidence of lipodystrophy. Monitor for evidence of ovarian hyperstimulation.

Trophic hormones and the adrenal cortex

■ MECHANISM OF ACTION

Tetracosactide (tetracosactrin) is an adrenocorticotrophin hormone (ACTH) analogue used to diagnose impaired adrenal function and to treat a range of inflammatory disorders. This drug stimulates the adrenal cortex to release corticosteroids. The advantage of this approach is that rather than treating the condition with an exogenously administered glucocorticoid, the release of a variety of corticosteroid substances with differing activities from the adrenal cortex is stimulated (see Chapter 58).

◆ COMMON ADVERSE EFFECTS

A common side effect of this therapy is hypersensitivity, especially in patients susceptible to allergy. Other side effects may occur as a result of elevated levels of glucocorticoids and mineralocorticoids, including fluid retention, hypertension and electrolyte imbalances.

✚ CLINICAL CONSIDERATIONS

It is advisable to have emergency equipment close by in case anaphylaxis occurs. In the diagnostic use of tetracosactide, failure to observe a rise in plasma cortisol concentration to at least 500 nmol/l 30 minutes after administration may be indicative of adrenal insufficiency.

Disorders of growth hormone secretion

GROWTH HORMONE HYPOSECRETION

A deficiency of growth hormone can result in children of short stature. Such children can be treated with a form of growth hormone called **somatropin**, which is synthesised using recombinant DNA technology. Somatropin can also be used in adults with growth deficiencies and in genetic disorders characterised by deficient growth, e.g. Turner's syndrome.

■ MECHANISM OF ACTION

Somatropin, acting as growth hormone, stimulates skeletal and cellular growth. It does this in concert with other hormones that influence growth, such as thyroid, gonadal and adrenal hormones. Somatropin triggers the release of insulin-like growth factors (somatomedins) from the liver that mediate normal cell growth. It also influences nutrient metabolism by stimulating amino acid uptake into cells, and it induces lipolysis. At high pharmacological doses,

somatropin can induce insulin-like effects on carbohydrate metabolism.

◆ COMMON ADVERSE EFFECTS

Common adverse effects include antibody formation, lipoatrophy (breakdown in subcutaneous skin, which leads to depressions at the injection site), local irritation at the injection site and fluid retention.

✚ CLINICAL CONSIDERATIONS

Before the availability of this technology, growth hormone (and other pituitary hormones) was extracted from the pituitary glands of human cadavers. The extracts were impure preparations of the hormones and, despite the best efforts of the manufacturers, sometimes were contaminated with infectious agents. A number of reports have emerged over recent years indicating that some human pituitary extracts used to treat defects in growth and fertility in the 1960s and 1970s were contaminated with a virus that causes a degenerative brain illness known as Creutzfeldt–Jakob disease (CJD). This condition takes decades to manifest, but, once it does, affected individuals die within months.

Although somatropin products are now made using DNA technology, synthesis and purification processes are still likely to be slightly different for each brand. It is advisable, therefore, to remain with the same brand during treatment.

Adverse reactions of somatropin can be minimised by starting at one-third to one-half of the recommended dosage and then increasing gradually according to the clinical response. The parents or caregiver of a child receiving somatropin should monitor the child for limping, as this may be an indication of a slipped capital epiphysis.

As with all preparations, it is important to rotate injection sites to prevent lipoatrophy.

The National Institute for Health and Clinical Excellence has provided guidance on when growth hormone should be used in adults and children and how its use should be monitored.

GROWTH HORMONE HYPERSECRETION

An excess of growth hormone, known as acromegaly, is treated using the synthetic somatostatin agonists **octreotide** and **lanreotide**.

■ MECHANISM OF ACTION

Somatostatin, which is secreted by the hypothalamus and the pancreas, inhibits the secretion of growth hormone and gastropancreatic peptide hormones. Lanreotide is relatively specific for peripheral rather than central somatostatin receptors and has demonstrated selectivity for the secretion of growth hormone over insulin secretion.

◆ COMMON ADVERSE EFFECTS

The main side effects are irritation and pain at the injection site, but these drugs are also known to cause gastrointestinal discomfort.

✚ CLINICAL CONSIDERATIONS

Octreotide is administered subcutaneously. As it is a peptide, it can be administered only parenterally. It is now available as a 'dialled dosage' pen-injection system in the style of insulin syringes for more convenient administration.

Octreotide is also beneficial in the therapy of gastropancreatic endocrine tumours characterised by hypersecretion of glucagon, insulin, gastrin and vasoactive intestinal hormones (see Chapter 76).

The action of the agonists is more prolonged than that of somatostatin. Lanreotide has been developed as a prolonged slow-release preparation that can be administered intramuscularly. When using octreotide or lanreotide long term, monitor thyroid function.

Lanreotide is also licensed for the treatment of thyroid tumours.

Disorders of prolactin secretion

Three drugs derived from the ergot alkaloids (see Chapter 30) – **bromocriptine**, **lisuride** and **cabergoline** – have been found to suppress the release of prolactin from the anterior pituitary.

■ MECHANISM OF ACTION

These drugs act by stimulating central dopamine receptors in the pituitary involved in regulating prolactin secretion. They are useful in the treatment of conditions involving high blood prolactin levels, such as amenorrhoea and galactorrhoea, and for the inhibition of postpartum lactation. Bromocriptine is no longer recommended, however, for the inhibition of postpartum lactation. For patients who cannot take or tolerate bromocriptine, cabergoline has been proposed as an alternative. Bromocriptine also reduces the levels of growth hormone in patients with acromegaly and is used as an adjunct in the treatment of this condition. Furthermore, the central dopaminergic stimulation makes these drugs important in the treatment of parkinsonism (see Chapter 36).

Lisuride has antiserotonergic activity, suppressing the secretion of not only prolactin but also ACTH. Such an action makes this drug less specific than the others. Lisuride is used in the treatment of Parkinson's disease.

◆ COMMON ADVERSE EFFECTS

Common adverse effects of this group are mild, affecting the gut (nausea and vomiting) and the central nervous system (insomnia, dizziness, drowsiness and headache). Excessive daytime sleepiness can also occur with dopaminergic drugs,

and patients should be warned that if they experience this effect they should not drive or operate machinery.

The Commission on Human Medicines has advised that ergot-derived dopamine-receptor agonists (i.e. bromocriptine, cabergoline, lisuride, pergolide) have been associated with pulmonary, retroperitoneal and pericardial fibrotic reactions. Patients should be monitored for dyspnoea, persistent cough, chest pain and abdominal pain. Lung function tests are suggested if the drugs are to be used long term.

✚ CLINICAL CONSIDERATIONS

Treatment is usually started at a low dose with the evening meal and increased gradually to prevent adverse effects. Contraceptive measures should be considered if pregnancy is unwanted in female patients of child bearing age who are being treated for hyperprolactinaemia.

Clinical uses of posterior pituitary hormones

The posterior pituitary gland produces the peptide hormones antidiuretic hormone (ADH), also known as vasopressin, and oxytocin. The effects of these hormones are listed in Table 56.1. Both hormones are available in synthetic forms for clinical use. The advantage of using synthetic forms over extracted natural hormones is that they are free of diseases such as CJD and contamination by the other posterior pituitary hormones. Furthermore, like insulin, the posterior pituitary hormones are peptides and cannot be administered orally.

VASOPRESSIN

Synthetic vasopressin, available as **desmopressin**, is used in the treatment of diabetes insipidus, which is characterised by ADH hyposecretion.

■ MECHANISM OF ACTION

ADH stimulates water reabsorption from the collecting ducts back into the bloodstream. It plays a significant role in concentrating urine in order to conserve water. It also stimulates vasoconstriction (especially of arterioles, capillaries and small venules), which is helpful during haemorrhage in order to reduce blood loss. The effects on smooth-muscle contraction also extend to the gastrointestinal tract, making ADH useful in the treatment of postoperative abdominal distension. Terlipressin, a derivative of vasopressin, may be used in cases of bleeding from oesophageal varices.

Interestingly, high doses of desmopressin can be used to stimulate blood clotting in patients with certain coagulation disorders. The drug stimulates sustained elevations of clotting factor VIII and von Willebrand factor and therefore is useful in treating haemophilia A and certain types of von Willebrand disease. It is also used in the therapy of some platelet disorders, as it decreases clotting time; however, the mechanism for this has not yet been identified.

◆ COMMON ADVERSE EFFECTS

Common adverse reactions to treatment with desmopressin are allergic reactions, tachycardia and decreased blood pressure due to its vasodilatory action at high concentrations. Caution is indicated in any condition where a drop in blood pressure is undesirable.

✚ CLINICAL CONSIDERATIONS

Desmopressin is available as an injectable solution, oral formulation and nasal formulations. Intranasal administration of desmopressin can be by a nasal spray or by the rhinyle delivery system, which facilitates better control of dosage than the spray.

Restrict fluid intake if desmopressin is used for renal function testing or nocturnal enuresis. Monitor fluid balance to evaluate the effectiveness of drug treatment. Response to thirst is of particular concern in unconscious, sedated and postoperative patients, and in patients with hypothalamic lesions and craniopharyngiomas.

OXYTOCIN

The smooth-muscle stimulant **oxytocin** is used to initiate labour, promote delivery of the placenta and control postpartum haemorrhage. It has been used to promote breast-milk let-down in some disorders of lactation. The ergot alkaloid **ergometrine** (see Chapter 30) can also be used in the management of third-stage labour in combination with oxytocin. Ergometrine is an antiserotonergic agent, which produces a longer-lasting contraction of uterine muscle than oxytocin. It has some α-adrenergic agonist action, which may account for its ability to control haemorrhage. The increase in smooth-muscle tone also constricts the uterine vasculature, which contributes to the reduced risk of postpartum haemorrhage.

◆ COMMON ADVERSE EFFECTS

Allergic reactions, cardiovascular spasm and hypotension are associated with the use of oxytocin. This drug is contraindicated when the fetus is in distress or positioned abnormally.

Adverse reactions of the oxytocin–ergometrine combination include nausea, vomiting, abdominal discomfort and, less frequently, hypertension.

✚ CLINICAL CONSIDERATIONS

Oxytocin administration requires continuous monitoring of the fetus. In practice, the use of oxytocin alone has replaced the use of the combined product of oxytocin and ergometrine because of the greater incidence of nausea and vomiting with the combined product.

CLINICAL MANAGEMENT

Pituitary hormone drugs

Assessment

- Assess for hypersensitivity and allergic reactions to drug therapy, which are common with these drugs.
- Obtain baseline vital signs and compare with subsequent observations. Also assess fluid input and output and fluid balance.
- Exercise caution in patients with coronary heart disease and elderly patients who have been ordered desmopressin, as desmopressin can cause spasm of the coronary arteries, leading to chest pain.

Planning

- The patient will be free of the pituitary disorder with the appropriate drug therapy and/or surgical treatment.

Implementation

- Monitor vital signs, conscious state and fluid balance.
- Have emergency drugs and equipment available to treat allergic and hypersensitivity reactions.
- Monitor hormonal levels under consideration by blood or urine tests.

Trophic hormones (gonads)

- For the infertile female patient on trophic hormones such as gonadorelin, follitropin alfa or beta, human chorionic gonadotrophin (hCG) and urofollitrophin, monitor the follicular development and oestrogen secretion for adjustment of dose and prevention of ovarian hyperstimulation. Ovarian hyperstimulation syndrome may rarely lead to the development of large ovarian cysts, which are prone to rupture, ascites, pleural effusion, thromboembolism and death.

Trophic hormones (adrenal cortex)

- For the patient on tetracosactide, monitor the rise in plasma cortisol concentration 30 minutes after administration. Failure to observe a rise to 500 nmol/l or greater may reflect adrenal insufficiency.

Drugs and growth hormone

- Monitor the height and weight regularly for patients on somatropin. Also monitor blood glucose levels.
- Somatropin is synthesised entirely by recombinant DNA technology. As purification processes may differ, however, it is important not to change brands during treatment, as this may increase the antibody response and complicate long-term follow-up of medication safety.
- While the patient is on somatropin, it is important to monitor for limping, as this may be indicative of a slipped capital epiphysis.
- In the patient who fails to respond to somatropin treatment, test for antibodies to somatropin.
- For the patient on octreotide, monitor thyroid function during long-term treatment.
- Avoid abrupt withdrawal in patients receiving octreotide, as this may lead to biliary colic and pancreatitis.

Drugs affecting prolactin

- For patients on bromocriptine, monitor mental status, including manifestations of depression, such as lack of interest in appearance, withdrawal, anorexia and insomnia.
- For patients on bromocriptine, check faeces and vomitus for occult blood.

Posterior pituitary hormones

- For patients with diabetes insipidus, monitor fluid balance through input and output. Monitor serum sodium levels and the specific gravity of urine. In diabetes insipidus, the specific gravity of urine is 1.000–1.003, and the output is characteristically large and dilute.
- For the use of oxytocin during labour, monitor the platelet count, full blood examination, serum electrolytes and haemoglobin levels.
- Do not leave a female patient in labour unattended during intravenous oxytocin administration. Monitor vaginal bleeding and fetal heart sounds.
- Regularly monitor observations to determine adequacy of intravenous desmopressin dose. An inadequate dose will lead to diuresis, low specific gravity of urine and thirst. A high dose will induce increased blood pressure, low serum sodium level, and intestinal and uterine cramping. Regular observations are particularly important for patients in whom the thirst mechanism is not operating effectively, such as unconscious, sedated or postoperative patients.

Patient teaching

Trophic hormones (gonads)

- Teach the patient to keep a record of basal body temperature and consistency of vaginal mucus.
- Provide emotional support and reassurance. Treatment is often prolonged and results may be discouraging.
- If pregnancy is suspected, notify the doctor immediately, as these drugs should then be discontinued.
- For patients on clomifene, advise avoidance of driving and operating heavy machinery.

Trophic hormones (adrenal cortex)

- Advise the patient to adhere to the drug regimen. Discontinuation of treatment can cause hypofunction of the gland. The dose should be tapered gradually and not stopped abruptly.
- Advise patients with diabetes mellitus to carefully monitor blood glucose levels, as the insulin dose may need to be raised.

Drugs and growth hormone

- Teach the patient's family to monitor and record the patient's weight and height.
- The ideal time for administration of these drugs is at night, when blood cortisol levels are low; this will increase the responsiveness to the drugs.
- Warn the patient that these drugs can cause pain at the injection site. Injection sites should be rotated regularly to prevent lipoatrophy.
- Instruct patients with diabetes mellitus to carefully monitor blood glucose levels, as a change in diet or insulin dose may be required.
- Advise the patient on octreotide that gastrointestinal adverse effects may occur at the start of treatment; however, these subside spontaneously after 10–14 days. Injecting the octreotide preparation between meals or at bedtime also tends to reduce gastrointestinal problems.

Drugs affecting prolactin secretion

- Instruct the patient to take these drugs with meals to reduce the incidence of gastric irritation.
- Advise the patient to avoid driving and operating heavy machinery if drowsiness develops.
- Advise the patient on measures for possible constipation, dry mouth and postural hypotension, which may occur with this drug.
- Advise the patient to avoid alcohol.

Posterior pituitary hormones

- Instruct the patient on the appropriate method for intranasal application of desmopressin.
- Instruct the parents of the child who is taking desmopressin for nocturnal enuresis to restrict the child's intake of fluid, especially at night.

Evaluation

- Evaluate the effectiveness of the drug therapy in returning the hormonal balance more closely to normal.

SUMMARY

- There are a number of drug groups used to mimic and block pituitary hormone function.
- Drugs used to stimulate gonadotrophin activity (luteinising hormone (LH) and follicle-stimulating hormone (FSH)) can be extracted from human urine or produced synthetically. These drugs are used in the treatment of fertility, hypogonadism and reproductive diseases.
- Chronic administration of gonadotrophin-releasing hormone (GnRH) agonists and partial oestrogen agonists will lead to suppression of gonadotrophin release.
- Somatropin is an analogue of growth hormone (GH), tetracosactrin is an anologue of adrenocorticotrophic hormone (ACTH) and desmopressin is a synthetic form of antidiuretic hormone (ADH, vasopressin).
- Dopamine agonists inhibit prolactin secretion, while the somatostatin agonists inhibit growth hormone release.
- The ergot alkaloid ergometrine can be combined with oxytocin in the management of labour for prolonged uterine contraction and to reduce postpartum bleeding.
- When using drugs that replace or stimulate the release of gonadotrophins, close monitoring of follicular development and oestrogen alongside meticulous titration of dosage must occur to prevent ovarian hyperstimulation syndrome.
- Many of the drugs used to alter pituitary function are peptides that cannot be administered orally. They must be injected, although some may be administered intranasally.

1 For each of the following hormones, indicate from which part of the pituitary gland it is released and its effects:
   (a) oxytocin;
   (b) prolactin;
   (c) follicle-stimulating hormone;
   (d) antidiuretic hormone.

2 For each of the following endocrine agents, name the target tissue it acts on:
   (a) bromocriptine;
   (b) follitropin;
   (c) tetracosactrin.

3 Name the hormone(s) that each of the following endocrine agents mimics:
   (a) buserelin;
   (b) tetracosactride;
   (c) octreotide;
   (d) nafarelin.

4 What is the major complication associated with using hormones extracted from cadavers?

5 Dimitra Kiriakopoulos, a 35-year-old patient with infertility problems, is placed on clomifene in an attempt to stimulate ovulatory function. What patient education would you offer Ms Kiriakopoulos?

6 Mary Zielinski, a 55-year-old patient, has diabetes insipidus. Is this the same as diabetes mellitus? What medication is used to control diabetes insipidus? Explain its action.

7 What assessment would you make to evaluate the effectiveness of somatropin?

8 Why is a fluid-balance chart maintained for a patient receiving desmopressin?

9 Peta Maritzos, 23 years old, is 11 days overdue for the birth of her first child. She is administered oxytocin intravenously to induce labour. What observations should you monitor closely during therapy?

10 Jennifer Elidel is 26 years old and is participating in an in vitro fertilisation programme. She is receiving treatment with clomifene to stimulate ovum production. What is the mechanism of action of clomifene? What is the most serious adverse effect associated with this treatment? State the clinical manifestations of this effect.

11 Janice Brown, a 35-year-old woman who wants to feed her baby with formula milk, is commenced on metergoline. What patient education would you provide Ms Brown?

56 DRUG SUMMARY TABLE: DRUGS AND PITUITARY GLAND

FAMILY NAME	GENERIC NAME	TRADE NAME(S)
Trophic hormones (gonads)	Buserelin	Suprecur
	Goserelin	
	Leuprorelin	
	Triptorelin	
	Clomifene (clomiphene)	
		Clomid
	Gonadorelin	HRF injection
	Human chorionic gonadotrophin (hCG)	Pregnyl
		Choragon
	Menotrophins	Menogon
		Menopur
	Lutropin alfa	Luveris
	Nafarelin	Synarel Nasal Spray
	Follitropin alfa	Gonal-F
	Follitropin beta	Puregon
Gonadotrophin-releasing hormone anatagonists	Cetrorelix	Cetrotide
	Ganirelix	Orgalutran
Trophic hormones (adrenal cortex)	Tetracosactide (tetracosactrin)	Synacthen
		Synthacen Depot
Drugs and growth hormone	Lanreotide	Somatuline LA
		Somatuline Autogel
	Octreotide	Sandostatin
	Somatropin	Genotropin
		Humatrope
		Norditropin
		Saizen
		Zomacton
Drugs and prolactin	Bromocriptine	Parlodel
	Cabergoline	Dostinex
Posterior pituitary hormones	Desmopressin	DDAVP
		Desmotabs
		Desmospray
		Nocutil
	Terlipressin	Glypressin
	Oxytocin	Syntocinon
	+ Ergometrine	Syntometrine
	Vasopressin (ADH)	Pitressin

THE THYROID AND THE PANCREAS

57

CHAPTER FIFTY-SEVEN

OBJECTIVES

After completing this chapter, the reader should be able to:

- **outline the physiological effects of the hormones produced by the thyroid gland and the pancreas;**
- **identify the endocrine agents that act on these endocrine glands;**
- **describe the actions and properties of the endocrine agents at each gland and, in general, the conditions they are used to treat;**
- **describe the mechanisms of action and adverse effects of the drugs used to alter glucose absorption and utilisation.**

KEY TERMS

Calcitonin
Diabetes mellitus
Hypercalcaemia
Hyperthyroidism
Hypothyroidism
Osteoporosis
Paget's disease
Pancreas
Thyroid hormones
Thyroid

THIS CHAPTER DEALS WITH AGENTS THAT AFFECT THE thyroid gland and the pancreas, including insulin.

DRUGS AFFECTING THE THYROID GLAND

The major effects of the thyroid hormones are listed in Table 57.1. In this section, the agents used in the treatment of hypothyroid and hyperthyroid conditions are described. The application of another thyroid hormone, calcitonin, is also explored.

Hypothyroid states

■ MECHANISM OF ACTION

The approach used in the correction of hypothyroid states is thyroid hormone replacement therapy. In most cases, the therapy will be maintained for the rest of the person's life. Treatment may involve the administration of either **L-thyroxine** (T_4) or **liothyronine** (L-triiodothyronine, T_3). The effects of L-thyroxine (levothyroxine sodium) are more prolonged (lasting approximately 1 week) than those of liothyronine (lasting up to 48 hours). L-Thyroxine preparations are cheaper than liothyronine. Liothyronine is approximately ten times more active in the body, however. L-Thyroxine is converted into L-triiodothyronine within peripheral tissues. Therefore, the principal body effects of thyroid hormones are manifested as a consequence of liothyronine's action. As it is more potent, liothyronine may be cardiotoxic in patients with pre-existing heart disease. Levothyroxine is the treatment of choice for maintenance therapy. Liothyronine, with its rapid onset of action, is given by intravenous injection in cases of hypothyroid coma, together with intravenous fluids, hydrocortisone and treatment of any infection. Assisted ventilation is also often necessary.

◆ COMMON ADVERSE EFFECTS

The adverse effects associated with thyroid hormone replacement therapy are the same as the effects of hypersecretion listed in Table 57.1.

✚ CLINICAL CONSIDERATIONS

Clinical responses related to the body's metabolic rate, such as normal heart rate and normal gastrointestinal function (i.e. absence of constipation or diarrhoea), are useful indicators of the appropriate dosage.

The need for thyroid replacement therapy is usually lifelong, except in some cases of postpartum thyroiditis. Patients need to be educated about vigilance with therapy to ensure restoration of the euthyroid (normal) state. When checking thyroid-stimulating hormone (TSH) levels to evaluate the effectiveness of therapy, allow 6 weeks following adjustment of dosage, as thyroxine has a very long half-life.

Metabolism of many drugs is affected by a hypothyroid state. It is advisable, therefore, to administer lower doses of other medications until normal thyroid function is established. If symptoms of hyperthyroidism occur during treatment (e.g. palpitations, insomnia, flushing, sweating, weight loss), then the medication is stopped for 1 week and then recommenced at a lower dose.

Hyperthyroid states

There are two ways to reduce the effects of hypersecretion of thyroid hormones. The first is to reduce the levels of circulating thyroid hormones by blocking their synthesis. This is achieved using antithyroid agents, such as the thionamides, iodide and other drugs; **carbimazole** is the agent most frequently used in the UK. The other way to reduce the effects of hypersecretion is to produce symptomatic relief by using beta-blockers.

THIONAMIDES

■ MECHANISM OF ACTION

Carbimazole and **propylthiouracil** are members of the thionamide family; they are also known as thioureylenes. They prevent the incorporation of iodine into the peptide structure of the hormones and block the peripheral conversion of thyroxine into the more active triiodothyronine. Because these drugs block the synthesis rather than the secretion of thyroid hormones, they have no effects on preformed or exogenously administered thyroid hormones. Carbimazole is used more widely because it is physiologically more active than propylthiouracil. Some investigators suggest that these agents also possess a therapeutically beneficial immunomodulating action, which modifies the underlying pathophysiology.

◆ COMMON ADVERSE EFFECTS

The adverse effects of this treatment are the same as the effects of hyposecretion listed in Table 57.1.

✚ CLINICAL CONSIDERATIONS

The thyroid gland is capable of storing large amounts of preformed hormones. Thus, the clinical effects of therapy will not be apparent until these stores are depleted. This will take about 3–4 weeks after the start of therapy.

High doses of antithyroid drugs are used for about 4–6 weeks to establish normal thyroid function and thereafter are decreased to the lowest possible dose to maintain the euthyroid state.

Propylthiouracil may be used in patients developing sensitivity to carbimazole. Mild adverse effects, such as pruritus and rashes, may occur during the early stages of therapy. These skin problems may respond to a course of antihistamines or a change in antithyroid treatment. Agranulocytosis is a rare but very serious adverse effect that may occur irrespective of dose, age and duration of treatment. It is more likely to occur during the first three months

TABLE 57.1 MAJOR EFFECTS OF THYROID HORMONE (T_4 AND T_3) IN THE BODY

Process or system affected	Normal physiological effects	Effects of hyposecretion	Effects of hypersecretion
BMR and temperature regulation	Promotes normal oxygen consumption and BMR; calorigenesis; enhances effects of catecholamines and sympathetic nervous system	BMR below normal; decreased body temperature; cold intolerance; decreased appetite; weight gain; decreased sensitivity to catecholamines	BMR above normal; increased body temperature; heat intolerance; increased appetite; weight loss; increased sensitivity to catecholamines; may lead to hypertension (high blood pressure)
Carbohydrate, lipid, protein metabolism	Promotes glucose catabolism; mobilises fats; essential for protein synthesis; enhances liver secretion of cholesterol	Decreased glucose metabolism; elevated cholesterol and triglyceride levels in blood; decreased protein synthesis; oedema	Enhanced catabolism of glucose and fats; weight loss; increased protein catabolism; loss of muscle mass
Nervous system	Promotes normal development of nervous system in fetus and infant; necessary for normal adult nervous system function	In infant, slowed/deficient brain development, retardation; in adult, mental dulling, depression, paraesthesias, memory impairment, listlessness, hypoactive reflexes	Irritability, restlessness, insomnia, overresponsiveness to environmental stimuli, exophthalmos, personality changes
Cardiovascular system	Promotes normal functioning of heart	Decreased efficiency of pumping action of the heart; low heart rate and blood pressure	Rapid heart rate and possible palpitations; high blood pressure; if prolonged, leads to heart failure
Muscular system	Promotes normal muscular development, tone and function	Sluggish muscle action; muscle cramps; myalgia	Muscle atrophy and weakness
Skeletal system	Promotes normal growth and maturation of skeleton	In child, growth retardation, skeletal stunting/ malproportion, retention of child's body proportions; in adult, joint pain	In child, excessive skeletal growth initially, followed by early epiphyseal closure and short stature; in adult, demineralisation of skeleton
Gastrointestinal system	Promotes normal gastrointestinal motility and tone; increases secretion of digestive juices	Depressed gastrointestinal motility, tone and secretory activity; constipation	Excessive gastrointestinal motility; diarrhoea; loss of appetite
Reproductive system	Promotes normal female reproductive ability and normal lactation	Depressed ovarian function; sterility; depressed lactation	In females, depressed ovarian function; in males, impotence
Integumentary system	Promotes normal hydration and secretory activity of skin	Skin pale, thickened and dry; facial oedema; hair coarse and thin; nails hard and thick	Skin flushed, thin and moist; hair fine and soft; nails soft and thin

BMR, basal metabolic rate.

Source: From *Human Anatomy and Physiology*, 2nd edn, by Elaine N Marieb. Copyright © 1992 by The Benjamin/ Cummings Publishing Company, USA.

of treatment. The monitoring of blood counts is not a reliable way of detecting agranulocytosis because of its rapid onset. Patients are advised to contact the doctor immediately if they develop fever, mouth ulcers or a sore throat. Carbimazole should be stopped promptly if there is any evidence of neutropenia.

IODIDE

Short-term iodide solution has been used for 10–14 days before surgery for hyperthyroidism. Iodine should not be used for long-term therapy, as its antithyroid activity tends to decline. Radioactive iodide (^{131}I) is used increasingly in the treatment of hyperthyroid states in patients of all ages. This is especially useful where medical therapy is problematic or compliance, in patients with cardiac disease and in patients who relapse following thyroidectomy.

■ MECHANISM OF ACTION

In conjunction with other antithyroid drugs, iodide solution (as either **potassium iodide** or strong **iodine** [Lugol's] solution) reduces the vascularity and increases the firmness of the thyroid gland. This was once believed to make surgical removal less problematic, but there is little evidence of a beneficial effect.

Iodide has been used as an adjunct therapy in acute hyperthyroid states such as thyrotoxicosis and thyorotoxic crisis (thyroid storm). High doses of iodide produce a potent, immediate inhibition of thyroid hormone release; it does this by decreasing iodide transport into the thyroid and through inhibition of certain steps in the synthesis of thyroid hormones. This effect is short-lived, however, lasting only 2 days. This is termed the 'escape' mechanism and is due to adaptations made by the thyroid gland.

Radioactive iodide, like the stable dietary iodide, is taken up rapidly and preferentially into the thyroid. It destroys the functional thyroid tissue. It can be used to completely destroy the thyroid gland or to reduce thyroid hormone synthesis and release to normal levels.

◆ COMMON ADVERSE EFFECTS

Overdosage of iodide therapy can lead to iodism. The clinical manifestations of this condition are very much like those of a head cold and include a metallic taste, burning sensations in the mouth and throat, sore gums, sneezing and increased salivation. Patients should also be monitored for hypersensitivity reactions.

✚ CLINICAL CONSIDERATIONS

The major considerations associated with radioactive iodide therapy are that it should not be used during pregnancy and the possibility of increasing the risk of cancer development in patients receiving treatment. There is little evidence to show an increase in cancer mortality in patients who receive radioactive iodide treatment.

The use of iodide solutions delays the commencement of therapy with radioactive iodide because the former reduces the level of uptake of the latter.

OTHER DRUGS

Iodinated radiological contrast agents, such as **iopanoic acid** and **sodium ipodate**, the corticosteroid **dexamethasone** and **lithium carbonate** are also useful antithyroid agents in acute hyperthyroid conditions. They are used for preoperative therapy.

■ MECHANISM OF ACTION

The iodinated contrast agents and dexamethasone act to inhibit the peripheral conversion of thyroxine into triiodothyronine. Lithium carbonate inhibits secretion of the thyroid hormones from the thyroid. They are regarded as second-line therapy in some countries, particularly for patients who are allergic to the thionamides.

BETA-BLOCKERS

■ MECHANISM OF ACTION

As many of the effects of hyperthyroidism are related to increased adrenergic stimulation (i.e. palpitations, cardiac dysrhythmia, tremor, anxiety), β-adrenergic receptor blockers such as **propranolol** and **nadolol** are indicated as adjuncts in the acute care of patients in crisis (see Chapters 26, 44 and 48). These agents have no effect on the circulating levels of thyroid hormones, but they block the effects of excess thyroid hormone on peripheral tissues. Propranolol also blocks the peripheral conversion of thyroxine into triiodothyronine and provides rapid relief from thyrotoxic symptoms. Beta-blockers are also useful in supraventricular arrhythmias due to hyperthyroidism. Propranolol has been used with iodine to prepare hyperthyroid patients for surgery, but it is better to make the patient euthyroid with carbimazole.

◆ COMMON ADVERSE EFFECTS

Bradycardia, hypotension, constipation, cold extremities, headache, fatigue and sleep disturbances are common adverse effects of these agents. They are contraindicated in patients with chronic lung disease and asthma.

Altered levels of blood calcium

In conditions characterised by elevated blood levels of calcium (hypercalcaemia, active Paget's disease), the parenteral administration of **calcitonin** may be indicated. The use of calcitonin in these conditions and in osteoporosis, however, has been largely superseded by more convenient oral agents called the bisphosphonates.

CALCITONIN

■ MECHANISM OF ACTION

Calcitonin is a hormone produced by the thyroid gland that inhibits bone resorption and the release of calcium ions into the blood, while promoting the uptake of these ions back into bone. Its effects on blood calcium levels are rapid but only short-acting. At present, the available clinical forms of calcitonin are either highly purified calcitonin extracted from pig thyroid tissue (porcine calcitonin) or a wholly synthetic version based on the amino acid sequencing found in salmon calcitonin (salcatonin). Salcatonin is reported to be 10–40 times more potent than mammalian forms of calcitonin. As peptides, these preparations are available as injectable formulations because they cannot be administered orally.

Teriparatide is a recombinant fragment of parathyroid hormone that has been introduced for the treatment of some cases of postmenopausal osteoporosis.

◆ COMMON ADVERSE EFFECTS

Common adverse effects of treatment include dose-related nausea, vomiting and dizziness, and local inflammation at the injection site.

✚ CLINICAL CONSIDERATIONS

Adverse effects relating to nausea and vomiting can be reduced by giving the drug subcutaneously rather than intramuscularly. Adjustment of the dosage frequency from once to twice daily, administration at bedtime and co-administration of an antiemetic agent may also help with decreasing the incidence of adverse effects. Patients should avoid operating machinery and driving, as these medications can cause dizziness.

BISPHOSPHONATES

The bisphosphonates include **etidronate**, **alendronate** and **risedronate**. They are used as first-line treatment in postmenopausal osteoporosis and may also be used in the prophylaxis and treatment of steroid-induced osteoporosis, Paget's disease, hypercalcaemia of malignancy and bone metastases in breast cancer.

■ MECHANISM OF ACTION

The bisphosphonates inhibit bone breakdown and resorption, thus reducing the rate of bone turnover. These drugs are absorbed into hydroxyapatite crystals in bone, become incorporated into the bone matrix and are taken up by osteoclasts, the bone cells responsible for bone resorption. As a result, the function of these bone cells is impaired.

◆ COMMON ADVERSE EFFECTS

The prototype of this group, etidronate, tends to inhibit the process of bone mineralisation and may induce osteomalacia. Gastrointestinal disturbances are commonly associated with bisphosphonate therapy.

✚ CLINICAL CONSIDERATIONS

The bisphosphonates are characterised by poor oral absorption. Orally administered bisphosphonates must be taken on an empty stomach. Water may be consumed if they are given orally. Patients need to remain upright for at least 30 minutes after administration of alendronate or risedronate in order to prevent oesophagitis, oesophageal erosions and ulcers. As an alternative, a number of these agents can be administered parenterally.

If bisphosphonates are used for the treatment of Paget's disease or osteoporosis, ensure that the patient maintains an adequate intake of calcium and vitamin D.

Osteoporosis

Osteoporosis is characterised by low bone mass and deterioration of bone tissue, leading to increased fragility and risk of fractures. This risk increases exponentially with age; in patients surviving over the age of 80 years, 30 per cent of women and 25 per cent of men will suffer a fractured hip. Oestrogen deficiency is a major factor in the development of postmenopausal osteoporosis in women but also to some extent in men. Osteoporosis is most commonly seen in postmenopausal women and in people taking long-term corticosteroids. People at risk should make sure their intake of vitamin D and calcium is maintained, if necessary by dietary supplementation.

The bisphosphonates are effective for preventing postmenopausal osteoporosis. Hormone replacement therapy (HRT) is also an option if there is a lack of response to other therapies. HRT is not considered as first-line therapy for the prevention of osteoporosis in people over 50 years of age. Calcitonin may be considered in people intolerant of bisphosphonates.

Guidance from the National Institute for Health and Clinical Excellence (NICE) recommends the use of bisphosphonates for the secondary prevention of osteoporotic fractures in susceptible postmenopausal women. In those who cannot tolerate these drugs or have sustained a fracture despite treatment, NICE recommends the selective oestrogen receptor modulator **raloxifene** as an alternative. The parathyroid hormone fragment teriparatide is suggested as an alternative in people over the age of 65 years with an extremely low bone density.

STRONTIUM RANELATE

This is a new oral treatment for women with postmenopausal osteoporosis. It is being promoted as the only drug to increase bone formation and decrease bone resorption.

■ MECHANISM OF ACTION

This drug is composed of two atoms of strontium combined with a carrier molecule – ranelic acid. The mechanism of action of this drug in osteoporosis has not been established; however, there is limited replacement of calcium by strontium in the bone over the long term.

◆ COMMON ADVERSE EFFECTS

Side effects include nausea and diarrhoea, but these decrease with treatment. Headaches, dermatitis and eczema are also reported. The rate of venous thrombosis was slightly increased in trials (3.3 per cent versus 2.2 per cent with placebo).

✚ CLINICAL CONSIDERATIONS

The evidence so far indicates that this drug may reduce fractures, but it needs to be compared with established treatments. The drug has not been on the market long enough to fully assess its worth, but it could be a useful alternative to bisphosphonates if these cannot be taken. Patients with a predisposition to thromboembolism should not receive strontium ranelate.

DRUGS AFFECTING THE PANCREAS

The three principal hormones produced by the pancreas are insulin, glucagon and somatostatin. Insulin and glucagon are involved in nutrient metabolism, primarily the regulation of blood glucose levels. Insulin reduces blood glucose levels by facilitating its uptake into muscle and connective tissue cells (it does not play a principal role in glucose uptake into brain, liver or kidney cells) and by inhibiting the hepatic processes of glycogenolysis (breakdown of glycogen into glucose) and gluconeogenesis (formation of glucose by the conversion of amino acids and free fatty acids). The converse is true of glucagon: it acts primarily on the liver to raise blood glucose levels by stimulating glycogenolysis and gluconeogenesis. Somatostatin inhibits all endocrine secretions from the pancreas; it is produced by the hypothalamus and the pancreas. Somatostatin is the only one of these three hormones not used clinically. The somatostatin agonists **octreotide** and **lanreotide** are used instead, because they are longer-acting; their uses and adverse effects are described in Chapter 56.

All these hormones are peptides, which are destroyed by the proteolytic hormones in the gut if administered orally. Therefore, in clinical use, they must be administered parenterally.

Hyperglycaemic agents

Glucagon is used to treat drug-induced hypoglycaemic states where intravenous glucose cannot be given. If the hypoglycaemic patient is fully conscious and not drowsy, glucose 10–20 g may be given by mouth either in liquid form or as sugar. Two teaspoons of granulated sugar, or three sugar lumps, gives about 10 g glucose. Glucogel™ (previously Hypostop Gel™) is an alternative form of glucose that is absorbed through the buccal musoca and is commonly used by paramedics.

■ MECHANISM OF ACTION

Glucagon raises blood glucose levels by activating glycogenolysis and gluconeogenesis in the liver. Glucagon also relaxes the smooth muscle of the gastrointestinal tract, which results in reduced gastrointestinal motility and muscle tone. Glucagon acts on specific receptors to stimulate adenylate cyclase, and so its actions are similar to those of beta-adrenergic stimulation with adrenaline. Its metabolic effects are more pronounced than its cardiovascular actions, increasing the rate and force of contraction of the heart but less so than adrenaline.

◆ COMMON ADVERSE EFFECTS

Nausea and vomiting are the principal adverse reactions associated with glucagon therapy.

✚ CLINICAL CONSIDERATIONS

The muscle-relaxant properties of glucagon make it useful during endoscopic and radiographic procedures involving the gut.

The preparation needs to be protected from light and heat.

Glucagon may be administered by subcutaneous, intramuscular or intravenous injection; the intramuscular route is normally used. A hypoglycaemic patient should respond to glucagon within 10–15 minutes following administration. If there is no response, intravenous glucose is given as well. After the patient has responded, oral carbohydrates are given to prevent hypoglycaemia from recurring and to restore liver glycogen. During administration, it is important to assess serum potassium levels, because hypokalaemia may occur with large doses. Glucagon is not appropriate in patients with chronic hypoglycaemia, as seen in liver disease.

Glucagon may occasionally be used in the treatment of anaphylaxis when the patient is taking beta-blockers and does not respond well to the administration of adrenaline.

Diabetes mellitus

Diabetes mellitus is a metabolic condition that affects the way the body handles carbohydrates, proteins and fats. It is not a single disease but a group of conditions characterised by an imbalance between insulin demand and insulin availability or responsiveness. In the UK in 2004, approximately 1.8 million people were known to have diabetes; there are likely to be at least another 1 million who have undiagnosed diabetes.

The two most common forms of diabetes mellitus are type 1 (previously known as insulin-dependent diabetes mellitus, IDDM) and type 2 (previously known as non-insulin-dependent diabetes mellitus, NIDDM). Other types of diabetes mellitus are associated with endocrine diseases and acquired during pregnancy (gestational diabetes).

Type 1 diabetes accounts for about 20 per cent of cases of diabetes mellitus. It is characterised by an absolute deficiency of insulin. Histological examination of the pancreas of a person with type 1 diabetes shows a dramatic deficiency in beta islet cells and significant fibrosis of islet tissue. Type 1 diabetes is linked to an autoimmune attack on beta islet cells. Antibodies to these cells are produced, which, over a period of time, lead to beta-cell destruction. These antibodies may be present years before the condition manifests. As for other autoimmune disorders, there is evidence of a genetic predisposition for the development of this condition. When susceptible individuals are exposed to the right trigger (say, a particular viral infection), then the condition develops. The peak age for diagnosis of type 1 diabetes is around puberty, but it can manifest at any age. Affected individuals show marked deviations from normal blood glucose levels, which lead to acute episodes of hyperglycaemia. The typical body form of a person with type 1 diabetes is lean.

Type 2 diabetes accounts for around 80 per cent of cases of diabetes mellitus. It is characterised by a relative insulin deficiency, where not enough insulin is produced when needed or insulin is destroyed before it can be used. Importantly, it is also linked to the development of cellular insulin resistance caused by a decrease in the number of insulin receptors on peripheral tissues (such as muscle and adipose tissue). In these people, the level of insulin in the blood may be above normal (hyperinsulinaemia). The peak age for diagnosis of type 2 diabetes is around 40 years, but it can manifest at any age. The typical body form of a person with type 2 diabetes is obese; indeed, obesity is an important factor in the pathophysiology of this type of diabetes, contributing to the alteration in tissue responsiveness. Heredity is an important risk factor in type 2 diabetes; having a family member with this form of diabetes increases the risk of an individual also developing it. Acute hyperglycaemic episodes can develop in people with type 2 diabetes.

Diabetes mellitus is associated with long-term complications. It is a common cause of blindness, kidney impairment, neuropathy and cardiovascular disease. Diabetes mellitus is managed using drug therapy, dietary restriction and exercise. The drugs used in the treatment of diabetes mellitus are termed hypoglycaemic agents.

Hypoglycaemic agents

There are two types of hypoglycaemic agent. They are classified according to the manner in which they are administered: parenteral and oral. Insulin is the sole representative of the parenteral type.

INSULIN

■ MECHANISM OF ACTION

Insulin lowers blood glucose levels by facilitating glucose uptake into body cells. It inhibits glycogenolysis and gluconeogenesis in the liver and stimulates glycogenesis. Insulin also affects the metabolism of proteins and fats. It stimulates amino acid uptake into cells and, subsequently, protein synthesis, and it promotes fat storage.

For people with diabetes mellitus, insulin therapy helps them control blood glucose levels. In the short term, this reduces the onset of hyperglycaemia. In the long term, better blood glucose control reduces the development of chronic complications, such as impaired peripheral nervous system function, renal impairment, cardiovascular disease, visual problems, increased susceptibility to infection and impaired wound healing.

◆ COMMON ADVERSE EFFECTS

The adverse effects of insulin treatment are hypoglycaemia, lipodystrophy, allergic reactions and insulin resistance. Hypoglycaemia results from an overdose of insulin or a mismatch in blood glucose level with the appropriate dose of insulin. This can occur as a consequence of missing a meal or increased metabolic demand caused by strenuous exercise or stress. Lipodystrophy is a localised effect at the injection site, which appears to be associated with contaminants in the preparation. The injected insulin dissolves the subcutaneous fat in the injection site, leaving a depression in the skin (lipoatrophy), or causes local enlargement of subcutaneous fat deposits (lipohypertrophy). Insulin resistance occurs as a consequence of insulin antibodies forming in the blood, due mainly to contaminants. This means that a substantial portion of the injected insulin is destroyed in the blood, requiring an increase in dose to attain the desired effect. It is as if the patient becomes resistant to the prescribed dose of insulin. The incidences of lipodystrophy, allergy and resistance have fallen as a result of using human insulin and increasing the purity of the animal forms of insulin.

Lipodystrophy can be avoided by thorough massage of the site after injection and the methodical rotation of injection sites. Slight pharmacokinetic variation in the action of insulin has been observed from one body region to another (e.g. onset of action after injection into the abdomen compared with that after injection into the thigh). In order to minimise this variation, the insulin user can inject into a number of discrete injection sites within a particular body region, for example starting with a thigh before moving to the other thigh and then another region, such as the abdomen.

✚ CLINICAL CONSIDERATIONS

The peptide hormone insulin cannot be administered orally, as it would be destroyed by proteolytic gut enzymes. Therefore, it must be injected via the intravenous or subcutaneous route. Common body regions used for subcutaneous injection include the thigh, abdomen, upper arm and buttock. The fastest rate of absorption and onset of action occurs through abdominal administration. The skin is pinched to reduce the chance of injecting into a blood vessel.

There are a number of different types of insulin available for commercial clinical use. Essentially, the regular form of insulin is a highly soluble crystal of zinc insulin at an acidic pH of around 3.5. The drug is more active physiologically if its pH is made neutral, and this is achieved by mixing the insulin with either an acetate or a phosphate buffer. This form of insulin is known as neutral or soluble insulin. As it is highly soluble in solution, it has a clear appearance and may be administered either subcutaneously or intravenously. This insulin preparation forms complexes of six insulin molecules, called a hexamer. Once injected subcutaneously, the hexamer must be broken up to be absorbed into the bloodstream. This delays the onset of action of the insulin for half an hour or more.

The chemical and pharmacokinetic properties of regular insulin can be altered by attaching other molecules to it. The insulin must be freed of these attachments at the injection site before absorption into the bloodstream is possible. This separation takes time, delaying the onset of physiological effects and prolonging the duration of action. Such pharmacokinetic changes are brought about either by varying the concentration of zinc in acetate buffer to produce the lente insulins (**lente insulin**, **ultralente insulin**) or by using complexes of zinc insulin and protamine in a phosphate buffer (**isophane insulin**, **NPH insulin**). The greater the concentration of zinc or the presence of protamine in the insulin preparation, the more prolonged the duration and delayed the action of the insulin. Insulin preparations are therefore categorised as short-acting or rapid-acting (neutral and soluble insulin), intermediate-acting (lente and isophane insulins) and long-acting (ultralente insulin). Importantly, the additional attachments decrease the solubility of regular insulin. Lente and isophane insulins are relatively insoluble and in solution form solid particles in suspension. The appearance of these forms of insulin is cloudy. They can be administered only subcutaneously and require thorough mixing before injection. These longer-acting preparations of insulin also form hexamers, further delaying their onset of action.

Fast-acting analogues of human insulin are now available. They are called ultra-rapid-acting insulins. **Insulin lispro** and **insulin aspart** are analogues currently available in the UK. In these preparations, the sequencing of amino acids near the carboxyl terminal of the insulin molecule is manipulated (see Figure 57.1). These changes do not alter the physiological action of the molecule. In insulin lispro, the sequencing of proline and lysine is reversed. In insulin aspart, the proline is substituted for an aspartate; as a consequence, the preparation does not form hexamers. Instead, it remains a monomer (a single molecule) and is absorbed more quickly from the subcutaneous injection site. Its onset of action is 5–15 minutes, which means that it can be administered at mealtimes rather than half an hour before. Peak action is about 1 hour after injection. This profile resembles physiological insulin release more closely and gives better postprandial (after meals) glucose control, while leading to less risk of hypoglycaemia between meals, as the duration of action is 3–5 hours. Ultra-rapid-acting insulins have a clear appearance and can also be injected intravenously.

Long-acting analogues are also available in the form of **insulin glargine** and **insulin detemir**. These both have three amino acid substitutions and a slow onset of action (1–1.5 hours). They provide a basal level of insulin throughout the day that is steady and does not peak – again, this is much closer to the natural background insulin release by the body. Boluses of fast-acting analogue insulin are given with meals.

Historically, there have been three sources of insulin for clinical use: bovine, porcine and human. Insulin can be extracted from the pancreas of the ox (bovine form) and the pig (porcine form). More recently, through the advent of recombinant DNA (rDNA) technology, the human gene for insulin production has been incorporated into the genetic material of the bacterium *Escherichia coli* or the yeast *Saccharomyces cerevisiae*. The subsequent population of microbes readily produces low-antigenic 'human' insulin, which can be extracted for commercial use. A semisynthetic form of human insulin can also be derived from the porcine form of insulin. The sequence of amino acids in porcine insulin differs from the human sequence by only one amino acid. This amino acid can easily be substituted for that found in the human sequence.

The relative onset of action after administration, peak effects and durations of all insulin preparations are listed in Table 57.2.

Current clinical trials are investigating the efficacy of new formulations of insulin and novel delivery devices. We may see the introduction of insulin–fatty acid complexes for prolonged insulin action, radio-controlled implantable insulin pumps and oral, nasal and inhaled insulin formulations.

As the human forms of insulin are readily available and relatively cheap to produce, the animal forms are being phased out. People with newly diagnosed diabetes are often prescribed the human forms of insulin, and many older patients are gradually being transferred from animal to human forms of insulin. Some patients have reported

FIGURE 57.1 SITES OF AMINO ACID SUBSTITUTION IN THE INSULIN MOLECULE

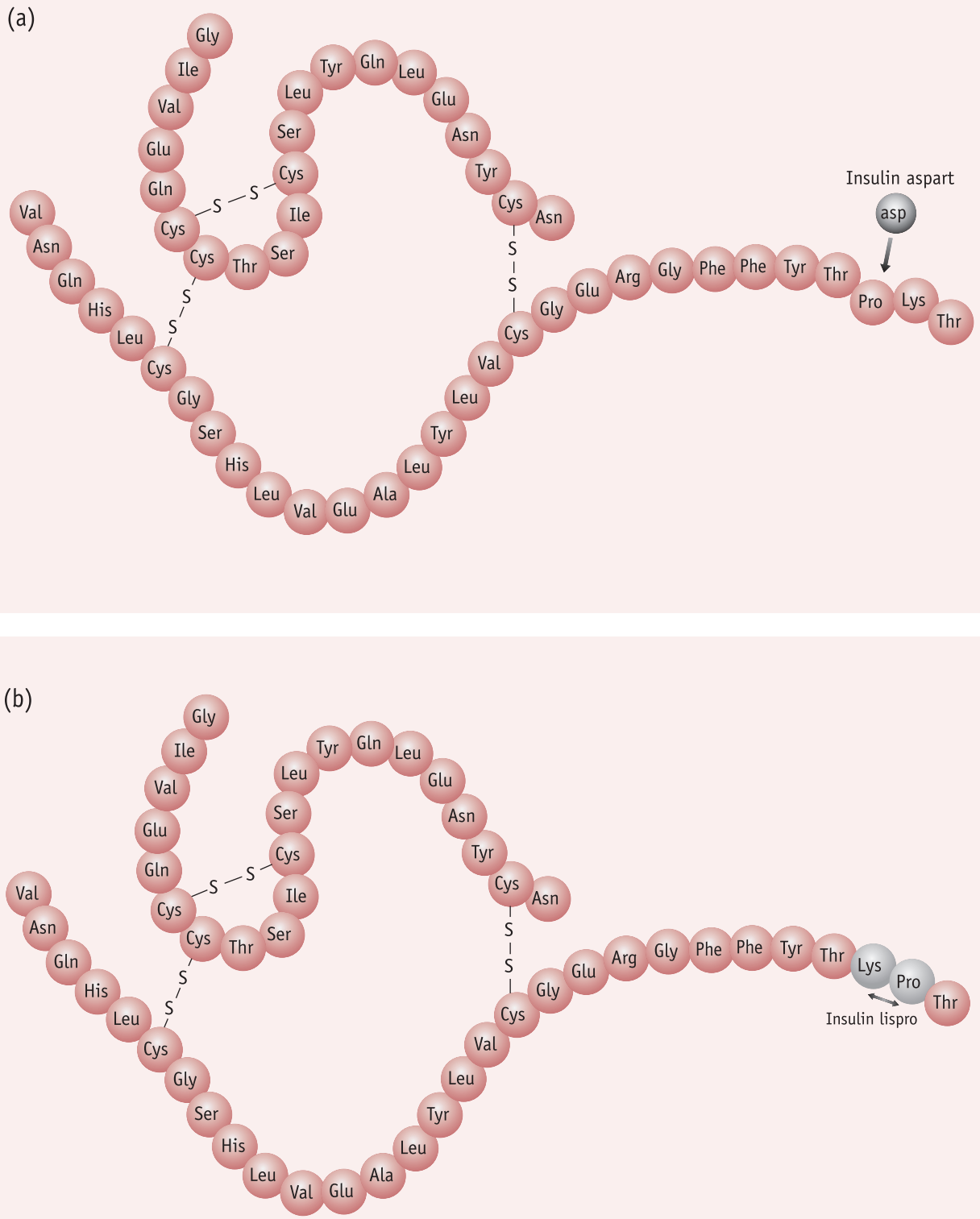


TABLE 57.2 INSULIN PREPARATIONS AND THEIR PHARMACOKINETICS

Insulin preparation	Onset time (hours)	Peak effect (hours)	Duration (hours)	Trade name(s)
Ultra-rapid-acting				
Insulin aspart	0–0.25	1–3	3.5–5	NovoRapid
Insulin lispro				Humalog
Rapid-acting				
Soluble insulin (neutral insulin)	0.5–1	About 4	6–8	**Human insulins**
				Actrapid
				Humulin S
				Velosulin
				Animal insulins
				Hypurin Bovine Neutral
				Hypurin Porcine Neutral
				Pork Actrapid
Intermediate-acting				
Insulin zinc suspension: 3 parts amorphous, 7 parts crystalline (lente)	1–3	7–15	Up to 24	Hypurin Bovine Lente Monotard
Isophane insulin (protamine)	1–2	4–12	16–24	Insuman Basal Humulin I Hypurin Porcine Hypurin Bovine Hypurin Isophane Insulatard Pork Insulatard
Long-acting				
Insulin zinc suspension (crystalline) (ultralente)	4–6	10–30	24–36	Ultratard
Protamine Zinc Insulin				Hypurin Bovine Protamine Zinc
Longer-acting analogue insulins				
Glargine	1–1.5 (no pronounced peaks)		24	Lantus
Detemir	No pronounced peaks		24	Levemir
Premixed biphasic insulin				
Neutral : isophane	0.5	4–12	Up to 24	
10 : 90 (10% neutral, 90% isophane)				Mixtard 10
20 : 80				Humulin 20/80
				Mixtard 20
30 : 70				Humulin M3
				Mixtard 30
				Pork Mixtard 30
				Hypurin Porcine 30/70
40 : 60				Mixtard 40
50 : 50				Mixtard 50
Insulin lispro : insulin lispro protamine				
25 : 75	0.25	4–12	18–24	Humalog Mix25
50 : 50				Humalog Mix50
Insulin aspart : insulin aspart protamine				
30 : 70	0.33	1–4	Up to 24	NovoMix 30

In mixed insulins, the first figure is the percentage of soluble or fast-acting insulin in the mix; the second figure is the percentage of intermediate-acting insulin in the mix.

that symptomatic warning of impending hypoglycaemia is less pronounced after transfer from the animal forms.

Important drug interactions with insulin therapy include these with corticosteroids, diuretics (loop and thiazide), thyroid hormone replacement and oral contraceptives. In each case, the insulin dose may need to be changed following close monitoring of the blood glucose concentration. If an insulin user also requires treatment with a beta-blocker, the manifestations of any hypoglycaemic episode may be masked, consequently delaying recovery. Table 57.3 shows medications that may increase or decrease blood glucose concentrations.

Slower-acting intermediate insulins can be mixed with rapid-acting or ultra-rapid-acting insulin preparations in the same syringe at the time of administration or may be premixed by the manufacturer. The purpose of this approach is two-fold: first, it reduces the number of injections the person with diabetes must administer when both types of insulin are required; second, it provides continuity in blood insulin levels in the absence of endogenous insulin production. The rapid-acting form simulates the postprandial endogenous secretion of insulin, and the intermediate-acting form simulates basal endogenous blood levels between meals. This regimen is not without problems, however. The presence of an intermediate-acting insulin with a rapid-acting form can lead to excess protamine molecules or zinc ions attaching to the relatively unbound insulin of the latter preparation, thus delaying its absorption from the injection site. In other words, the pharmacokinetic profile of the rapid-acting insulin becomes more like that of an intermediate-acting form. Such a change in action could be deleterious for the patient in terms of control of blood sugar levels.

The diminished effect of rapid-acting insulin is also minimised if the mixed insulins are administered immediately after being drawn up rather than being used later in the day. The premixed forms of insulin tend to be used in the treatment of stable diabetes mellitus, when blood sugar levels tend to remain within a reasonable, somewhat predictable range, and where any diminution of rapid-acting insulin will not result in catastrophe. In order to avoid contamination of the rapid-acting vial of insulin by the cloudy intermediate-acting insulin, it is advisable to draw up the clear form before the cloudy form. In this way, no intermediate-acting insulin is introduced into the clear vial, which would diminish the activity of the rapid-acting preparation.

APPROACHES TO INSULIN THERAPY

Full insulin therapy is associated with type 1 diabetes mellitus. Individuals with type 2 diabetes may require temporary insulin therapy, however, during illness or may require long-term treatment if they cannot maintain good glycaemic control using oral hypoglycaemic drugs. More people with type 2 diabetes are being prescribed insulin as the pancreas eventually becomes less able to produce sufficient quantities of insulin.

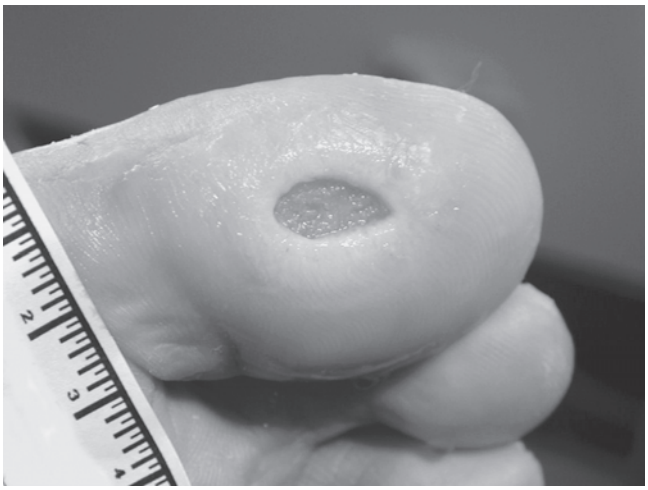
All patients commencing insulin therapy must be provided with education and support regarding the effects of insulin, administration, monitoring of blood glucose levels and diet. Good management of diabetes involves good control of blood glucose levels, avoidance of

TABLE 57.3 MEDICATIONS THAT MAY RAISE OR LOWER BLOOD GLUCOSE CONCENTRATION

Increase blood glucose levels	Decrease blood glucose levels
Atypical antipsychotics	Alcohol
β_2 Agonists	Angiotensin-converting enzyme inhibitors
Danazol (antiandrogen)	Anabolic steroids
Glucocorticoids (corticosteroids)	Disopyramide (antidysrhythmic)
Nicotinic acid	Mefloquine (antimalarial agent)
Oral contraceptives	Monoamine oxidase inhibitors
Pentamidine (toxic to pancreatic cells)	Octreotide (somatostatin agonist)
Phenothiazine antipsychotics	Pentamidine (raises insulin levels) (anti-infective agent)
Somatotropin (growth hormone)	Perhexiline (antianginal agent)
Thiazide diuretics	Quinine (antimalarial agent)
Thyroid hormones	High-dose salicylates

FIGURE 57.2 CHRONIC COMPLICATION OF DIABETES MELLITUS

This foot ulcer in a diabetic patient has occurred following unstable blood glucose control.



hypoglycaemia and hyperglycaemia (the latter contributing to chronic microvascular complications), and promotion of normal growth and development in children with diabetes mellitus. Hyperglycaemia can contribute to the development of chronic microvascular complications, such as foot ulcers (see Figure 57.2). Individuals with diabetes mellitus also need to be made aware of the effects on blood glucose levels of exercise, illness, stress and diet. At certain times, insulin requirements may change. Regular monitoring of blood glucose levels is required in order to avoid chronic complications and acute problems associated with hypoglycaemia and hyperglycaemia. Although blood glucose levels for different individuals vary, an ideal value for a fasting blood glucose level is less than 6 mmol/l, while an ideal range for a random blood glucose level is 4–8 mmol/l. The glycosylated haemoglobin (HbA_{1c}) level should also be determined every 3–6 months, which gives some indication of the glycaemic control over the past 2–3 months. As there is a relationship between the HbA_{1c} level and the incidence of microvascular complications, regular monitoring is important. An ideal HbA_{1c} level is 7.0 per cent or less.

INSULIN REGIMENS

A person with type 1 diabetes requires full substitution therapy, comprising at least two injections of insulin per day. The overall aim is to produce a glycaemic profile as near to normal as possible. The starting dose depends on the age, weight and lifestyle of the individual.

For many patients, the development of injection pen devices has made the administration of insulin simpler, more convenient and more flexible. These devices contain prepackaged insulin cartridges and replaceable needles. They may be used to administer a range of insulin preparations.

The following are the most common insulin regimens used, together with some of their advantages and disadvantages:

TWICE-DAILY SOLUBLE AND ISOPHANE

For adults, the usual total daily dose is 0.3 IU/kg of part rapid-acting and part intermediate-acting insulins – 30 per cent rapid acting and 70 per cent intermediate acting is commonest. Two-thirds of the insulin dose is usually given before breakfast and one-third before the evening meal. Injections should be more than 10 hours apart.

Only two injections are needed daily, but there is little flexibility, as lunch has to be eaten on time otherwise there is a risk of hypoglycaemia.

TWICE-DAILY ISOPHANE

This regimen is used mostly in older patients with type 2 diabetes who now need insulin. There is less risk of hypoglycaemia, and good glucose control can be achieved.

BASAL/BOLUS REGIMEN

This involves four injections per day. Rapid-ultra-rapid-acting insulin is administered before breakfast, lunch and the evening meal, and intermediate-acting or long-acting analogue insulin is administered at bedtime. This bedtime dose of longer-acting insulin has been shown to be beneficial by suppressing overnight glucose production in the liver.

Glycaemic control may not be better than with twice-daily insulin in some cases, but greater flexibility of lifestyle is possible with this regimen, especially if fast-acting analogue insulins are used before meals. Dose can be adjusted according to the size of each meal and if exercise is taken.

CONTINUOUS SUBCUTANEOUS INSULIN INFUSION (CSII) PUMP

A small pump is attached to the abdomen via a cannula and a continuous supply of basal insulin is delivered with boluses when food is consumed. This regimen has the inconvenience of wearing the pump but most closely matches physiological insulin delivery and also allows greater flexibility. The insulin pump is not used widely in the UK and is not available to everybody on the National Health Service (NHS).

ORAL HYPOGLYCAEMIC AGENTS

There are four chemical categories of orally administered agents that act to lower blood sugar levels: the sulphonylureas, the biguanides, the thiazolidinediones (glitazones) and the meglitinides. These drugs fall into two categories and either increase insulin secretion from the pancreas (sulphonylureas, meglitinides) or increase insulin sensitivity

in peripheral tissues (biguanides, glitazones). Reducing carbohydrate absorption may also help. The sulphonylureas were derived from the sulphonamide group of antibiotics. None of these drugs actually lowers blood sugar directly; rather, they act indirectly by increasing the effectiveness or mimicking the intracellular effects of endogenous insulin. Therefore, it is clear that these drugs can be used only in the treatment of type 2 diabetes, not in the therapy of type 1 diabetes characterised by an absolute deficiency of insulin.

SULPHONYLUREAS

Available sulphonylureas include **chlorpropamide**, **glibenclamide**, **gliclazide**, **glimepiride**, **glipizide** and **tolbutamide**.

■ MECHANISM OF ACTION

The sulphonylureas act in three ways, by (i) stimulating the release of insulin from the pancreas – their main action; (ii) weakly inhibiting the process of gluconeogenesis (forming glucose from amino acids and fatty acids) in the liver; and (iii) perhaps increasing the number of insulin receptors on target cells.

As they stimulate the secretion of endogenous insulin, they are also known as insulin secretagogues. They bind to potassium channels in the pancreatic beta-cell membrane and inhibit potassium efflux. This results in depolarisation of the cell membrane, calcium ion influx and the release of stored insulin from the beta cell. This leads to an immediate release of preformed insulin granules; these drugs also extend the second phase of insulin secretion. Although all the drugs in this group have a similar mode of action, they differ in their half-lives and routes of elimination.

◆ COMMON ADVERSE EFFECTS

The effects of the sulphonylureas are shown in Figure 57.3. Adverse reactions include hypoglycaemia due to overdosage and individual factors (lifestyle and diet), allergic skin reactions, depression of bone marrow and gastrointestinal disturbances. It appears that the longer the drug's half-life, the greater the risk of hypoglycaemia developing.

✚ CLINICAL CONSIDERATIONS

With all oral hypoglycaemic agents, blood glucose and glycosylated haemoglobin levels should be checked regularly to determine the therapeutic response of the agent. During times of increased stress, such as infection, fever, surgery and trauma, blood glucose levels may alter. Many drugs can affect blood glucose levels and therefore increase the risk of either hypoglycaemia or hyperglycaemia when used in combination with an oral hypoglycaemic agent (see Table 57.3).

Sulphonylureas should be administered with food to minimise the risk of hypoglycaemia. The dose is increased at weekly intervals until glucose control is achieved. Substitution of one sulphonylurea agent for another does not usually improve glucose control. More effective management is achieved by combined treatment with other groups of oral hypoglycaemics or with insulin. Drugs with a long half-life such as glibenclamide are not suitable for use in elderly patients due to the risk of hypoglycaemia.

MEGLITINIDES

Meglitinides approved for use in the UK are **repaglinide** and **nateglinide**.

■ MECHANISM OF ACTION

These drugs are known as prandial insulin releasers as they stimulate rapid short-term insulin secretion during meal times. As a consequence, postprandial blood glucose levels are reduced. They are insulin-stimulating agents or insulin secretagogues. Like the effect of the sulphonylureas, this effect of the meglitinides is associated with the drug binding to potassium channels (at a different site from the sulphonylureas) in the pancreatic beta-cell membrane. The beta-cell depolarises, leading to calcium influx and the release of stored insulin from the cell. Meglitinides can be taken immediately before a meal to reinstate the initial surge in insulin release that is lost in type 2 diabetes.

◆ COMMON ADVERSE EFFECTS

Common adverse reactions include gastrointestinal disturbance and hypoglycaemia. These drugs may also induce elevated liver enzyme levels.

✚ CLINICAL CONSIDERATIONS

Repaglinide and nateglinide have a rapid onset and a short duration of action. They have been shown to be as effective as the oral hypoglycaemic agent **metformin** in controlling blood glucose levels. In combination with metformin, HbA_{1c} levels have reportedly been reduced. When used in combination with other drugs, blood glucose levels may be affected (see Table 57.3).

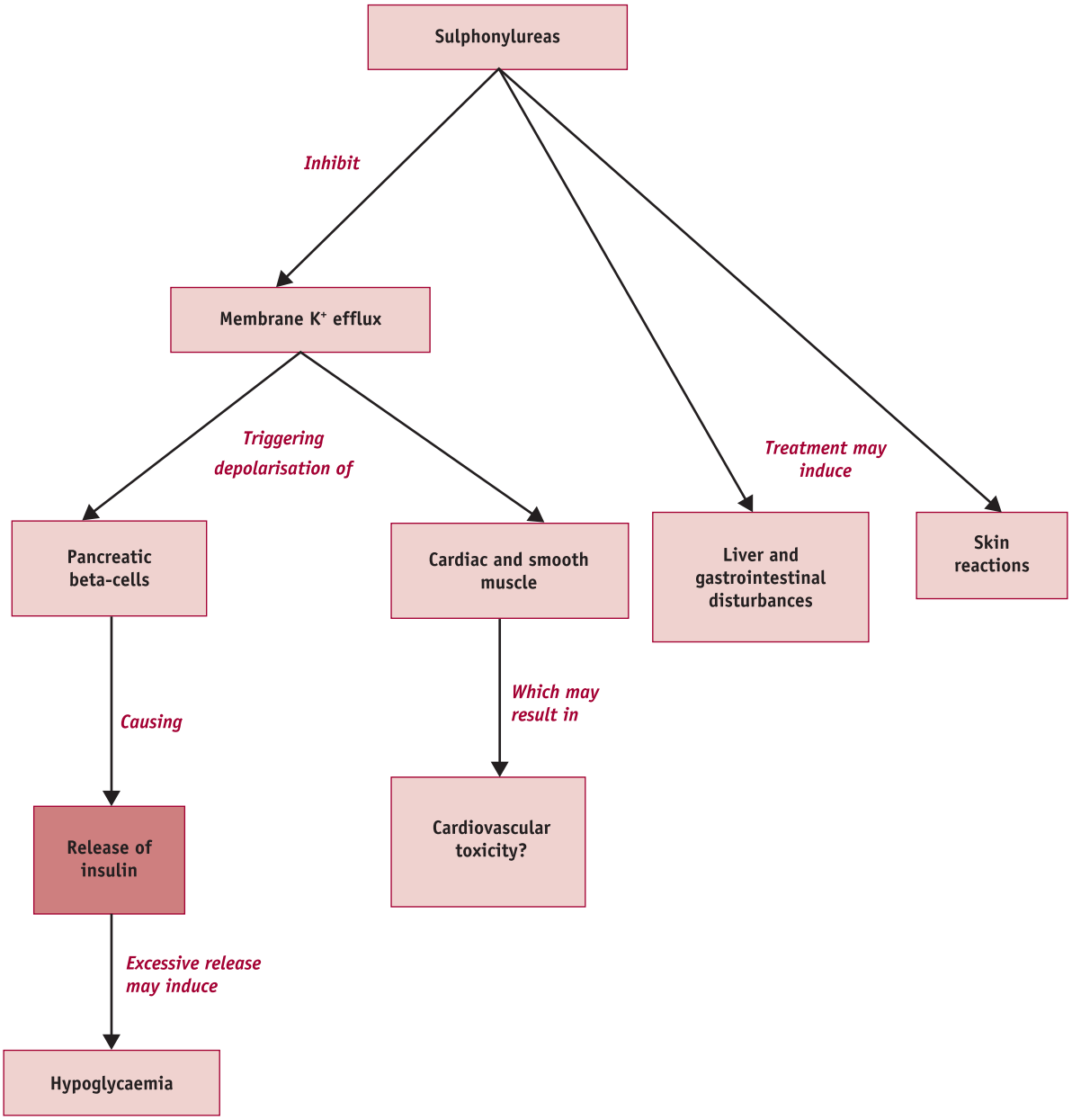
The drugs are taken in three divided doses immediately before meals in order to prevent gastric irritation and to minimise the chance of hypoglycaemia. Hypoglycaemia is the most common adverse effect occuring with this therapy. If a patient skips a meal, the drug dose associated with that meal is not taken in order to prevent hypoglycaemia from occurring. The drugs may be suitable for people with an irregular lifestyle who do not eat at the same time each day.

BIGUANIDES

At the time of writing, there is only one biguanide available for the treatment of diabetes mellitus in the UK. **Metformin** is indicated in the treatment of type 2 diabetes, either alone or in combination with other hypoglycaemic agents.

FIGURE 57.3 FLOWCHART SHOWING THE EFFECTS OF THE SULPHONYLUREAS

Desired therapeutic effect shown in the darker shaded box.



It is the most extensively used oral agent used in type 2 diabetes throughout the world.

MECHANISM OF ACTION

Metformin acts by promoting glucose uptake into cells through enhanced insulin-receptor binding and decreases the production of glucose in the liver, probably via decreased gluconeogenesis. It requires the presence of insulin to be effective and does not stimulate insulin release. Some researchers argue that metformin also slows absorption of glucose from the gut, inhibits glucagon secretion and stimulates tissue glycolysis. It tends to stabilise body weight or lead to weight loss, unlike the sulphonylureas, which, through their stimulation of insulin, tend to cause weight gain. Metformin has been the drug of choice in people with type 2 diabetes and who are overweight for many years.

Metformin also creates small improvements in the blood lipid profile – triglycerides and low-density lipoprotein

(LDL) fall and high-density lipoprotein (HDL) shows a small increase. Results of the UK Prospective Diabetes Study (UKPDS) showed that patients taking metformin had a 39 per cent reduced risk (compared with those taking other oral hypoglycaemic agents) of myocardial infarction after 10 years.

◆ COMMON ADVERSE EFFECTS

The effects of the biguanides are shown in Figure 57.4. Common side effects include a tendency towards drug tolerance and acidosis, the latter due to a build-up of lactic acid in the blood, especially in elderly patients and in individuals with hepatic, renal or cardiovascular disease. Gastrointestinal disturbances such as nausea and vomiting may occur when treatment commences, but these are usually transient in nature. Metformin does not usually induce hypoglycaemia. Therefore, it is probably better to refer to it as a euglycaemic rather than a hypoglycaemic agent, as it restores a normal blood glucose level.

✚ CLINICAL CONSIDERATIONS

Biguanides should be taken with meals to minimise the effects of gastric irritation. As metformin has a slow onset, glucose control may take up to 2 weeks to establish. Alcohol intake should be limited with metformin, as the combination can increase the chance of lactic acidosis, a rare but often fatal condition characterised by anorexia, nausea, vomiting, abdominal pain, cramps and weight loss. The incidence of true lactic acidosis with metformin is low (about 0.03 cases per 1000 patient-years), and these cases are usually due to poor prescribing. When lactic acidosis does occur, it has a high mortality rate. Metformin should not be used in renal insufficiency, as the drug accumulates. The incidence of lactic acidosis is also increased in any disease where tissue perfusion is poor, such as cardiogenic shock.

THIAZOLIDINEDIONES (GLITAZONES)

The thiazolidinediones **pioglitazone** and **rosiglitazone** are approved for use as oral hypoglycaemic agents in the UK. They can be used as monotherapy when a person's diabetes mellitus cannot be controlled by non-pharmacological therapies or in combination with metformin or a sulphonylurea.

■ MECHANISM OF ACTION

The thiazolidinediones improve body cell sensitivity to insulin via the stimulation of a receptor, peroxisome proliferator activated receptor (PPAR), in skeletal muscle, liver and fat cells. The receptor modulates the activity of genes programmed to reduce hyperglycaemia and hyperinsulinaemia. Simpler, non-chemical names for this drug group are insulin sensitisers and insulin mimetics. As the problem in type 2 diabetes is usually insulin resistance, these drugs should be extremely useful therapeutically.

◆ COMMON ADVERSE EFFECTS

The effects of the thiazolidinediones are shown in Figure 57.5. Common adverse reactions include oedema, mild anaemia (thought to be due to plasma volume expansion) and weight gain. The first thiazolidinediones, **trioglitazone**, was introduced in 1997 but withdrawn in 2000 following reports of fatal hepatotoxicity. Although this has occurred only rarely with the two drugs now licensed, hepatic function must be monitored closely during therapy for signs of hepatic impairment. Mild hypercholesterolaemia may be observed during treatment with rosiglitazone. Drug interactions between oral contraceptives and pioglitazone may result in loss of contraception.

◆ CLINICAL CONSIDERATIONS

Liver enzyme levels should be checked before thiazolidinedione therapy commences. These agents must not be used in patients with elevated baseline levels of liver enzymes. These agents are contraindicated in patients who have liver transaminase levels greater than 2.5 times the upper limit of normal. For patients with normal liver enzyme levels, enzyme levels should be monitored every 2 months for the first year and then periodically thereafter.

The patient should be advised to contact their doctor if they develop unexplained signs and symptoms, such as dark urine, jaundice, abdominal pain, nausea, vomiting, anorexia and fatigue. These signs and symptoms may be indicative of liver problems.

POSTPRANDIAL HYPOGLYCAEMIC AGENTS

Another drug, **acarbose**, may be useful in people with type 2 diabetes who do not respond to dietary control alone or if the oral hypoglycaemic agents are contraindicated or not tolerated. Acarbose may also be used to reduce postprandial glucose rises in type 1 diabetes, although it is not often used for this purpose.

■ MECHANISM OF ACTION

Acarbose is a complex carbohydrate molecule of microbial origin that competes with disaccharides and polysaccharides in the intestines for the binding sites of carbohydrate enzymes. As a consequence, these carbohydrates cannot be broken down into absorbable monosaccharides. Absorption of carbohydrates is delayed and the postprandial rise in blood glucose is reduced. The absorption of monosaccharides from foodstuffs is unaffected by this drug, because monosaccharides do not require further enzymic breakdown. In clinical trials, acarbose, either alone or in combination with an oral hypoglycaemic agent, has been shown to produce small reductions in the level of HbA_{1c}. As the site of action is within the intestines, it is advantageous that the active drug is largely unabsorbable.

FIGURE 57.4 FLOWCHART SHOWING THE EFFECTS OF THE BIGUANIDES

Desired therapeutic effect shown in the darker shaded box.

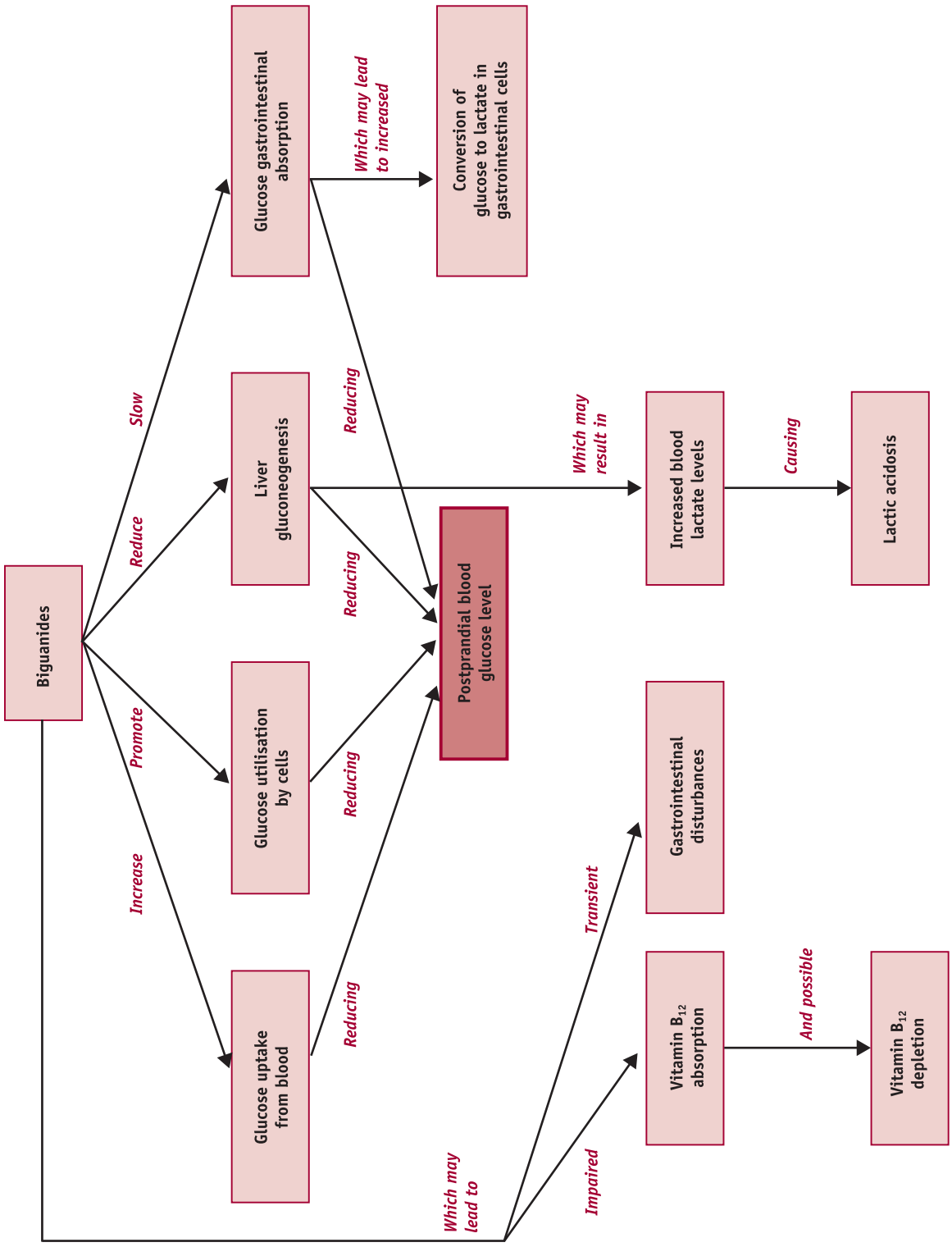
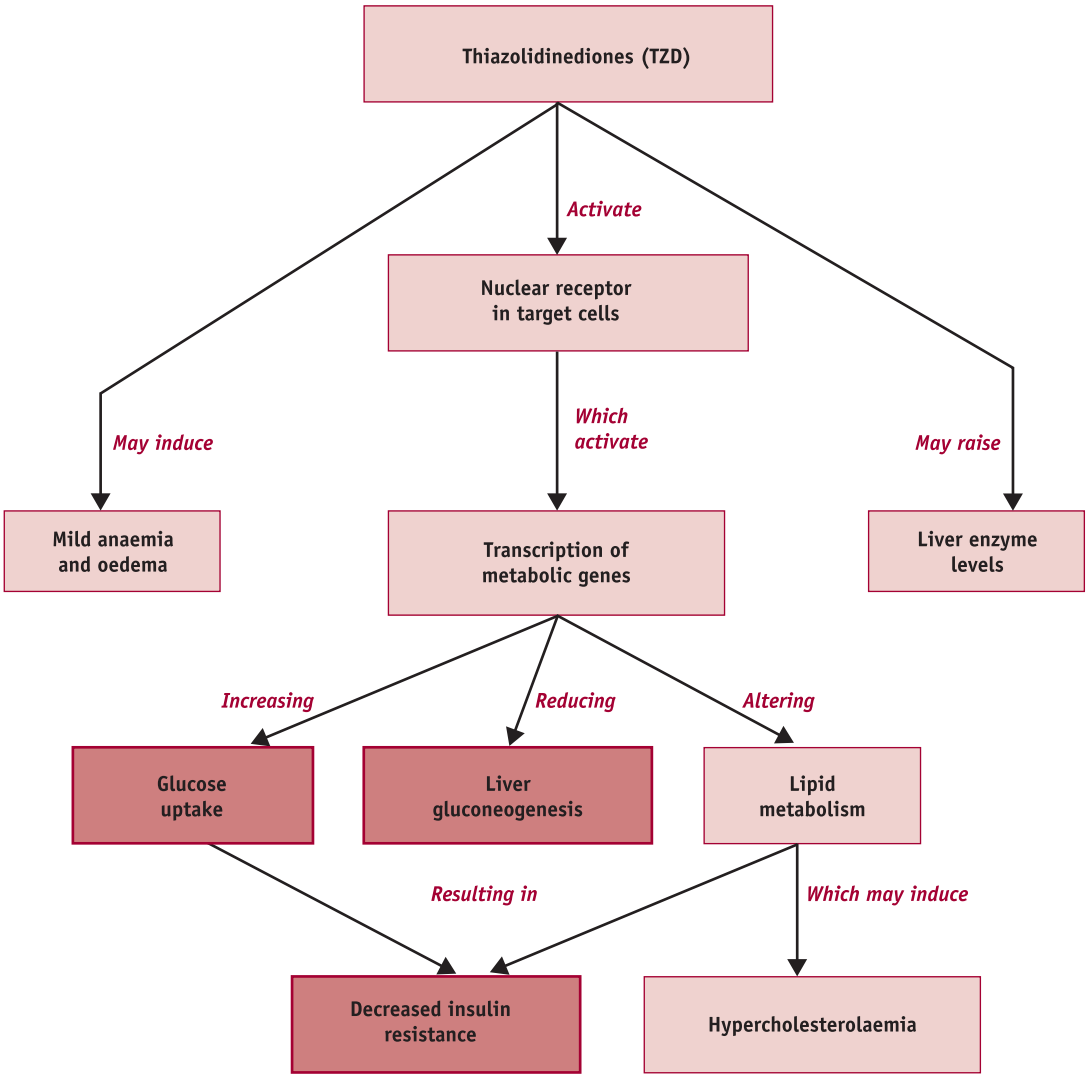


FIGURE 57.5 FLOWCHART SHOWING THE EFFECTS OF THE THIAZOLIDINEDIONES

Desired therapeutic effects shown in the darker shaded boxes.



◆ COMMON ADVERSE EFFECTS

The common adverse effects of acarbose are gastrointestinal and are associated with large amounts of undigested carbohydrate in the gut. They include flatulence, diarrhoea and abdominal discomfort. These effects are dose-dependent.

✚ CLINICAL CONSIDERATIONS

During acarbose therapy, blood glucose and HbA_{1c} levels should be checked regularly to determine the therapeutic response of the agent. During times of increased stress, such as infection, fever, surgery and trauma, blood glucose levels may alter. When used in combination with other drugs, blood glucose levels may be affected (see Table 57.3).

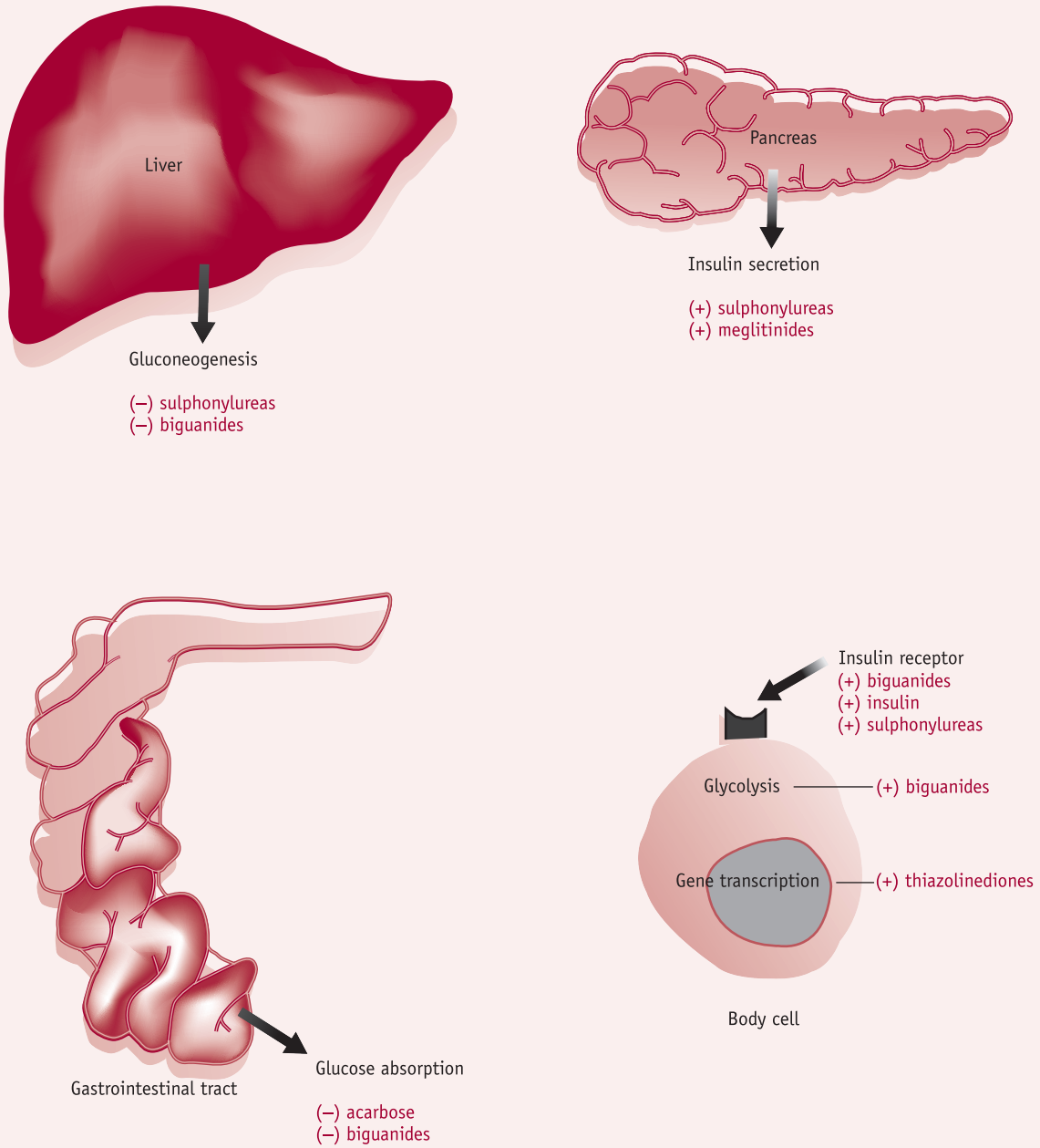
Plasma transaminase levels are monitored during acarbose therapy for the first 6 months and the dose is decreased if enzyme levels are elevated.

Gastric irritation associated with acarbose can be reduced by starting at a low dose and increasing the dose slowly, according to response. Acarbose is swallowed whole with liquid immediately before a meal or with a few mouthfuls of food.

Hypoglycaemia may occur with combined treatment of acarbose with sulphonylureas, repaglinide or insulin. If hypoglycaemia occurs, glucose rather than sucrose should be given.

A summary of the sites of action of the hypoglycaemic agents is shown in Figure 57.6.

FIGURE 57.6 SITES OF ACTION OF THE HYPOGLYCAEMIC AGENTS



CLINICAL MANAGEMENT

Thyroid drugs

Assessment

- Obtain a history of the drugs the patient is currently taking. Note that thyroid drugs enhance the action of oral anticoagulants, sympathomimetics and tricyclic antidepressants, and decrease the effects of oral hypoglycaemics and cardiac glycosides.
- Use thyroid hormone with care in elderly patients as they are very sensitive to its effects. A 25 per cent drop in dosage is often warranted in elderly patients.
- Assess for manifestations of hyperthyroidism, including fever, increased pulse, systolic hypertension, nausea, vomiting, diarrhoea, agitation, tremors, anxiety, restlessness, confusion and heat intolerance.
- Assess for manifestations of hypothyroidism, including dry and scaly skin, decreased hair growth, lowered pulse, decreased exercise tolerance, loss of appetite, constipation, abdominal distension, slurring of speech, lethargy, confusion and cold intolerance.
- Assess vital signs and compare with subsequent observations.
- Obtain baseline interpretations of the level of mood, weight, level of energy and response to changes in temperature. Compare with interpretations obtained after commencement of therapy.

Planning

- The patient's manifestations of hyperthyroidism or hypothyroidism will be alleviated during a course of prescribed therapy.
- The patient's thyroid gland will be restored to a normal or near-normal functioning state.

Implementation

- Continue to monitor vital signs, weight and thyroid function during therapy.
- Monitor level of mood, level of energy and response to temperature.
- Check thyroid function tests.
- Monitor for manifestations of thyroid crisis, including raised pulse, dysrhythmias, fever, heart failure, flushed skin, apathy, confusion, behavioural changes and, later, hypotension and vascular collapse. Thyroid crisis may occur after a thyroidectomy, abrupt withdrawal of antithyroid drugs, excess ingestion of thyroid hormone, and failure to give an antithyroid drug before thyroid surgery.
- For thyroid hormones, monitor the electrocardiogram (ECG) at regular intervals.
- When administering radioactive iodine, wear rubber gloves and follow the institutional policy for handling of radioactive substances.
- Monitor for manifestations of iodism (excessive iodine), including metallic taste, sneezing, swollen and tender thyroid gland, vomiting and bloody diarrhoea.
- For antithyroid drugs, monitor for tingling of fingers and toes. Inspect the patient for skin changes and hair loss.
- Monitor for manifestations of hypercalcaemia and hypocalcaemia during calcitonin therapy. Monitor serum electrolyte levels.
- Beta-blockers can be used for relief of hyperthyroid symptoms, such as tachycardia, tremor and sweating. Their use should be avoided in patients with asthma or heart failure.
- Metabolism of many drugs is often reduced in hypothyroidism. To avoid toxicity problems, the dose of drugs (other than thyroid therapy) should be lowered until the patient achieves a euthyroid status.

Patient teaching

- Advise the patient about the manifestations of hyperthyroidism and hypothyroidism. Both conditions can occur from treatment of hyperthyroidism and hypothyroidism.
- If possible, teach the patient how to monitor pulse rate and to report any marked rise or fall in rate.

Hypothyroid therapy (thyroid drugs)

- Advise the patient that the full benefit is established after several weeks of therapy.
- Instruct the patient to take the drug at the same time each day, preferably before breakfast. Food tends to inhibit the absorption rate of the drug.
- Instruct the patient to avoid foods that can inhibit thyroid secretion, such as strawberries, peaches, pears, cabbage, turnips, brussels sprouts, cauliflower, radishes, peas and spinach.
- Doses should be taken early in the day to prevent night-time insomnia.
- Advise the patient to report manifestations of hyperthyroidism, which may be due to drug overdosing.

- Advise the patient to consult the pharmacist and doctor before taking any over-the-counter preparations.
- Advise female patients to keep a record of menstruation, as menstrual irregularities may occur.

Calcitonin

- Advise the patient that administering the drug at night may decrease the feeling of flushing.
- Teach the patient how to administer injectable preparations subcutaneously.
- Advise the patient on a low-calcium diet if required.

Thionamides

- Instruct the patient to report manifestations of agranulocytosis (loss of white blood cells), including fever, sore throat, chills and unexplained bleeding and bruising. The patient should have a full blood examination to check for leucopenia.
- Alert the patient to other side effects of antithyroid drugs, such as rash, hives, nausea, alopecia, petechiae, ecchymosis and weakness.
- Advise the patient to take the drug with meals to decrease the incidence of gastric irritation.
- Instruct the patient about the importance of not stopping the drug abruptly, as this could bring about a thyroid crisis.
- A rare but serious adverse effect of antithyroid therapy is agranulocytosis. The regular monitoring of blood cell counts is probably not very beneficial, as the onset of agranulocytosis is rapid. Advise the patient to contact the doctor immediately if fever, mouth ulcers, sore throat or rash develops.

Iodine preparations

- Advise the patient about the effects of iodine and its presence in shellfish, iodised salt and certain over-the-counter cough preparations.

Evaluation

- Evaluate the effectiveness of the drug in restoring the function of the thyroid gland to a normal or near-normal state.
- Evaluate the patient's and family's knowledge of the clinical manifestations of hyperthyroidism and hypothyroidism.

Drugs used to treat altered blood calcium levels

Assessment

- Assess the patient with Paget's disease for the following symptoms: severe bone pain, presence of complications (e.g. pathological fractures, osteoarthritis), and raised levels of plasma alkaline phosphatase and urinary hydroxyproline.
- Calcitonin may require dosage reduction when used in patients with renal impairment.
- Bisphosphonates are contraindicated in conditions of hypocalcaemia. Assess calcium levels before treatment.
- Assess patients on alendronate and risedronate for oesophageal and gastric conditions such as oesophagitis, oesophageal ulcers and gastritis. There is an increased risk of oesophageal disorders in these patients.

Planning

- The patient will begin to experience pain relief and reduced incidence of complications.

Implementation

- Ensure adequate intake of calcium and vitamin D to prevent the risk of secondary hyperparathyroidism.
- Continue treatment of calcitonin therapy for 3–6 months.
- Restart calcitonin therapy if symptoms reappear.
- Monitor levels of plasma alkaline phosphatase and urinary hydroxyproline before calcitonin treatment and at 3-monthly intervals during treatment.
- Ensure bisphosphonates are consumed on an empty stomach with a glass of water.
- Following administration of alendronate or risedronate, the patient should remain upright for about 30 minutes.
- Bisphosphonate therapy should cease if the patient experiences pain on swallowing or worsening heartburn.

Evaluation

- Monitor the effect of calcitonins in alleviating symptoms, such as severe bone pain.
- Monitor the effect of bisphosphonates in alleviating symptoms of Paget's disease, osteoporosis, hypercalcaemia of malignancy, osteolytic bone metastasis and ossification due to spinal injury.

Drugs for diabetes mellitus

Assessment

- Obtain a patient history of oral hypoglycaemics and/or insulin used, with dosage and times administered. Also obtain a patient history of other drugs taken, as several drugs can cause a rise in glucose levels.
- The risk of hypoglycaemia following the use of glibenclamide and chlorpropamide is relatively high in elderly patients and in patients with renal or hepatic impairment. Avoid use of these sulphonylureas in such patients.
- During pregnancy, oral hypoglycaemic drugs should be replaced with insulin. Insulin lispro should be avoided, however, because of its unknown effects during pregnancy.
- Determine history of infection and other illness.
- Assess baseline vital signs and compare with subsequent observations.
- Assess the patient about to commence metformin for renal and hepatic impairment and other major illnesses (e.g. severe infection, trauma, heart failure, respiratory failure, alcohol abuse). Metformin is contraindicated in these conditions, as it may cause the rare but often fatal problem of lactic acidosis.

Planning

- The patient's blood glucose will be within normal levels.
- The patient will have a good understanding of the medication, method of administration and manifestations of hyperglycaemia and hypoglycaemia.

Implementation

- Monitor vital signs, weight and blood glucose levels. Note that sulphonylureas increase cardiac function and oxygen consumption, which can lead to cardiac dysrhythmias.
- Monitor for long-term effects of diabetes, including ulcers in the lower extremities and neuropathy.
- Monitor the condition of skin and nails, skin turgor, level of consciousness, decreased sensation and decreased reflexes.
- Monitor for manifestations of hyperglycaemia and hypoglycaemia.
- For patients on oral hypoglycaemic drugs, monitor for a full blood examination, platelet count and liver function tests.
- The patient with diabetes should have a haemoglobin (HbA_{1C}) test every 3 months to determine long-term control of blood glucose levels.
- Administer oral hypoglycaemic drugs with food to minimise gastric upset.
- Store insulin in the refrigerator when not in use. Remove from the refrigerator for a few minutes before using; warming insulin to room temperature reduces injection discomfort. Roll the vial gently between the palms before use. Do not shake.
- Note the expiry date for insulin. The expiry date after commencing use of a vial is 1 month.
- Administer short-acting insulin (e.g. neutral insulin) 30 minutes before a meal and ultra-short-acting insulin (e.g. insulin lispro) immediately before a meal.
- For a patient on thiazolidinedione therapy, check liver enzymes at the start of treatment and then every 2 months for the first year, and periodically thereafter.
- Monitor plasma transaminase levels monthly for the first 6 months of therapy with acarbose.

Patient teaching

- Instruct the patient to recognise manifestations of a hypoglycaemic reaction (e.g. nervousness, sweating, tremors, rapid pulse, hunger, weakness) and manifestations of a hyperglycaemic reaction (e.g. thirst, sweet and fruity breath odour, abdominal pain, increased urine output, nausea and vomiting).
- Teach the patient how to check a blood glucose level using a blood-glucose-monitoring machine. Blood glucose levels should be checked about four times daily; more frequent monitoring is required if levels are not within the normal range. Urinary testing of ketones and glucose is not routinely recommended by diabetes associations, as this method does not provide an accurate reflection of blood glucose levels.
- Impress on the patient the importance of maintaining a well-balanced diet with the dietary restrictions specified by the health-care team. Delaying or missing a meal can lead to hypoglycaemia. Alcohol should be avoided.
- Explain to the patient the use of orange juice and sugar-containing drinks and foods when a hypoglycaemic reaction occurs.
- The patient should always carry a source of sugar when away from home.

Insulin

- Review with the patient the possible changes in routine during times of stress, illness, surgery and infection. Stress usually causes an elevation in blood glucose levels, and adjustments to the insulin dose are

often required. The patient should consult their doctor or diabetic educator about changes to diet or insulin.
- Teach the patient the importance of tracking up and down the same site for insulin administration to maintain effective, uniform absorption and to prevent lipodystrophy.
- When administering long-acting and short-acting insulin preparations together, advise the patient to follow this schedule: With one syringe, air is put in the cloudy (long-acting) insulin, and then air is put in the clear (short-acting) insulin. Fluid is drawn up into the syringe from the clear insulin and then fluid is drawn up from the cloudy insulin. This sequence prevents contamination of the clear insulin with remnants of cloudy insulin.
- Impress on the patient that insulin controls but does not cure diabetes. Insulin therapy is, therefore, required long-term.

Oral hypoglycaemic drugs

- Teach the patient that oral hypoglycaemic drugs are not the same as insulin. Rather, they enhance the effectiveness of insulin.
- Instruct the patient on chlorpropamide not to ingest alcohol, as a disulfiram-like reaction may occur. Manifestations include blurred vision, sweating, chest pain, headache, respiratory difficulty, nausea, vomiting, fainting and confusion.
- Explain that insulin might be needed instead of, or as a supplement to, the oral hypoglycaemic agent at times of infection, stress and surgery.
- Explain to the patient that photosensitivity may occur. Impress on the patient the importance of using sunblock, wearing protective clothing and a hat, and avoiding the sun during the hottest time of the day (see Table 11.19 in Chapter 11 for further information).
- Advise the patient to contact their doctor if dark urine, jaundice, abdominal pain, nausea, vomiting, anorexia or fatigue develops during thiazolidinedione therapy, as this may indicate hepatic dysfunction.

Postprandial hypoglycaemic agents

- Advise the patient on acarbose to swallow the tablet whole with liquid just before a meal or to chew it with the first few mouthfuls of food. These measures will avoid the adverse effects of flatulence, abdominal pain, distension and diarrhoea. Explain that antacids do not generally assist with such gastrointestinal problems and may reduce the effectiveness of acarbose.
- Advise the patient on repaglinide to take the medication with meals in order to prevent gastrointestinal disturbances.

Evaluation

- Evaluate the effectiveness of the drug therapy in ensuring that blood glucose levels are at an acceptable level.
- Evaluate the patient's knowledge of the clinical manifestations of hypoglycaemia and hyperglycaemia. Determine whether the patient knows what measures to take before these conditions become severe.
- Evaluate the patient's knowledge of the possible long-term effects of diabetes and measures to take to prevent these effects from occurring. These measures include foot care, avoiding smoking, maintaining dietary control and monitoring blood glucose levels carefully.

SUMMARY

- Endocrine disorders associated with the thyroid gland are either hypothyroid or hyperthyroid states.
- The usual therapy in hypothyroid conditions is thyroid hormone replacement. The conditions usually require lifelong therapy.
- Thyroxine (T_4) and triiodothyronine (T_3) can be used, but T_4 has a more prolonged action and can be converted into T_3 in the periphery.
- If symptoms of hyperthyroidism occur during treatment, the medication is stopped for a week and then recommenced at a lower dose.
- In hyperthyroid conditions, treatment usually involves inhibiting the synthesis and/or release of thyroid hormones using antithyroid drugs or blocking the peripheral effects of excessive thyroid hormone levels using beta-blockers.
- Antithyroid drugs include the thionamides, iodide solution, radioactive iodide and iodinated contrast media.
- High doses of antithyroid drugs are used for about 3–4 weeks to establish normal thyroid function. Dosage is decreased thereafter.

- Calcitonin, obtained from pigs and salmon, can be used to lower blood calcium levels in hypercalcaemia and active Paget's disease. It should be administered parenterally because it is inactivated if given orally.
- Patients on calcitonin should avoid operating machinery and driving, as this medication can cause dizziness.
- The bisphosphonates prevent bone resorption. These drugs inactivate osteoclasts, the bone cells responsible for bone breakdown.
- Oral bisphosphonates have a low bioavailability and must be taken on an empty stomach with a glass of water.
- Insulin lowers blood glucose levels by facilitating glucose transport into body cells. It is an important drug in the management of diabetes mellitus.
- There are four main types of insulin preparation: ultra-rapid-acting (the insulin analogues), short-acting (neutral insulin), intermediate-acting (lente and isophane insulins) and long-acting (ultralente) insulins, including long-acting analogues such as glargine.
- Common adverse reactions of insulin include hypoglycaemia and lipodystrophy.
- Insulin is usually given by subcutaneous injection, but in emergencies ultra-rapid-acting or short-acting insulin may be administered intravenously.
- Insulin is given by subcutaneous injection into the abdomen, thigh, upper arm or buttock. The fastest rate of absorption and onset of action occurs through abdominal administration. Rotate sites to prevent lipodystrophy.
- For patients with type 2 diabetes mellitus, a number of oral hypoglycaemic agents are available. The main oral hypoglycaemic drug groups are the sulphonylureas, biguanides, thiazolidinediones and meglitinides.
- Acarbose is a postprandial hypoglycaemic agent that slows the absorption of glucose from the gut.
- Blood glucose and glycosylated haemoglobin levels should be checked regularly for all hypoglycaemic agents.

1 For each of the following endocrine agents, name the tissue(s) on which it acts, the effects desired and one clinical application:
(a) liothyronine;
(b) carbimazole;
(c) calcitonin;
(d) iodide;
(e) bisphosphonates.

2 Explain why the pancreatic hormones cannot be administered orally.

3 Compare and contrast the following insulin preparations: lente, neutral, isophane, insulin lispro and ultralente.

4 What are the advantages and disadvantages of using premixed insulin preparations?

5 Explain why someone with type 1 diabetes cannot be treated with the oral hypoglycaemic agents.

6 Nanette Miodouchowski, a 45-year-old patient, commences L-thyroxine to treat a hypothyroid condition. What assessment would you undertake to determine the effectiveness of treatment?

7 (a) John Wong is a 38-year-old patient with Paget's disease. He is receiving therapy with calcitonin for acute bone pain. Outline the patient education associated with this therapy.
(b) What drug group might be considered an alternative treatment for John's condition? What is the major advantage of this group over calcitonin?

8 Vicki Renaldo, a 14-year-old student, is diagnosed with diabetes mellitus. She is receiving Actrapid™ 15 units, three times during the day, and Protophane™ 13 units at night. Her mother asks the diabetic educator why Vicki must have insulin injections when other people they know with diabetes do not require insulin injections. What would the diabetic educator say?

9 Develop a clinical management and teaching plan for Vicki Renaldo (from question 8) that emphasises the following aspects: checking blood glucose levels, administration technique, recognising manifestations of hypoglycaemia and hyperglycaemia, and strategies during times of illness and exercise.

10 Stanley McDougall, a 55-year-old bookshop owner, takes glibenclamide for type 2 diabetes. Develop a clinical management and teaching plan for Mr McDougall, emphasising the following aspects: dietary measures, knowledge of adverse effects, and evaluation of the drug's effectiveness.

11 What changes in insulin dosage are required during times of illness and stress? Explain your answer.

12 Margaret Smith is a 60-year-old woman with type 2 diabetes. She has been managing her condition by dietary measures and therapy with the oral hypoglycaemic agent glicazide. She is experiencing some problems with the control of postprandial blood glucose levels. Her doctor prescribes acarbose. What advice would you give regarding Margaret's preparation for the nature and type of common adverse effects she might experience?

57 DRUG SUMMARY TABLE: THE THYROID AND THE PANCREAS

FAMILY NAME	GENERIC NAME	TRADE NAME(S)
Thyroid hormones	Liothyronine (L-triiodothyronine)	Tertroxin Triiodothyronine
	Levothyroxine	
Drugs that alter blood calcium levels	Calcitonin	Miacalcic
Bisphosphonates	Alendronic acid	Fosamax Fosamax Once Weekly
	Etidronate	Didronel
	Pamidronate	Aredia
	Risedronate	Actonel
	Sodium clodronate	Bonefos Loron
	Tiludronic acid	Skelid
	Zoledronic acid	Zometa
	Strontium ranelate	Protelos
Antithyroid drugs	Carbimazole	Neo-Mercazole
	5% Iodine solution + 10% Potassium iodide	Lugol's Solution
	Potassium iodide	
	Propylthiouracil (PTU)	
Beta-blockers	Metoprolol	Betaloc Lopresor
	Nadolol	Corgard
	Propranolol	Inderal
Somatostatin agonists	Lanreotide	Somatuline LA
	Octreotide	Sandostatin
Hyperglycaemic agents	Glucagon hydrochloride	GlucaGen HypoKit

FAMILY NAME	GENERIC NAME	TRADE NAME(S)
Oral hypoglycaemic agents		
Sulphonylureas	Chlorpropamide	
	Glibenclamide	Daonil
		Semi-Daonil
		Euglucon
	Gliclazide	Diamicron
	Glimepiride	Amaryl
	Glipizide	Glibenese
		Minodiab
	Gliquidone	Glurenorm
	Tolbutamide	
Biguanides	Metformin	Glucophage
		Glucophage SR
Thiazolidinediones	Pioglitazone	Actos
	Rosiglitazone	Avandia
	+ Metformin	Avandamet
Meglitinides	Nateglinide	Starlix
	Repaglinide	NovoNorm
Oral postprandial agents	Acarbose	Glucobay

THE ADRENAL CORTEX AND THE GONADS

58

CHAPTER FIFTY-EIGHT

OBJECTIVES

KEY TERMS

Adrenal cortex
Agonists
Androgens
Antagonists
Contraception
Electrolyte balance
Glucocorticoids
Gonads
Mineralocorticoids
Oestrogens
Progesterone

After completing this chapter, the reader should be able to:

- **outline the physiological effects of the hormones produced by the adrenal cortex and the gonads;**
- **identify the endocrine agents that act on each of these endocrine glands;**
- **describe the actions and properties of the endocrine agents at each of these glands and, in general, the conditions they are used to treat.**

THIS CHAPTER DEALS WITH DRUGS AFFECTING THE ADRENAL cortex and the gonads.

DRUGS AFFECTING THE ADRENAL CORTEX

The adrenal cortex secretes three types of corticoid: glucocorticoids, mineralocorticoids and gonadocorticoids. The effects of these hormones are listed in Table 58.1. Two types of adrenocorticoid, glucocorticoids and mineralocorticoids, are used clinically in the treatment of adrenocortical insufficiencies. These conditions (e.g. Addison's disease) are characterised by a deficiency in the secretion of one or more corticosteroid hormones. The glucocorticoids are also important in the treatment of numerous inflammatory and immune disorders. Examples of these include cancers (especially haematological), eye inflammations, inflammatory bowel diseases, rheumatoid arthritis, dermatitis, and autoimmune and allergic disorders.

MECHANISM OF ACTION

The glucocorticoids are potent immunosuppressants used to prevent organ-transplant rejection (see Chapter 75). They can also be used to promote lung maturation in premature infants. Specific immunosuppressant anti-inflammatory effects of the glucocorticoids include a reduction in the size and substance of lymph nodes and spleen, inhibition of helper T-cells (which enhance the immune response), inhibition of protein synthesis (affecting antibody and cytokine production), inhibition of eicosanoid biosynthesis (inflammatory mediator production; see Chapter 30), a decrease in neutrophil and macrophage responsiveness (affecting phagocytosis), stabilisation of mast-cell membranes and impairment of fibroblast activity (affecting the healing process).

At high doses, parenteral corticosteroids are useful in the treatment of hypovolaemic shock. Corticosteroids are known to increase the responsiveness of tissues to the catecholamines noradrenaline and adrenaline, thus enhancing sympathetic nervous system effects. Reportedly, they also directly increase the tone of precapillary sphincters and endothelial cells within the vasculature of peripheral tissues. This counteracts the net movement of fluid out of the intravascular compartment into the interstitium that often occurs during fluid-replacement therapy.

COMMON ADVERSE EFFECTS

The effects of the glucocorticoids are summarised in Figure 58.1. Adverse reactions associated with glucocorticoid therapy derive from the agents' effects on metabolism and immunity and the degree to which they affect electrolyte and water levels. These reactions tend to be more common during high-dose and prolonged systemic therapy. Metabolic effects include elevated blood glucose

FIGURE 58.1 EFFECTS OF GLUCOCORTICOIDS

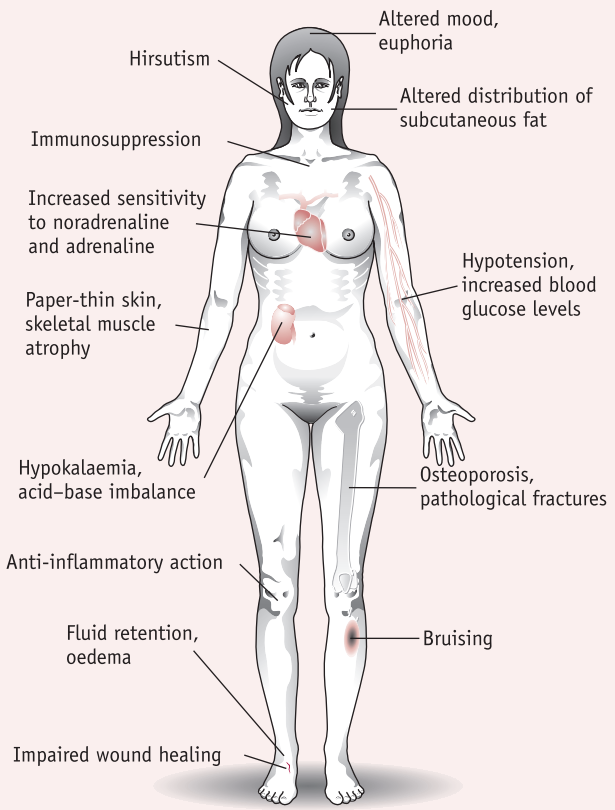


TABLE 58.1 ADRENOCORTICAL HORMONES AND THEIR EFFECTS

Hormone	Effects
Mineralocorticoids Aldosterone	Sodium and water retention; increase blood volume and blood pressure
Glucocorticoids Cortisone Hydrocortisone (cortisol)	Increase blood glucose levels; mobilise fats; stimulate protein catabolism; depress immunity and inflammatory responses; enhance tissue responses to noradrenaline and adrenaline
Gonadocorticoids Androgens	Influence patterns of body hair growth; effects in adults yet to be elucidated fully, but may be involved in the female sexual response

levels, protein catabolism and lipolysis. The elevation in blood glucose levels may lead to an exacerbation of diabetes mellitus and require an adjustment of hypoglycaemic therapy. Protein catabolism can, in the short term, result in a negative nitrogen balance; in the long term, it may cause a loss of bone mass that eventually leads to osteoporosis and pathological fractures. Skeletal muscle atrophy and fragile paper-thin skin may also occur as a result of prolonged protein catabolism. Lipolysis leads to a rise in plasma fatty acid levels, but after prolonged use the distribution of subcutaneous fat may be altered, leading to the development of the characteristic 'moonface' and 'buffalo hump'. The suppression of immune processes can result in an increased susceptibility to infection and impaired wound healing. Contraindications associated with corticosteroid therapy include systemic fungal infections and a history of hypersensitivity to these drugs. Patients must be monitored for any signs of infection.

Adverse effects associated with altered fluid and electrolyte levels include oedema (both localised and systemic), increased blood pressure, hypernatraemia and hypokalaemia. As a result of hypokalaemia, metabolic alkalosis may develop. Individuals with cardiovascular conditions must be monitored closely during this therapy. Hirsutism can also be a problem during therapy. Allergic reactions, such as rash, may occur. Patients with peptic ulcers may experience an exacerbation of the condition due to increased gastric acid secretion.

✚ CLINICAL CONSIDERATIONS

The glucocorticoids are classified according to their duration of action; there are short-acting, intermediate-acting and long-acting forms. Cortisol (**hydrocortisone**) and **cortisone** are the only naturally occurring glucocorticoids used clinically; both possess mineralocorticoid activity (i.e. cause retention of sodium and water, as well as excretion of potassium). The other clinical corticosteroids are synthetic and are modified for increased anti-inflammatory activity (see Table 58.2) and bioavailability. Most have negligible mineralocorticoid activity, the exceptions being **fludrocortisone** and **prednisolone**. Prednisolone cause some retention of sodium and water but to a lesser degree than cortisol. Fludrocortisone is a potent mineralocorticoid with significant anti-inflammatory action. It is used to promote water and salt retention in patients with adrenal insufficiency. Most corticosteroids are available in oral, injectable and topical (e.g. cream/ointment, eye drops, nasal/inhalable spray) forms. A number of topical corticosteroid preparations contain additional therapeutic agents (see the drug summary table at the end of this chapter). Because of the immunosuppressant action of the corticosteroids, such preparations often contain an antimicrobial substance. The type of additional agent depends on the nature of the condition being treated and the site of administration. As examples, preparations designed for ophthalmic and nasopharyngeal application may also include a decongestant, while anorectal corticosteroid creams and ointments may incorporate a local anaesthetic for pain relief.

Adverse effects are minimised if the corticosteroid is applied topically. Some individuals are predisposed to rises in intraocular pressure when these agents are applied to the eye (see Chapter 18), and prolonged application to the skin can cause cutaneous atrophy. Furthermore, if the integrity of the tissue surface to which the corticosteroid is applied becomes damaged, greater systemic absorption will result.

When therapeutic doses of corticosteroids are used, it is advisable to measure the patient's blood glucose level, weight, blood pressure and electrolyte levels before treatment and then weekly during the first month of treatment. The patient should be reviewed regularly for signs of infection.

If the oral dose exceeds 15 mg daily of prednisolone or equivalent dose, the patient may benefit from receiving

TABLE 58.2 CORTICOSTEROID POTENCIES COMPARED WITH HYDROCORTISONE

Corticosteroid	Anti-inflammatory activity	Mineralocorticoid activity
Hydrocortisone	1	1
Cortisone	0.8	1
Methylprednisolone	3.3–7.5	–
Prednisolone	4.2–5	0.3–0.8
Triamcinolone	5	–
Fluocortolone	5	–
Budesonide	17–20	–
Dexamethasone	25–30	–
Betamethasone	25–40	–
Alcometasone	50	–
Fludrocortisone	10	250

gastric acid suppressive therapy, such as **omeprazole** or **ranitidine**, to prevent gastric ulcer formation.

When chronic therapy or repeated therapy is initiated, preventive measures for osteoporosis should be given. Baseline measures of bone density should be considered for these patients.

If an individual has been on systemic corticosteroid therapy for at least 3 weeks, the dose is reduced gradually and not withdrawn abruptly due to the possibility of acute adrenal suppression. The hypothalamus, pituitary gland and adrenal cortex will need time to allow the adrenal response to recur naturally.

Adrenal cortex antagonists

SPIRONOLACTONE

The steroid **spironolactone** is a useful diuretic agent in the treatment of essential hypertension, heart failure and other oedematous conditions (see Chapters 44 and 47). Spironolactone is also used in the treatment of hirsutism in women when non-drug therapy has failed, in heart failure and in primary hyperaldosteronism.

■ MECHANISM OF ACTION

Spironolactone is an antagonist to the endogenous mineralocorticoid aldosterone and promotes the excretion of sodium and water while retaining potassium. Its action in hirsutism is due to the inhibition of steroid production, in this case excess androgens secreted by the ovary.

In heart failure, spironolactone has been shown to reduce mortality and hospitalisation rates. There is evidence that spironolactone may contribute to an amelioration of the pathophysiological process underlying the development of heart failure (see Chapter 48).

◆ COMMON ADVERSE EFFECTS

Adverse reactions include hyperkalaemia, rashes and endocrine imbalances resulting in increased breast development in men and menstrual irregularities in women.

✚ CLINICAL CONSIDERATIONS

Serum potassium levels should be monitored during spironolactone therapy. Menstrual irregularities need to be monitored. It is important to note that elderly patients are more susceptible to postural hypotension and hyperkalaemia during spironolactone therapy.

METYRAPONE

Another antagonist used for both diagnostic and therapeutic purposes is **metyrapone**. This is used to treat conditions associated with excessive production of adrenal cortex hormones, such as Cushing's disease and hyperaldosteronism.

■ MECHANISM OF ACTION

Metyrapone prevents the synthesis of the glucocorticoid hormones hydrocortisone (cortisol) and corticosterone within the gland. As a result of the inhibition of synthesis of these hormones, there is a marked rise in plasma adrenocorticotrophic hormone (ACTH) levels. Its diagnostic value, therefore, lies in differentiating the level at which dysfunction of the pituitary-adrenocortical axis has occurred.

◆ COMMON ADVERSE EFFECTS

Common adverse reactions include gastrointestinal disturbances, dizziness and headache. Contraindications for use are hypersensitivity and conditions characterised by adrenocortical insufficiency.

✚ CLINICAL CONSIDERATIONS

In patients in whom the function of the adrenal cortex or anterior pituitary is severely impaired, metyrapone can induce transient adrenal insufficiency, which can be overcome by administering a glucocorticoid. As prolonged therapy can also induce hypertension, blood pressure should be monitored.

DRUGS AFFECTING THE GONADS

The reproductive, somatic and metabolic effects of the gonadal hormones (androgens, oestrogens, progestins) are summarised in Table 58.3.

Oestrogen-only preparations

The main use of oestrogens is as replacement therapy when ovarian production is deficient as a result of primary failure (i.e. primary hypogonadism) or age-related changes (i.e. after menopause). In the former, oestrogens stimulate the secondary sex characteristics and menses. Oestrogen-only preparations can also be used as a postcoital contraceptive ('morning-after' contraceptive) and are discussed later in this chapter. Oestrogens are available in oral, injectable and intravaginal forms and as transdermal patches and subcutaneous implants. The intravaginal formulations act topically to raise urogenital oestrogen levels. In so doing, these forms restore premenopausal vaginal pH and return the morphology and function of the urogenital epithelium to a premenopausal condition. Examples of the intravaginal formulations include pessaries, creams and an elastic polymer vaginal ring.

The most convenient route of administration is oral; the preferred oral forms are the natural oestrogens (**oestriol**, **oestradiol**, **conjugated equine oestrogens**) rather than the synthetic oestrogens (**ethinyloestradiol**, **mestranol**). The synthetic forms are more potent but are more likely to affect liver function adversely. Administration of the hormone via the transdermal, intranasal, subcutaneous and

TABLE 58.3 SUMMARY OF HORMONAL EFFECTS OF OESTROGENS, PROGESTERONE AND TESTOSTERONE

	Oestrogen	Progesterone	Testosterone
Major source	Ovary: developing follicles and corpus luteum	Ovary: mainly corpus luteum	Testes: intersitial cells
Stimulus for release	FSH (and LH)	LH	LH and declining levels of inhibin produced by sustentacular cells
Feedback effects exerted	Both negative and positive feedback exerted on anterior pituitary release of gonadotrophins	Negative feedback exerted on anterior pituitary release of gonadotrophins	Negative feedback suppresses release of LH by anterior pituitary (and perhaps release of GnRH by hypothalamus)
Effects on reproductive organs	Stimulates growth and maturation of internal and external genitalia and breasts at puberty; maintains adult size and function of reproductive organs; promotes proliferative phase of uterine (menstrual) cycle; rising levels stimulate production of watery (crystalline) cervical mucus and activity of fimbriae and cilia of uterine tubes; promotes oogenesis and ovulation by stimulating formation of FSH receptors on follicle cells and acts with FSH to induce formation of LH receptors on follicle cells; stimulates capacitation of sperm in female reproductive tract via effect on vaginal, uterine and tubal secretions	Cooperates with oestrogen in stimulating growth of breasts and in regulating uterine cycle (promotes secretory phase of uterine cycle); stimulates production of viscous cervical mucus	Stimulates growth and maturation of internal and external genitalia at puberty, and maintains their adult size and function; required for normal spermatogenesis; suppresses mammary gland development
During pregnancy	Stimulates mitoses of myometrial cells, growth of uterus and enlargement of external genitalia and mammary glands; acts with relaxin (placental hormone) to induce softening and relaxation of pelvic ligaments and pubic symphysis	Quiets myometrium and acts with oestrogen to cause mammary glands to achieve mature milk-producing state (stimulates formation of alveoli)	
Somatic effects	Stimulates lengthening of long bones and feminisation of skeleton (particularly pelvis); inhibits bone resorption and then stimulates epiphyseal closure; promotes hydration of skin; stimulates female pattern of fat deposit and appearance of axillary and pubic hair		Stimulates growth spurt at puberty; promotes increased bone mass and skeletal mass and then epiphyseal closure at end of adolescence; promotes growth of larynx and vocal cords and deepening of voice; enhances sebum secretion and hair growth, especially on face, axillae, genital region and chest

TABLE 58.3 SUMMARY OF HORMONAL EFFECTS OF OESTROGENS, PROGESTERONE AND TESTOSTERONE (*continued*)

	Oestrogen	Progesterone	Testosterone
Metabolic effects	Generally anabolic effects; stimulates Na^+ reabsorption by renal tubules, hence inhibits diuresis; enhances HDL (and reduces LDL) blood levels (cardiovascular-sparing effect)	Promotes diuresis (antioestrogenic effect); increases body temperature	Generally anabolic effects; stimulates haematopoeisis; enhances basal metabolic rate (BMR)
Neural effects	Feminises brain		Responsible for sex drive (libido) in both sexes; masculinises brain; promotes aggressiveness

FSH, follicle-stimulating hormone; GnRH, gonadotrophin-releasing hormone; HDL, high-density lipoprotein; LDL, low-density lipoprotein; LH, luteinising hormone.
Source: From *Human Anatomy and Physiology*, 2nd edn, by Elaine N Marieb. Copyright © 1992 by The Benjamin/Cummings Publishing Company, USA.

intravaginal routes avoids the effects of first-pass metabolism; therefore, lower doses are required when oestrogen is administered in these ways. In transdermal application and subcutaneous implantation, the hormone is absorbed continuously into the blood, resulting in less fluctuation in blood concentration than that seen with daily oral administration. Transdermal patches are convenient to apply, have to be changed only a couple of times a week, and may be worn while bathing; however, rashes are common and adhesiveness may be poor in warmer climates.

◆ COMMON ADVERSE EFFECTS

A number of adverse effects are associated with oestrogen-only therapy, including breast tenderness, nausea, headaches, gastrointestinal disturbances, fluid retention (contributing to weight gain and hypertension), thrombosis development and breakthrough bleeding. The manifestations of headache and gastrointestinal disturbance may be minimised by using the transdermal route of administration. Patients who opt for oestrogen replacement therapy may be at higher risk of the development of breast cancer and, in women with intact uterus, endometrial cancer. The risk of endometrial cancer and the incidence of breakthrough bleeding experienced by some women can be minimised by using oestrogen–progestin combinations (see later in this chapter). For women who take oestrogen-only replacement therapy, the doctor is encouraged to use the lowest possible dose to produce the desired effects, in order to reduce the occurrence of adverse effects.

✚ CLINICAL CONSIDERATIONS

When using oestrogen patches, they should be applied to clean, dry, intact skin below the waist or on the upper buttock. Different skin sites should be used for successive applications.

If long-term therapy is required for hormone replacement, a progestogen is included to prevent endometrial hyperplasia, which can lead to endometrial carcinoma. Women who have had a hysterectomy are not at risk of endometrial carcinogenic problems and therefore do not require the addition of a progestogen agent. When using hormones for replacement, two regimens may be used. A sequential form of therapy involves the use of continuous oestrogen, plus progestin for 10–14 days each month or for 14 days every 3 months. A continuous form of therapy involves continuous oestrogen plus continuous progestin.

Oestrogen replacement therapy does not provide contraceptive protection. It may be advisable to use a low-dose oral contraceptive until menopause occurs and then to consider changing to a hormone replacement regimen. If nausea occurs during oestrogen therapy, suggest the patient takes the tablets with food or try a patch or gel. The presence of heavy withdrawal bleeds usually requires a reduction in the oestrogen dose.

Oestrogenic drugs with mixed activity

SELECTIVE OESTROGEN RECEPTOR MODULATORS

Drugs in this group induce oestrogen-like effects in some tissues and produce antioestrogenic effects in others. **Tamoxifen**, **raloxifene** and **toremifene** are members of this group. Tamoxifen is used in the treatment and prevention of breast cancer, and toremifene is used in the treatment of breast cancer (see Chapter 76); raloxifene is used to prevent osteoporosis.

■ MECHANISM OF ACTION

Tamoxifen has traditionally been regarded as an anti-oestrogen; however, it appears to produce a weak oestrogenic effect on bone, endometrium, coagulation and blood lipid profile. The antioestrogenic effect of tamoxifen is relatively specific to breast tissue. The tissue-selective nature of its oestrogenic activity has led to a revised classification as a selective oestrogen receptor modulator (SERM). Tamoxifen also increases the activity of the cytokine transforming growth factor-beta, which has a role in fighting cancer and may contribute to its anticancer action (see Chapter 75).

The SERMs raloxifene and toremifene are analogues of tamoxifen. They have both oestrogen agonist and antagonist activity. They produce oestrogen-like effects in bone and on lipid metabolism, but they block oestrogen action in breast and uterine cells. As raloxifene inhibits bone resorption, it is indicated in the treatment of post-menopausal loss of bone tissue. Compared with oestrogen, raloxifene is associated with a lower risk of breast cancer and uterine hyperplasia and a comparable blood lipid profile.

◆ COMMON ADVERSE EFFECTS

Common adverse effects include hot flushes, thromboembolism, dizziness, gastrointestinal disturbances and leg cramps. Contraindications for use include pregnancy, history of active thromboembolism activity and drug hypersensitivity.

✚ CLINICAL CONSIDERATIONS

Due to the increased risk of thromboembolism, patients embarking on prolonged travel should be advised to move around at regular intervals on the journey. Treatment should be stopped if illness or injury leads to prolonged immobilisation.

TIBOLONE

Tibolone is a steroid agent with oestrogen-like activity used to prevent osteoporosis and alleviate menopausal symptoms.

■ MECHANISM OF ACTION

Tibolone is related to the natural sex hormones and has oestrogenic, antioestrogenic, androgenic and progestogenic activity on selected tissues. On the vagina and bone, it has been shown to have oestrogenic effects. This action makes it useful for decreasing menopausal symptoms and preventing bone loss. It has progestogenic and antioestrogenic activity on the breast, reducing the risk of breast cancer.

◆ COMMON ADVERSE EFFECTS

Common adverse effects of tibolone include headache, dizziness and vaginal bleeding.

✚ CLINICAL CONSIDERATIONS

Tibolone therapy should not be commenced until 12 months after the last menstrual period to prevent irregular bleeding.

Progestin-only preparations

Progestins refer to the group of pharmacological agents with progesterone-like action. The members of this group are semisynthetic and synthetic forms of progesterone. They are also known as progestogens.

■ MECHANISM OF ACTION

Progestin-only preparations produce both suppression of ovarian function and inhibition of ovulation. They are, therefore, useful in treating hirsutism due to excess androgen production by the ovary, and endometriosis. As progestins promote the development of the endometrium, they can be used in uterine hypoplasia and amenorrhoea associated with a poorly developed endometrium. Progestin-only preparations are indicated in the treatment of premenstrual syndrome and threatened/habitual abortion. The effectiveness of progestin therapy in these conditions has not been demonstrated convincingly, however.

Progestin-only preparations are used as contraceptives (see Table 58.4) when oestrogen administration is either not recommended or not tolerated. Longer-term injectable progestin-only contraceptive preparations, which do not require daily dosing, are now available. These formulations may require dosing only once every 3 months or once every 3 years in the case of **etonogestrel**. The 'mini-pill' is a low-dose progestin-only preparation. A disadvantage of this approach is that ovulation may not always be inhibited, increasing the likelihood of conception.

◆ COMMON ADVERSE EFFECTS

The adverse effects associated with progestins are not dissimilar to those observed during oestrogen therapy. Weight gain, increased blood pressure, breast tenderness and nausea have been reported. As some older synthetic progestins (**norgestrel**, **etynodiol** (ethynodiol) and **norethisterone**) are related closely to the structure of androgens, acne and hirsutism may also be observed.

✚ CLINICAL CONSIDERATIONS

For maximum protection with progestin-only contraceptives, the patient must take the same dose around the same time each day. Such compliance is essential for effective contraception. These preparations have some benefits over oestrogen–progestin contraceptives in that the hormone dose is low, they may be tolerated by women who cannot take the oestrogen–progestin combinations and they may be used safely while breast feeding.

Using depot **medroxyprogesterone acetate** as a contraceptive may be inappropriate if pregnancy is planned within a year, because of a possible delayed return of the

TABLE 58.4 PROGESTIN-ONLY CONTRACEPTIVE PREPARATIONS

Progestin (dose)	No. of tablets	Trade name(s)
Levonorgestrel		
30 μg	28	Microval
750 μg	2	Levonelle-2 (for postcoital contraception)
1.5 mg	1	Levonell One Step
Norethisterone		
350 μg	28	Noriday Micronor
Ethynodiol diacetate		
500 μg	28	Femulen 28
Etonogestrel		
68 mg (every 3 years)	Injectable	Implanon Implant
Medroxyprogesterone		
150 mg (every 3 months)	Injectable	Depo-Provera
Norethisterone enantate	Injectable	Noristerat
(Lasts 8 weeks – given as short-term contraception, e.g. following vasectomy)		

normal ovulatory cycle. An intrauterine device is appropriate to use in women who experience dysmenorrhoea, as it reduces the incidence of painful menstruation. For women who use a progestin implant as a contraceptive device, removal within 3 years is essential because of the risk of a future ectopic pregnancy.

Women using progestin for hormone replacement and who experience bleeding should have their progestin dose increased. Women who are intolerant of menstruation during hormone replacement may benefit from having a continuous progestin dose rather than a sequential regimen. Alternatively, less frequent withdrawal bleeds can be achieved by using a progestin for 14 days every 3 months.

Oestrogen–progestin combinations

The most widespread use of oestrogens and progestins is as oral contraceptives. Oral contraceptives are the most effective form of contraception available, with low failure rates (around 1 per cent). Users must, however, weigh up the benefits against the risks involved. On the plus side, there have been significant reductions in the effective dose of the constituent hormones since the oral contraceptives first appeared, resulting in relatively mild acute side effects. In addition, the packaging and presentation make oral contraceptives easy and convenient to use. Despite these benefits, it is the long-term effects that cause the greatest community concern. An increased risk of thromboembolism, heart disease, cerebrovascular accident, atherosclerosis, liver disease, infertility and certain forms of cancer with long-term oral contraceptive use has been the established view. Recent research does not support this, but the risk of cardiovascular complications is certainly higher in women who smoke cigarettes.

The oral contraceptives may also be beneficial in the treatment of selected menstrual disorders characterised by irregular, painful and heavy periods, may offer protection against iron deficiency anaemia and ovarian and cervical cancer, and may be useful in the treatment of uterine fibroids and ovarian cysts.

MECHANISM OF ACTION

The mechanism of action of oestrogen–progestin combinations is to suppress the secretion of the pituitary gonadotrophic hormones follicle-stimulating hormone (FSH) and luteinising hormone (LH). As a consequence, fertilisation cannot occur, because ovulation is inhibited. Moreover, the steroid combination induces changes to the reproductive tract itself, which contributes to the prevention of pregnancy. The cervical mucus becomes more hostile to sperm penetration and the endometrial lining more resistant to implantation.

The physiological effects of the oral contraceptives are widespread and in many cases similar to those changes that occur in pregnancy. The size of the ovary decreases and it may become less responsive to gonadotrophic hormones. Effects that may result from the action of oestrogens include breast enlargement and tenderness; enhancement of blood clotting; increased heart rate, blood pressure, serum iron

levels and blood lipid levels; skin pigmentation; and impairment of liver function and bile flow.

◆ COMMON ADVERSE EFFECTS

The most common adverse effects are nausea and vomiting, which usually subside as use is continued. Less frequent side effects are those detailed in the sections on oestrogen-only preparations, including breast changes, weight gain, changes in blood pressure, headache, breakthrough bleeding and mid-cycle spotting, and an increased incidence of vaginal infections. As some of the synthetic progestins are derived from androgens, acne and hirsutism may occur.

Contraindications are as for oestrogen therapy: evidence of thromboembolism, vascular disease, cardiac or hepatic dysfunction and oestrogen-dependent tumours preclude the use of oral contraceptives.

✚ CLINICAL CONSIDERATIONS

There are a number of different oral contraceptives containing an oestrogen–progestin combination. All preparations provide 21 days' supply of hormones, and some include 7 days' worth of pharmacologically inert tablets, adding up to 28 days of treatment. Generally, they fall into three categories according to whether the dose of progestin or oestrogen is modified during the menstrual cycle. The first category comprises the monophasic preparations, where the dose of both hormones is fixed from day 1 to day 21. The second category is the biphasic preparations, where the 21 days are divided into two phases; the dose of oestrogen is constant for all 21 days, but the dose of progestin is increased from day 11 to day 21. The third category is the triphasic preparations, where the treatment period is divided into three phases; the dose of progestin is altered at least once, and sometimes twice, over the 21 days. The dose of oestrogen may also change once over the three phases, but it usually remains constant. The combined oral contraceptives currently on the market are listed in Table 58.5.

For effective contraception, it is important to take oral contraceptives as directed, with each dose interval no longer than 24 hours. If a dose is missed, it is important to take it as soon as possible. If two doses are missed, then they should both be taken as soon as the person remembers. In either situation, the next dose should be taken at its usual time. As a further precaution, an additional method of contraception should be used or abstinence practised until seven consecutive doses of hormone have been taken or, if there are fewer than seven doses left, until the pack is finished. If one or more doses of the pharmacologically inert tablets are missed, there is no impact on the effectiveness of the contraception as long as the hormone-containing tablets are started on time. Tables 58.6–58.8 provide information about what to do when a dose of an oral contraceptive is missed and the process involved in changing between the various types of contraceptive pills.

If the oestrogen–progestin preparation is for contraception, the patient should be shown which are the hormone tablets and which are the inactive sucrose tablets, and advised to start the active tablets on day 1 or 2 of menses for immediate effect. If certain symptoms occur, the patient is advised to stop taking the pill. These symptoms include severe or sudden pain in the chest, sudden blurred vision or loss of sight, and unexplained tenderness or pain in the leg. If the woman smokes while on the pill, she is advised to stop smoking or change the method of contraception. The combined use of smoking and oestrogen places the woman at greater risk of developing a blood clot. The pill does not protect against sexually transmitted diseases, and patients are advised to take precautions by using condoms.

The continuous use of oestrogen and progestin for hormone replacement is recommended for women who are more than 2–3 years postmenopause. Of these women, generally half will experience irregular bleeding in the first 6 months of treatment and most will be amenorrhoeic after 12 months.

Postcoital contraception

Hormonal contraception involves the use of levonorgestrel, a progestogen-only preparation. It is used as a means of postcoital or emergency contraception and is also known as the 'morning-after pill'. It is administered as a single dose of 1.5 mg as soon as possible after coitus, preferably within 12 hours, but it is 90 per cent effective up to 72 hours after intercourse. It may also be used 72–120 hours after unprotected intercourse (unlicensed use), but efficacy decreases with time. These drugs act to desynchronise the menstrual and ovarian cycles by inhibiting ovulation or preventing the fertilised egg from successfully implanting within the endometrium. Nausea and vomiting are often associated with this therapy, and the administration of an antiemetic may be necessary; **domperidone** is preferred. If vomiting occurs within 3 hours of administration, a replacement dose may be given.

Effectiveness of emergency contraception is reduced by enzyme-inducing drugs and a larger dose may be needed (see the *British National Formulary*, BNF). If the patient is taking antibiotics that are not enzyme inducers, then a larger dose is not needed.

Postmenopausal hormone replacement therapy

Oestrogen–progestin preparations are recommended as hormone replacement therapy (HRT) for menopausal and postmenopausal women with intact uterus. Short-term therapy has been found to relieve the physical discomfort that some menopausal women experience, such as hot flushes, sweating and atrophic vaginitis.

The use of longer-term combination HRT for postmenopausal women is controversial. The rationale for

TABLE 58.5 ORAL CONTRACEPTIVE PREPARATIONS

Oestrogen (dose)	Progestin (dose)	No. of tablets	Trade name(s)
Ethinyloestradiol–levonorgestrel			
Monophasic			
30 µg	150 µg	21	Microgynon 30 Trinordiol
		+7 inert	Microgynon 30 ED
Triphasic			
30 µg	50 µg	6	Logynon
40 µg	75 µg	5	
30 µg	125 µg	10	
		+7 inert	Logynon ED
Ethinyloestradiol–norethisterone			
Monophasic			
35 µg	500 µg	21	Norimin Brevinor
		21	Ovysmen
Biphasic			
35 µg	500 µg	7	BiNovum
35 µg	1000 µg	14	
Triphasic			
35 µg	500 µg	7	Synphase
35 µg	1000 µg	9	
35 µg	500 µg	5	
35 µg	500 µg	7	TriNovum
35 µg	750 µg	7	
35 µg	1000 µg	7	
Mestranol–norethisterone			
Monophasic			
50 µg	1000 µg	21	Norinyl-1
Ethinyloestradiol–desogestrel			
Monophasic			
20 µg	150 µg	21	Mercilon 21
30 µg	150 µg	21	Marvelon 21
30 µg	150 µg	21	Ovranette
Ethinyloestradiol–gestodene			
Monophasic			
20 µg	75 µg	21 +7 inert	Melodene 28
30 µg	75 µg	21	Femodene Minulet
		+7 inert	Femodene ED
Triphasic			
30 µg	50 µg	6	Trinordiol
40 µg	75 µg	5	
30 µg	125 µg	10	
Ethinyloestradiol–drospirenone			
Monophasic			
30 µg	3000 µg	21	Yasmin
Ethinyloestradiol–cyproterone acetate			
Monophasic			
35 µg	2000 µg	21	Dianette (licensed for severe acne)

TABLE 58.6 ADVICE ON MISSED DOSE OF AN OESTROGEN–PROGESTIN COMBINED ORAL CONTRACEPTIVE PILL

Up to 12 hours late	More than 12 hours late
• Take the pill as soon as you remember. No additional contraceptive precautions are required.	• Take the pill as soon as you remember. Take the next pill at the usual time. Continue with the daily administration of the pill but also take contraceptive precautions for 7 days. If the 7 days extend into the inactive pill or pill-free week, do not have a break from using pills. • If diarrhoea or vomiting occurs, this should be regarded as having missed a pill and contraceptive precautions should be taken for the next 7 days. • If the missed pill occurs during the 7 days following the inactive pill or pill-free week, and there has been unprotected intercourse, emergency contraception should be sought from the doctor.

TABLE 58.7 ADVICE ON MISSED DOSE OF A PROGESTIN-ONLY CONTRACEPTIVE PILL

More than 3 hours late
• Take the pill as soon as you remember. Continue with daily pill administration. Additional contraceptive precautions are required for the following 48 hours. • Note that if diarrhoea or vomiting occurs, this should be regarded as having missed a pill and contraceptive precautions should be taken for the next 48 hours. • If unprotected intercourse has occurred, this should be regarded as a missed pill and emergency contraception should be sought from the doctor.

TABLE 58.8 PROCESS FOR CHANGING CONTRACEPTIVE PILLS

Change	Requirement
From a combined oral contraceptive pill to a higher-dose or same-dose pill	Take as before, including the inactive pills
From a combined oral contraceptive pill to a lower-dose pill	Skip the inactive pills and start taking the active pills
From a progestin-only pill to a combined oral contraceptive pill	Start taking the active combined pill without a pill-free interval
From a combined oral contraceptive pill to a progestin-only pill, depot injection or progestin implant	Start the progestin-only pill or depot or insert the implant on the day immediately following the last active pill of the combined oral contraceptive pill
If emergency contraceptive pill is required (ethinyloestradiol–levonorgestrel or levonorgestrel)	Consider the emergency pill as one dose of oral contraception and continue with the pill pack

such therapy is that it offers protection against osteoporosis, cardiovascular disease and some cancers. An international clinical study (the Women's Health Initiative trial; see JE Rossouw *et al.* (2002) 'Risks and benefits of estrogen plus progestin in healthy postmenopausal women', *Journal of the American Medical Association*, 228, 321–33) investigating the health risks and benefits was abandoned, however, because it found that the risks outweighed the benefits. Although the study confirmed that HRT did protect against osteoporosis and colon cancer, it also revealed an increased relative risk of breast cancer and thromboembolic episodes. Rather than reducing the incidence of cardiovascular disease, the study showed a relative increase of heart attacks and strokes. The Commission on Human Medicines advises that for the treatment of menopausal symptoms, the benefits of short-term HRT outweigh the risks in most women, but in healthy women with no symptoms the risks outweigh the benefits. The minimum effective dose should be used for the shortest duration of time, and treatment should be reviewed at least annually. Alternative treatments should be considered for osteoporosis (see below and Chapter 57). HRT does not prevent coronary heart disease or protect against cognitive decline and should not be used for these purposes.

HRT may be used in women who have experienced surgical or early natural menopause (before the age of 45 years). It should be given until the age of about 50 years (approximate natural menopause). Oestrogen-only preparations can be used by women who have had a hysterectomy. (Oestrogen-only preparations stimulate endometrial proliferation in women with an intact uterus, which can lead to breakthrough bleeding and increase the risk of developing endometrial cancer.) Oestrogen-only therapy was not shown to increase the risk of breast cancer in the Women's Health Initiative trial, but this arm of the trial was also stopped early because of a slightly increased incidence of stroke in the women in the trial. Hormones do appear to protect women and to reduce the risk of cardiovascular disease perhaps through their action of lowering blood cholesterol levels, but this is an area that is still not understood fully.

For protection against osteoporosis, bisphosphonates are first-line therapy, and the selective oestrogen receptor modulator raloxifene or the steroid derivative tibolone may be more appropriate and a safer therapy (compared with HRT) for this condition, although the latter is also likely to carry some of the risks of HRT.

✚ CLINICAL CONSIDERATIONS

In combination HRT, the progestin must be given for at least 12 days of the 28-day cycle. Compliance with therapy can be enhanced by the use of combination packs of oestrogen and oestrogen–progestin tablets. Combination HRT therapy is also available as daily oestrogen and progestin tablets. This form of treatment almost completely inhibits endometrial proliferation, resulting in amenorrhoea.

The intravaginal route is recommended for topical oestrogen treatment of postmenopausal vaginitis. Oestrogen is absorbed well through the highly vascular vaginal mucosa, and systemic effects may be observed, however.

Androgens and anabolic agents

Anabolism is the formation of larger, more complex molecules from smaller simple molecules. In order for body structures such as bones, muscles and skin to grow, anabolic reactions must take place.

■ MECHANISM OF ACTION

Anabolic agents facilitate body growth. Endogenous androgens, such as testosterone, produce anabolic effects on muscles, bones and skin, but this is only part of their action. Androgens are necessary for the development of male secondary sexual characteristics: the growth and maintenance of the male genitalia, the process of spermatogenesis, the acquisition of a deeper voice, body hair growth and the inhibition of mammary gland growth. Androgens also affect brain function by influencing spatial perception, sex drive (libido) and levels of aggression.

Having noted the major functions of testosterone, it is interesting to remember that the female human is not free of testosterone. The human adrenal gland and ovaries produce testosterone. The role of testosterone in women has not yet been elucidated fully; however, we do know that testosterone is necessary for libido and the appearance of pubic and axillary hair in women.

All anabolic agents are androgens. The relative androgenic : anabolic activity of testosterone is equivalent (1 : 1). The synthetic anabolic agents have been modified, however, to produce relatively strong anabolic but weak androgenic effects. As androgenic activity is always present, these agents are referred to more correctly as anabolic-androgenic steroids (AASs). **Nandrolone** is the most potent, with anabolic activity between four and six times greater than that of its androgenic activity. Nandrolone is used in the UK for the treatment of some apalstic anaemias. AASs are useful in promoting growth and enhancing healing after surgery, trauma and long periods of immobilisation when used in conjunction with appropriate dietary measures and exercise. They are not used clinically for this in the UK, but these effects have led to abuse by athletes to gain a competitive edge in performance by using higher than normal doses. It is argued by some people that these drugs produce enough gain in strength and aggression to enhance sporting performance at the national and international level. This is yet to be supported convincingly by drug studies in the area, and their use as body-building drugs is quite unjustified. More worrying is that AASs are also being abused by adolescent males to improve self-esteem

and confidence (see Chapter 24 for a full discussion of their abuse).

◆ COMMON ADVERSE EFFECTS

Adverse effects associated with the use of these drugs other than masculinising effects on women (hirsutism, deepening of the voice, clitoral enlargement, acne, menstrual irregularities) include sodium and water retention (which may lead to increased blood pressure and oedema), excessive sexual stimulation, increased aggressiveness, premature closure of the epiphyseal plate in prepubertal boys, prostatic hyperplasia in older men, baldness and jaundice. Prolonged or high-dose usage can damage the liver and may increase the risk of liver cancer.

In males, through negative feedback on the hypothalamic-pituitary axis, these agents inhibit LH secretion. This may result in testicular atrophy and subsequently induce infertility. Used in high doses, AASs lead to higher circulating levels of oestrogens in males. This can lead to feminisation, characterised by gynaecomastia. After prolonged use of these agents in women, the masculinising effects may not be reversible.

This treatment is contraindicated in pregnancy and in patients with prostate cancer.

✚ CLINICAL CONSIDERATIONS

Androgens are used as replacement therapy in conditions where endogenous androgen levels are inadequate, such as hypopituitarism and hypogonadism. This treatment promotes and maintains the male secondary sex characteristics. Testosterone may also be combined with oestrogen therapy for young women after surgical menopause, where there is a persistent lack of libido. In such instances, a dose of testosterone is selected that will not produce masculinising effects.

Androgens and AASs have been used in conjunction with oestrogens in the treatment of osteoporosis (this is no longer advocated), to stimulate growth in prepubertal children and in some forms of anaemia. The masculinising effects of anabolic agents on females, however, prohibit prolonged or high-dose therapy. These drugs are also used in the treatment of some tissue-specific neoplasms (see Chapter 76).

Androgens and anabolic steroids should be used cautiously in patients with diabetes, cardiac, renal or hepatic disease, epilepsy, migraine and other conditions that are aggravated by fluid retention. In children, wrist X-rays need to be undertaken to determine the level of bone maturation; periodic X-rays then need to be taken to monitor the extent of maturation.

Watch for signs of virilisation, which could be irreversible despite prompt discontinuation of therapy. When these preparations are used to promote erythropoiesis in refractory anaemia, ensure the patient has an adequate iron intake. Instruct males to report priapism, reduced ejaculatory volume and gynaecomastia. All patients should take their weight regularly and report any large gains, which could be indicative of fluid retention.

Sex hormone antagonists

INHIBITORS OF OESTROGEN SYNTHESIS

Danazol and **gestrinone** are synthetic hormones used in the treatment of endometriosis. Danazol is also used in the therapy of menorrhagia and refractory mastalgia.

■ MECHANISM OF ACTION

Danazol and gestrinone act on the hypothalamic-pituitary-gonadal axis to suppress LH and FSH secretion (see Figure 58.2). As a consequence, ovarian function is suppressed and gonadal hormone secretion is reduced. Endometrial proliferation, which underlies endometriosis, is inhibited and menstrual bleeding is thus reduced because the shed layer is not as thick. Danazol has no oestrogenic activity and gestrinone has some antioestrogenic activity.

◆ COMMON ADVERSE EFFECTS

The adverse effects are those associated with low levels of oestrogen, including hot flushes, skin reactions and dizziness. Danazol and gestrinone have some weak androgenic and progestin activity. Therefore, the side effects often observed include fluid and sodium retention, weight gain, hirsutism, acne and deepening of the voice.

✚ CLINICAL CONSIDERATIONS

Patients taking these drugs need to be advised to use non-hormonal forms of contraception during treatment. As these drugs induce weight gain, it may be helpful for the patient to keep a food history. An appropriate exercise programme should offset weight gain. Provide advice to the patient regarding methods to remove unwanted hair and skin care for acne prevention.

ANTIOESTROGENS

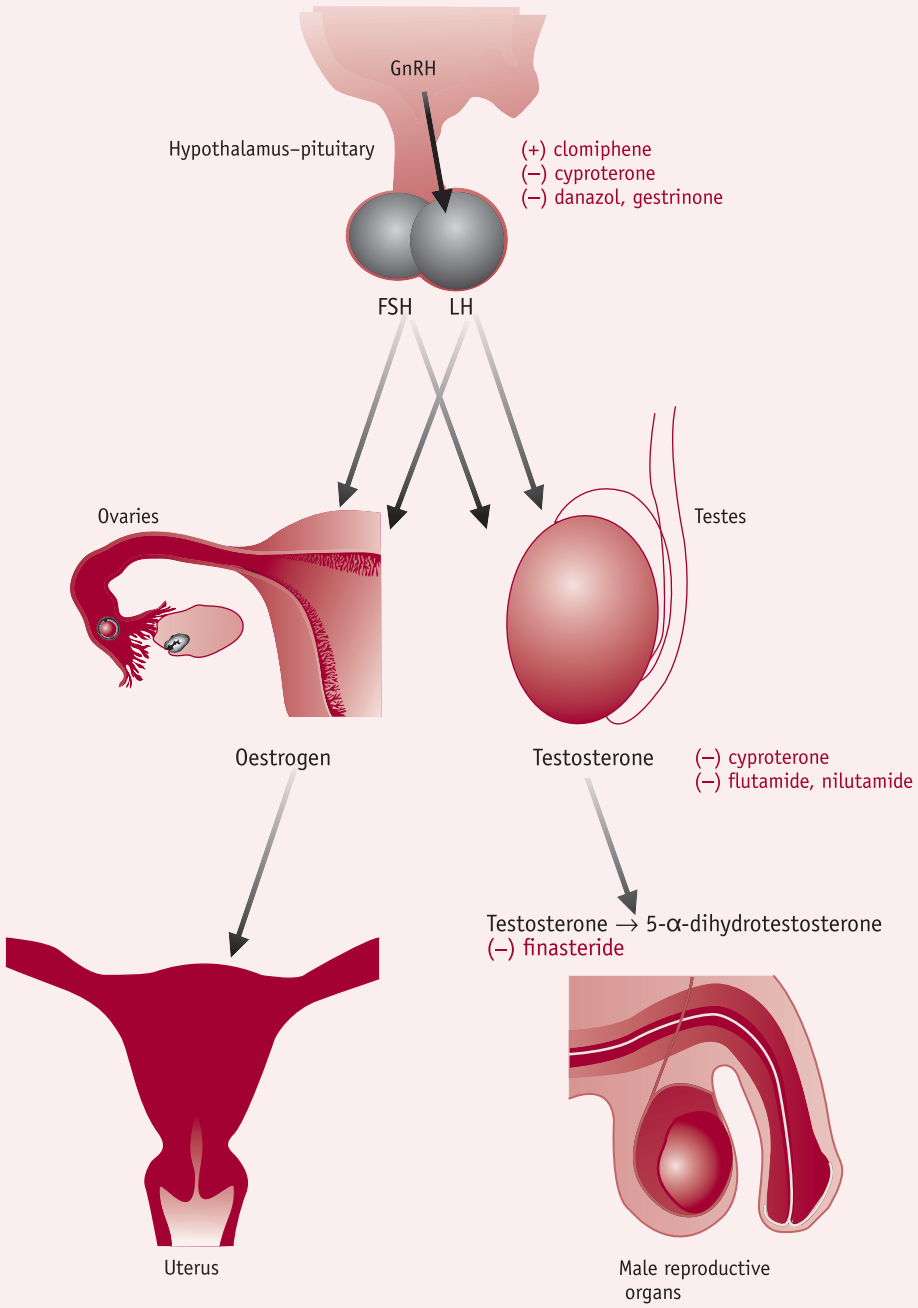
Clomifene (clomiphene) is an antioestrogenic agent used as an ovulatory stimulant (see Chapter 56).

■ MECHANISM OF ACTION

Clomifene is a weak partial oestrogen agonist. In binding to oestrogen receptors, it prevents access of endogenous oestrogen to its receptors. As a consequence, the action of endogenous oestrogen is diminished. Clomifene is relatively selective for oestrogen receptors in the anterior pituitary and its binding inhibits the negative feedback influence of oestrogens on gonadotrophin secretion. LH and FSH secretion is increased, resulting in follicular development and increased oestrogen secretion in the ovaries (see Figure 58.2). Here lies an interesting paradox: the antioestrogen produces marked rises in plasma oestrogen levels.

FIGURE 58.2 SITES OF ACTION OF SEX HORMONE ANTAGONISTS

Sex hormone antagonists can act at the hypothalamic-pituitary level or at the level of the reproductive organs. (+) = stimulatory effect, (–) = inhibitory effect.



FSH, follicle-stimulating hormone; GnRH, gonadotrophin-releasing hormone; LH, luteinising hormone.

◆ COMMON ADVERSE EFFECTS

Common adverse effects associated with this treatment include ovarian enlargement, hot flushes, abdominal bloating, distension and pain, nausea and vomiting, visual disturbances and breast soreness.

✚ CLINICAL CONSIDERATIONS

Before starting treatment with clomifene, liver function is checked. If visual blurring occurs, treatment is stopped. Ovarian hyperstimulation may occur in women with polycystic ovary disease, particularly if pregnancy takes place

during the cycle when clomifene was given. Pregnancy rates are very poor in severe polycystic ovary disease.

ANTIANDROGENS

Cyproterone, **flutamide** and **nilutamide** are androgen receptor antagonists, while **finasteride** and **dutasteride** inhibit the synthesis of an important metabolite of testosterone with androgenic activity. These agents are used to treat conditions characterised by excessive androgen action or androgen-dependent cancers, such as prostate cancer.

■ MECHANISM OF ACTION

Cyproterone acetate is an androgen antagonist at its target tissues. It also has some progesterone activity that leads to the suppression of LH and FSH through negative feedback to the pituitary.

Finasteride and dutasteride are enzyme inhibitors and block the conversion of testosterone into the potent metabolite 5-α-dihydrotestosterone (see Figure 58.2). The development of prostatic hypertrophy is linked strongly to the action of 5-α-dihydrotestosterone. Finasteride is also proving useful as a treatment for male-pattern baldness.

Flutamide is purely an androgen receptor antagonist (see Figure 58.2) and has no effects at oestrogen, progesterone or corticoid receptors. Flutamide is selective for androgen receptors on the male accessory structures such as the prostate, and so it does not inhibit spermatogenesis or sex drive.

◆ COMMON ADVERSE EFFECTS

Common adverse effects of cyproterone in men include decreased spermatogenesis and gynaecomastia; in women, effects include impaired ovulation. The adverse reactions of finasteride include impotence, decreased libido and impaired ejaculation.

Flutamide tends to induce gastrointestinal disturbances, gynaecomastia, breast tenderness and galactorrhoea. Nausea, dizziness and impaired adaptation to changes in light intensity are apparent as the treatment starts but wane as therapy continues.

✚ CLINICAL CONSIDERATIONS

The main uses of cyproterone are to treat the masculinisation of women, characterised by acne, hirsutism and alopecia, and as a form of chemical castration to control excessive or deviant sexual behaviour in men. Cyproterone acetate has applications in the treatment of precocious puberty in boys and in prostatic cancer (see Chapter 76). Cyproterone acetate is also available in combination with ethinyloestradiol. The combined action of oestrogen and progesterone inhibits ovulation and is used as an oral contraceptive (see Table 58.5).

Finasteride has been shown to reduce the size of the prostate and is indicated in benign hypertrophy. The androgen antagonist flutamide is also used to treat advanced cases of prostate cancer.

When using sex hormone antagonists, it is important to monitor liver enzymes at baseline and then every 6 months. Although liver failure occurs rarely with these agents, the patient should be advised to see their doctor immediately if they develop yellowing of the skin or eyes, dark urine or itching. Due to the risk of hepatotoxicity, cyproterone use in prostate cancer is restricted to short courses unless the patient is not responsive to other treatments.

CLINICAL MANAGEMENT

Drugs affecting the adrenal cortex

Assessment

- Obtain a history of peptic ulcer, glaucoma, cataracts, psychiatric disorders, hepatic disease, renal disease and diabetes. Caution should be used when administering corticosteroids in patients with these conditions, as the condition may worsen. Corticosteroids should not be used in patients who have systemic fungal infection or who are on immunosuppressant therapy.
- Obtain baseline vital signs and compare with subsequent observations.

Planning

- The patient's inflammatory condition will be alleviated.

Implementation

- Monitor vital signs during treatment. These drugs may cause infection, which may manifest as changes in the vital signs. Changes can include a fast, thready pulse, increased respiration and decreased blood pressure.
- Monitor for manifestations of oedema during therapy. Auscultate lung sounds for crackles. Other manifestations of oedema include moonface, puffy

eyelids and dependent oedema of the arms, legs and sacral area.
- Monitor for manifestations of depression, such as lack of interest in personal appearance, withdrawal from activities, insomnia and lack of appetite. Depression may arise from the condition being treated or from the use of drugs affecting the adrenal cortex.
- Perform a full blood examination, and monitor haemoglobin, serum electrolyte and blood glucose levels.
- Monitor the body and skin carefully, noting colour and character of the skin, distribution of fat and muscle, presence of bruises, rashes, purpura and petechiae, and the condition of the hair and nails.
- Monitor for manifestations of infection, which may occur with drugs that affect the adrenal cortex.
- Monitor carefully for adverse effects from corticosteroids when therapy has lasted for more than 10 days and with high doses. These drugs should be weaned slowly and not stopped abruptly; adrenal crisis may result otherwise.
- Monitor for changes in muscle strength. These drugs may cause muscle wasting.
- Wear gloves to apply topical preparations to patients to prevent absorption through your skin.
- Apply topical preparations thinly in order to reduce effects from systemic absorption.
- Use care when moving and positioning immobilised patients in order to prevent fractures and bruising. Maintain pressure area care. Pad the cot sides if present.
- An increase in glucocorticoid therapy is required during illness and times of stress, such as during surgery and with infection.

Patient teaching

- Advise the patient to take the drug as ordered. The drug should not be stopped abruptly. Instead, the doctor will organise the dose to be reduced over 1–2 weeks.
- Advise the patient to eat foods high in potassium, including fresh and dried fruits, vegetables and nuts.
- Advise the patient not to have any immunisations while taking the drugs, unless these have been approved by the doctor.
- Advise the patient to take oral drugs with food to prevent gastric irritation. Antacids and other anti-ulcer drugs may be prescribed to lessen the risk of ulceration.
- If weight gain is an issue following commencement of therapy, a change in the dose or drug may be warranted. A low-sodium and high-potassium diet may also help.
- Large doses of these drugs may increase the patient's susceptibility to infection. Warn the patient about this possibility. Instruct the patient to notify the doctor of fever, cough, sore throat and injuries that do not heal.
- Tell the patient to avoid contact with people with active respiratory infections as these drugs suppress the immune system.
- Advise the patient to inform other health-care professionals that they are taking these drugs, especially before surgery.
- Teach the patient to recognise adverse effects of these drugs, which may include moonface, puffy eyelids, dependent oedema, increased bruising, dizziness, bleeding and menstrual irregularity.
- Inform female patients that menstrual irregularities may occur with long-term therapy; advise these patients to document their menstrual history.
- Warn patients with diabetes to monitor blood glucose levels carefully.
- The doctor should be notified if the patient notices the faeces are tarry or if coffee-ground emesis occurs.
- Advise the patient to avoid activities that may cause bruising.

Evaluation

- Evaluate the effectiveness of drug therapy as demonstrated by a decrease in inflammation.
- Evaluate the incidence of adverse effects, especially when the patient receives high doses of the drug over a long period.

Drugs affecting the gonads

Assessment

- Assess the patient's vital signs, weight, haemoglobin, haematocrit, full blood examination and serum electrolyte levels. Compare with subsequent observations.
- For female patients, obtain a history of weight, description of menstrual cycle, assessment of breasts, previous contraceptive measures taken and previous pregnancies.

- In male patients receiving androgen therapy for reduced androgen production, obtain a history of the secondary sexual characteristics. If the androgen therapy is for its anabolic effects, determine the patient's nutritional needs, level of mobility and food and fluid intake.
- For patients taking drugs for premenstrual tension, obtain a history of manifestations, such as weight gain, headache and increased appetite.
- For patients taking drugs for endometriosis, obtain a menstrual history and characteristics of pain. Check the patient's plans for pregnancy and identify the patient's pregnancy status.
- For patients taking drugs for menopause, assess the family history for osteoporosis, the patient's menstrual history and the patient's current experience with the climacteric. Determine the patient's feelings about menopause.
- Assess the patient on oestrogens for a history of cerebrovascular disease, coronary artery disease, asthma, diabetes, hypertension, and thyroid and liver disease. Caution should be exercised in the presence of any of these conditions.
- Assess patients on progestins for a history of diabetes, epilepsy, varicose veins, hypertension, asthma, obesity, depression, migraine, and cardiac and renal disease. Note also whether the female patient is over the age of 35 years and smokes or over the age of 44 years and does not smoke. Caution should be exercised in the presence of these conditions.
- Note that the use of oestrogens is contraindicated in children who have not completed their bone growth, in pregnancy, in thromboembolic disease, in breast cancer and in undiagnosed vaginal bleeding.
- Note that the use of progestins is contraindicated in undiagnosed vaginal bleeding, thromboembolic disease, breast cancer and pregnancy.
- Note that the use of androgens is contraindicated in breast and prostatic cancer, pregnancy, hepatic and cardiac disease, myocardial infarction, coronary artery disease, infants and children.

Planning

- Planning depends on the reason for administration. It is anticipated that the patient will obtain some alleviation or relief of the condition requiring treatment, e.g. endometriosis, menopausal symptoms, carcinoma of the breast, erectile dysfunction, osteoporosis, delayed puberty, male climacteric, or lack of anabolic development.

Implementation

- Monitor the patient's vital signs, weight, haemoglobin, haematocrit, full blood examination and serum electrolyte levels.
- For female patients, monitor body weight and the menstrual cycle.
- For patients taking drugs for premenstrual tension, monitor the incidence of manifestations such as weight gain, headache and increased appetite during therapy.
- For patients taking drugs for endometriosis, monitor the characteristics of menstrual pain during therapy.
- For patients taking drugs for menopause, monitor for the manifestations normally associated with menopause, such as hot flushes.
- For patients taking an oestrogen preparation for long-term hormone replacement therapy (HRT), a progestogen should be added to prevent endometrial hyperplasia and endometrial carcinoma. This practice is not necessary for women who have had a hysterectomy.
- For patients on oestrogens, monitor for leg pain, changes in vision or speech, sudden onset of chest pain, shortness of breath, numbness of leg or arm, and dizziness, as these are manifestations of pulmonary embolus and other thromboembolic conditions.
- For patients on sex hormone antagonists, monitor for hirsutism, weight gain, oedema in dependent areas and development of acne.
- For patients on androgens or anabolic agents, and with osteoporosis or tissue wasting, determine the nutritional intake. Ensure adequate intake of protein, vitamins, minerals and energy.
- In male patients receiving androgen therapy for its anabolic effects, monitor nutritional intake and level of mobility.
- For patients on androgens or anabolic agents, restrict sodium if oedema develops. Record body weight at the same time daily.
- For patients on androgens or anabolic agents, ensure that they consume adequate fluids to prevent kidney stones: 3–4 l of fluid a day is necessary to prevent kidney stones as a result of hypercalcaemia. Patients confined to bed require a range of motion exercises; ambulatory patients need to perform weight-bearing exercises.
- Patients on androgens or anabolic agents for tissue wasting should reduce stressors and have plenty of rest, as stress hormones are catabolic.

Patient teaching

Oestrogens and progestin therapy for menopausal manifestations

- Ensure that the patient has had a thorough breast examination, pelvic examination and Pap smear test before starting therapy.
- Advise the patient that warm weather and stress can exacerbate the vasodilation that produces hot flushes.
- Advise the patient on methods to cope with vasodilation, including using a fan, wearing cotton clothes, cutting caffeine intake, drinking cool fluids and avoiding spicy foods. A vitamin E supplement may help, although this should not be taken by patients with hypertension or rheumatic heart disease.
- Teach the patient how to perform a breast self-examination, and stress the need to do it regularly.
- Encourage the patient to visit the doctor or community health centre every 6–12 months. She should expect a blood pressure check and breast and pelvic examinations to be performed.
- Suggest that the patient wears cotton underwear and pantyhose with a cotton gusset, and to avoid douching and feminine deodorant spray products. The use of yoghurt containing *Acidophilus* bacteria in the vagina can maintain the natural flora of the environment.
- Advise the patient to use a water-soluble vaginal lubricant to prevent painful intercourse.
- Suggest that the patient reduces the use of antihistamines and decongestants if she is experiencing vaginal dryness.
- Suggest to the patient that she carry sanitary pads or tampons with her in case of breakthrough bleeding.
- Advise the patient to report any heavy bleeding to the doctor and to have her haemoglobin and haematocrit checked. The patient should also report bleeding that occurs between menstrual periods, or a return of bleeding after cessation of menstruation.
- Instruct the patient to stop treatment and contact her doctor if she experiences headaches, visual problems, chest pain, heaviness in her legs and breast lumps.
- Advise the patient to undertake consistent exercise, to eat a well-balanced diet with calcium-rich foods, and to avoid alcohol and smoking.
- Advise the patient that patch formulations should be applied to clean, dry, intact skin. The upper buttock is the preferred site; alternative sites should then be used for subsequent applications in order to prevent skin irritation.
- Instruct the perimenopausal patient that progestogen treatment may result in heavy menses initially.

Oral contraceptives

- Counsel the patient not to smoke due to the increased cardiovascular risk.
- Advise the patient to use a barrier method of contraception for the first 2 weeks of therapy or if a tablet has been missed.
- Instruct the patient to take the tablet at the same time each day in order to develop a routine and prevent forgetfulness.
- For patients who experience amenorrhoea after stopping the pill, explain that the majority of women will have regular periods within 12–18 months.
- Advise the patient to weigh herself at home and to report any weight gain or oedema.
- Inform the patient that this contraceptive method does not work as a barrier to sexually transmitted disease.
- Patients who are breast feeding should take progestin-only therapy, as oestrogens can adversely affect the infant.
- Advise patients on a progestin-only preparation that the tablet must be taken within 3 hours of the same time each day, otherwise the tablet is considered as a missed dose.
- Check to see whether the patient wears contact lenses, and advise on ways to cope with dry eyes from decreased tearing.
- Instruct the patient to report any breakthrough bleeding and spotting as the dose or type of oral contraceptive may need to be changed.
- Inform the patient that menstrual flow may be less in amount and duration, as oral contraceptives cause thinning of the endometrium.
- Advise the patient to always inform her doctor that she is taking an oral contraceptive because of the possibility of drug interactions with other therapies.

Androgens and anabolic agents

- Oral androgens should be taken with meals to reduce gastric upsets.
- Patients need to be advised on skin hygiene measures to reduce the severity of acne.
- Patients on androgens should report priapism (painful, prolonged erection), as the dose then needs to be reduced. Patients should also report decreased flow of urine, as androgens can cause prostatic hypertrophy.
- Wrist X-rays should be taken of children to determine the extent of their bone maturation.

Sex hormone antagonists

- Inform the male patient on flutamide that gynaecomastia may occur. Provide reassurance and support. A change in therapy may be required.
- Advise the male patient on finasteride that decreased libido and impaired ejaculation may occur. As this is a very sensitive issue, male patients may feel reluctant to speak about their symptoms. Reassurance and emotional support are important.
- Advise the male patient on flutamide that it may cause gynaecomastia, breast tenderness and galactorrhoea, which could be embarrassing.

Evaluation

- Evaluate the patient's compliance with therapy.
- Determine the effectiveness of therapy for a specific condition. This condition may be for the purpose of contraception, the alleviation of the manifestations of endometriosis, menopause, menorrhagia, or the promotion of body growth.

SUMMARY

- Corticosteroids are used widely as anti-inflammatory agents and immunosuppressants. They can also be used in the management of hypovolaemic shock.
- Systemic use of corticosteroids can lead to a range of serious adverse effects affecting fluid and electrolyte balance, immunity, metabolism and the integrity of skin and bones.
- For systemic use of corticosteroids, it is advisable to measure the blood glucose levels, weight, blood pressure and electrolyte levels before treatment and then weekly during the first month of treatment.
- Review the patient regularly for signs of infection.
- The adrenal cortex antagonists spironolactone and metyrapone can be used in the management of cardiovascular disease, oedema and hyperadrenal states.
- Oestrogens are used as replacement therapy in deficient states and as contraceptives.
- Oestrogen preparations are available as natural and synthetic forms. The synthetic forms are more potent but can adversely affect liver function.
- Oestrogenic drugs with mixed activity may be useful as ovulatory stimulants to prevent osteoporosis and treat breast cancer.
- If long-term oestrogen replacement therapy is required, a progestogen is included to prevent endometrial hyperplasia and carcinoma.
- Progestins (or progestogens) are useful as contraceptives and to treat endometriosis and hirsutism in women.
- For effective contraception using progestin-only preparations, compliance with dosage and time of administration is necessary.
- Oestrogen–progestin combinations are used as oral contraceptives and in postmenopausal hormone replacement therapy.
- Oestrogen–progestin contraceptives suppress gonadotrophin secretion, which results in inhibition of ovulation. They also make the endometrium more resistant to implantation and the cervical mucus more hostile to sperm.
- The contraceptive pill does not protect against sexually transmitted diseases, and patients are advised to use condoms.
- The use of oestrogen–progestin combinations for postmenopausal women is controversial. There are benefits in protection against osteoporosis and colon cancer, but there is an increased relative risk for cardiovascular disease, breast cancer and thromboembolism.
- Androgens are used as replacement therapy in deficient states and to treat poor sex drive in young women. Anabolic steroids stimulate the growth of muscle, bone and red blood cell production. All anabolic steroids retain some androgenic activity.

1. List ten specific conditions in which the glucocorticoids are indicated.
2. Name ten adverse effects associated with corticosteroid therapy and link each one to the physiological effects of this group.
3. How can the serious adverse effects of corticosteroid therapy be avoided?
4. Indicate the therapeutic uses of the following gonadal hormones:
   (a) oestrogens;
   (b) androgens;
   (c) progestins;
   (d) oestrogen–progestin combinations.
5. State the common adverse effects associated with administration of the following gonadal hormones:
   (a) androgens;
   (b) progestins;
   (c) oestrogens.
6. Carmella Fernandez, a 35-year-old patient with inflammatory bowel disease, commences prednisolone to alleviate some of the manifestations of her condition. What patient education would you offer Ms Fernandez?
7. What precautions would you take when applying a corticosteroid cream to frail skin?
8. Helen Van Der Graaf, a 25-year-old secretary, rings the family-planning clinic in a distressed state. She forgot to take her oral contraceptive tablet this morning and it is now mid-afternoon. What further information would you solicit from Ms Van Der Graaf? What would you advise her to do?
9. Why would you advise a patient not to smoke while taking the oral contraceptive pill?
10. Brenda Locoid, 20 years old, visits the family-planning centre in which you are working. She is seeking advice about changing from an oestrogen–progestin contraceptive to a progestin-only contraceptive. What can you tell her about the advantages and disadvantages associated with such a change?
11. Julie Smith, an 18-year-old student, visits the community health centre requesting a script for oral contraception. What assessment would you perform on Ms Smith? Provide rationales for your answer.
12. Joseph Binks is 72 years old and is about to commence flutamide therapy for his prostate cancer. What are the potential adverse reactions to this therapy? What patient education and support would you offer Joseph to prepare him for these effects?

58 DRUG SUMMARY TABLE: THE ADRENAL CORTEX AND THE GONADS

FAMILY NAME	GENERIC NAME	TRADE NAME(S)
Oral and parenteral corticosteroids	Betamethasone	Betnesol
		Betnelan
	Budesonide	Entocort
	Cortisone	
	Dexamethasone	
	Fludrocortisone	Florinef
	Hydrocortisone	Efcortesol
		Solu-Cortef
	Methylprednisolone	Depo-Medrone
		Medrone
		Solu-Medrone
	Prednisolone	Deltastab
		Delacortril Enteric
	Triamcinolone	Adcortyl
		Kenalog
Topical corticosteroids	Alcometasone	Modrasone
	Beclometasone	Beclazone
		Beconase
		Nasobec
		Qvar
	Betamethasone	Betacap
		Betnelan
		Betnesol
		Betnovate preparations
		Bettamouse
		Diprosone
		Vista-Methasone
	Budesonide	Budenofalk
		Entocort
		Pulmicort
		Rhinocort
	Clobetasone	Eumovate
	Desonide	
	Dexamethasone	Maxidex
	Diflucortolone	Nerisone
	Fluclorolone	
	Fludrocortisone	Florinef
	Fluorometholone	FML Liquifilm
	Fluticasone	Flixonase
		Flixotide
		Nasofan
	Hydrocortisone	Colifoam Rectal
		Dioderm
		Efcortelan
		Locoid

FAMILY NAME	GENERIC NAME	TRADE NAME(S)
		Mildison lipocream
		Solu-cortef
	Methylprednisolone	
	Mometasone	Asmanex
		Elocon
		Nasonex
	Prednisolone	Deltacortril
		Deltastab
		Pred Forte
		Predsol preparations
		Predfoam
	Triamcinolone	Adcortyl in orabase
		Kenalog in orabase
		Nasacort
Topical corticosteroids with other agents	Betamethasone	
	+ Clioquinol	Betnovate-C
	+ Clotrimazole	Lotriderm
	+ Fusidic acid	FuciBET
	+ Neomycin	Betnesol-N
	+ Salicylic acid	Diprosalic
	Budesonide	
	+ Eformoterol	Symbicort
	Dexamethasone	
	+ Framycetin, gramicidin	Sofradex
	+ Neomycin, polymyxin B	Maxitrol
	+ Tobramycin	Tobradex
	Flumetasone + clioquinol	Locorten-Vioform
	Fluocortolone	
	+ Cinchocaine	Ultraproct
	+ Chlorquinaldol	Locoid C
	+ Cinchocaine	Proctosedyl
	+ Ciprofloxacin	
	+ Clioquinol	
	+ Colistin, neomycin	
	+ Lignocaine	Germoloids HC
	+ Miconazole	Daktacort
	+ Natamycin, neomycin	
	+ Cinchocaine, clemizole	Scheriproct
Adrenocorticoid antagonists	Metyrapone	Metopirone
	Spironolactone	Aldactone
Oestrogens	Ethinyloestradiol	
	Oestradiol	Angeliq
		Estracombi
		Evorel Conti
		Femapak
		Femoston-conti
		Kliovance
		Novofem

FAMILY NAME	GENERIC NAME	TRADE NAME(S)
		Nuvelle
		Tridestra
		Trisequens
	Oestradiol valerate	Cyclo-Progynova
	Oestriol	Hormonin
Selective oestrogen receptor modulators	Raloxifene	Evista
	Tamoxifen	Nolvadex
		Soltamox
	Toremifene	Fareston
Oestrogenic agent with mixed activity	Tibolone	Livial
Progestins (progestogens)	Dydrogesterone	Duphaston
	Ethynodiol	Femulen
	Etonogestrel	Implanon implant
	L-Norgestrel	Levonelle
		Microlut
		Mirena
		Norgestron
		Postinor-2
	Medroxyprogesterone	Depo-Provera
		Farlutal
		Provera
	Megestrol acetate	Megace
	Norethisterone	Micronor
		Noriday
		Noristerat
		Primolut N
		Utovlan
	Progesterone	Crinone
		Cyclogest
		Gestone
Androgens/anabolic agents	Mesterolone	Pro-Viron
	Nandrolone decanoate	Deca-Durabolin
	Testosterone	Andropatch
		Nebido
		Restandol
		Striant SR
		Testosterone enantate
		Testim
		Testogel
		Virormone
	Testosterone esters (mixed)	Sustanon
Mixed hormone preparations	Oestrogens, medroxyprogesterone	Menoprem
	Oestradiol, norethisterone	Estracombi
		Estrapak
		Kliovance
		Trisequens
	Oestradiol, dydrogesterone	Femoston
	Oestradiol, cyproterone acetate	

FAMILY NAME	GENERIC NAME	TRADE NAME(S)
Sex hormone antagonists	Clomiphene	Clomid
	Cyproterone	Androcur
		Cyprostat
	Danazol	Danol
	Finasteride	Propecia
		Proscar
	Flutamide	Drogrenil
	Gestrinone	Dimetriose

HYPERURICAEMIA AND GOUT

59

CHAPTER FIFTY-NINE

OBJECTIVES

After completing this chapter, the reader should be able to:

- **define hyperuricaemia and describe its consequences;**
- **outline the major characteristics of gout;**
- **state the major pathophysiological steps involved in gouty arthritis;**
- **name the types of drug used in the treatment of hyperuricaemia and gout;**
- **compare the similarities and differences in the actions of the non-steroidal anti-inflammatory drugs and colchicine;**
- **define a uricosuric agent and briefly outline its action;**
- **define a uricolytic agent and briefly outline its action;**
- **state the action of allopurinol and its application to the treatment of hyperuricaemia and gout;**
- **state the types of adverse effect commonly expected when anti-inflammatory drugs, uricosuric agents and allopurinol are used.**

KEY TERMS

Hyperuricaemia
Gouty arthritis
Inflammation
Purines
Uric acid
Xanthine oxidase

HYPERURICAEMIA IS A METABOLIC CONDITION CHARACTERISED BY ELEVATED serum levels of uric acid. Uric acid is a product of the metabolism of the purines adenine and guanine, which are essential components of nucleic acids and the energy-storage molecules adenosine triphosphate (ATP) and guanosine triphosphate (GTP). Any processes involving cell destruction (e.g. cancer chemotherapy) or the rapid turnover of cells (e.g. in cancers such as leukaemia and lymphoma) can lead to increased purine turnover and, eventually, hyperuricaemia. Serum uric acid levels are controlled by the kidneys. The glomeruli filter uric acid. It is completely resorbed into the blood and then secreted into the urine. Illnesses such as renal failure can also lead to hyperuricaemia.

Uric acid is not particularly water-soluble in the kidney filtrate or blood. Being a weak acid, it is more soluble at an alkaline pH. It tends to crystallise in acidic environments and at temperatures lower than 37 °C. It therefore readily precipitates as urate (a salt of uric acid) crystals in the joints of the periphery, especially the toes and ankles, which are often cooler than other areas of the body, and within the rather acidic environment of the kidney filtrate. These uric acid crystals are known as tophi (singular: tophus). The formation of tophi can result in gouty arthritis and kidney-stone formation. Although hyperuricaemia is usually associated with gout, it can also exist as a long-term asymptomatic condition in some individuals without producing deleterious effects.

Gout is a genetic disorder often associated with a diet rich in purines and with alcohol consumption. The prevalence of gout in the UK is reported to be around 14 per 1000, and the male/female ration is 3.6 to 1. The prevalence in men over the age of 65 years is approaching 7 per cent. The ingestion of large amounts of alcohol (elevating blood lactate levels) can lead to metabolic acidosis; the lactic acid competes with the uric acid for secretion into the kidney filtrate. Patients with gout are advised to avoid purine-rich foods and alcohol because such a diet can precipitate an attack of gouty arthritis. Examples of foods with a high purine content include offal, sardines and anchovies; foods with moderately high levels of purines that should be limited include meat, seafood, lentils, spinach and peas.

Episodes of gouty arthritis occur when the tophi enter the joint cavity. Initially, the crystals are taken up by the synovial membrane cells, which then release inflammatory mediators, such as prostaglandins and cytokines (see Chapter 75), and lysosomal enzymes. The release of these mediators triggers a typical inflammatory response: vasodilation, increased capillary permeability, phagocytosis (by neutrophils and macrophages) and the secretion of more inflammatory mediators. These events account for the swelling, redness, warmth and pain associated with acute inflammation. The activation of phagocytes can actually exacerbate the situation. When activated, the macrophages secrete acids, which lower the pH of the environment, leading to a vicious cycle of further precipitation of the relatively insoluble uric acid (i.e. more tophi) and additional inflammation. In time, episodes of gouty arthritis lead to cartilage and bone destruction.

In addition to dietary measures, treatment of hyperuricaemia and gout involves drugs. Two approaches are used, often concurrently. First, the acute gouty arthritis is controlled by administration of anti-inflammatory agents, such as **colchicine** and the non-steroidal anti-inflammatory drugs (NSAIDs). It is important to distinguish drugs used in the treatment of acute attacks from those used in long-term control. The latter may actually exacerbate and prolong the acute symptoms if they are started during an attack. The long-term approach is more preventive and involves reducing blood uric acid levels by either promoting the excretion of uric acid through the kidneys or preventing the catabolic conversion of purine metabolites into uric acid. Acute hyperuricaemia induced by cancer chemotherapy can be treated using a uricolytic agent.

ANTI-INFLAMMATORY AGENTS

Non-steroidal anti-inflammatory drugs

A number of NSAIDs, both new and established, have been tried successfully in the treatment of acute gouty arthritis. Well-established agents commonly used are **diclofenac**, **etoricoxib**, **indometacin** (indomethacin), **ketoprofen**, **naproxen**, **piroxicam** and **sulindac**. These are given in high doses in an acute attack. Aspirin is not indicated in gout.

■ MECHANISM OF ACTION

The NSAIDs inhibit the prostaglandin synthesis involved in mediating the inflammatory response (see Chapter 40). As a consequence, the manifestations of acute gouty arthritis subside within a matter of hours.

In addition to its anti-inflammatory activity, the salicylate **diflunisal** increases the excretion of uric acid. This makes it a useful NSAID in the treatment of gout.

◆ COMMON ADVERSE EFFECTS

Important side effects of these drugs include gastrointestinal distress and bleeding, headache, confusion, dizziness, hypersensitivity, renal disturbances, fluid and electrolyte imbalances, and haematological reactions such as thrombocytopenia

and aplastic anaemia. Contraindications for use include peptic ulceration, blood dyscrasias and allergy.

✚ CLINICAL CONSIDERATIONS

Instruct patients with recurrent acute attacks to self-medicate with an NSAID at the earliest sign of an attack, as long as NSAID use is not contraindicated. The full dose of the agent is used during the acute attack and continued for about a week after the gout has settled.

NSAIDs should not be used in patients with renal failure or gastric conditions, as these drugs may worsen renal function and are associated with a high incidence of gastrointestinal irritation. Taking the drug with meals may reduce the problem of gastrointestinal irritation.

High doses of aspirin should be avoided, because this may increase plasma urate levels, therefore precipitating acute gout.

Intra-articular corticosteroids

The injectable corticosteroids **betamethasone**, **methylprednisolone** and **triamcinolone** can be used to relieve an acute attack of gout (unlicensed use).

■ MECHANISM OF ACTION

The corticosteroids are potent anti-inflammatory agents that suppress immune function. They affect the responsiveness of immune cells and inhibit inflammatory mediator synthesis (see Chapter 58).

◆ COMMON ADVERSE EFFECTS

The corticosteroids may induce local and systemic adverse effects, including irritation at the injection site, brief joint discomfort, flare reactions, headache and flushing.

✚ CLINICAL CONSIDERATIONS

The patient should be advised to limit the use of the joint after treatment so that the therapeutic effects are maximised and further joint damage is minimised.

Other anti-inflammatories

COLCHICINE

Colchicine is an alkaloid derived from the autumn crocus, *Colchicum autumnale*, which is used in the management of gout. It is probably as effective as the NSAIDs, but its use is limited by the development of toxicity.

■ MECHANISM OF ACTION

Colchicine is an anti-inflammatory agent, but its action is more specific than that of the NSAIDs. Colchicine is taken up by leucocytes and disables the microtubules, components of the cytoskeleton. The release of cellular secretions, mitosis and cell movement are all dependent on microtubules. The release of enzymes from lysosomes and the synthesis of leukotriene B_4, a potent chemotactic factor that attracts neutrophils to the site, are inhibited. As a consequence, leucocyte migration to the site of inflammation and the processes of phagocytosis are inhibited. The vicious cycle of phagocyte-mediated tophi formation is also suppressed.

◆ COMMON ADVERSE EFFECTS

The most common side effects of colchicine are gastrointestinal, including nausea, vomiting, abdominal pain and diarrhoea. The diarrhoea associated with this therapy has led to increased usage of the NSAIDs in favour of colchicine. Importantly, none of the anti-inflammatory agents acts to reduce hyperuricaemia.

✚ CLINICAL CONSIDERATIONS

Gastrointestinal effects, such as nausea, vomiting and diarrhoea, are an indication of acute overdose. Treatment should be stopped immediately if these symptoms occur. Other toxic symptoms include muscle weakness and ascending paralysis. Colchicine can be given with meals to reduce the incidence of gastrointestinal effects.

Joint inflammation subsides within 48 hours in most individuals. Colchicine is reserved for acute gout when NSAIDs and corticosteroids are contraindicated. Patients should be advised not to take alcohol with this medication, as the efficacy of therapy may become impaired.

URICOSURIC AGENTS

Drugs that enhance the excretion of uric acid are known as uricosuric agents. The major drug used for this purpose is **probenecid**, which is available on a named-patient basis and is used to prevent nephrotoxicity with **cidofovir**, used in the treatment of cytomegalovirus infection in patients with acquired immunodeficiency.

■ MECHANISM OF ACTION

The mechanism by which excretion is enhanced is by blocking the tubular reabsorption of urates into the blood (see Figure 59.1).

◆ COMMON ADVERSE EFFECTS

The adverse effects associated with these drugs include gastrointestinal irritation, which may result in nausea and vomiting. It can cause allergic reactions in the form of rashes and, infrequently, it can induce kidney stones. Rarely, aplastic anaemia and renal impairment may develop.

✚ CLINICAL CONSIDERATIONS

It is important that the patient maintains an adequate fluid intake during the first few months of treatment in order to reduce the risk of uric acid kidney stones. If required,

FIGURE 59.1 MECHANISM OF ACTION OF URICOSURIC AGENTS

This figure shows how excess uric acid is absorbed from the kidney tubule into the surrounding blood vessels. This action leads to the formation of uric acid crystals, which can cause gouty arthritis. After treatment with a uricosuric agent, the reabsorption of uric acid into blood vessels is blocked and the amount of uric acid excreted in the urine is increased.

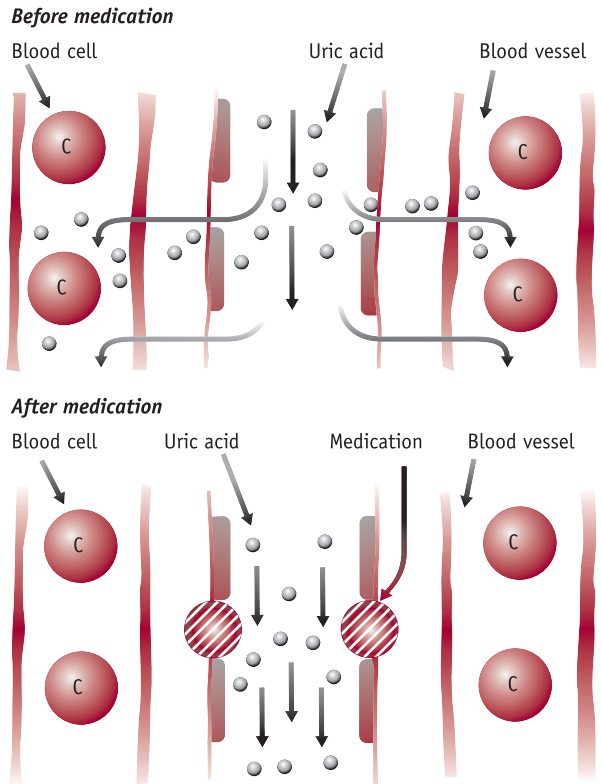
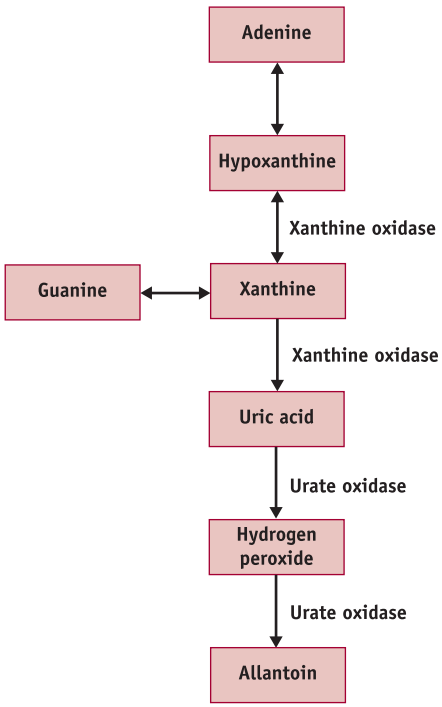


FIGURE 59.2 PURINE METABOLISM

This figure shows the metabolism of the purines adenine and guanine, where the end product is uric acid. Xanthine oxidase is the enzyme that catalyses the conversion to uric acid at two points in the pathway. Inhibition of this enzyme leads to the accumulation of the more water-soluble substance xanthine, which can be converted back into either adenine or guanine. Uric acid can also be converted into allantoin, which is more easily excreted.



urinary alkalisers (see below) can be given to decrease the risk further.

Renal function tests and a complete blood examination should be undertaken regularly as these agents have the potential to cause renal failure and blood disorders.

INHIBITION OF URIC ACID FORMATION

Uric acid is the endpoint of purine metabolism. It is formed from the catabolism of the purine metabolite xanthine under the influence of the enzyme xanthine oxidase.

■ MECHANISM OF ACTION

The chemical **allopurinol** inhibits xanthine oxidase, resulting in lower blood levels of uric acid. The advantage of this approach is two-fold: (i) xanthines are more water-soluble, leading to fewer crystals in the blood; and (ii) the excess xanthine can be reconverted into purines (see Figure 59.2).

◆ COMMON ADVERSE EFFECTS

The kinds of adverse reaction associated with other drugs used in gout are also observed when allopurinol is used. Allopurinol is, however, tolerated well and therefore used widely. Gastrointestinal irritation (nausea, vomiting, diarrhoea) and rashes are common. Rarely, aplastic anaemia has been reported.

✚ CLINICAL CONSIDERATIONS

One important aspect of allopurinol treatment to consider is that when therapy begins, the incidence of acute gouty attacks is increased. This occurs as urate crystals are drawn out of the tissues and into plasma. To minimise this complication, colchicine or an NSAID should be given concurrently for the first 2 months of treatment.

Allopurinol should never be started during an acute attack, and the patient should wait until a gout attack has settled before starting treatment with allopurinol. Allopurinol is usually started 2–3 weeks after an acute attack. Changes in uric acid levels can aggravate and prolong an attack. The uric acid level should be checked after 4 weeks of treatment and then the dose adjusted. The uric acid level should be less than 0.38 mmol/l. Once the treatment has been normalised, it should continue at the current dose even during times of an acute attack. The patient is advised to stop therapy and see a doctor if a rash or swollen lips or swollen mouth develops. Plenty of fluids should be consumed to prevent the development of kidney stones.

Sulfinpyrazone (sulphinpyrazone) can be used instead of allopurinol, or with it in resistant cases.

URICOLYTIC AGENTS

Acute hyperuricaemia can also occur during chemotherapy of haematological cancers. A novel agent called **rasburicase** is approved in the UK as treatment for this condition.

■ MECHANISM OF ACTION

When malignant haematological cells are subjected to chemotherapy, the rapid tumour-cell lysis can lead to acute hyperuricaemia. This is due to the large-scale breakdown of cell purines. The enzyme urate oxidase breaks down uric acid into the water-soluble metabolite allantoin (see Figure 59.2). Allantoin is excreted more easily and rapidly from the kidneys. Rasburicase is a form of urate oxidase synthesised using recombinant DNA technology and, as such, is regarded as a uricolytic agent. The intermediate substance produced during this reaction is hydrogen peroxide, which can produce adverse effects.

◆ COMMON ADVERSE EFFECTS

Common adverse reactions include fever, nausea and vomiting. Methaemoglobinaemia and haemolytic anaemia have been observed during therapy. The latter effect appears to be due to the action of hydrogen peroxide.

✚ CLINICAL CONSIDERATIONS

Rasburicase is infused over 30 minutes. It is given once daily for 5–7 days. If methaemoglobinaemia or haemolytic anaemia occurs, the treatment must be discontinued. The large-scale lysis of malignant cells can also lead to hypocalcaemia, hyperphosphataemia and hyperkalaemia. Patients should be monitored for these conditions.

OTHER CONCURRENT MEASURES

When a preventive approach is used in the treatment of gout, fluid intake must be increased in order to help flush out the excess uric acid within the body and inhibit crystal formation. Another measure often employed is to prevent crystalluria by administering a urinary alkaliniser. The rationale for this is that the uric acid remains more soluble in an alkaline environment.

■ MECHANISM OF ACTION

Sodium bicarbonate and **citric acid** (or its sodium salt) are used as urinary alkalinisers in some countries. After absorption, citric acid/sodium citrate is metabolised rapidly into carbon dioxide, which is then converted into sodium bicarbonate.

CLINICAL MANAGEMENT

Drugs used in hyperuricaemia and gout

Assessment

- Assess the patient for a history of gastric, renal, cardiac or liver disorders. Caution should be exercised concerning the administration of these drugs in these conditions. Drug dosage and selection may need to be changed.
- Assess the patient's baseline vital signs and compare with subsequent observations.
- Assess body weight.
- Determine the patient's history of previous attacks and any family history of gout.

Planning

- The patient will be free of the manifestations of gout, including pain, and swelling and tenderness of the joints surrounding the big toe, ankle, knee and elbow.
- The patient's uric acid level will fall and the patient will experience fewer recurrences of gout.

Implementation

- Monitor serum uric acid levels.
- Monitor the patient's fluid balance, including input and output. Monitor urine output. As antigout drugs and uric acid are excreted through the urine, the patient is predisposed to the development of kidney stones. If necessary, urinary alkalinisers can be used.
- Inspect patients on colchicine for hair loss and skin changes. Also monitor serum creatinine levels, full blood examination, platelet count, liver function tests and urea and uric acid levels.
- Monitor patients on allopurinol for rash, other skin changes and vision changes. Also monitor serum creatinine levels, full blood examination, platelet count, liver function tests and urea and uric acid levels. Allopurinol should be stopped if a rash develops, if the liver function tests are elevated, or if there are any signs of hypersensitivity.
- Monitor patients on probenecid for skin changes. Monitor liver function tests, serum creatinine and urea and uric acid levels.
- Monitor the patient's gastrointestinal manifestations of gastric pain, vomiting, nausea and diarrhoea while the patient is on antigout therapy. Administer therapy with food.
- Ensure that the patient consumes at least 2 l of fluid daily (as long as there are no pre-existing fluid restrictions for other conditions, such as cardiac or renal disease).
- Ensure that the patient has an increased urine output (e.g. at least 2 l daily) to prevent the development of kidney stones.
- Before commencing a course of allopurinol, wait until the gout attack has settled, as changes in uric acid concentration may exacerbate or prolong the acute attack.

Patient teaching

- Advise the patient to increase fluid intake (about 2–3 l daily) to aid excretion of uric acid and prevent the formation of kidney stones.
- Advise the patient to limit alcohol intake, as heavy alcohol consumption produces lactic acid, which inhibits uric acid secretion into urine.
- Advise the patient not to take aspirin, as low doses (1–2 g/day) inhibit uric acid secretion into the urine. Paracetamol can be used instead for pain relief.
- Encourage the patient to take the drug with food to prevent gastric upset.
- Advise patients to avoid foods with a high purine content as uric acid is produced when purine is metabolised. Foods with high purine levels include offal, sardines, mincemeat, anchovies, shrimp, scallops, broth, consommé, gravies, herring, mackerel and yeast.

Colchicine and allopurinol

- Instruct the patient to report changes in urine colour (indicating haematuria), bruising, bleeding, nose bleeds, blood in bowel motions, fever, sore throat and abdominal pain. The patient should see the doctor for investigation of these manifestations.

Colchicine, allopurinol and probenecid

- Instruct the patient to report jaundice and to see the doctor if it occurs.

Allopurinol

- Instruct the patient not to take vitamin C preparations while on allopurinol, as vitamin C increases the acidity of urine, which may lead to the formation of kidney stones.

Probenecid

- Instruct the patient to avoid driving and operating heavy machinery if dizziness occurs.
- The patient may be prescribed an alkalising agent such as sodium bicarbonate to take with probenecid. Inform the patient that this agent causes alkalisation of the urine and prevents crystallisation of uric acid.

Evaluation

- Evaluate the effectiveness of therapy as indicated by a lowered serum uric acid level, prevention of further attacks, and decreased pain of an acute attack.
- Evaluate the patient's compliance in consuming adequate fluids and avoiding foods containing high levels of purine.

SUMMARY

- Hyperuricaemia is characterised by elevated serum uric acid levels.
- Gout is a genetic disorder usually associated with a diet rich in purine and alcohol ingestion and is characterised by acute arthritis.
- Anti-inflammatory agents such as non-steroidal anti-inflammatory drugs, corticosteroids and colchicine can be used in the treatment of gouty arthritis.
- Gastrointestinal irritation and renal disturbances are important adverse effects of non-steroidal anti-inflammatory drugs that should be monitored.
- Signs of colchicine toxicity include nausea, vomiting, diarrhoea, muscle weakness and ascending paralysis. If gastrointestinal effects occur, the medication should be stopped immediately.
- The uricosuric agent probenecid enhances the excretion of uric acid, and the xanthine oxidase inhibitor allopurinol lowers the blood uric acid levels.
- Ensure that the patient has an adequate fluid intake during the first few months of probenecid or allopurinol treatment.
- Renal function and a complete blood examination should be undertaken regularly during probenecid therapy.
- Urinary alkalisers, such as sodium bicarbonate, may help prevent the uric acid crystal formation that leads to attacks of gout.

1 Compare and contrast the terms 'hyperuricaemia' and 'gout'.

2 What is a tophus?

3 For each of the following indicate, where possible, the grouping to which the drug belongs and briefly describe its respective mechanism of action:
(a) allopurinol;
(b) colchicine;
(c) sodium bicarbonate;
(d) indomethacin.

4 For each of the drugs listed below, outline its role in the treatment of gout:
(a) allopurinol;
(b) colchicine;
(c) sodium bicarbonate;
(d) indomethacin.

5 Which of the above drugs have no role in the treatment of hyperuricaemia? Why?

6 What dietary restrictions would you advise for a patient with gout?

7 What patient education would you provide to prevent manifestations of gastric disturbance, a common adverse effect of antigout medications?

8 Why should patients increase their fluid intake when taking antigout medications?

9 Yang Sun-Young, a 50-year-old lecturer, is diagnosed with gout. He commences probenecid to treat his condition. What characteristics of his urine would you monitor? Explain.

10 Anne Hemin, 45 years old, is receiving chemotherapy for an advanced lymphoma. She receives rasburicase therapy before and during the cancer treatment. What kind of drug is rasburicase and how does it work? What serious adverse effects should be monitored during rasburicase therapy?

11 Frank Smits, 65 years old, is commencing therapy with allopurinol for his gout. As part of his preparation for administering this drug at home, you advise him to watch for any signs of excessive bleeding and the presence of blood in his stools and urine. Why? What action do you advise him to take if this occurs?

59 DRUG SUMMARY TABLE: HYPERURICAEMIA AND GOUT

FAMILY NAME	GENERIC NAME	TRADE NAME(S)
Non-steroidal anti-inflammatory agents	Diflunisal	Dolobid
	Indometacin	Flexin Continus
	Naproxen	Synflex
	Sulindac	Clinoril
	Tenoxicam	Mobiflex
Other anti-inflammatory agents	Colchicine	
Intra-articular corticosteroids	Betamethasone	
	Methylprednisolone	Depo-Medrone
		Solu-Medrone
	Triamcinolone	Kenalog
Uricosuric agents	Probenecid	
Xanthine oxidase inhibitors	Allopurinol	Zyloric
Uricolytic agent	Rasburicase	Fasturtec

OBESITY

60

CHAPTER SIXTY

OBJECTIVES

After completing this chapter, the reader should be able to:

- **define obesity and outline how it is measured;**
- **list the health risks associated with being obese or overweight;**
- **describe the factors determining energy intake and expenditure;**
- **outline the role of leptin in monitoring nutritional status;**
- **discuss non-pharmacological methods of weight control;**
- **discuss the use of anorectic drugs;**
- **identify problems associated with anorectics;**
- **outline the actions of other drugs used in the treatment of obesity.**

KEY TERMS

Body mass index
Energy balance
Hypothalamic feeding centres
Leptin
Neuropeptide Y
Nutrition

OBESITY IS A CONDITION ASSOCIATED WITH EXCESSIVE levels of body fat. It is the scourge of the developed world and is considered an important public health issue. A measure of obesity is the body mass index (BMI), which is a reliable indicator of body fat levels. The BMI is an integer calculated by dividing the body weight in kilograms by the square of the height in metres. A person with a BMI of 30 or above is considered obese. An overweight individual has a BMI of between 25 and 30.

Overweight and obese people have higher rates of cardiovascular disease, diabetes mellitus and cancer. Other problems associated with obesity are gastro-oesophageal reflux, sleep disorders and chronic joint pain. There is a direct correlation between BMI and cardiovascular disease, and in some countries the morbidity and mortality associated with obesity is on a par with that associated with smoking. Being overweight is now ranked second to cigarette smoking as the greatest killer in the early twenty-first century, and obesity-related deaths may actually overtake smoking-related deaths in the next few years. There is also growing concern about the increasing rates of childhood obesity. Fat children can grow into endomorphic adults and, in general, thin children grow into mesomorphic adults. Children brought up with a high intake of processed food and fast food are consuming amounts of fat well beyond their bodily needs.

An additional problem of obesity is that it can lead to depression, not only because of the health aspects but also because of the social aspects, for example buying clothes to fit or receiving ridicule from other members of society. The depressed obese person may then seek solace by eating more, thus creating a vicious circle from which it is difficult to escape.

Many nutritional scientists, both medical and non-medical, now recognise that in many cases obesity is a disease rather than the person simply being greedy for food. The term 'metabolic syndrome' has been given to such cases where insulin resistance plays an important part (see Chapter 57).

In the UK, approximately one in five adults is obese – a figure that has trebled over the past 20 years. Two-thirds of adults over the age of 45 years are either overweight or obese. In 1972, the average male waist girth was 78 cm; at the time of writing, it is 86 cm. Extrapolation shows that in 2032, the average male girth could be as large as 103 cm.

The causes of obesity are complex and involve an interplay between genetic, physiological and lifestyle factors. A person's body mass is a product of their energy intake and expenditure. In order to better understand the non-pharmacological and pharmacological management of obesity, it is useful to explore the notion of energy balance.

ENERGY BALANCE

A person is said to be in energy balance when food intake equals the energy consumed by body cells. When this occurs in an adult, the person will neither gain nor lose weight, assuming that fluid intake equals fluid output. Daily variation in energy intake and expenditure does occur, but as long as this energy balance can be maintained, body weight will remain stable.

Regulation of food intake

Our understanding of the physiological regulation of food intake is far from complete. In humans, there are two feeding centres located in the hypothalamus. One is associated with hunger and stimulates eating; the other is associated with satiety (sense of fullness) and inhibits eating. The hunger centre is always active but is intermittently inhibited by the satiety centre.

These centres respond to neuroendocrine and paracrine signals, blood nutrient levels and psychosocial influences. Stimuli that can trigger eating include particular tastes and smells associated with foods, low blood glucose levels and cold ambient temperature. Stimuli that inhibit eating include hot ambient temperature, distension of the gastrointestinal tract, malaise and sympathetic nervous system activity.

The hypothalamic centres respond to a number of chemical mediators. A hypothalamic peptide called neuropeptide Y is a potent stimulant of feeding. It is thought to act by inhibiting the satiety centre. Neuropeptide Y is also produced within the gut. The monoamine neurotransmitters noradrenaline and serotonin tend to inhibit eating. Cholecystokinin (CCK), a gastrointestinal hormone, is secreted in response to the presence of triglycerides within the small intestines. CCK rapidly stimulates the satiety centre in the hypothalamus to stop eating. Some investigators have suggested that the eating disorder bulimia may be associated with impaired CCK secretion. The pituitary hormone melanocyte-stimulating hormone (MSH) and the hypothalamic hormone corticotrophin-releasing hormone (CRH) also appear to suppress appetite. The role of neuropeptides in appetite regulation is still being researched. Leptin is a hormone that acts as an appetite suppressant. It is a member of the cytokine family and is produced in and released by fat cells. Leptin receptors are found in the hypothalamus. Although the amount of leptin produced is proportional to the amount of body fat, obese people appear resistant to the effects of leptin (see below).

One cannot discount the significance of psychosocial factors on eating. Culture has a powerful influence on our body image and the kinds of food we eat. Furthermore, the eating habits of children are influenced greatly by their parents and peers, setting patterns that are likely to continue into adulthood.

Energy expenditure

The rate of cellular metabolism determines the use of energy by the body. It can be measured as oxygen consumption and body temperature. Factors that increase metabolism include physical activity (especially strenuous exercise), sympathetic nervous system stimulation and increased

body temperature. Hormones such as adrenaline and the thyroid hormones also increase metabolic rate. Age and gender further influence metabolism. Metabolic rate is lower in non-pregnant women than in men and tends to decrease with age.

When a person expends energy in excess of their energy intake for a sustained period, they lose weight in the form of tissue mass. It is desirable that this loss in body mass involves a loss of fat rather than of lean tissue.

MONITORING NUTRITIONAL STATUS

It appears that adipose cells provide important information to the brain about body fat levels by secreting leptin, which appears to play a significant role in regulating body weight and metabolism. The levels of circulating leptin appear to correlate with a person's percentage of body fat and BMI, providing the body with an index of nutritional status. Receptors for leptin are located in the hypothalamic feeding centres, providing long-term inhibition of neuropeptide Y secretion and inducing MSH synthesis. Leptin also appears to increase energy expenditure. Research in humans and mice has shown that leptin levels decrease during dieting; this is consistent with a loss in fat tissue. Glucocorticoids and insulin appear to modulate leptin expression. Currently, there is conjecture as to whether reduced leptin receptor sensitivity may contribute to the development of obesity. There is significant interest in the use of leptin in, or the development of leptin analogues for, the treatment of obesity and associated conditions.

Leptin may also play a role in reproduction and inflammation. In mice, leptin stimulates the secretion of gonadotrophin-releasing hormone from the hypothalamus, which triggers the secretion of luteinising hormone (LH) and follicle-stimulating hormone (FSH). A link has been suggested between leptin deficiency and amenorrhoea in very thin girls. In mice, leptin is pro-inflammatory, enhancing T-cell proliferation, phagocytosis and cytokine production.

MANAGEMENT OF OBESITY

Pathological changes such as hyperlipidaemias and hypertension are often a direct result of obesity and need separate treatment (see Section X). No studies have demonstrated conclusively the effectiveness of complementary therapies in causing weight loss, and no details of these substances are given in this chapter.

Non-pharmacological strategies

By far the best and safest way to lose weight is by following a sustainable and realistic programme involving diet and exercise (see Table 60.1). Foods that should be avoided (within reason) are mainly the fats. Bear in mind that the diet requires essential fatty acids, and so fat cannot be eliminated completely from the diet. See Chapter 43 for more on fats in the diet.

TABLE 60.1 SUGGESTIONS FOR SAFE AND EFFECTIVE WEIGHT LOSS

- Do not crash diet: you will most likely regain the lost weight within 5 years.
- Aim for small, slow losses of around 1 kg per week or less.
- Cut down on dietary fats, especially saturated fat.
- Increase your intake of fresh fruit, vegetables and wholegrain foods.
- Consume less alcohol.
- Eat less takeaway and snack food.
- Exercise for at least 30 minutes a few times every week and introduce more movement into your day.
- Do not eliminate any food groups: choose from a wide range of foods every day instead.

It is also important that one does not equate calorific values of fats with those of protein and carbohydrate foodstuffs. When carbohydrate and amino acids are converted into adipose tissue, energy is needed for this process. It is also easier for the body to use stored glycogen as energy than to use fat stores. There is no conclusive evidence that high-protein, low-carbohydrate and low-fat diets are effective. Likewise, fad diets such as the grapefruit diet are of dubious value. Dieticians advise that sudden spurts of exercise use carbohydrate stores, whereas steady exercise uses fat stores. This means that steady, non-strenuous exercise, for example brisk walking as opposed to sauntering, is more appropriate than playing squash for weight loss.

Pharmacological strategies

Current treatments address the energy imbalance underlying weight gain by the following means: suppressing appetite, reducing nutrient intake or absorption, inducing gastrointestinal tract distension and raising metabolism.

STIMULANT ANORECTICS

Anorectics are drugs that suppress the appetite. They are also termed appetite suppressants, anorexigenic drugs and anorexiants.

The majority of appetite suppressants are central nervous system (CNS) stimulants. The original anorectics were the amphetamines, but due to their addictive properties these drugs are not recommended for this purpose now. The more recent anorectics are also CNS stimulants but have

fewer addictive properties, although they still can produce both physical and psychological dependence.

■ MECHANISM OF ACTION

These drugs probably depress the hunger reflex indirectly. The site of action of these drugs is the sympathetic nervous system, and they act as sympathomimetics (see Chapter 26). They produce euphoria, irritability and insomnia, with an urge to get things done and expend energy. This feeling of wellbeing and the activity urge tend to make one forget about food and eating. Whether this is a direct or indirect effect on the feeding centres is not clear, but these drugs do help reduce weight by curbing the appetite.

Phentermine, **fenfluramine** and **dexfenfluramine** act by increasing the release of monoamines, mainly noradrenaline, in the CNS. They have been associated with heart-valve disease and carry a rare but serious risk of pulmonary hypertension. Fenfluramine and dexfenfluramine were withdrawn in the UK in 1997, but phentermine remained on the market. In 2000, all these agents were withdrawn in the European Community and are no longer available by prescription. No new safety problems were discovered, but the risks of their use were seen to outweigh the benefits. **Sibutramine**, originally developed for the treatment of depression, inhibits the reuptake of serotonin as well as dopamine and noradrenaline. It is indicated for use as an anorectic in people with a BMI above 30 and in people with a BMI of 27 or above in the presence of other risk factors. Whether sibutramine has a future in the management of obesity remains to be seen, but it is unlikely to offer any benefit over the anorectics already available.

◆ COMMON ADVERSE EFFECTS

Sibutramine is structurally related to the amphetamines; it has some stimulant properties and can cause insomnia. It can have adverse effects on the cardiovascular system and has been implicated in the deaths of at least two people in the UK. Addiction is always a problem with CNS stimulants, and rebound depression is common after abrupt withdrawal. Insomnia can be a problem if this drug is administered to decrease appetite for the evening meal. Other common effects are dry mouth, constipation, headache, insomnia, elevated blood pressure, tachycardia and a 'spaced-out' feeling.

✚ CLINICAL CONSIDERATIONS

Stimulant anorectic agents should be avoided in individuals with untreated hypertension and cardiac dysfunction. Patients should avoid consuming sibutramine in the evening because of its tendency to cause insomnia. The drug is not licensed for use for longer than a year.

Sibutramine may cause clinically significant increases in blood pressure and heart rate, and monitoring is recommended in all patients during treatment. In the first 3 months, blood pressure and heart rate should be checked every 2 weeks; this may be reduced to every month for the next 3 months, and at least every 3 months thereafter. Treatment should be discontinued if resting heart rate increases by 10 beats/minute or more or blood pressure increases by 10 mmHg or more on two consecutive visits. In patients with previously well-controlled hypertension, treatment should be discontinued if the blood pressure exceeds 145/90 mmHg on two consecutive visits.

PLANT-DERIVED ANORECTICS

Plant substances that swell in the presence of liquids are being promoted as useful in the management of weight reduction. Several types of these substances are available. **Methylcellulose**, a derivative of cellulose, has the capacity to absorb large amounts of liquid and promote a sense of fullness, which may discourage further eating. As methylcellulose is non-calorigenic, it does not cause weight gain. **Extracts of grain** and of **citrus fruit fibre** are also available. These products should be taken before food and consumed with an adequate liquid intake, otherwise they may lead to constipation or intestinal obstruction. Bulk-forming agents should be taken while sitting up and at least a few hours before bedtime to allow adequate passage through the gastrointestinal tract and to prevent lodging in the oesophagus. **Guar gum** has caused oesophageal obstruction when taken with small amounts of fluid. The role of these substances in the dietary control of weight loss is controversial.

LIPASE INHIBITORS

ORLISTAT

■ MECHANISM OF ACTION

Orlistat is a long-acting non-competitive inhibitor of lipase (gastric, pancreatic and intestinal), which renders fats in the diet unabsorbable and lowers blood fat levels. The use of this drug means that triglycerides in the diet are not broken down in the ileum and thus enter the colon unchanged to be excreted with the faeces.

◆ COMMON ADVERSE EFFECTS

The bacteria in the colon break down the unabsorbed triglycerides for their own use and in doing so produce a lot of gas and fatty acids of low molecular weight. The excess gas can lead to embarrassing flatulence, and the fatty acids can increase the osmolarity of the colon contents, thus acting like an osmotic laxative. This can be lessened to a certain extent by minimising fat consumption to

approximately 30 per cent of caloric intake. It has been suggested that these side effects, along with rectal incontinence, which are socially embarrassing, will reinforce the necessity to cut down fat intake rather than a desire to cease using the drug.

✚ CLINICAL CONSIDERATIONS

For maximum benefit, the medication should be taken with three main meals daily. If the a meal is missed, the dose associated with that meal is not taken. The patient is advised to follow a low-kilojoule diet high in fruit and vegetables with about 30 per cent of the energy intake as fat. Flatulence associated with fat content in stools can be minimised by lowering the fat intake. Administering a fibre supplement can further reduce this problem.

Orlistat is used for significantly obese patients and in people for whom obesity is a risk factor, for example patients with hypercholesterolaemia, type 2 diabetes mellitus or hypertension. Research has shown that orlistat combined with a biguanide (see Chapter 57) is particularly useful in the treatment of obese diabetic patients. Patients should be informed that treatment is usually long-term and the possible gastrointestinal disturbances should be explained. Orlistat is contraindicated in malabsorption syndrome and in cholestasis. Evidence that orlistat is implicated as a causal agent of breast cancer is scant. When using orlistat, supplementation of the diet with the fat-soluble vitamins may be advisable. If required, this multivitamin supplement should be taken at least 2 hours away from orlistat. The National Institute for Health and Clinical Excellence (NICE) has recommended that treatment with orlistat should continue for longer than 6 months only if at least 10 per cent of body weight has been lost since treatment started.

The use of **evening primrose oil** capsules between meals, once a day, may prevent essential fatty acid deficiency, although at the time of writing there is no real evidence that linoleic or linolenic acid deficiency is a problem.

MISCELLANEOUS DRUGS AND FOOD SUPPLEMENTS USED IN WEIGHT CONTROL

Many other compounds have been tried with limited success in an attempt to help patients lose weight. **L-Thyroxine** (see Chapter 57) increases metabolic rate, and thus in theory the patient will burn off more joules. Prolonged use can lead to pituitary suppression and then to hypothyroidism on discontinuation of the drug. Its use in dietary regimens is not recommended. The antidepressant **fluoxetine** (see Chapter 35) has been used with some success in bulimia, its mechanism of action being to inhibit serotonin reuptake at the synapse. The biguanide **metformin** (see Chapter 57) reduces glucose absorption from the gastrointestinal tract and thus allows one to eat carbohydrate as 'empty calories'. This can leave fermentable sugars in the gut from which the natural bacterial flora can produce excessive gases and thus flatulence. Metformin also affects glucose metabolism in the body and can induce hypoglycaemia in non-diabetic patients. The use of metformin in patient with type 2 diabetes is sometimes advantageous if the person is overweight and, when combined with dietary changes and orlistat, the weight loss can be dramatic.

A great deal of interest is being focused on adrenergic receptors in adipose tissue, which appear to be β_3 receptors (distinguishing them from the other β receptors mentioned in Chapter 26). Agonists to these receptors, if specific enough, will not affect the cardiovascular or respiratory systems and may help the patient burn off extra joules exactly from where this is wanted. Time will tell whether anything comes of this research.

Other drugs of even more dubious value in weight loss are the laxatives, local anaesthetics and diuretics. **Benzocaine** sucked as a lozenge is supposed to dull one's sense of taste in order to discourage eating. The use of diuretics to aid weight loss cause a spurious loss of weight that is regained on the next fluid intake. Use of diuretics can also cause dehydration. Likewise, laxative use can lead to dehydration due to the acceleration of gut contents through the gastrointestinal system. This accelerated passage is enough to induce water loss but not to inhibit digestion and absorption.

ARTIFICIAL SWEETENERS

Artificial sweeteners as a replacement for sugar in drinks and sweets curbs caloric intake, although it may be better to try to adapt to drinking tea and coffee without a sweetening agent. Artificial sweeteners are available in liquid form suitable for the preparations of desserts and other sweets. There are also many products on the market that contain non-absorbable simple sugars such as **sorbitol** and **mannitol**. These two sugars consumed in excess can produce diarrhoea (see Chapter 54). Another sugar based on the pentose xylose is **xylitol**; this sugar alcohol may help to prevent dental caries and is often included in low-calorie chewing gum. The two most common sweeteners used in beverages are **saccharin** and **aspartame**. Saccharin is devoid of calories; aspartame has some calories, being a derivative of a tripeptide, but as it is consumed in minute quantities the caloric count is negligible. Saccharin is disliked by many people, who perceive a bitter aftertaste following its consumption. Some scaremongers decry these sweeteners as dangerous. In the 1970s, saccharin was banned in the USA because experiments in rats showed that it could induce bladder cancer. The amount given to rats was equivalent to a person taking the substance in quantities of 1000 tablets a day – but the consequences of consuming 1000 teaspoons of sugar per day (~5 kg)

make one shudder! People with diabetes have been using saccharin for the past century and there is no evidence of an increase in bladder cancer among this cohort. Likewise, aspartame has its detractors, but it is difficult to see how a tripeptide derivative could be dangerous except in phenylketonuria, as it contains phenylalanine (see Chapter 63).

In summary, the best and safest way to lose weight is still by dieting and exercising. All pharmacological methods of weight control should be accompanied by dietary advice. This is doubly important because long-term therapy is inadvisable and there is always a tendency to regain weight when drug therapy is ceased. An important premise in obesity is that if energy expenditure is less than energy intake, then one will gain weight.

It was stated in an article on obesity from *Drug Safety* in 1999 that 'there is clearly a need for an efficient pharmacological treatment offering an acceptable safety profile. Such treatment is not available at present.' This still holds true today.

CLINICAL MANAGEMENT

Central nervous system stimulants

Assessment

- Assess whether the patient has a history of malabsorption syndrome or cholestasis. Orlistat is contraindicated in these conditions. Verify the order with the doctor.
- Patients with hypertension or heart-related problems should not take sibutramine.
- Establish baseline vital signs, including blood pressure and pulse rate and rhythm. Compare with subsequent observations.
- Establish baseline body weight and compare with subsequent observations.

Planning

- Through a combined programme of supervised medication use (if required), exercise and diet, the patient will achieve a gradual weight loss.
- The patient will not experience the adverse effects attributed to central nervous system stimulants.

Implementation

- Monitor the patient for the effects of central nervous system stimulants on behaviour modification.
- Monitor effects on body weight.

Patient teaching

Bulking agents

- Advise the patient taking a bulking agent that it should be consumed with a glass of water to encourage adequate dissolution.
- To prevent constipation from bulking agents, the patient should be instructed to observe measures that prevent constipation, such as a high-fibre diet, adequate fluid intake and exercise (refer to Table 11.4 in Chapter 11 for further preventive measures for constipation).
- Instruct the patient to take a bulking agent while sitting up and at least a few hours before bedtime, in order to allow adequate passage through the gastrointestinal tract and prevent lodging in the oesophagus.

Orlistat

- Minimise the incidence of flatulence with orlistat by reducing the intake of fats.
- Fat-soluble vitamin supplementation may be necessary for a patient on orlistat.
- The administration of evening primrose oil may prevent fatty acid deficiency. A multivitamin preparation containing fat-soluble vitamins may also be required.

Stimulant anorectics

- Instruct the patient taking a stimulant anorectic not to consume more than two cups of caffeinated coffee per day.
- Instruct the patient that these agents have abuse potential and should be used as a short-term measure. Tolerance to the effects of these drugs occurs within a few weeks, and so weight loss cannot depend on these drugs alone.
- Instruct patients not to consume sibutramine in the evening, because it may cause insomnia.

Evaluation

- Evaluate the effectiveness of the drug to decrease weight.
- Evaluate the tendency of the drug to produce adverse effects, especially those of a central stimulatory nature.

SUMMARY

- Being obese or overweight is a major contributor to mortality and morbidity in developed countries.
- Energy balance relates to the relationship between food intake and energy expenditure. When intake and expenditure is equal, there is no net change in body weight.
- Food intake is regulated by an interplay between the hypothalamic feeding centres and a mix of neuroendocrine and paracrine signals, blood composition and psychosocial factors.
- Leptin is a protein secreted by adipose cells that has a long-term influence on appetite and metabolism. The circulating levels of leptin correlates with body fat levels and is thought to provide the body with an index of nutritional status.
- Non-pharmacological treatment of obesity should comprise a realistic and sustainable programme involving diet and exercise.
- Pharmacological treatment of obesity should be concurrent with an appropriate increase in physical activity and dietary advice.
- Many other preparations are used in weight control, including bulking agents and artificial sweeteners.

1. Why should a dietary fibre supplement be avoided in patients with coeliac disease?
2. Why should bulk-forming agents be taken with plenty of water?
3. Why should anorectics not be taken for prolonged periods?
4. Why are amphetamines not indicated for use as anorexiants?
5. Why do amphetamines lead to a decrease in appetite?
6. Natalie Naylor, a 50-year-old woman, has commenced a course of orlistat as part of a combined weight-loss programme. What information would you provide Ms Naylor about preventing problems associated with orlistat?
7. Why is it not advisable for a person who has just consumed a methylcellulose drink to go straight to bed?

60 DRUG SUMMARY TABLE: OBESITY

FAMILY NAME	GENERIC NAME	TRADE NAME(S)
Central nervous system appetite suppressants	Orlistat Sibutramine	Xenical Reductil
Intestinal bulking agents	Grain and citrus fruit Methylcellulose	

CASE STUDY XII.1

Miss GH was reading as many articles on slimming and diets in women's magazines as she could get her hands on. This became an obsession, so much so that she started to shed the kilograms at an alarming rate, trying out one diet after another. Her weight fell from 60 kg to 40 kg (her recommended weight was 55 kg). She was still not satisfied and managed to get hold of dexamfetamine tablets, which she took daily. Her menstrual periods stopped, she developed hirsutism and she became depressed because she still thought of herself as fat. Her parents at last managed to get her to visit her general practitioner, who referred her to a psychiatrist; anorexia nervosa was diagnosed.

Her depression and severely agitated state was so bad that she was suicidal, and immediate electroconvulsive therapy (ECT) was given. This, together with fluoxetine, trifluoperazine and orphenadrine, soon improved her mood. She needed three ECT treatments, which involved the use of propofol and suxamethonium injections. Even though her mood had improved, she was still not eating, and so she was given some insulin injections, which, together with psychotherapy, quickly improved her appetite. She was discharged from hospital after 6 weeks, although she was still on fluoxetine.

With weekly visits to her psychiatrist, she continued to improve both physically and mentally, and the fluoxetine was gradually withdrawn; after a year, she was no longer on drug therapy. Her periods soon returned to normal, as did her physical appearance.

QUESTIONS

1 *Why would Miss GH want to take dexamfetamine tablets?*

2 *What is fluoxetine, and how is it thought to act?*

3 *Why was ECT given concurrently with fluoxetine in the initial stages of therapy?*

4 *Why would trifluoperazine be prescribed?*

5 *Why would orphenadrine be prescribed?*

6 *Name a long-term adverse effect of trifluoperazine.*

7 *Why would propofol be used in preference to thiopentone (tip: propofol is covered in Chapter 41)?*

8 *Why was suxamethonium administered?*

9 *Why was the fluoxetine withdrawn gradually?*

CASE STUDY XII.2

Ms FT is 30 years old and presents to her doctor with the following clinical manifestations: weight loss, tremor, anxiety, insomnia, talkativeness, palpitations, heat intolerance and sweating. A large goitre is also evident. Blood tests revealed elevated free thyroxine but suppressed thyroid-stimulating hormone (TSH) levels. Antibodies to the TSH receptor were also detected.

Ms FT was referred to an endocrinologist, who diagnosed Graves' disease. Ms FT commenced treatment with high doses of the thionamide carbimazole as well as the beta-blocker propranolol.

After 8 weeks, the dose of the thionamide was reduced. The beta-blocker treatment ceased. Treatment continued for 2 years without evidence of remission. Ms FT's endocrinologist advised that surgery was the best long-term option. For a few days before surgery, iodine solution was administered.

The surgery was successful and Ms FT became euthyroid.

QUESTIONS

1 *What type of thyroid imbalance is Graves' disease?*

2 *Describe the mechanism of action of the thionamides.*

3 *What advice should be given to patients taking thionamides regarding the onset of clinical effects? What is the underlying reason for this?*

4 *What adverse effect must be monitored for closely during the first weeks of thionamide therapy?*

5 *State three common adverse effects of thionamide treatment.*

6 *What is the rationale for the use of a beta-blocker in this condition?*

7 *What is the purpose of administering iodine solution before thyroid surgery, and what is the mechanism of action of this agent?*

CASE STUDY XII.3

Ms HN is 17 years old and has made an appointment with her family doctor to discuss emergency contraception. At the consultation, Ms HN is clearly distressed and explains that she had unprotected sexual intercourse with her boyfriend on the previous night and that she is not on the pill. The doctor prescribes Postinor-2, a high-dose progestin-only preparation, and provides Ms HN with instructions on dosage and adverse effects. The doctor also asks Ms HN to consider the possibility of taking the pill from now on. Ms HN agrees that this is a good idea, and so her doctor adds an oestrogen–progestin combination oral contraceptive to the prescription. The emergency contraception was successful.

Ms HN revisits her doctor after several months of starting to take the pill. She has suffered no ill-effects associated with taking the pill, but she is in a panic because she has missed a dose a day earlier and wants to know what she should do. Furthermore, she has been talking to friends and they have told her about progestin-only oral contraceptives. Ms HN wants to know whether they might be better than the oestrogen–progestin combination she is taking.

QUESTIONS

1 *How effective is postcoital contraception?*

2 *High-dose progestin-only preparations are one form of hormone-based emergency contraception. Are there any other hormone-based alternatives? If so, compare the efficacy and adverse effects of these with progestin-only preparations.*

3 *What is the mechanism of action of postcoital progestin-only contraceptives?*

4 *How would Ms HN be able to tell that the emergency contraception was successful?*

5 *What patient education should be provided to Ms HN about using an oestrogen–progestin oral contraceptive?*

6 *What is the mechanism of action of oestrogen–progestin oral contraceptives?*

7 *What is the failure rate associated with the appropriate use of an oestrogen–progestin contraceptive?*

8 *Describe the benefits and the risks associated with oestrogen–progestin combination contraceptives.*

9 *Do oestrogen–progestin oral contraceptives offer protection against sexually transmitted diseases?*

10 *What should Ms HN be told regarding the missed dose of her oral contraceptive?*

11 *What are the advantages and disadvantages of the progestin-only oral contraceptives?*

CASE STUDY XII.4

Mr WD, a 44-year-old man, has been experiencing fatigue for the past 4 months. He puts this down to being busy at work over this period. Over the past 2 days, he has been urinating frequently and drinking more fluids than he usually does. He decides to go to the doctor.

The doctor completes a physical examination. Mr WD has no history of unexplained fatigue or kidney problems. He does not smoke, but he enjoys about five glasses of wine a week. He has a normal blood pressure, he does not have a fever, there is no evidence of oedema and his pulses are normal. His height is 173 cm, weight is 89 kg and body mass index is 29.7 kg/m^2. He is overweight and does not exercise regularly. His blood glucose level was found to be 13 mmol/l. Mr WD's father and one of his aunts have diabetes mellitus. Mr WD is referred to an endocrinologist, who makes a diagnosis of diabetes mellitus.

At the diabetes clinic, Mr WD is provided with information about the disease, as well as a dietary and exercise programme. At the next consultation, Mr WD is still having trouble with fluctuating blood glucose levels and is told that his glycosylated haemoglobin level is elevated. He is prescribed oral hypoglycaemic drug therapy – the biguanide metformin and the postprandial agent acarbose.

Several months pass and Mr WD appears to have better control of his daily blood glucose levels, but a problem has arisen with hyperglycaemia developing overnight. Mr WD is prescribed an isophane insulin to remedy this problem.

QUESTIONS

1 *What type of diabetes mellitus do you think Mr WD has? Why?*

2 *Briefly outline the pathophysiology of this type of diabetes mellitus.*

3 *Describe the mechanisms of action of the hypoglycaemic agents prescribed for Mr WD.*

4 *Outline the patient education provided to Mr WD regarding this therapy.*

5 *Describe the properties of isophane insulin and its pharmacokinetics.*

6 *What are the common adverse effects of insulin therapy?*

7 *Outline the patient education associated with insulin therapy.*

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American Society for Reproductive Medicine www.asrm.org

Association of Reproductive Health Professionals www.arhp.org

British Diabetic Association www.diabetes.org.uk

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Hormone Foundation www.hormone.org

International Diabetes Institute www.idi.org.au

International Obesity Task Force www.iotf.org

National Diabetes Education Program www.ndep.nih.gov

National Institute of Diabetes and Digestive and Kidney Disease: Endocrine and Metabolic Diseases www.endocrine.niddk.nih.gov

North American Association for the Study of Obesity www.naaso.org

North American Menopause Society www.menopause.org

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NUTRITIONAL AND NATURAL THERAPIES

Man shall not live by bread alone.

ST MATTHEW 4

Good nutrition is necessary for good health. The nutrients required for adequate nutrition include vitamins, minerals, amino acids, fats and carbohydrates. Sometimes circumstances arise where adequate nutrition cannot be maintained by eating. This might be due to conditions such as a digestive disorder, surgery, coma or nausea and vomiting. At other times, a patient may not be relied on to eat a healthy diet or even sufficient food. Under conditions such as these, nutritional support may be required, supplied by either the enteral (via the gastrointestinal tract) or parenteral (intravenous) routes.

As well as being involved in disease processes, some of these nutrients can be used as therapeutic substances, not only as dietary supplements but also as drugs. In this section, we examine the functions and uses of vitamins (Chapter 61), minerals (Chapter 62) and amino acids (Chapter 63). The principles of enteral and parenteral nutritional therapy are also described (Chapter 64).

Chapter 65 deals with a variety of herbal medicines that may have a therapeutic value. This chapter is not intended to be a guide to natural therapies, but as more people take these herbs it is important that health-care professionals have some knowledge of the common herbal preparations. Natural therapies are now used more than over-the-counter and prescription drugs.

XIII

VITAMINS

61

CHAPTER SIXTY-ONE

OBJECTIVES

After completing this chapter, the reader should be able to:

- **list the functions, uses and dangers of vitamin A;**
- **name the functions and uses of members of the vitamin B group;**
- **name the functions and use of ascorbic acid;**
- **list the functions, uses and dangers of vitamin D;**
- **outline the relationship between vitamin D, parathyroid hormone and calcium metabolism;**
- **describe the functions of vitamins E and K.**

KEY TERMS

Fat-soluble vitamins
Over-the-counter medicines
Water-soluble vitamins
Vitamin supplementation

THE WORD 'VITAMIN' IS DERIVED FROM THE TERM 'VITAL amine'. It was initially believed that these substances, found in foodstuffs and necessary to the diet, were organic amines. This is not strictly true, as many vitamins discovered since are not amines. Vitamins are a very diverse group of organic substances needed for many metabolic processes that take place in the body. Many vitamins, especially those of the B group, function as coenzymes.

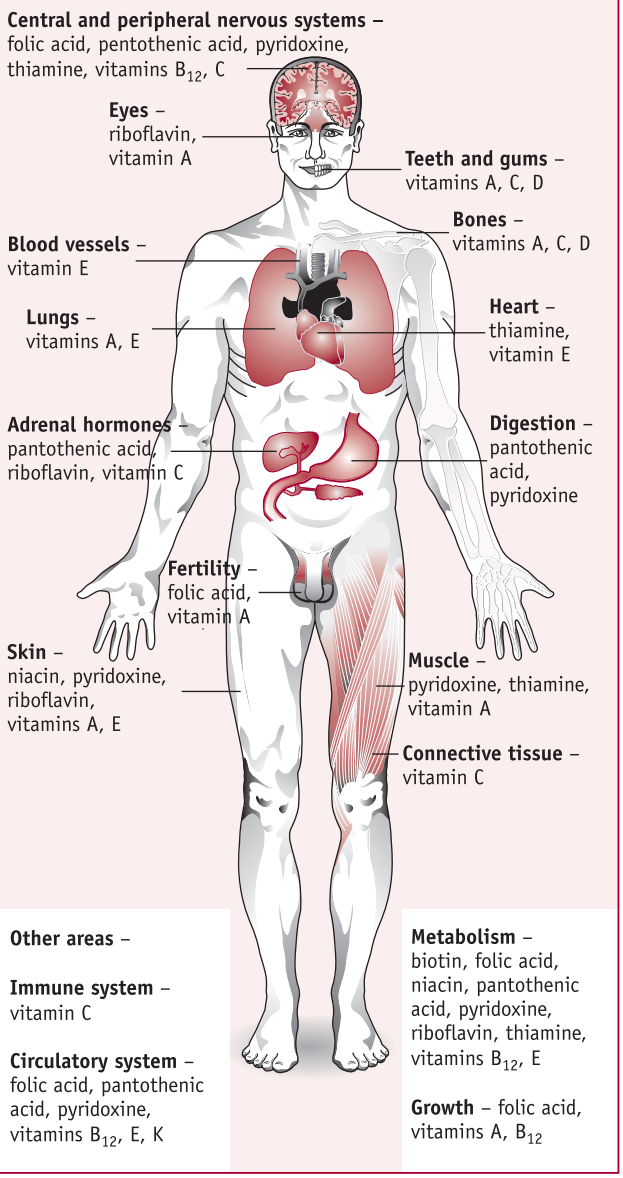
In view of the many bottles of vitamin preparations that are sold in pharmacies, supermarkets and healthfood shops, it is important that health-care professionals know something about them and the many apparent fallacies associated with them. Vitamins consumed in food cannot be termed drugs, but when taken as supplements they can be so classified. They are thus included in most pharmacology textbooks.

Most authorities classify vitamins into two main groups: fat-soluble and water-soluble. The fat-soluble vitamins are A, D, E and K; the rest are water-soluble. The fat-soluble vitamins depend on bile for their absorption (true for any lipid), and any disturbance in bile formation can lead to vitamin deficiencies.

Apart from absorption difficulties, this division is not necessary, as many synthetic preparations of the so-called fat-soluble vitamins are, in fact, water-soluble. The one advantage of this classification is to remind us that with the naturally occurring fat-soluble vitamins, their absorption from the gastrointestinal tract can be upset by disorders of fat absorption. Another anomaly in this classification system is the expectation that the fat-soluble vitamins are stored for considerable periods of time in the body, whereas the water-soluble ones are not. For example, vitamin B_{12}, a water-soluble vitamin, can be stored for months in the liver. Conversely, stores of the fat-soluble vitamin K can be depleted in only 10 days. When dealing with the vitamins, it is just as easy to start with vitamin A and deal with them in alphabetical order. In textbooks describing vitamins, you will come across the terms 'recommended daily allowance' (RDA), 'recommended daily intake' (RDI) and 'recommended nutrient intake', which are all supposed to be the minimum amount of that vitamin required in order to avoid deficiency symptoms. These figures can be misleading, as they vary from country to country, indicating that we are not sure just how much of a particular vitamin is needed by the human body. RDIs vary according to the age and physical condition of the person. For example, during pregnancy, a woman requires larger quantities of folic acid, while smokers require greater amounts of vitamin C compared with non-smokers. This has been made official in the USA, where the RDA of vitamin C is higher for smokers than for non-smokers. Figure 61.1 shows the areas of the body on which each vitamin has its major effect.

There is also evidence that some vitamins taken in greater than the recommended amounts may help in the prevention of other disease states not normally associated with vitamin deficiencies. The use of mega-doses of vitamins, as advocated by some people, is potentially dangerous. There is no convincing evidence that mega-doses of any vitamins have any benefits. You may see on labels in healthfood shops the names of 'vitamins' that are not included here, as they are not true vitamins. Names such as 'vitamin P' are misnomers.

FIGURE 61.1 ORGANS AND BODY SYSTEMS ON WHICH EACH VITAMIN HAS ITS MAJOR EFFECT



VITAMIN A

Vitamin A belongs to a group of chemicals known as retinoids. Some of these, after various chemical modifications, are very potent drugs, used mainly in the treatment of psoriasis and acne (see Chapter 78). It is important to note that retinoids are drugs related to vitamin A and should not be thought of as vitamins per se, and vice versa. The scientific name for vitamin A is **retinol**, a name that gives a clue to one of its functions and its chemical nature. That is, vitamin A is an alcohol needed for the normal functioning of the retina. The main sources of retinol in the diet are liver, dairy products, egg yolk and fatty fish. Polar-bear liver is so high in retinol that it must be considered toxic, as early Arctic explorers found out to their

detriment; this is why Inuit people avoid eating that part of the polar bear. Retinol is not found in plant products, but most plants contain carotenoids, which act as provitamins and can be converted into retinol in the intestinal wall and liver. The principal carotenoid in the plant kingdom is **beta-carotene**, which gets its name from carrots – the colour of carrots is due to the presence of this compound. Any vegetable or fruit that has an orange colour will probably contain this provitamin. Beta-carotene is also found in green vegetables, its colour being masked by the high amount of chlorophyll present. After carrots, spinach has the highest concentration of beta-carotene of all other commonly eaten fruit and vegetables.

The functions of retinol in the body are at least two-fold:

- It is needed for the formation of visual purple, a light-sensitive pigment of the retina of the eye. In the retina, retinol is first converted into its aldehyde form, retinal. This combines with proteins called opsins, resulting in the formation of four types of coloured compound called visual pigments. You may remember that the retina is dark due to the presence of these pigments. This colour is visible on ophthalmoscopy. These visual pigments change their chemical nature when excited by light energy by a very complicated series of reactions. It is not necessary to go into detail here, except to explain briefly the function of one of these pigments, which is greatly affected by vitamin A deficiency. The pigment visual purple, or rhodopsin, is found in the rods of the retina. This pigment is sensitive to low-intensity light, as occurs in semidarkness. When low-intensity light acts on rhodopsin, the photochemical changes result in graded potentials. These stimulate neurotransmitter release, and the message is recorded, via the optic nerve, in the visual centre of the brain as a picture. If rhodopsin is lacking, this series of events is inhibited, and night blindness (or nyctalopia) results. (Hence the belief that carrots help one to see in the dark.)
- Vitamin A is needed for the normal growth and differentiation of epithelial tissues and probably the differentiation of all tissues. It is involved primarily with the normal functioning of mucus-secreting epithelial cells. In the absence of vitamin A, these cells become keratinised. As mucus-secreting cells of the respiratory and genitourinary tract are part of the body's defence system, deficiency can lead to an increase in infections. The cornea can become keratinised, which leads to a condition called xerophthalmia (dry eyes). This in turn can cause permanent blindness. The mechanism of action of retinol and the retinoids is at the nuclear level and may affect gene expression. Note that deficiency causes two different defects in the eye.

Both natural and synthetic retinoids have been used to treat disorders of the skin. **Etretinate** and **acitretin** are retinoids that have been useful in the treatment of psoriasis, while **tretinoin** and **isotretinoin** have been used successfully to treat severe acne.

The retinoids and the carotenoids have been used experimentally in the treatment of some cancers. For example, beta-carotene is being used in Australia to treat mesothelioma of the lung, caused by asbestos. There is also a suggestion that people with diets containing fruit and vegetables high in beta-carotene have a lower incidence of certain cancers and cardiovascular disease. Most studies that have compared blood retinol levels at baseline between people who subsequently developed lung cancer and those who did not have found no statistically significant association between low serum retinol and risk of lung cancer. Any positive action of beta-carotene may be due in part to its antioxidant effect and this would also apply to vitamins C and E. Many chemicals found in a normal diet may have carcinogenic potential when oxidised; beta-carotene may prevent these changes from occurring. Likewise, atherosclerosis and cardiac dysrhythmias may be due to a lack of certain unsaturated fatty acids, such as linoleic acid. Even if linoleic acid is present in the diet, it can be oxidised in vivo; beta-carotene and other antioxidants may prevent this from happening.

The retinoids can be toxic if taken in excess, and they are teratogenic. Toxicity can result from taking only ten times the RDA for several months. Symptoms of toxicity are varied and can include excessive peeling of the skin, hyperlipidaemia, hypercalcaemia and hepatotoxicity; ultimately, death can result. An acute dose of about 200 mg can cause immediate toxicity, resulting in increased cerebrospinal pressure. This can cause severe headache, blurring of vision and bulging of the fontanelle in infants.

Beta-carotene is not nearly as toxic as the retinoids. The main symptom of ingesting too much beta-carotene is that one turns orange. This condition is known as carotenaemia and has resulted from people consuming an abnormally high amounts of carrots (usually as the juice) in their diet.

A large-scale placebo-controlled trial carried out in the USA using beta-carotene was terminated prematurely as it appeared that the subjects taking the active compound showed an increase rather than a decrease in certain cancers. This was also noted in a Finnish study. Future mega-vitamin studies with beta-carotene are unlikely to go ahead until the potential hazards are clarified.

As a point of interest, the pigment lycopene found in red fruits, such as tomatoes, is an antioxidant and, like carotene, may help to reduce the risk of cancer of the prostate.

✚ CLINICAL CONSIDERATIONS

Acute toxicity of vitamin A relates to doses exceeding the RDI. Doses that do not exceed the RDI are rarely toxic.

As adverse reactions usually occur only with toxicity, assess for these effects on a periodic basis. It is important to also assess vitamin A intake from all sources, including food and vitamin supplementation, in order to determine the amount consumed by the individual. Vitamin A is a fat-soluble vitamin that may accumulate in the body.

THE VITAMIN B GROUP

It is better practice to call the vitamins in this group by their names rather than by numbers, except perhaps for vitamin B_{12}, which is dealt with more fully in Chapter 50. All members of this group act as coenzymes, usually after being derivatised. They are grouped together, as many are found in similar foodstuffs.

Vitamin B_1 (thiamine)

Anyone who takes multivitamin preparations will be aware of the distinctive smell of some of them. This is due to **thiamine**, which, like many sulphur-containing compounds, is slightly malodorous. (Compounds containing sulphur very often have the prefix thio-.) The major dietary sources of thiamine are pork, beef, liver, unrefined grain products, yeast products and nuts, especially brazil nuts.

Thiamine is converted into a pyrophosphate, which functions as a coenzyme in some important carbohydrate metabolic processes. The metabolism of alcohol depends on thiamine pyrophosphate. As the triphosphate, it is needed for normal nerve function.

Deficiency of thiamine leads to the disease beri-beri, a Singhalese word for weakness. This is a symptom of deficiency. Beri-beri is found in societies that rely on rice as a staple food. When natural rice grains are refined, the vitamin-bearing part of the grain is removed and thiamine deficiency can occur. Beri-beri is less common today, as foods are often fortified with vitamins. Beri-beri is categorised into two types, depending on whether the deficiency is chronic or acute. In chronic deficiency (dry beri-beri), the essential feature is a polyneuropathy of the peripheral nerves, with a resultant loss in motor control. In acute deficiency (wet beri-beri), there is cardiac enlargement and, eventually, cardiac failure.

In developed societies beri-beri-like symptoms occur in alcoholics who also consume an inadequate diet. As other vitamins may also be lacking, various symptoms may occur in addition to those of beri-beri. The most disturbing feature is an encephalopathy known as Wernicke–Korsakoff syndrome. This results in poor memory, apathy and eye disturbances. There has been a suggestion that vitamin supplements should be added to beer to help prevent this condition.

Thiamine toxicity can occur if very large doses are taken for long periods of time, and this can result in hepatotoxicity.

Some reports suggest that when taken in moderate doses of 100 mg three times a day, thiamine produces a substance in sweat that insects do not like. Because of this, it may be an effective insect repellent, although this is disputed by some vitaminologists.

Apart from being a component of multivitamin preparations, thiamine is available as **vitamin B_1**. For severe beri-beri, thiamine can be administered intravenously; care should be taken with this mode of administration, as anaphylaxis has been reported.

✚ CLINICAL CONSIDERATIONS

Thiamine malabsorption commonly occurs in patients with alcoholism, cirrhosis and gastrointestinal disease. The first few doses of thiamine should be given parenterally to ensure maximal absorption and good clinical response in these patients. Patients who regularly consume more than 60 g of alcohol daily should be considered at risk of developing thiamine deficiency. As glucose administration may precipitate Wernicke's encephalopathy, parenteral thiamine should be given before glucose for those patients at risk of encephalopathy. It is important to adhere to the recommended dose schedule, as higher doses may not be utilised fully. After tissue saturation, thiamine is excreted in urine as pyrimidine.

Vitamin B_2 (riboflavin)

Riboflavin is so named because it contains a ribose moiety as part of the molecule and is yellowish in colour (Latin: *flavus*, yellow). Patients using riboflavin supplements should be warned that their urine may be bright yellow. The main dietary sources are dairy products, liver and yeast products; almonds are a good source and many other plant products contain reasonable amounts. In the body, riboflavin is converted into several different coenzymes, principally flavin mononucleotide (FMN) and flavin adenine dinucleotide (FAD). Both of these are important in the metabolism of fats, carbohydrates and proteins, being hydrogen carriers from various metabolites into the respiratory chain.

Deficiency of riboflavin causes cheilosis (fissures on the lips) and stomatitis (cracks in the angles of the mouth). Glossitis (inflammation of the tongue) and seborrhoeic dermatitis, mainly of the face and scrotum, and decreased resistance to infections can occur.

Riboflavin is sensitive to light and foodstuffs. Vitamin supplements containing riboflavin should be kept out of direct sunlight. There is no known danger associated with excessive consumption of riboflavin.

It is important to remember that if catecholamines (adrenaline, dopamine and their derivatives) are to be measured in urine, then riboflavin in excess might interfere with the analysis.

✚ CLINICAL CONSIDERATIONS

Riboflavin deficiency usually accompanies deficiencies in other vitamins of the B complex group. A multivitamin supplement may therefore be required. This vitamin should be protected from light and air. Inform the patient that the absorption of riboflavin is improved when it is taken with meals and that it may cause bright yellow or orange discoloration of urine.

Vitamin B_3 (nicotinamide) and nicotinic acid

Nicotinamide (also known as **niacinamide**) and **nicotinic acid** (also known as **niacin**) are chemically slightly different but function exactly the same as vitamins. This vitamin has no relationship to nicotine as far as action on the body is concerned. (Part of the nicotine molecule has a pyridine ring associated with it and nicotinic acid has this ring too, as shown in Figure 61.2.) Humans can actually make some of this vitamin from the amino acid tryptophan. Not enough is produced, however, to meet daily requirements, so adequate dietary intake is needed. The main food sources are liver, yeast products, peanuts, wholegrain cereals and fish; tuna is exceptionally high in this vitamin.

Nicotinamide is converted into two very widespread coenzymes: nicotinamide adenine dinucleotide (NAD) and nicotinamide adenine dinucleotide phosphate (NADP). Both are important as hydrogen carriers in oxidative pathways. NADP is commonly used in biosynthetic pathways.

The vitamin, as nicotinic acid, is used in large doses to treat hyperlipidaemias (see Chapter 43). Some experts say that even only slightly higher than normal levels help in reducing triglycerides and cholesterol, but the evidence for this is not conclusive. The RDA for nicotinic acid is 10–20 mg; a dose of 100 mg per day has been recommended by natural therapists for reducing triglycerides and cholesterol. This is still far below the doses recommended by lipidologists. Because of the adverse effects of these higher doses of nicotinic acid, it has been used more recently at lower doses in combination with a cholesterol-lowering statin (**simvastatin**).

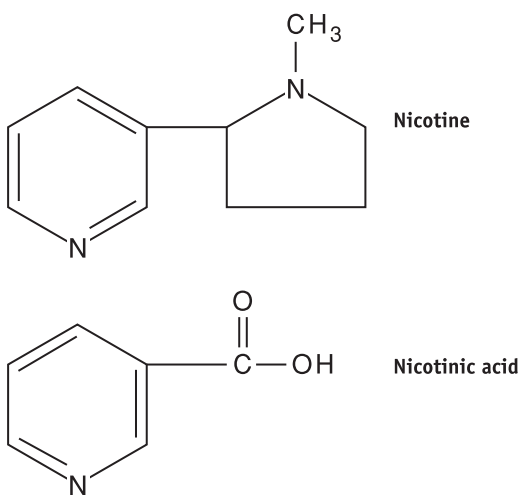
Some psychiatrists have promoted mega-doses for the treatment of schizophrenia, but the scientific evidence for this is lacking.

Deficiency of nicotinamide causes pellagra, an Italian term for rough skin. Pellagra is not seen normally in developed countries. The symptoms are often referred to as 'the three Ds': dementia, dermatitis and diarrhoea.

The problems of excessive intake of these vitamins depend on the form in which they are taken. Moderate doses of nicotinic acid (about 100 mg), especially on an empty stomach, can cause intense peripheral vasodilation. This results in an uncomfortable, itchy, warm sensation on the skin, and headaches and syncope due to the reduction in blood pressure. This effect is only short-lived and consequently nicotinic acid is of no use in hypertension. Many derivatives of nicotinic acid have been produced, and are still used, with doubtful beneficial effects, to treat peripheral vascular problems such as Raynaud's disease and chilblains. Nicotinic acid in large doses can lead to peptic ulcers, diabetes mellitus, cardiac dysrhythmias and hepatic failure. In view of its potential adverse effects at doses of 100 mg and above, nicotinic acid is being made available only on prescription in many countries. Nicotinamide appears not to have any of these effects. It has been suggested that athletes should not take too much of this vitamin as it hastens glycogen breakdown in muscle tissue, which could ultimately affect their performance.

Apart from in the preparations used for the treatment of hyperlipidaemias mentioned in Chapter 43 and in multivitamin preparations, nicotinic acid is sold by its chemical name.

FIGURE 61.2 STRUCTURAL FORMULAE OF NICOTINE AND NICOTINIC ACID



✚ CLINICAL CONSIDERATIONS

To minimise gastrointestinal effects involving nausea, vomiting and diarrhoea, nicotinic acid should be given with meals. Advise the patient that the flushing and warmth that occur with peripheral vasodilation may subside with continued use. In view of its potential to cause serious adverse effects relating to the cardiac, hepatic and endocrine systems, it should be stressed that nicotinic acid is a potent medication and the patient must adhere to the correct dosage schedule at all times.

Vitamin B_5 (pantothenic acid)

The name 'pantothenic' is of Greek derivation and means 'all over the place'; that is, **pantothenic acid** occurs

ubiquitously in both the plant and animal kingdoms. Deficiencies are unknown in the natural situation. The vitamin is needed for the formation of coenzyme A, which is required in numerous biochemical processes.

Artificially induced deficiency in human volunteers results in abdominal pains, vomiting, cramps and personality changes. Presumably, in view of the importance of coenzyme A, death would occur eventually. It has been noted that in black rats fed a diet deficient in pantothenic acid, the fur turns grey. Entrepreneurs have used this as a basis for including either the acid or its alcohol derivative, **pantothenol**, in preparations to restore hair colour. These preparations are sold, but there is no evidence that the agent helps to normalise grey hair in humans.

Very large doses of pantothenic acid have been known to result in diarrhoea.

✚ CLINICAL CONSIDERATIONS

As pantothenic acid is readily available in most plant and animal sources, it is very difficult for individuals to have a deficiency in this vitamin. It is available generally in multivitamin preparations, and a diet rich in fruit, vegetable, cereal and meat sources ensures adequate intake of pantothenic acid. By complying with the dosage schedule for multivitamin preparations, diarrhoea caused by high doses of this vitamin can be eliminated.

Vitamin B_6 (pyridoxine)

There are different forms of **pyridoxine**, all of which have similar activity, as they can be interconverted in the body. The main forms are **pyridoxal** and **pyridoxamine**. The various forms of pyridoxine are distributed widely in animal and plant products, making deficiency rare. The vitamins are converted into pyridoxal phosphate, an important coenzyme in amino-acid metabolism. It is needed for the conversion of tryptophan to nicotinic acid.

This vitamin reputedly has several therapeutic uses. It is used routinely in patients on **isoniazid** therapy to prevent neuritis developing (see Chapter 69). There has been some success with its use in treating hyperemesis gravidarum (nausea of pregnancy), particularly when given parenterally, and in the suppression of lactation (given orally). Pyridoxine can help in haemoglobin formation in cases of sideroblastic anaemia. Other, more controversial and doubtful uses are in the treatment of premenstrual tension, sickle cell anaemia, carpal tunnel syndrome and asthma. Women taking oral contraceptives need to take extra pyridoxine.

Deficiency is rare, but in infants fed milk deficient in this vitamin epileptiform seizures have occurred. In adults, peripheral neuritis, dermatitis, anaemia and weight loss occur with deficiency.

There are several important drug interactions with pyridoxine. The conversion of **levodopa** to dopamine (see Chapter 36) can be increased in the periphery by pyridoxine. Therefore, it is important that patients with Parkinson's disease are warned not to take vitamin supplements without first consulting their doctor. People taking **hydralazine** or **penicillamine** may need pyridoxine supplementation, as these drugs inhibit the conversion of pyridoxine into pyridoxal phosphate. Increasing pyridoxine intake can alleviate this inhibition.

Pyridoxine in large doses (2–3 g daily) for prolonged periods can lead to peripheral neuropathy. This has become a problem for women overzealous in using pyridoxine for the treatment of premenstrual tension.

Apart from being present in many multivitamin preparations, pyridoxine is also available under its chemical name.

✚ CLINICAL CONSIDERATIONS

The optimal dose of pyridoxine is dependent on the amount of isoniazid consumed. As this vitamin can cause seizures, an antiseizure drug may also be required when pyridoxine is used to treat isoniazid toxicity. Patients taking high doses of this vitamin (2–6 g daily) may experience difficulty in walking because of diminished proprioceptive and sensory function. Prolonged high doses may also cause peripheral neuropathy and toxicity. It is, therefore, advisable to avoid unnecessary use.

Biotin

Biotin, like pantothenic acid and pyridoxine, is widespread in the foods we eat, and deficiency is almost unknown. It is also made by the natural flora of the intestine. Raw eggs contain the protein avidin, which has an affinity for biotin. Deficiencies have occurred extremely rarely in people with a diet consisting mainly of raw eggs. Cooking eggs destroys avidin, and therefore the normal consumption of eggs does not affect biotin absorption. Biotin functions as a coenzyme in metabolic pathways involving carboxylation reactions.

Deficiency, which is usually induced experimentally, results in anorexia, vomiting and dermatitis.

Biotin seems devoid of any toxic action if taken in excess. Abuse of this vitamin does not seem to be common, as no great healing properties have been attributed to it.

✚ CLINICAL CONSIDERATIONS

As with pantothenic acid and pyridoxine, biotin is readily available in many food sources. It may be present in a multivitamin preparation; however, by consuming a balanced diet, it is unlikely that an individual would experience a deficiency in biotin.

Folic acid

Folic acid, sometimes referred to as folacin (although folacin is actually a mixture of folic acid and its derivatives), was

initially discovered as a factor present in the proprietary yeast extract Marmite™ when Marmite was found to alleviate the symptoms of some types of anaemia. A search was made for the factor, which was folic acid. This type of anaemia is often associated with pregnancy, especially in women who have a diet lacking in leafy vegetables. The name 'folic' is derived from the Latin *folium*, meaning 'leaf'.

Folic acid is found in nearly all plant products. The only reasonable supplies obtained from non-vegetarian sources are in liver, with a small amount also being found in crab meat.

Deficiency of folic acid causes megaloblastic (or macrocytic) anaemia. This is one of the most common deficiency states and is discussed along with other aspects of folic acid in Chapter 50. There have been many reports linking congenital deformities of the nervous system, such as spina bifida, to low folic acid intake in pregnancy. There is little doubt that this is so, and so folic acid supplementation before and during pregnancy is strongly advised. This use of folic acid has been recommended for many years by some physicians, but absolute proof has been forthcoming only recently.

Adequate intake of folic acid can reduce the plasma concentration of the amino acid derivative homocysteine, a possible risk factor for coronary heart disease and stroke. Research has shown that 500 μg folate per day reduces the risk of stroke in high-risk patients by 20 per cent. Vitamin B_6 supplementation also affects homocysteine levels and has been shown to reduce the risk of heart disease in women.

High-dose folate may reduce the incidence of adenomatous polyps in the colon. It also reduces the incidence of gastric cancer in dogs. Whether the latter can be extrapolated to humans is not yet clear.

✚ CLINICAL CONSIDERATIONS

For women considering pregnancy, folic acid should be taken for at least 1 month before the anticipated conception and for at least the first 3 months after conception to decrease the incidence of neural tube defects. For women who have had a child with a neural tube defect, in women with a family history of this condition, and in woman taking antiepileptic medications (which can decrease the absorption of folic acid), the oral dose is 5 mg daily. For women with no previous history of neural tube defects and in women not taking antiepileptic medication, the oral dose is 0.5 mg daily. Folic acid should be stored at room temperature and protected from heat and light. It is important to exclude vitamin B_{12} anaemia before administering folic acid to treat megaloblastic anaemia. High doses of folic acid can correct the anaemia of vitamin B_{12} deficiency but cannot correct the associated neurological damage.

Vitamin B_{12} (hydroxocobalamin)

This vitamin is often found as **cyanocobalamin** in pharmaceutical preparations, which, until recently, was the only form of the vitamin obtainable. When vitamin B_{12} was first isolated from liver in 1948, it was as cyanocobalamin, so called because the molecule was associated with a cyanide group. Several years passed before it was discovered that the extraction process had changed the naturally occurring **hydroxocobalamin** into the unnatural cyanocobalamin. As far as we are concerned, there is no difference in activity between the two forms. When cyanocobalamin was first marketed, it was under the name Cytamen™; when hydroxocobalamin came along, the manufacturers named it Neo-Cytamen™ (*neo* meaning 'new'). Both are still used today. Hydroxocobalamin, as the name implies, has a cobalt atom present in its molecular structure.

This vitamin is found only in animal products, being originally made by bacteria in the gut of herbivores. As so little of the vitamin is needed (2 μg per day), dietary deficiencies are exceedingly rare, even in vegetarians, as there are adequate amounts present in all dairy products and eggs. Deficiencies have been known to occur in vegans (people who eschew all forms of animal products), a diet that can be dangerous, especially in infants. Only very few vegans become deficient in hydroxocobalamin, however, as plant products are usually contaminated with some animal material, which will provide enough of the vitamin. Deficiency symptoms of hydroxocobalamin may not appear until 5 years or more after its exclusion from the diet, as the body stores enough in the liver to last this time.

In spite of this, hydroxocobalamin deficiency is not rare, because there may be malabsorption of the vitamin. As discussed in Chapter 50, the stomach produces an intrinsic factor (factor of Castle) necessary for the absorption of the vitamin in the ileum. This factor may be absent or lacking in gastritis and after partial or total gastrectomy.

Deficiency of hydroxocobalamin results in a megaloblastic anaemia similar to that caused by folic acid deficiency. Associated with the anaemia in this case is irreversible damage to the myelin sheath of peripheral nerves and in spinal tracts. To differentiate between this type of anaemia and that caused by folic acid deficiency, it is called pernicious or addisonian anaemia. Folic acid in high doses can mask the megaloblastic anaemia in pernicious anaemia, but the myelin degeneration will continue unabated. The use of hydroxocobalamin and cyanocobalamin in this type of anaemia is discussed more fully in Chapter 50.

✚ CLINICAL CONSIDERATIONS

It is advisable to confirm the diagnosis and the cause of vitamin B_{12} deficiency before use. Causes of vitamin B_{12}

deficiency include pernicious anaemia, total or partial gastrectomy, ileal disease or resection, certain drugs and inadequate diet. If the cause of deficiency is malabsorption, then the vitamin should not be given orally, as absorption will be limited. As this vitamin can cause hypokalaemia and cardiac arrest with high doses, monitor potassium levels at the start of therapy and correct hypokalaemia as required. As vitamin B_{12} can mask folic acid deficiency, it is important to determine whether the individual is also deficient in folic acid. If the cause of vitamin B_{12} deficiency is pernicious anaemia, then lifelong treatment is needed.

VITAMIN C (ASCORBIC ACID)

Vitamin C is **ascorbic acid**. Unlike most other mammals, humans do not have the ability to make it, and so we must obtain vitamin C through our diet. This vitamin is viewed by some to be a panacea, curing all ills and even increasing one's intelligence. On the shelves of pharmacies and healthfood shops, the array of vitamin C preparations is staggering. There is a great deal of debate regarding the ideal vitamin C intake, with some practitioners advocating up to 10 g or more per day, but the RDA is about 50 mg per day. The Linus Pauling Institute recommends an intake of at least 400 mg daily – the amount that they claim has been found to fully saturate plasma and circulating cells. As this is a water-soluble vitamin, anything above the required amount is simply producing expensive urine, although the antioxidant properties may be better at high blood levels of the vitamin.

It is doubtful that all of the beneficial effects attributed to ascorbic acid have a scientific basis. There is, however, evidence that it may do more than only prevent scurvy, the name given to the deficiency state of this vitamin.

Ascorbic acid is, like the carotenoids and retinoids, an antioxidant. Any of its proposed benefits, such as lowering the incidence of atherosclerosis, may be due to its protective effect on unsaturated fatty acids. Ascorbic acid accelerates the absorption of iron from the intestine, keeping it in its more absorbable ferrous (Fe^{2+}) state rather than the ferric (Fe^{3+}) state. Ferrous iron is easily reduced to the ferric state in the anaerobic conditions of the intestine. Other needs for ascorbic acid are in the biosynthesis of catecholamines and the adrenal steroid hormones. Plasma ascorbate levels are reduced in times of stress owing to the increased synthesis of these compounds, and it is probable that dietary intake of vitamin C should be increased during these times. The best-known function of ascorbic acid is that relating to its deficiency disease. It is essential for the production of the protein collagen. Collagen, being the main structural protein of many types of connective tissue, is constantly being replaced in normal tissue turnover and even more so in tissue injury.

The two best sources of vitamin C are capsicum peppers and guavas – not citrus fruits as is commonly believed; kiwi fruit are also very high in ascorbic acid. Most vegetables contain ascorbic acid, and therefore scurvy is not common today, although it can occur in colder climates, where fresh fruit and vegetables are not easily obtainable in winter. Ascorbic acid is very labile, and both heat and long-term storage cause its degradation. Inuit people are thought to suffer from mild vitamin C deficiency due to their mainly carnivorous diet.

The symptoms of scurvy are due to the degeneration of connective tissue, and the body disintegrates before death ensues. Scurvy was very common among early sailors, who had no fresh fruit and vegetables available while at sea for several months. Dr James Lind was the first person to encourage sailors to eat citrus fruit on long voyages. He advocated the use of limes, hence the nickname 'limeys' for British sailors. In his time, Lind was scoffed at, even though his research was sound. Captain James Cook was instrumental in promoting the avoidance of scurvy and made his men grow wheat on board his ships for consumption of the shoots.

The response of scurvy to treatment with ascorbic acid is dramatic. The name 'ascorbic' means 'without scurvy', and anything that prevents this disease is said to be antiscorbutic.

If large doses of ascorbic acid are used, plenty of water should be taken at the same time to avoid the formation of oxalate kidney stones, an adverse effect that is strongly genetically determined. Diarrhoea and gastritis can occur with large doses. As ascorbic acid is a reducing compound and similar to glucose in structure, large amounts present in the urine can give false-positive results when testing for glucose. Other reported problems such as tooth enamel being slowly dissolved and rebound scurvy remain to be confirmed.

There is no evidence that ascorbic acid, even in high doses, prevents the common cold, but the symptoms and the duration of the disease may be lessened. Patients who have had a stroke show a lower than normal plasma concentration of ascorbic acid, but whether this is of any importance in the aetiology of stroke is still a matter for conjecture. There is also a tenuous association between low plasma levels of ascorbate and stress.

✚ CLINICAL CONSIDERATIONS

Vitamin C is contraindicated in patients with allergy to tartrazine or sulphites. Large doses are contraindicated in women. As vitamin C can increase the absorption of iron, this interaction can be used for therapeutic benefit. To prevent faintness and dizziness, intravenous infusions of vitamin C should not be given too rapidly. Renal calculi associated with vitamin C therapy can be minimised by ensuring the patient has an adequate fluid intake.

VITAMIN D

Vitamin D is unique among the vitamins as it is not always necessary in the diet and acts as a prohormone. As long as enough ultraviolet (UV) radiation, in the form of sunlight, irradiates the skin, sufficient vitamin D can be made for our needs. The precursors for this process can be obtained from cholesterol or sterols in vegetable sources. Once vitamin D is made, it is modified chemically by the liver and then the kidneys. Vitamin D acts on other parts of the body, as would a hormone. The pathways for these syntheses, transformations and actions are shown in Figure 61.3. The end product is 1,25-dihydroxycholecalciferol, or **calcitriol**.

When the precursor for vitamin D is obtained from the diet, it is known as ergosterol. This is converted into **vitamin D_2**, or **calciferol**, in the skin by the action of UV light. The action of UV light on 7-dehydrocholesterol, the body's precursor, forms **cholecalciferol**, or **vitamin D_3**. (Vitamin D_1 has been relegated to the history books, as it was a mixture of both forms, originally thought to be only one compound.) 'Calciferol' means 'calcium-bearing'. Both forms are equipotent in humans. Vitamin D is present in high concentrations in fish and fish products, especially cod and halibut liver oils. Only very small amounts are present in dairy products, which are usually fortified with synthetically prepared vitamin D_2. This is particularly important in some countries in the northern hemisphere, where the climate prohibits skin exposure to the sun.

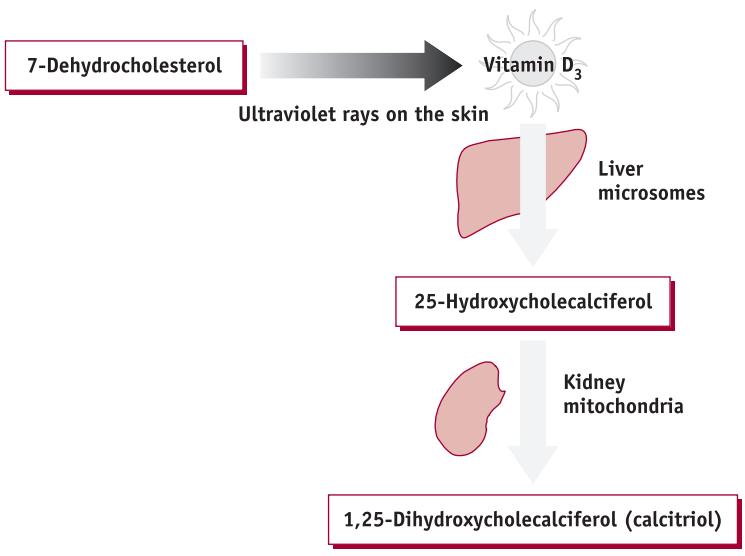
The function of calcitriol in the body is to regulate nearly all aspects of calcium and phosphate use by the body, from absorption to excretion. The proper function of calcitriol also depends on the presence of parathyroid hormone (PTH). (For details on this, see a physiology textbook.) The controlling factor for calcitriol synthesis is hypocalcaemia. If this occurs, then more calcitriol and PTH are produced. This causes some demineralisation of bone and increased calcium absorption from the intestine. Without the controlling influence of vitamin D on calcium metabolism, bone mineralisation is decreased.

In children, this results in rickets. The long bones, especially in the legs, remain in a semicartilaginous state and bend outwards because of the weight of the body, which leads to bow legs and other bone deformities. This was common during the Second World War in Glasgow due to a lack of sunlight and fortified dairy products. There are still people in Glasgow who had childhood rickets. In adults, deficiency causes osteomalacia, a condition not unlike osteoporosis, where bones fracture easily. In Middle Eastern countries, this still occurs in some women who, owing to their religious beliefs, keep their bodies completely covered.

Vitamin D is one of the most dangerous vitamins, and, if taken in excess, it causes death. One of the main symptoms of vitamin D hypervitaminosis is hypercalcaemia, which leads to deposition of bone in soft tissues and kidney damage. Neurological problems can also be caused, leaving some children permanently retarded. This happened in post-war Britain, when many children were overdosed with cod liver oil and orange juice supplemented with vitamin D. Excessive exposure to sunlight does not cause hypervitaminosis D but may result in melanomata.

The only therapeutic use of vitamin D is in the treatment of osteomalacia and rickets, although it can be used to help reduce osteoporosis in postmenopausal women.

FIGURE 61.3 VITAMIN D METABOLISM



Substances with vitamin D activity are termed antirachitic. **Calcipotriol**, a derivative of vitamin D, is used in the treatment of psoriasis (see Chapter 78). In 2001, a team of researchers from San Francisco reported that supplementary vitamin D in postmenopausal women drastically reduced (~30 per cent) cardiovascular deaths. It has also been suggested that adequate vitamin D intake may decrease the risk of autoimmune diseases.

✚ CLINICAL CONSIDERATIONS

Monitor the patient's eating and bowel activities, because dry mouth, nausea, vomiting, metallic taste and constipation may be early signs of toxicity. Malabsorption of vitamin D from inadequate bile or hepatic dysfunction may require the addition of bile salts to the therapeutic regimen. High doses of vitamin D can cause hypercalcaemia, which may require aggressive diuresis and intravenous hydration. Impaired renal function and bone demineralisation can also occur, especially at high doses. It is advisable to monitor serum calcium, phosphorus, potassium and urea levels when high therapeutic doses are used. Vitamin D is a fat-soluble vitamin that may accumulate in the body.

VITAMIN E (THE TOCOPHEROLS)

There are several tocopherols with **vitamin E** activity, the most abundant in animal tissue being **alpha-tocopherol**. The word 'tocopherol' comes from the Greek words for 'childbirth' and 'to bear' because a lack of vitamin E causes spontaneous abortions in rats. When first reported, this led to many myths about vitamin E. It was thought that vitamin E was needed for normal fertility in humans, leading to charlatans claiming it had aphrodisiac qualities and could improve sexual potency in men. This has no basis, and there is no evidence that vitamin E deficiency leads to abortion in humans.

The function of vitamin E is mainly as an antioxidant in cell membranes, preventing the oxidation of unsaturated fatty acid constituents. Many factors, such as radiation, light, pollution and cigarette smoke, can induce chemical changes in the body's chemicals, resulting in free radicals, highly reactive substances that are lacking in electrons. To try to stabilise themselves, free radicals capture electrons from other chemicals, such as unsaturated fatty acids. In the process, they oxidise the acids. Free radicals are thought to play a part in the degenerative changes seen in many diseases, including atherosclerosis and cancer. Vitamin E may help to 'mop up' these free radicals, slowing down the degenerative changes. Vitamin E also appears to be necessary for haemoglobin formation.

Vitamin E is found principally in plant foods. Wheatgerm is particularly high in vitamin E, which explains its popularity in health foods. Most vegetable oils also contain appreciable amounts of vitamin E.

Deficiency of vitamin E is rare but can lead to anaemia in babies, especially premature infants. In deficient adults, erythrocytes may have a shortened lifespan.

Vitamin E is relatively non-toxic and may cause problems only in the mega-dose range of about 1000 mg per day in adults (the RDI is 10 mg per day). At this range, interference with thyroid function and a prolonging of blood clotting time may occur. The role of vitamin E in many skin formulations to reduce scarifying and wrinkles appears to be unfounded.

✚ CLINICAL CONSIDERATIONS

Assess the patient with liver or gall-bladder disease for response to therapy. Adequate bile is essential for vitamin E absorption. Warn patients against self-medicating with large doses because thrombophlebitis may occur. This is a fat-soluble vitamin that may accumulate in the body.

VITAMIN K

The 'K' in this vitamin is derived from the German word for coagulation, *koagulierung*, as the vitamin is needed for this process in the blood. **Vitamin K** exists in at least two naturally occuring forms: phylloquinone, which is found in plants, and menaquinones, which are made by gut bacteria and found in animal tissues. Menadione and phytomenadione are synthetic forms of Vitamin K. These forms are often abbreviated to vitamins K_1, K_2 and K_3, respectively. As much of our vitamin K is made by intestinal bacteria, the RDI is not known with any certainty. One of the major causes of vitamin K deficiency is the use of broad-spectrum antibiotics, which kill the intestinal bacteria, thus stopping that supply.

Vitamin K is needed for the formation of a number of biologically important proteins, including osteocalcin, which is involved in calcium metabolism. Prothrombin is probably the most important of these proteins. As discussed in Chapter 46, this is one of the initiating factors in the blood-clotting cascade after being converted to thrombin. Lack of vitamin K leads to an increased prothrombin time, with the resultant tendency to haemorrhage. The coumarin group of drugs, such as **warfarin**, are vitamin K antagonists. They are useful in preventing thrombotic episodes. Newborn babies are susceptible to a lack of vitamin K until their intestinal flora have been established. It is common practice to administer a vitamin K supplement during the first days of life. Until recently, vitamin K was given parenterally, but there were reports that administration by this route was associated rarely with an increase in liver cancer, which led to the administration of the vitamin by the oral route. More recently, studies in the USA and Sweden have refuted this claim, and the use of parenteral vitamin K is regarded as appropriate by many authorities.

There is no indication for vitamin K therapy, except in the newborn and in deficiency states.

Excess vitamin K has caused problems when administered prophylactically to babies, when it can cause haemolysis. This is particularly the case with the synthetic menadione. Mega-doses in adults can lead to haemorrhagic problems – rather paradoxically. Vitamin K as menadione (menaphthone) is available as tablets, and phytomenadione is available in a parenteral form and as tablets.

✚ CLINICAL CONSIDERATIONS

Monitor the prothrombin time to determine the effectiveness of therapy. If severe bleeding occurs, other treatment measures may be required, such as fresh frozen plasma or whole blood. The intravenous route should be avoided, as anaphylaxis and transient hypotension can occur with fast intravenous administration. For this reason, the intramuscular and oral routes are preferred. This is a fat-soluble vitamin that may accumulate in the body.

CLINICAL MANAGEMENT

Vitamins

Assessment

- Obtain the patient's dietary history, including foods consumed, food preparation, coping patterns and knowledge about nutrition.
- Assess the presence of debilitating disease and gastrointestinal disorders.
- Assess the patient's height and weight.
- Assess for the presence of manifestations indicative of the vitamin deficiency.
- Obtain baseline diagnostic studies of the specific vitamin deficiency, e.g. serum folic acid levels.

Planning

- The patient's vitamin deficiency will be amended by the intake of a vitamin supplement and a well-balanced diet.

Implementation

- Continue to monitor diagnostic studies for the specific vitamin deficiency (e.g. serum folic acid levels) in a patient receiving a therapeutic dose of a particular vitamin.
- Monitor the manifestations indicative of the vitamin deficiency to determine the effect of therapy.
- Chewable tablets should be chewed thoroughly before swallowing.
- Take care when administering fat-soluble vitamins to children, as they are more sensitive to high doses.
- It is important to adjust phosphase supplements in patients with vitamin-D-resistant rickets.
- Avoid calcium supplementation in combination with vitamin D at a therapeutic dosage unless dietary intake of calcium is clearly inadequate.

Patient teaching

- Encourage the patient to maintain a food diary to assist in the monitoring of food intake.
- Advise the patient to adopt a well-balanced diet.
- Advise the patient to check the expiry date of vitamin preparations at the time of purchase, as vitamin potency and effectiveness are reduced if the preparations are past their expiry date.
- Instruct the patient not to consume an excessive amount of alcohol, as this can cause vitamin B deficiencies.
- Advise the patient not to take excessive doses of vitamins. When discontinuing excessive doses of vitamins, the doses should be reduced gradually to prevent a vitamin deficiency.
- Explain that large doses of vitamin C do not cure or prevent colds.
- Recommend folic acid for female patients of childbearing age for at least 1 month before anticipated conception and for at least the first 3 months of pregnancy to prevent neural tube defects in the fetus. Further information should be sought from the patient's obstetrician or midwife.
- Alert the patient that taking large doses of vitamin C with aspirin or sulphonamides, and even on its own, can cause kidney stones.
- For the patient taking a vitamin D preparation for a therapeutic cause, advise the patient to avoid consuming over-the-counter preparations that contain vitamin D substances.
- Advise the patient with pernicious anaemia that lifelong therapy with monthly vitamin B_{12} injections is required.

Evaluation

- Evaluate the effectiveness of vitamin therapy in addressing a vitamin deficiency.
- Determine whether the patient's diet includes the appropriate foods required for a well-balanced diet.

SUMMARY

- Vitamins are necessary constituents of the diet.
- Lack of vitamins in the diet leads to deficiency diseases.
- The fat-soluble vitamins A and D are toxic in large amounts.
- The water-soluble vitamins are relatively non-toxic in large amounts, but the consumption of large amounts is inadvisable as most can cause adverse effects.
- Some vitamins and their derivatives can be used in the pharmacological treatment and/or prevention of certain disease states.

1. Why may patients on cholestyramine therapy have some vitamin deficiencies?
2. Carotene is widespread in the plant kingdom. Would you expect mushrooms to be a good source? Why?
3. Why would one consider polar-bear liver to be poisonous?
4. Why do individuals with an alcohol problem often become deficient in the B vitamins?
5. Why are multiple B vitamin deficiencies not unusual?
6. What food preparative processes are harmful to the ascorbic acid content of foods?
7. Ascorbic acid is available as the free acid, sodium salt and calcium salt. Suggest what problems may be associated with each, if taken excessively. What advantage might the salts have over the free acid?
8. What is the difference between osteomalacia, osteoporosis and rickets?
9. Why is calciferol given to elderly patients by injection?
10. Why is vitamin D deficiency uncommon in Australia?
11. Define the term 'antioxidant'. Why are antioxidants of importance in the body?
12. Alberto Ripaldi, a 55-year-old patient, is admitted to hospital with chronic liver disease. The doctor orders an intravenous infusion of 10% glucose with vitamin B complex and vitamin C. Why is this infusion administered?
13. Jack Jones, a 22-year-old professional basketball player, takes 1 g vitamin C daily. What product education would you offer Mr Jones?
14. As a midwife in the delivery suite, you are required to administer an intramuscular vitamin K preparation to Massoud Hussein, a newborn boy. Why is this preparation administered?
15. What potential problem is associated with the administration of mega-doses of vitamin C in a patient who is also taking aspirin or sulphonamides?
16. What are the common names of vitamins B_1, B_2, B_6 and B_{12}? What are the uses of these vitamins?

MINERALS

62

CHAPTER SIXTY-TWO

OBJECTIVES

KEY TERMS

Elemental ions
Macrominerals
Microminerals
Mineral supplementation

After completing this chapter, the reader should be able to:

- **describe the role of trace elements in human metabolism and disease;**
- **outline the role of fluoride in the prevention of tooth decay and osteoporosis;**
- **describe the role of zinc salts in therapeutics.**

IT IS STILL UNCLEAR JUST HOW MANY MINERALS, OR elemental ions, the human body requires for normal functioning. Some minerals are found as contaminants in almost everything we eat and therefore find their way into the body, where they can be detected using the techniques available to the analytical chemist, such as atomic absorption spectrophotometry. The presence of an element in tissues therefore does not imply a function. Conversely, as some minerals are needed in minute quantities, it is difficult to say that all those present are not needed by the body.

In this chapter, we look at some of the minerals that have been proven to have a function in humans, with particular emphasis on those that can be used therapeutically. Minerals can be divided into two groups, depending on the relative requirements by the body. Those that are needed in fairly large quantities are termed 'macrominerals' and include calcium, phosphorus, magnesium, sodium, potassium and chloride. The others are the 'micronutrients' or 'microminerals' and include iron, iodine, zinc, copper, fluorine, sulphur, selenium, chromium, manganese and molybdenum. Cobalt is not dealt with here as it is an integral part of the vitamin B_{12} molecule and is dealt with in Chapter 61. Normally, the metallic minerals (and some other elements) are referred to as if they were in the atomic state, but the ionic or organic state is implied.

THE MACROMINERALS

Calcium

Calcium is the most plentiful element in the body, being a major constituent of the inorganic part of bone. In the remainder of the body, it participates in many biochemical reactions, including the mechanisms of blood clotting, neural transmission and muscular contraction (including of cardiac muscle). It is of vital importance that calcium levels in the blood are controlled strictly. Too much calcium leads to cardiac failure (calcium chloride is included in the lethal injection given in judicial killing in some US states), but too little calcium leads to tetany, which, if severe, can result in fatal muscular convulsions. Both vitamin D and parathyroid hormone (PTH) can normally keep the calcium levels constant, principally by mobilising calcium from bone if hypocalcaemia is present and shunting it back into bone in hypercalcaemia. Both hypocalcaemia and hypercalcaemia are due to factors involving either vitamin D or PTH. Benign hypercalcaemia due to excessive absorption of calcium may result in calcification of soft tissues and renal damage. Lack of calcium in the diet results in osteoporosis, in which bone is less dense, brittle and weak. In women, osteoporosis can also result from lack of oestrogens after oophorectomy or menopause.

Calcium is usually ubiquitous in the diet, but only a few foods provide reasonable amounts; dairy products are the best sources. Various factors affect the absorption of calcium from the intestine. Vitamin D and PTH are needed for absorption (see Chapter 61). Some foods, such as unrefined cereals, contain phytic acid, which combines with calcium, rendering it unabsorbable. Oxalic acid, which is present in spinach and rhubarb, also has this property. These foods are problematic only if eaten excessively, however.

Osteoporosis after the menopause is the most common condition in developed countries caused by a disturbance in calcium metabolism. This condition is not usually due to a lack of calcium but to a lack of oestrogens, which are necessary for normal bone metabolism. As discussed in Chapter 58, the use of **oestrogen** replacement therapy in postmenopausal women can help prevent this condition, but this therapy is not without adverse effects. The use of calcium supplements premenopausally and postmenopausally to build up calcium stores is advocated by some but denounced by others. There is evidence that moderate calcium supplementation along with exercise can help prevent osteoporosis. For an unknown reason, calcium citrate may be the best form of calcium to take orally. The bisphosphonates also have a role in the management of osteoporosis (see Chapter 57).

Calcium, usually as the chloride, is given intravenously in severe hypocalcaemia and in cardiac resuscitation. When used intravenously, care must be taken with digitalised patients owing to calcium's synergism with the cardiac glycosides. As the carbonate, it is incorporated into some antacids (see Chapter 53).

As calcium is necessary for normal blood clotting, anticoagulants used in vitro work by combining with the calcium. Commonly used forms are **ethylene diamine tetra-acetic acid** (EDTA), the oxalates and citrates. Note that when citrated blood is used in blood transfusions, hypocalcaemia may result.

✚ CLINICAL CONSIDERATIONS

Calcium solutions should not be injected intramuscularly or subcutaneously because they are extremely irritant and may cause tissue necrosis. Different oral preparations of calcium are available that may influence patient adherence, for example chewable and effervescent tablets. Patient preferences should be sought to ensure good compliance. Intravenous injection of calcium gluconate is preferred to that of calcium chloride because the former causes less local irritation and has a more gradual onset of action. When administering intravenous calcium, titrate the dose to pulse rate, blood pressure and electrocardiogram (ECG) changes.

Phosphorus

As **phosphorus** is so widespread in the diet, deficiencies are rare and are usually due to secondary factors.

Phosphorus, apart from being (with calcium) an important constituent of bone, is involved in numerous biochemical reactions when combined with vitamins and either purine or pyrimidine bases. The latter are integral components of the nucleic acids and are involved in many biosynthetic and energy-involving pathways.

Phosphorus deficiency can occur in the abuse of antacids containing aluminium compounds. Aluminium combines with phosphates to produce aluminium complexes, which renders the phosphates unavailable for absorption. This effect is utilised in the rare condition of hyperphosphataemia, whereby aluminium salts can be given to the patient to indirectly lower the phosphate levels in the blood. Deficiency of phosphorus causes blood-cell dyscrasias, muscular weakness and bone pain. Excessive amounts of phosphorus in the diet can lead to calcium deficiency by preventing the incorporation of calcium into bone and increasing its renal excretion.

Substances called glycerophosphates are sometimes included in tonics. It is doubtful whether they contribute to any beneficial effect.

✚ CLINICAL CONSIDERATIONS

Phosphorus is usually administered in the form of phosphate ion preparations, which often contain sodium and potassium. Consideration should be given to the sodium and potassium content before administering these to patients with electrolyte imbalance, impaired renal function or

cardiac failure. Soft-tissue calcification may occur with intravenous administration of phosphate ions, which is less likely to occur if the infusion is given slowly. Excessive doses of phosphorus may produce hypocalcaemia in some cases. This effect is reversible with a dosage adjustment. Oral effervescent preparations should be dissolved in water.

Magnesium

Magnesium takes part in many biochemical reactions, acting as a coenzyme, and considerable amounts can be stored in bone. Magnesium deficiency can result from malabsorption problems and can occur in alcoholics. Slight deficiency causes nausea and apathy, whereas more severe deficiency can lead to sudden death from cardiac failure. It has been suggested that borderline magnesium deficiency can occur in areas with soft water and in people who use water softeners on their taps.

In healthy individuals, the ingestion of large amounts of magnesium as laxatives, antacids or nutritional supplements appears to be harmless. If the kidneys are not functioning properly, however, hypermagnesaemia may result, which can lead to lethargy, slurring of speech and unsteadiness. Spasmodic contractions of the coronary arteries can lead to sudden death. Oral magnesium salts are used in combination with aluminium to counter the constipating effects of aluminium. This combination can be used to decrease the high phosphate levels that occur in renal disease.

Magnesium supplementation has been reported to increase the solubility of calcium salts in the urine and may decrease the incidence of renal calculi in people predisposed to these caliculi.

Magnesium sulphate can be used for the recurrent seizures of eclampsia and may be used in women with pre-eclampsia.

✚ CLINICAL CONSIDERATIONS

When administering intravenous magnesium, watch for severe respiratory depression and signs of heart block. Respirations should be over 16 breaths per minute before the dose is given.

As magnesium is absorbed poorly from the gastrointestinal tract, it acts as an osmotic laxative and so the patient should be cautioned about the diarrhoea that may occur with magnesium therapy. Oral aluminium therapy can lead to constipation, while oral magnesium therapy can cause diarrhoea; the combined use of aluminium and magnesium can decrease the incidence of these gastrointestinal effects.

Sodium, potassium and chloride

Sodium, **potassium** and **chloride** are the main electrolytes of the body. Sodium is found mainly in the extracellular fluid and potassium in the intracellular fluid. These cations are normally associated with the chloride anion. The cations are involved in the maintenance of osmotic balances between the various body compartments and of an electrochemical potential difference between the intracellular and extracellular compartments. This potential difference is necessary for the transport of other ions into and out of cells, and in neural conduction. Apart from being associated with the sodium and potassium ions, chloride ions are needed for the production of hydrochloric acid in the stomach.

A dietary deficiency of sodium and chloride ions is unknown; the problem with sodium is normally associated with an excess, although hyponatraemia can occur with diuretic use and in diabetes insipidus (see Chapter 47). If excess sodium is taken in the diet, usually by its addition to food as table salt, the kidneys excrete the excess, but this can lead to hypertension in susceptible individuals. The kidneys need water to excrete the excess sodium, hence the thirst caused by high-sodium foods such as salted peanuts. This leads to hypervolaemia, which on a long-term basis can lead to hypertension. Drinking seawater leads to dehydration, as the kidneys remove the extra salt by the excretion of essential body water. Most individuals can tolerate sodium in the diet at levels above that required, but it may be prudent for us to cut down on sodium intake. Several studies have shown that a reduction in salt intake in hypertensive individuals is beneficial; 'lite' salts are available consisting of potassium chloride and sodium chloride for people who still want the salty taste.

There is a misconception that during hot weather the intake of extra sodium as salt tablets is advisable. This may be helpful only in athletes and in people doing strenuous work. In such people, it is probably better to encourage the consumption of low-fat milk, fruit juices and sports drinks, which contain sodium and potassium, respectively, in a more palatable form. Sodium chloride tablets can irritate the stomach.

The role of potassium in body function, the causes and consequences of an imbalance and the uses of potassium clinically are addressed fully in Chapter 49. Potassium deficiency can result from the use of some diuretics, which promote urinary potassium excretion. This can cause cardiac dysrhythmias, and so it is important that people on such diuretics take some form of potassium supplement. Severe diarrhoea can also cause hypokalaemia. Potassium chloride is an irritant to the stomach mucosa, and so tablets are enteric-coated. The chloride is also irritant to the intestinal mucosa, and so problems can still occur. Another danger with potassium supplementation is hyperkalaemia, which is just as serious as hypokalaemia. If possible, diuretic-induced hypokalaemia is best treated by encouraging the patient to consume a high-potassium diet. Foods high in potassium include fruit juices, bananas, wholegrain cereals and nuts. Another way around this problem is to use a potassium-sparing diuretic (see Chapter 47) in conjunction with dietary changes.

✚ CLINICAL CONSIDERATIONS

Sodium and chloride are commonly found in intravenous fluids. For example, 0.9% normal saline is an isotonic fluid used to replace extracellular fluid. Sodium, potassium and chloride are found in oral preparations, including effervescent tablets and granules. Although there is the potential for fluid retention and circulatory overload, care should be taken when administering sodium-containing preparations to patients with conditions associated with fluid retention. Such conditions include renal failure, hepatic dysfunction and cardiac disease. Patients taking medications that tend to raise serum potassium levels (e.g. potassium-sparing diuretics) need to exercise care when using other medications containing potassium.

THE MICROMINERALS

Iron

Iron, as a micronutrient, is needed for the formation of haemoglobin and is used as a haematinic (an agent that raises haemoglobin levels and red blood cells). Iron is needed for the formation of some of the cytochromes and myoglobin, which have a similar haem portion to haemoglobin.

Iron exists in two ionic states, depending on its oxidative state: the ferrous (iron II) ion (Fe^{2+}) and the ferric (iron III) ion (Fe^{3+}). The ferrous ion is the one utilised by the body and, as the ferrous ion is easily oxidised to the ferric ion, antioxidants such as ascorbic acid help in the absorption of iron from the intestines. Iron is present in most meats, legumes, shellfish and wholegrains. As with calcium, the latter may not readily give absorbable iron due to the presence of phytic acid. Iron can accumulate in body tissues, and overload can occur with the ingestion of large amounts, which could be obtained from foodstuffs cooked in iron pots; this is the case with some African beers, which are brewed in iron vessels – consumption over a period of time can lead to haemochromatosis, a potentially fatal disease, in which iron deposits are found in many tissues.

✚ CLINICAL CONSIDERATIONS

Iron preparations are best consumed on an empty stomach because this allows for maximum absorption. Alternatively, the iron may be given with orange juice or after food to assist in decreasing gastrointestinal symptoms. Milk and antacids should be avoided with iron consumption. To prevent iron from staining the teeth, tell the patient to drink an iron elixir through a straw. Caution the patient not to substitute one iron salt for another, as amounts of elemental iron vary among preparations. As iron can be constipating, check with the patient about the number and consistency of bowel motions passed each day. To prevent constipation, the patient should be encouraged to eat plenty of fruit and vegetables and to drink lots of fluids. Monitor the haemoglobin level and haematocrit during therapy to determine the clinical response. Explain to the patient that iron may turn the stools black but that this effect is harmless.

Iodine

Iodine, being part of the thyroid hormones thyroxine and triiodothyronine, is discussed more fully in Chapter 57. This appears to be the only function of iodine in humans. An unusual aspect of iodine is that even though the dietary source is as iodide, this ion is converted into the element iodine during the iodination of the tyrosine molecule in thyroid hormone biosynthesis. The only other element used as such by the human body is oxygen.

The main sources of iodide in the diet are seafood and water. Deficiencies are common in areas away from the sea and where water levels are inadequate. Deficiency results in hypothyroidism and goitre. Excessive amounts of iodide can lead to similar conditions. Moderately high amounts of iodine in the diet can be bad for acne, and in areas where there are adequate amounts obtainable in the diet iodised salt should be avoided by people with acne.

Iodide, taken as iodine dissolved in potassium iodide solution, is useful when taken as a safety precaution in people who handle radioactive iodine. Iodine is preferentially taken up by the thyroid gland. If the gland, when saturated with normal iodine, is exposed to radioactive iodine, no more iodine can be taken and the radioactive iodine is excreted.

✚ CLINICAL CONSIDERATIONS

Oral Lugol's solution is a preparation taken for 7 days before thyroid surgery for Graves' disease. It is used to reduce the thyroid vascularity (see Chapter 57). Long-term use of this solution should be avoided, as it can exacerbate hyperthyroidism.

Zinc

Zinc is a component of many of the body's enzyme systems and is involved in the normal function of many physiological processes. Nearly all functional units of the immune system are affected deleteriously by zinc deficiency. Zinc plays a part in the maintenance of epithelial and tissue integrity through promoting cell growth and suppressing apoptosis and through its role as an antioxidant, protecting against free-radical damage during inflammatory responses. Research on zinc has shown it to be even more valuable than thought previously. Several studies have shown a reduction in cases of pneumonia, diarrhoea and malaria with zinc supplementation, especially in children. Zinc lozenges have been advocated for reducing the duration of the common cold, although

conclusive evidence for this is lacking. Similarly, nasal sprays of zinc appear to be of no value in upper respiratory tract infections. There is no conclusive evidence that zinc is beneficial in the treatment of acne.

Zinc is found in meat, eggs, oysters and, to a lesser extent, milk and wholegrain cereals. Like other divalent ions, it can complex with phytic acid. Zinc deficiency results in stunted growth and underdeveloped sex organs. (Perhaps this is why oysters are purported to have aphrodisiac properties.) Many other defects have been associated with zinc deficiency, and there are beliefs that it has panacean qualities, such as improving the senses of taste and smell, encouraging wound healing and restoring fertility. It appears that these claims are true only in cases of genuine dietary zinc deficiency, however. This may be so in children who eat little meat and in vegetarians, and so there may be a case for zinc supplementation here. Excess zinc supplementation can be dangerous as it can cause an increase in copper excretion, leading to copper deficiency (see below). Other problems with excessive zinc intake are atherosclerosis due to a rise in cholesterol and triglyceride levels, and gastric irritation. Mega-doses can result in acute toxicity and can be fatal. In view of this, it is recommended that zinc supplements should be no more than twice the recommended daily dose.

Zinc oxide is an astringent and is used in several proprietary topical preparations, such as zinc and castor oil ointment (see Chapter 78).

✚ CLINICAL CONSIDERATIONS

Prolonged use of zinc may lead to copper deficiency and anaemia. Therapy should be limited to short-term use. Instruct the patient to report signs of zinc hypersensitivity, including hives and shortness of breath. Monitor the effectiveness of zinc therapy, which should lead to a decreased incidence of skin lesions and improved wound healing.

Copper

Copper, like iron, is important for the synthesis of haemoglobin. Copper is not part of the haemoglobin molecule but is part of a coenzyme involved in the synthesis of haemoglobin. Copper is part of the molecule cytochrome oxidase, which is an integral part of the electron transport chain. Copper has its own protein, caeruloplasmin, for transporting it from the liver to the tissues. Good sources of copper are liver, shellfish, nuts and beans.

We need very little copper in the diet (about 2 mg daily) and copper deficiency is rare. Parts of Peru lack copper in the soil, and hence there is a general lack in the diet there, such that some Peruvian children have anaemia and bone disease. Excess zinc can cause copper deficiency, as can too much vitamin C, which blocks the absorption of copper.

Copper in excess is very toxic. Wilson's disease, or hepatolenticular degeneration, is a disease in which the body has a problem with normal copper balance and a build-up occurs in the tissues. This build-up of copper causes widespread tissue toxicity, with multiple symptoms. The drug **penicillamine** (D-penamine) can bind to copper and remove it from the tissues for excretion (see Chapter 21).

✚ CLINICAL CONSIDERATIONS

As the incidence of copper deficiency is relatively low, it does not need to be specifically replaced in the diet. Thus, copper tends to appear as a trace element in combination with other vitamins and minerals. Patients are advised to take these preparations in accordance with the required directions for use.

Fluorine

Fluorine is probably the most controversial of the microminerals, as it is added to many of the world's water supplies and must be consumed regardless of whether one wants to. There does not seem to be any doubt that, as a mineral, fluorine is an essential nutrient, not only to strengthen tooth enamel but also as a coenzyme for one or more enzyme systems. Many areas of the world have low fluoride concentrations in the soil and drinking water, and so people are deficient in the element, resulting in an increase in dental caries. There is also evidence that fluoride can strengthen bones in osteoporosis.

The fluoride ion is poisonous and can, even in amounts that occur naturally in some areas of the world, cause mottling of the teeth. This is the main argument put forward against fluoridation. Adherents to this view maintain that fluoride can cause many diseases, from warts to cancer, and that fluoridation is compulsory medication. Another argument against fluoridation is that the excess fluoridated water that ends up flushed into sewers and gardens may become an environmental pollutant. Fluoridation has been carried out in many parts of the world for many years with no untoward effects, the only noticeable outcome being a huge decrease in fillings in children's teeth. Even in areas where fluoride occurs naturally in water supplies at a higher concentration than that added artificially, there is no increase in morbidity, except for teeth mottling. The only food that contains reasonable amounts of fluoride is tea.

In areas where fluoride is low and municipalities do not add it to water supplies, it is prudent to treat children from birth with sodium fluoride tablets and to use fluoride toothpastes or mouthwashes. For osteoporosis and other demineralising bone diseases, a larger amount of fluoride is required.

✚ CLINICAL CONSIDERATIONS

Fluorine tablets may be dissolved in water, chewed or swallowed whole. Advise the patient that topical rinses and

gels should not be used by children younger than 3 years of age. For topical rinses and gels, instruct the patient to rinse around and between the teeth for about a minute and then to spit out. All preparations are most effective when used immediately after brushing teeth. Food and drink should be avoided for about 30 minutes after using a fluorine preparation.

Selenium

Selenium was for a long time considered too toxic an element to be an essential nutritional requirement, one of the problems being its implication as a carcinogen. It was not until the 1970s that it was noted that an area in China had a high incidence of oesophageal cancer, which was quickly linked to selenium deficiency. In the same area of China, the incidence of a cardiomyopathy called Keshan's disease is also high. Since these findings, many pathological events have been attributed to selenium deficiency, from sudden infant death syndrome (SIDS) to muscular dystrophy. It has also been shown that low plasma selenium levels are noted in men suffering from cancer of the prostate. There is now no doubt that selenium is an essential nutrient, being a key component of the glutathione peroxidase complex of enzymes, which are important in protecting tissues from oxidative damage. Selenium also suppresses the activity of a tumour-suppressing protein. Thus, like vitamin C and vitamin E, selenium is often classed as an antioxidant. Selenium and its implications in human disease is a topic being researched by scientists all over the world.

The best sources of selenium are seafood (especially mackerel), liver and kidney. Plant products are not a very good source, especially if grown in soil low in the element, as was the case in China. Selenium is very toxic if taken in excess. Selenium poisoning initially results in garlicky breath, followed by loss of hair and nails and disorders of the nervous system, which can result in death.

Selenium sulphide, as mentioned in Chapter 78, is a useful shampoo for the treatment of dandruff and seborrhoeic dermatitis.

✚ CLINICAL CONSIDERATIONS

Patients should be advised about the importance of adhering strictly to instructions and dosage relating to their selenium preparations to prevent selenium toxicity.

Chromium

Although not much is known about **chromium** as a micronutrient, it has long been considered essential. Trace amounts are necessary for what is known as the 'glucose tolerance factor', a metalloprotein essential for the normal functioning of insulin. It has been suggested that the lack of this may be associated with some cases of diabetes mellitus. Artificially induced chromium deficiency in animals results in a diabetic-like state.

Foods rich in chromium are yeast products, wholegrains, egg yolk, seafood and wine. It is unlikely that chromium deficiency is common in humans, and chromium supplements, as with selenium, should be treated with respect, being needed only in exceptional circumstances. Only 50 mg chromium salts per day can cause liver and kidney damage in experimental animals.

✚ CLINICAL CONSIDERATIONS

As the incidence of chromium deficiency is relatively low, it does not need to be specifically replaced in the diet. Thus, chromium tends to appear as a trace element in combination with other vitamins and minerals. Patients are advised to take these preparations in accordance with the required directions for use.

Manganese

The exact function of **manganese** in the human body remains unclear, but there does not seem to be any doubt that it is an essential nutrient. It is probably involved in several enzyme systems in the brain, bone, cartilage and heart.

Deficiency is unknown. Good sources are tea, nuts, vegetables and fruit.

✚ CLINICAL CONSIDERATIONS

Manganese tends to appear as a trace element in combination with other vitamins and minerals. Patients are advised to follow the directions when consuming these preparations.

Molybdenum

Molybdenum, an element many people have not even heard of, is an essential component of the enzyme xanthine oxidase. This enzyme, as discussed in Chapter 59, is involved in the formation of uric acid from the purine xanthine. Paradoxically, excess molybdenum in the diet can lead to a gout-like illness.

Molybdenum, like the other rarer micronutrients, is unlikely to present itself in a deficiency symptom, the daily requirements being so small. So far, there has been no recorded case of molybdenum deficiency. It is found in sufficient quantities in root vegetables, legumes, fruits and cereals.

✚ CLINICAL CONSIDERATIONS

Molybdenum may be present in preparations containing other vitamins and minerals. Patients should be advised to follow the instructions appropriately when consuming these preparations.

Sulphur

Sulphur is a natural component of the amino acids cysteine and methionine and, as such, is found in all proteins. Deficiency is therefore not a problem. The amino

acid cysteine, as the acetyl derivative (**acetylcysteine**), is particularly important in pharmacology and is dealt with in Chapters 22, 40 and 52. Sulphur is utilised by the body as sulphates in conjugation reactions, which are discussed in Chapter 14. Sulphur-containing organic compounds often have distinct smells.

✚ CLINICAL CONSIDERATIONS

If one maintains a diet containing adequate amounts of protein, sulphur deficiency should not be a problem.

Other elements

No doubt more of the 96 or so naturally occurring elements are needed for normal metabolism, but their function remains unknown. Elements such as **aluminium**, **silicon**, **tin**, **arsenic** and **vanadium** have been detected in human tissues, but whether they are contaminants or essential nutrients is unresolved. Many alternative therapists promote the use of small intakes of all or some of these elements, but absolute scientific proof that we need to supplement these in our diet is still lacking. Tin is almost certain to be an essential nutrient. Defective brain tissue in Alzheimer's disease (see Chapter 36) is high in aluminium, but whether this is the cause of the disease is doubtful. A probable explanation is that the pathologically affected tissue has an affinity for aluminium, which is a normal ion in the diet. Remember that a few decades ago selenium was considered a contaminant in human tissues that caused cancer, whereas in fact it may help to prevent some cancers.

CLINICAL MANAGEMENT

Minerals

Assessment

- Obtain the patient's dietary history, including foods consumed, food preparation, coping patterns and knowledge about nutrition.
- Assess the presence of debilitating disease and gastrointestinal disorders.
- Assess the manifestations of the condition affected by the mineral deficiency.
- Assess the patient's height and weight.
- Obtain baseline diagnostic studies of the specific mineral deficiency, e.g. iron levels.

Planning

- The patient's mineral deficiency will be amended by the intake of a mineral supplement and a well-balanced diet.

Implementation

- Continue to monitor diagnostic studies for the specific mineral deficiency, e.g. iron levels.
- Monitor the manifestations of the condition affected by the mineral deficiency.
- Administer an intramuscular iron injection using the Z-track technique to avoid leakage of iron into the subcutaneous tissue and skin. If contact is made with the skin, iron solution can irritate and stain the skin.

Patient teaching

- Encourage maintenance of a food diary to assist in the monitoring of food intake.
- Advise the patient about following a well-balanced diet. Mineral supplementation is not usually necessary for healthy individuals consuming a balanced diet.

Evaluation

- Evaluate the effectiveness of mineral therapy in addressing a mineral deficiency. For example, for iron therapy, the effectiveness is determined by evaluating whether the patient is fatigued or short of breath and by assessing the haemoglobin level.
- Determine whether the patient's diet includes the appropriate foods required for a well-balanced diet.

SUMMARY

- A few minerals are needed in relatively large amounts; these are called macrominerals.
- Many minerals are needed in small amounts; these are called microminerals.
- Deficiencies in microminerals can lead to deficiency disorders.
- Some microminerals are beneficial in preventing certain diseases not associated with a direct dietary deficiency.
- Large amounts of microminerals are associated with toxicities.

1. Arsenic and other poisonous minerals are found in human tissues. Does this mean they have biochemical roles?
2. What element acts as an antioxidant, and of which enzyme system is this element a part?
3. What are the symptoms of hypokalaemia and hyperkalaemia?
4. An 80-year-old patient takes frusemide 40 mg each morning, and one potassium supplement tablet in the morning and at night for congestive cardiac failure. She complains of a severe 'tummy upset', which you determine is due to the potassium supplement. What should she do to prevent this manifestation from occurring again?
5. Explain whether calcium tablets are of benefit in a postmenopausal woman who has a predisposition to osteoporosis.
6. Lee Chui-Yui, a 35-year-old patient, tells you that she often takes sodium chloride tablets during heat waves to replace fluid lost during sweating. What would be your response?
7. Explain the difference between the ferric and ferrous forms of iron. How would you evaluate the effectiveness of prescribed iron therapy?

AMINO ACIDS

63

CHAPTER SIXTY-THREE

OBJECTIVES

KEY TERMS

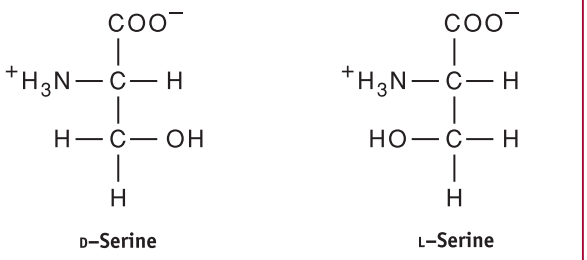
Amino acids
Disorders of metabolism
Phenylketonuria
Maple-syrup urine disease
Cystic fibrosis
Hepatic encephalopathy

After completing this chapter, the reader should be able to:

- **describe the difference between the D- and L-forms of amino acids;**
- **explain the significance of amino acids in disorders of metabolism;**
- **describe the treatment of metabolic disorders using the various amino-acid-free preparations;**
- **list the amino acids that can be used in therapeutics.**

AMINO ACIDS ARE NOT GENERALLY DISCUSSED AS SUCH IN pharmacology textbooks but, as some act as neurotransmitters, others are involved in drug metabolism and at least one is used as a drug, it is not inappropriate to deal with certain types in this chapter.

FIGURE 63.1 STEREOISOMERS OF SERINE



D–Serine L–Serine

Most amino acids occur in two possible forms, called optical isomers. Essentially, this occurs in molecules having a carbon atom with four different attachments, which can be arranged in two spatially distinct forms denoted D and L. Figure 63.1 shows this for the amino acid serine. The L stands for levorotatory (left) and the D for dextrorotatory (right) and describes the particular three-dimensional arrangement of the molecule. The difference between the two forms can be related to the handedness of the molecule. As an analogy, if you look at both your hands, you will see that they are anatomically identical but their arrangement in space is different. If you had a bucket of left hands and right hands, you would have no problem separating them from each other. D- and L-forms of amino acids are similar.

In glycine, there is no optical isomerism because two of the groups on the central carbon atom are identical. L-Amino acids represent the vast majority of amino acids utilised. D-Amino acids are found as components of the cell walls of bacteria.

With the sugars, such as glucose, there are also two forms, but the body uses only the D-forms. Some drugs exist in both forms, and usually one form is more active than the other. They may even act differently, pharmacologically speaking. The best example of this is quinidine, which is the D-form of quinine. Both forms of quinine have antimalarial properties, but only quinidine has significant effects on heart muscle and as such can be used as an antidysrhythmic (see Chapter 48).

There are at least eight essential amino acids required in the diet that cannot be synthesised within the body, namely isoleucine, leucine, lysine, methionine, phenylalanine, threonine, tryptophan and valine. In infants, arginine and histidine are also essential. It seems probable that histidine is also important in adults, as adults cannot make enough for their normal requirements. Amino acids in therapeutics are used mainly in dealing with nutritional problems where protein malnutrition occurs and also in parenteral feeding. As amino acids are the building blocks of proteins, it is usual to supplement the diet with protein-rich preparations, amino acids themselves usually being reserved for parenteral nutrition. It is beyond the scope of this book to deal with nutrition in detail, except to mention a few clinical problems related to metabolic disorders that can be encountered with amino acids in nutrition. Various inborn errors of metabolism exist, in which certain enzymes involved in amino acid metabolism are lacking. The most common is phenylketonuria (PKU), where phenylalanine metabolism is defective. Normally, excess phenylalanine is converted into the amino acid tyrosine, which, if not required by the body, can be broken down into intermediates that eventually enter the Kreb's cycle and produce energy for the body. In PKU, the enzyme phenylalanine hydroxylase is lacking because of a defective gene. This causes an excess of phenylalanine in the blood, which saturates the large neutral amino acid transporter that carries these amino acids into the brain, where they are required for protein and neurotransmitter synthesis. This reduced synthesis disrupts brain development in children, leading to mental retardation. The excess phenylalanine is converted instead into phenylketones, accumulation of which can also contribute to the mental retardation. The phenylketones are excreted in the urine, giving rise to the name for this condition. This makes the essential amino acid phenylalanine a potential poison, and the diet of people with PKU must be kept relatively phenylalanine-free by restricting dietary intake to a small amount sufficient for tissue building and repair. Aspartame (a sweetener in some foods and medicines) contributes to the phenylalanine intake and may affect control of PKU.

There are many other disorders of metabolism that affect different amino acids and, depending on the amino acid involved, dietary restriction may be necessary. Another such disease is maple-syrup urine disease (MSUD), in which the essential branched-chain amino acids leucine, isoleucine and valine are not metabolised and accumulate in the blood and, hence, the urine. It is very difficult to avoid these amino acids in protein-containing foods, and protein restriction is necessary. Patients with enzyme deficiencies must be fed a synthetic mixture of amino acids that does not contain those that cause problems.

ARGININE AND ORNITHINE

In hepatic encephalopathy, there is a build-up of ammonia in the blood (hyperammonaemia) due to an increase in deamination of certain amino acids. It is impossible and impractical to restrict all the amino acids from the diet, and one way to help this disorder is to increase the rate of urea formation in the liver. Urea is the chemical found in the urine and is synthesised from ammonia in the process of its detoxification. The two amino acids involved in the production of urea from ammonia are **arginine** and **ornithine**. Both of these can be used to counteract hyperammonaemia by accelerating urea formation. The administration of these amino acids by intravenous infusion has been known to induce anaphylaxis.

Arginine can stimulate the pituitary gland to produce growth hormone and has been used in some cases of pituitary insufficiency. It is also the precursor of nitric oxide, a chemical mediator involved in cell signalling (see Chapter 31).

CYSTEINE

Cysteine, a sulphur-containing amino acid, is usually encountered as a drug as its derivative **acetylcysteine**, which is used in paracetamol poisoning and in mucoviscidoses, such as cystic fibrosis.

The sulphydryl grouping (-SH) is an integral part of the cysteine molecule and is of great importance in protein and enzyme structure (see Chapter 16).

Cysteine solution as an eye instillation is effective in the treatment of corneal ulcerations.

GLUTAMIC ACID

Glutamic acid and **glutamine** have been used as dietary supplements. In patients undergoing major uncomplicated surgery on the lower gastrointestinal tract, total parenteral nutrition regimen may be supplemented with glutamine and alanine (L-alanyl-L-glutamine). As the monosodium salt, it is a common food additive – the infamous monosodium glutamate (MSG), which has been related to the condition known as 'Chinese restaurant syndrome', a reaction occurring after the consumption of some Chinese food. MSG has also been implicated in the aetiology of some asthmatic attacks and wheeziness. Many Chinese restaurants now indicate whether or not food contains MSG. The evidence for MSG being the culprit in the reactions mentioned is inconclusive and controversial. Glutamate is also an important excitatory neurotransmitter in the central nervous system (CNS) (see Chapter 32).

GLYCINE

Glycine has been used as a dietary supplement. Like all amino acids, it has buffering properties and has been used with antacids. Glycine is sometimes combined with aspirin to lessen gastric irritation that might result. Sterile solutions of glycine 1.5% in water, which are hypotonic and non-conductive, are used as urogenital irrigation solutions during certain surgical procedures. Glycine is also considered to be a neurotransmitter in the CNS.

HISTIDINE

Histidine is a basic amino acid that is essential for infant growth. Histidine and **histidine hydrochloride** are used as dietary supplements.

LYSINE

Lysine hydrochloride has been used in some countries to treat recurrent herpes simplex infections, but its efficacy is doubtful. It may also help to correct lysine deficiency in lysinuric protein intolerance.

TRYPTOPHAN

The amino acid **tryptophan** has been used as a drug, mainly because it is a precursor of serotonin, an important CNS neurotransmitter (see Chapter 30). Tryptophan can also be used to synthesise nicotinic acid, an important B group vitamin.

As serotonin is depleted in depression, tryptophan has been used in high doses (1 g thrice daily), with limited success in relieving depression. Serotonin appears to be a sleep inducer; until recently, tryptophan was used as a mild hypnotic. Being a naturally occurring amino acid, tryptophan has been promoted by many as a safe hypnotic and has been available as an over-the-counter (OTC) preparation in pharmacies and healthfood shops. The evidence for its hypnotic effect is conflicting, but at high doses it appears to increase sleep duration. Such high doses can cause nausea and headache.

It has been shown in rats and rabbits that deficiency in dietary tryptophan leads to homosexual mounting behaviour. This may be due to a lack of brain serotonin, but whether this is of significance in human homosexuality is not known.

In 1990, it was noticed in the USA that the intake of tryptophan was implicated in a syndrome called eosinophilia myalgia syndrome (EMS). As the name suggests, the symptoms are eosinophilia associated with severe muscle and joint pain. This syndrome has, in some instances, resulted in death. It is possible that tryptophan was not the cause of EMS and that it was a contaminant in one manufacturer's product, as only one brand caused the adverse effect. In many countries, preparations containing tryptophan were then either withdrawn from the market or their availability severely restricted or limited. In the UK, tryptophan is used concurrently with other antidepressant medication and when patients have failed to respond to other antidepressant drug treatment.

Melatonin is a related hormone secreted by the pineal gland and produced from tryptophan At night and during sleep, this hormone is present at ten times its concentration during daylight hours. There is some evidence that the intake of melatonin ensures natural onset of sleep, There is also an indication that it is effective in preventing or reducing jet lag in people travelling across several time zones. Melatonin is now available in many countries, but not the UK, as an OTC product.

CLINICAL CONSIDERATIONS OF AMINO ACIDS

Amino-acid preparations should be used only under strict medical supervision and in a dose determined by the doctor or dietician. With amino-acid powders, the preparation should be dissolved with a small amount of water and mixed to a smooth paste before gradual dilution to the final volume. The prepared feeds should be refrigerated and must not be kept for longer than 24 hours from the time of preparation. Patients are advised to shake or stir the mixture before consumption. All amino-acid powders must be stored in a cool, dry place before reconstitution and the container lid replaced firmly after use. Ensure that any amino-acid preparation given intravenously is covered by a black bag to protect it from light.

CLINICAL MANAGEMENT

Amino acids

Assessment

- Assess the patient's nutritional intake to determine whether protein intake needs to be restricted.
- Assess the patient's history of the condition requiring restriction of particular amino acids, e.g. phenylketonuria or alcoholic liver disease.

Planning

- In patients with hepatic encephalopathy, there will be a lower level of ammonia in the blood following arginine or ornithine administration and dietary protein restriction.
- For patients with a disorder of metabolism that affects particular amino acids, unaffected amino acids will be maintained within normal body levels following synthetic amino acid therapy.

Implementation

- Ensure that any amino-acid solution given intravenously is covered by a black bag to protect it from light, thus preventing degradation of amino acids.
- Before intravenous administration of arginine and ornithine, ensure that emergency equipment and drugs are close at hand in case of anaphylaxis.

Patient teaching

- Encourage the patient and their family to maintain a food diary to provide regulation of the foods consumed.
- Teach the patient and family about foods containing low amounts of protein to encourage self-care and responsibility for the patient's medical condition.

Evaluation

- For patients with hepatic encephalopathy, evaluate the level of ammonia in the blood following arginine and ornithine administration and dietary protein restriction.
- For patients with a disorder of metabolism that affects particular amino acids, evaluate the body levels of unaffected amino acids following synthetic amino acid therapy and dietary protein restriction.

SUMMARY

- All amino acids, except for glycine, can occur in two spatially distinct forms – the L-form and the D-form. The L stands for left and the D for right. These terms relate to the three-dimensional structure of the amino acid molecule. As far as humans are concerned, only the L-form is utilised by the body.
- The principal importance of amino acids in therapeutics lies not so much in administration of them but avoidance of some.
- There are several inborn errors of metabolism concerning the biochemistry of amino acids, and it is imperative that the amino acids concerned be avoided as much as possible in people with such disorders.

1 Explain the difference between the D- and L-forms of naturally occurring compounds.

2 Why is tryptophan no longer used as a hypnotic?

ENTERAL AND PARENTERAL NUTRITION

64

CHAPTER SIXTY-FOUR

OBJECTIVES

After completing this chapter, the reader should be able to:

- **state the indications for the use of enteral and parenteral nutrition;**
- **describe the nutritional constituents of enteral and parenteral nutrition;**
- **describe the precautions required in the delivery and reduction of enteral and parenteral nutrition;**
- **describe the complications of enteral and parenteral nutrition;**
- **explain the clinical management for a patient receiving enteral or parenteral nutrition.**

KEY TERMS

Enteral nutrition
Parenteral nutrition
Gastric tube
Enteric tube
Gastrostomy
Jejunostomy
Total parenteral nutrition

ADEQUATE NUTRITION IS REQUIRED FOR AN INDIVIDUAL TO maintain health and energy, resist illness and infection, facilitate the healing process and recuperate from disruptions of health. Nutritional support or replacement by enteral or parenteral routes can be prescribed for patients who are unable to orally ingest adequate nutriment.

ENTERAL NUTRITION

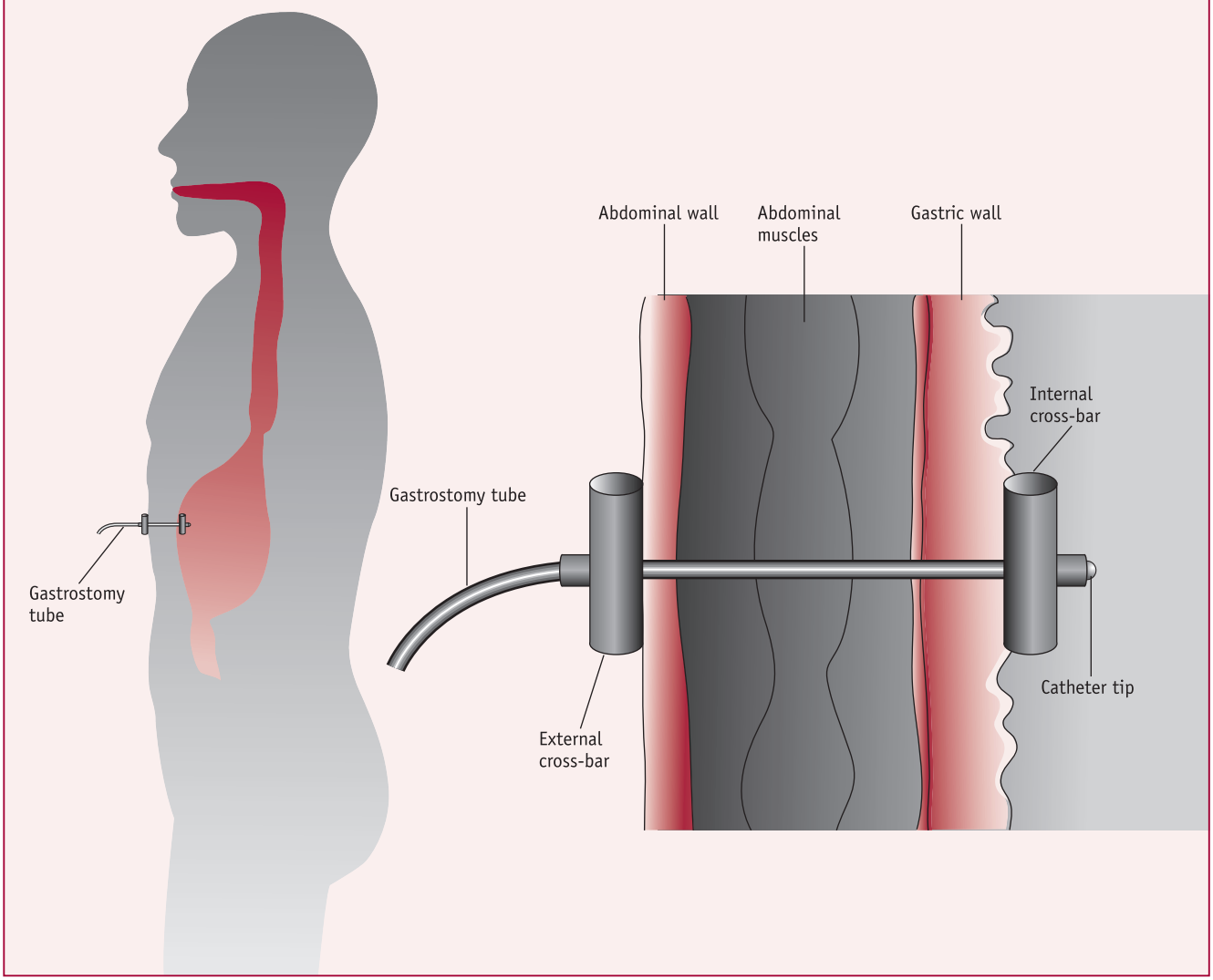
Enteral nutrition refers to the supply of nutrients via the gastrointestinal route. Enteral nutrition can be given through a gastric or enteric tube. Alternatively, a small-gauge tube can be placed below the gastro-oesophageal sphincter through a gastrostomy or jejunostomy procedure. When an opening is created into the gastric area, the tube used is termed a percutaneous endoscopic gastrostomy (PEG) tube (see Figure 64.1); if an opening is created into the jejunal area, the tube used is termed a percutaneous endoscopic jejunostomy (PEJ) tube. For short-term nutrition involving feeding for less than 6 weeks, a gastric or enteric tube is preferable. If feeding is required for long-term nutrition, however, then a PEG or PEJ tube is preferred.

Enteral feeding is used when swallowing is not possible but the patient has otherwise relatively normal gastrointestinal function. If the gastrointestinal function is not affected, then enteral nutrition is always preferred over parenteral nutrition as it involves fewer complications, is less expensive and needs less monitoring. Enteral nutrition also helps to maintain the integrity of the gut mucosa and mucosal structure and function. Furthermore, specific nutrients can be given enterally but not parenterally. These specific nutrients include glutamine, arginine, omega-3 fatty acids and proteins.

Enteral nutrition is commonly used in patients with impaired consciousness resulting from stroke or head injury. It can also be used in situations of hypermetabolism, such as severe burns and septic shock. It is also commonly used in patients with anorexia, malnutrition and severe impairment of chewing or swallowing.

Artificial nutritional support is needed when oral intake is likely to be absent for more than 5–7 days and, in malnourished patients, may be required earlier.

FIGURE 64.1 PERCUTANEOUS ENDOSCOPIC GASTROSTOMY (PEG) TUBE PLACEMENT



Types of enteral feed

In the early days of enteral feeding, vitamised normal food was commonly used. Now, there are several commercially available products that contain specific amounts of nutrients to cater for particular conditions. Producing feeds locally with the use of a liquidiser is not recommended, as there is an infective risk and the nutritional quality in terms of micronutrinets may be poor.

The general-purpose feeds are iso-osmolar with intact (not predigested) nutrients. Lactose is often excluded from enteral feeds due to the high incidence of lactose intolerance in the general population. Most commercial feeds contain 1.0 kcal/ml, but high-enegy varieties are available with 1.5 kcal/ml. Feeds are usually available in fibre-free and fibre-rich forms. Although feeds are nutritionally complete, dietetic expert advice should always be obtained.

In conditions where a normal diet is not tolerated, predigested feeds are used. Nutrients that require little digestion by the patient, produce little faecal residue and are almost totally absorbed are used. Nitrogen is provided in the form of short peptides or, in elemental feeds, as free amino acids. Elemental feeds are recommended in conditions such as short-bowel syndrome, gastrointestinal fistula and inflammatory bowel disease. They are generally not used unless specifically indicated, as they are fairly expensive and their use can lead to intestinal mucosal atrophy.

Special-purpose feeds contain much higher amounts of certain nutrients. These feeds often rely on high levels of protein to make up the bulk of energy requirements. Table 64.1 lists the preparations available as general-purpose, elemental and special-purpose feeds. Patients with respiratory failure are often given feeds with a low carbohydrate/fat ratio. This minimises carbon dioxide production. Patients with liver disorders may need low-sodium and low-volume feeds, but there is no evidence for low protein intake in this instance. Patients with renal disorders may require modified protein, electrolyte and volume feeds.

Guidelines for enteral feeding in hospital patients in the UK were commissioned by the British Society of Gastroenterology (BSG) and published in 2003 (see Further reading at the end of this section). These guidelines are evidence-based, but the emphasis is not only on protocols but also use of clinical judgement.

TABLE 64.1 TYPES OF ENTERAL FEED

Type of enteral feed	Examples
General-purpose	Enlive Plus Ensure Esmogen Fortifresh Fortimel Isosource
Elemental	Elemental 028 Extra Jevity Peptamen
Special-purpose	Clinutren Dialamine Enrich Ensure Plus Forticare Fortini Frebini Generaid Plus Modulen B Monogen Nepro Paediasure Prosure Osmolite Suplena

A more detailed list of products can be found in the *British National Formulary*.

Principles of management

PRESENCE OF BOWEL SOUNDS

Before enteral feeding can commence, usually bowel sounds must be present, but on occasion post-pyloric enteral feeding may be used postoperatively, even if apparent ileus is present. Initially, water may be given through the tube in the first few hours, usually at a rate of 30–60 ml an hour. The enteral feed is then commenced at 30 ml an hour and increased gradually to 60 ml an hour. Tube feeds are usually given by a continuous infusion, either over a 24-hour period or as a night-time supplement, as this results in less diarrhoea than bolus feeds. It is very important not to introduce the feed too quickly, as fasting decreases production of gastrointestinal enzymes. As the entry of food into the alimentary tract acts as the stimulus for release of these enzymes, it is advisable that the feed be introduced slowly.

PUMP FEEDING

Pump feeding is the most accurate method of delivering feed, allowing for a reduced residual volume and reduced risk of aspiration. Pumps allow for the feeding formula to be administered evenly and reduces the likelihood of the tube becoming clogged. Pump feeding is also the preferred method of feeding into the small bowel, as this environment does not tolerate large changes in volume infusion. For the administration of high-density feeds, a pump is also preferred due to the viscosity of the feeds.

POSITIONING OF TUBE

Commonly, enteral feeds are administered through a tube whose tip is positioned in the stomach (gastric tube) or whose tip remains in the duodenum of the small intestine (enteric tube). Enteric tubes are very fine and require a guiding wire in order to be manoeuvred into the correct position. As enteric tubes are so fine, they should never be aspirated or have medications administered through them, as these actions may destroy the integrity of the tube. Tubes inserted through the patient's nose are termed nasogastric or nasoenteric tubes, while tubes inserted through the mouth are called orogastric or oroenteric tubes. Gastroscopy and jejunostomy tubes are placed endoscopically into the stomach or the jejunum, respectively. This endoscopic procedure is performed by an experienced medical practitioner.

It is the nurse's responsibility to check the position of the gastric tube. This can be undertaken in two ways. First, the contents of the tube can be aspirated, which will indicate the presence of acidic fluid. The gastric pH, checked using pH paper, should be 4–5. Normal gastric pH varies around 1–3. As explained previously, this method for checking feed tolerance cannot be performed on enteric tubes. Second, a large volume of air (approximately 20 ml) can be passed quickly into the tube while simultaneously listening for gurgling sounds over the stomach with a stethoscope.

Again, it is important to understand that these measures for checking the tube's position cannot be performed on an enteric tube. Instead, an abdominal X-ray can be used to determine its position.

TOLERANCE FOR THE FEED

The patient's tolerance for the feed must be checked regularly. Tolerance refers to the absorption of the feed through the gastrointestinal tract to the blood vessels. To check for tolerance, stop the feed half an hour before the checking procedure is due to be performed. The gastric tube is then aspirated and the volume noted on the patient's fluid chart. Most of the fluid administered to the patient should have been absorbed, and the volume obtained is rather small. For patients with enteric tubes, the consistency of the stools can be used as an indication of tolerance for the feed. If the patient is passing well-formed bowel motions, then it may be assumed that the feed is tolerated. Table 64.2 details the measures taken for the management of intolerance of the feed.

TABLE 64.2 MANAGEMENT OF ENTERAL FEED INTOLERANCE

Problem	Action
Regurgitation or large return of gastric aspirate	If this occurs in the initial stage of administration of feed, persist if it has been some time since the patient has taken food orally If situation continues, decrease rate of infusion Always return large aspirate through tube in order to not upset gastrointestinal balance of secretions Raise head of patient's bed Avoid use of hyperosmolar feeds Insertion of fine-bore enteric tube may assist in decreasing the chance of regurgitation
Vomiting around tube	Refer to above measures Seek medical opinion; an antiemetic may be ordered, such as metoclopramide or prochlorperazine
Diarrhoea (liquid stools of frequency > 3 times a day)	Decrease rate of feed Microbiological culture of stools; administer antibiotic if microorganism not part of normal flora Seek medical opinion; codeine phosphate or loperamide may be ordered to alleviate diarrhoea Administer an iso-osmolar rather than a hyperosmolar feed Administer feed by continuous infusion rather than bolus Select feed with a low-fat content Remove feed from refrigerator about half an hour before administration to allow it to de-chill Determine whether diarrhoea is caused by one of the medications administered

ADMINISTRATION OF MEDICATIONS

Medications can be administered down a gastric tube. To perform this task, the feed is stopped temporarily and the tube flushed with water. The dissolved medication is then administered through the tube and the tube reflushed with water. The feed is subsequently resumed. It is important to note that enteric tubes are never aspirated and medications are never administered through them, as these procedures can damage the integrity of the tubing.

INSPECTION OF INSERTION SITE OF GASTROSTOMY AND JEJUNOSTOMY TUBES

It is important to inspect the skin surrounding the insertion site for healing, redness, swelling and the presence of drainage. If there is evidence of drainage, then the colour, amount, consistency and odour are noted. Any changes in the insertion site or lack of healing may be indicative of infection.

Complications of enteral nutrition

Complications associated with enteral nutrition are indicated in Table 64.3. Entry of the feed into the blood circulation is now quite rare, as the connections of enteral bags and of intravenous giving sets are not compatible. Several years ago, if an enteral feed had been connected to an intravenous set, it would certainly have resulted in the death of the patient.

Entry of the feed into the lungs is a more common complication. The tube should be inserted gently and the tip position confirmed by X-ray or by the methods explained earlier. Perforation of the oesophagus can occur during the insertion of an enteral tube. Insertion of a tube is normally the responsibility of a nurse, doctor or dietician. If you are required to insert a tube, never force the tube to overcome an area of obstruction. An X-ray can be used in difficult situations. To minimise aspiration, the patient should be fed while propped up at an angle of at least 30 degrees and should remain in this position for at least 30 minutes following the feed. Continuous feeding should be stopped overnight in patients at risk of aspiration.

In view of the particular makeup of feeds, the patient may experience electrolyte imbalances. Electrolyte levels should therefore be monitored regularly.

A common complication associated with enteral feeds is obstruction or clogging of the tube. To prevent clogging, the feed should be set at the correct rate and checked regularly for flow. Stasis of the feed can lead to clogging. The feeding tube can be flushed with tap-water or other ordered fluid every 4–6 hours. If clogging occurs, the tube is flushed with water. Some health-care institutions advocate the use of carbonated drinks such as cola for clearing obstructions. Research has shown that irrigation with carbonated drinks is no more effective than water. In fact, the acidic ingredients found in carbonated drinks could actually coagulate the proteins found in feeds and make the clogging worse. PEG and PEJ tubes have similar complications to those of gastric and enteric tubes. They are also more susceptible to causing problems relating to bleeding and peritonitis.

TABLE 64.3 COMPLICATIONS OF ENTERAL NUTRITION

Complication	Cause
Obstruction	Slow passage of feed through tube
Mechanical	Intracranial penetration Nasopharyngeal perforation Oesophageal perforation Pneumothorax Malposition of tube in oesophagus Tracheobronchial placement Accidental intravenous administration Bleeding (mainly PEG and PEJ tubes)
Gastrointestinal	Nausea and vomiting Diarrhoea Constipation
Metabolic	Electrolyte imbalance
Infection	Pulmonary aspiration Feed contamination Peritonitis (mainly PEG and PEJ tubes)

PEG, percutaneous endoscopic gastrostomy;
PEJ, percutaneous endoscopic jejunostomy.

Transition to oral feeding

After the health-care team decides that the patient is ready to make a transition to oral feeds, oral solids and fluids can be introduced slowly while enteral feeding continues. Enteral feeding should then continue until the oral intake is at least 4200 kJ (1000 kCal) or until the health-care team is confident that the patient's requirements will be met by the oral route.

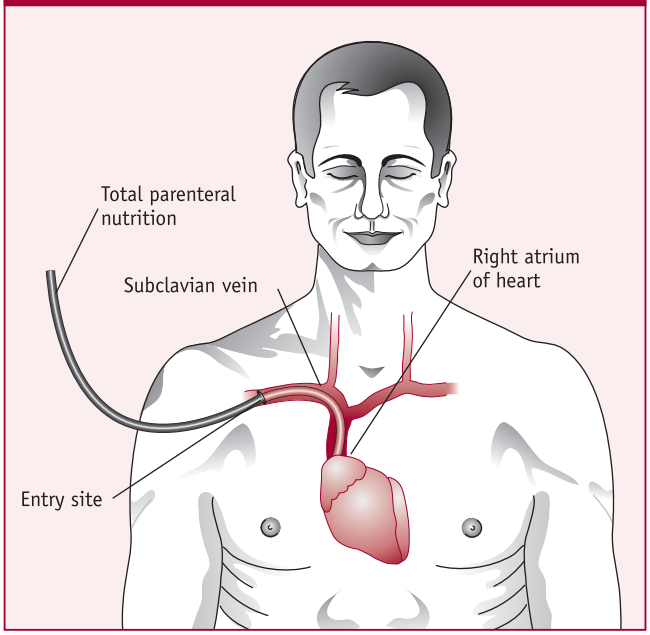
PARENTERAL NUTRITION

Parenteral nutrition involves the delivery of nutrition through the venous route (see Figure 64.2). This method is used if oral or enteral feeding is not adequate or not appropriate.

Indications

Parenteral nutrition is given to patients who are unable to tolerate nutrition by the gastrointestinal route. Table 64.4

FIGURE 64.2 TOTAL PARENTERAL NUTRITION THROUGH A CENTRAL VENOUS CATHETER IN THE RIGHT SUBCLAVIAN VEIN



shows the indications for parenteral nutrition. There are no contraindications, but renal and liver insufficiency need to be monitored carefully with the use of amino acids and lipids.

Delivery of parenteral nutrition

Parenteral nutrition can be delivered through a peripheral or central vein. Peripheral venous nutrition is used for patients with a lower energy requirement than those needing central venous nutrition. Components incorporated in peripheral venous nutrition commonly include 5% or 10% glucose, thiamine, vitamin C and vitamin B complex.

Central venous nutrition involves the delivery of nutrition through a large central vein using a central venous catheter (CVC). Examples of veins used include the subclavian and jugular veins. A central vein is selected for complete or total parenteral nutrition (TPN) and is used for patients with higher energy needs. Components incorporated in central venous nutrition include 25–50% glucose, amino acids, electrolytes, vitamins and trace elements. As TPN is a hypertonic solution (see Chapter 49), it must be administered centrally rather than peripherally in order to prevent damage to peripheral veins and surrounding tissues.

Intralipid™ (10% or 20%) is a fat emulsion that can be mixed with parenteral nutrition or given separately. It is an isotonic solution and can be administered peripherally and centrally.

Parenteral nutrition solutions are usually prepared under sterile conditions in hospital pharmacy departments. These solutions are often prepared with the particular mix required for an individual patient. The pharmacist makes up the solutions a few hours before it is required and takes it to the ward before use.

Management and complications of parenteral nutrition

Complications relating to CVC insertion include pneumothorax, blood-vessel perforation, thrombosis and air embolism. Before administration of the parenteral nutrition, a chest X-ray is required to check the integrity of blood vessels and the position of the central line.

Throughout the UK, there are approximately 500 patients on home parenteral nutrition (HPN). This is needed when patients are unable to absorb adequate fluid and nutrients to maintain independent health. HPN was introduced in the UK in 1977, and a number of patients have been receiving HPN successfully for up to 15 years. The most common cause necessitating HPN in Britain is short-bowel syndrome. The Department of Health (DH) published a guidance document for HPN in 2002, and this is available from the DH website.

TABLE 64.4 INDICATIONS FOR PARENTERAL NUTRITION

Type of indication	Examples
Hypermetabolism	Severe burns, septic shock, severe trauma
Obstruction in gastrointestinal tract	Adhesions, carcinoma of oesophagus
Paralytic ileus	Peritonitis, pancreatitis, post-gastrointestinal surgery
Malabsorption or short-bowel syndromes	Chronic diarrhoea
Inflammatory intestinal disease	Crohn's disease, ulcerative colitis
Cachexia	Anorexia, carcinoma
Organ failure	Liver failure, acute renal failure

TABLE 64.5 COMPLICATIONS OF PARENTERAL NUTRITION

Type of complication	Cause
Infection and sepsis	Catheter seeding blood-borne infection Contamination of catheter-insertion site during insertion Contamination of parenteral nutrition fluid Contamination of catheter-insertion site during dressing procedures
Insertion of central venous catheter	Air embolism Cardiac perforation Brachial plexus injury Catheter misplacement Central vein thrombophlebitis Endocarditis Haemothorax Pneumothorax Injury to large blood vessels Subcutaneous emphysema
Fluid imbalance	Fluid overload Fluid underload
Metabolic	Electrolyte imbalance Hyperglycaemia Rebound hypoglycaemia on sudden cessation of parenteral nutrition Trace element deficiencies Azotaemia

Table 64.5 provides a detailed list of complications arising from parenteral nutrition. Some of the more common complications are now considered.

INFECTION

Infection remains one of the most common complications of parenteral nutrition. The high glucose content renders the fluid an ideal breeding ground for microorganisms. Parenteral nutrition fluid is kept in the refrigerator. The fluid is removed from the refrigerator at least 30 minutes before administration. The fluids are ordered daily by medical and nursing staff from the hospital pharmacy. Building a bank of these fluids in the refrigerator only contributes to the problem of infection. Usually the solutions are marked with an expiry date and time, after which point the fluid should not be used.

The nurse is responsible for connecting the parenteral nutrition to the patient's venous line and maintaining its flow. Great care should be taken in connecting the bag using a non-touch technique. The CVC and lines should also be changed regularly according to hospital policy. A common requirement is for nurses to change lines every 48 hours and for doctors to change CVCs every week. When changing a soiled CVC dressing, the nurse should wear a sterile gown and gloves. The CVC tip undergoes a microbiological culture check when the CVC is removed. It is also important to observe closely and regularly for systemic and local infection. The whole infusion system should be used only for parenteral nutrition. This practice prevents unnecessary manipulation of infusion lines and ports.

HYPERGLYCAEMIA

In view of the high concentrations of glucose used in parenteral nutrition, hyperglycaemia is of particular concern. In order to monitor closely and accurately the high concentrations of glucose, it is preferable to infuse the fluid carefully using a volumetric pump. In this way, the patient is assured of receiving a particular volume each hour. Blood glucose levels should also be monitored regularly. Commonly, a glucose test is performed every 4 hours. If the blood glucose level rises above 10 mmol/l, the doctor will usually order an infusion of a short-acting form of **insulin**. In view of the small amounts of insulin required to stabilise glucose levels, the insulin is given by a volumetric pump. In addition to checking for high glucose levels, the nurse should monitor for manifestations of high glucose levels. These include confusion, lethargy, convulsions, nausea, vomiting and diarrhoea.

HYPOGLYCAEMIA

A rebound phenomenon can occur if the parenteral nutrition is stopped suddenly; this is also more common if the

patient is already receiving insulin. To prevent the occurrence of hypoglycaemia, the use of an infusion pump will ensure accurate delivery of the high concentration of glucose present in parenteral nutrition. Check regularly for kinking, clotting and displacement of the intravenous line, as these events hamper the flow of parenteral nutrition and therefore lower the amount of glucose delivered. As indicated already, blood glucose levels should be checked regularly. When the nutrition is discontinued, the amount delivered is tapered off slowly. Commonly, 10% glucose is given to the patient over 12 hours just before stopping the nutrition. Finally, it is important to be aware of the manifestations of hypoglycaemia, which include coma, seizures, weakness, tremors, increased anxiety and slurred speech.

FLUID OVERLOAD

Patients susceptible to fluid overload are patients with cardiac, renal and hepatic disease and elderly people. Patients without these conditions can safely tolerate 3000–4000 ml fluid daily. Any patient receiving parenteral nutrition should be weighed daily at the same time each day. This provides a check on fluid retention and weight gain expected from parenteral nutrition. A weight gain of 0.5–1 kg per week is considered desirable. The nurse also monitors strict fluid-balance charts, recording input and output of fluid.

FLUID UNDERLOAD

Dehydration may occur if the fluid is not infused at an adequate rate. Check for kinks, clots and line displacement, as these events can affect flow. Alternatively, the doctor may need to order an increase in fluid rate. The patient should also be assessed for manifestations of dehydration. These include thirst, decreased skin turgor, decreased urine output and decreased blood pressure.

PROTEIN OVERLOAD

Protein overload occurs because of the amino acid content of parenteral nutrition. Urea and creatinine levels are monitored regularly, as these are breakdown products of proteins. It may also be necessary to readjust the level of protein in the parenteral nutrition.

ELECTROLYTE IMBALANCE

Most common electrolyte imbalances involve those associated with sodium, potassium and phosphate. In monitoring electrolyte levels closely, regular analysis of blood electrolyte levels should be made.

CLINICAL MANAGEMENT

Enteral feeding

Assessment

- Establish a baseline assessment of the patient's body weight, history of weight loss and any manifestations of malnutrition, including wasted muscle mass and poor condition of hair and nails.
- Nutritional assessment should include the cause of weight loss, reason for increased metabolic requirements, and a record of medications that may have a catabolic effect. These medications may include cytotoxic therapy and steroids.
- Assess the patient for contraindications for enteral feeding, including patients who are able to tolerate oral foods and patients who have paralytic ileus, intestinal obstruction, severe intractable vomiting or oesophageal fistula.
- Baseline observations should include body weight, temperature, blood pressure, pulse and respiration. Compare with subsequent observations.

Planning

- The patient will obtain the necessary nutrients required for body nourishment.
- The patient will achieve a steady gain in body weight.

Implementation

- Regularly monitor observations such as vital signs, body weight, and condition of skin, hair, gums, mucous membranes and nails.
- Monitor the patient's fluid balance by documenting input and output.
- Laboratory tests that should be assessed include serum albumin, serum electrolytes, creatinine, urea, haemoglobin, haematocrit, folic acid, iron and lymphocyte count.
- Monitor the patient for crackles in the lungs, respiratory distress and frothy sputum to determine whether the feed has been aspirated.
- Regularly monitor for the presence of bowel sounds. Check also the frequency and consistency of bowel motions.
- Determine the positioning of enteric tubes by X-ray before administration of feed. Positioning of enteric tubes can be determined only by abdominal X-ray, as these tubes cannot be aspirated.
- Monitor the feeding tube for possible obstruction. Regularly check and maintain flow of the feed. If obstruction occurs, flush the tube with tap-water or other ordered fluid.

- Monitor the gastric tube placement and residual gastric return according to hospital policy or at least every 8 hours. Remember that an enteric tube cannot be aspirated.
- Elevate the head of the bed to at least 30 degrees in order to facilitate movement by gravity.
- Keep the fluid bag in the refrigerator when stored. Take the bag out about half an hour before administration and allow to de-chill to room temperature.
- Monitor for the incidence of diarrhoea. If this occurs, notify the doctor and dietician, who may order a lower concentration of feed or a slower rate of delivery.
- Maintain adequate nasal care and oral hygiene during administration.
- Inspect the insertion sites of percutaneous endoscopic gastrostomy (PEG) and percutaneous endoscopic jejunostomy (PEJ) tubes for redness, healing, swelling and the presence of drainage.

Evaluation

- Evaluate the patient's weight gain, which should be approximately 0.5–1 kg per week.
- The patient should exhibit improved strength, healthy gums, hair, nails and oral mucous membranes.
- Evaluate the presence of diarrhoea, aspiration and fluid volume excess or deficit. Measures should be implemented if these complications arise.

Parenteral feeding

Assessment

- Establish baseline assessment of the patient's body weight, history of weight loss and any manifestations of malnutrition, including wasted muscle mass and poor condition of hair and nails.
- Nutritional assessment should include the cause of weight loss, reason for increased metabolic requirements, and a record of medications that may have a catabolic effect. These medications may include cytotoxic therapy and steroids.
- Baseline observations should include body weight, temperature, blood pressure, pulse and respiration. Compare with subsequent observations.

Planning

- The patient will obtain the necessary nutrients required for body nourishment.
- The patient will achieve a steady gain in body weight.

Implementation

- Regularly monitor observations such as vital signs, body weight, and condition of skin, hair, gums, mucous membranes and nails.
- Monitor the patient's fluid balance by documenting input and output.
- Laboratory tests that should be assessed include serum albumin, serum electrolytes, creatinine, urea, haemoglobin, haematocrit, folic acid, iron and lymphocyte count. If lipid formulations are given, triglyceride levels are also assessed.
- Monitor blood glucose levels regularly (at least every 6 hours) to determine the effect of a high concentration of glucose in the parenteral nutrition.
- Strict asepsis should be used when administering nutrition, by:
  - changing the dressing as it becomes wet or dislodged;
  - changing the tubing and catheter site depending on institutional policy;
  - taking cultures of insertion site, catheter tip and patient's blood according to institutional policy;
  - reporting any elevations of body temperature.
- Store the bag in the refrigerator.
- Remove the fluid bag from the refrigerator about half an hour before it is required. Allow the fluid to come to room temperature before administration. Administration of fluid straight from the refrigerator can lower the blood temperature.
- Check the label for the expiry date, contents, patient's name, number sequence of bottle and appearance of solution.
- Place a black bag over the fluid bag to protect the substances from light during infusion.
- Monitor blood glucose levels. If blood glucose levels remain consistently high, an insulin infusion may need to be commenced.

Evaluation

- Evaluate the patient's weight gain, which should be approximately 0.5–1 kg per week.
- The patient should exhibit improved strength, healthy gums, hair, nails and oral mucous membranes.
- Laboratory values of various tests will remain within normal limits. If any laboratory value lies outside the expected range, the concentration of various substances may need to be changed.

SUMMARY

- Enteral nutrition refers to the supply of nutrients via the gastrointestinal route. It can be given through a gastric or enteric tube.
- There are three types of enteral feeds: general-purpose, elemental and special-purpose.
- Bowel sounds must be present before enteral feeding is commenced.
- Enteral feeds are administered through a tube whose tip is positioned in the stomach (gastric tube) or whose tip remains in the small intestine (enteric tube).
- Complications relating to enteral feeding involve obstruction, mechanical, gastrointestinal and metabolic concerns, and infection.
- Parenteral nutrition involves the delivery of nutrition through a peripheral or central vein.
- Forms of parenteral nutrition include total parenteral nutrition and Intralipid.
- Complications relating to parenteral nutrition involve infection, concerns surrounding the insertion of the central venous catheter, fluid balance and metabolic concerns.

1. Explain the difference between bolus enteral feeding and continuous infusion enteral feeding.
2. How would you know whether a patient tolerates the enteral feed being administered?
3. What measures would you take to prevent infection as a complication of parenteral nutrition?
4. Why is an enteral feed generally preferred over parenteral nutrition for a patient who is unable to tolerate food orally?
5. The doctor has ordered that the parenteral nutrition administered to Boris Makinshev over the past week can now be ceased. What would you do to prevent rebound hypoglycaemia?
6. In what kinds of patient are enteral feeds not suitable?
7. How would you administer an enteral feed to prevent regurgitation or a large return of aspirate from the gastric tube?
8. Your patient, Sally Jacoona, develops severe diarrhoea following her enteral infusion. What measures would you take to treat the condition? What comfort measures would you provide for Ms Jacoona during her bouts of diarrhoea? (See Table 11.15 in Chapter 11 for assistance.)

HERBAL MEDICINES

65

CHAPTER SIXTY-FIVE

OBJECTIVES

KEY TERMS

Alternative therapy
Conventional medicines
Drug interactions
Drug safety
Herbal medicines

After completing this chapter, the reader should be able to:

- **identify some common herbal medicines;**
- **list potential adverse effects with herbal medicines;**
- **describe the potential interactions between herbal medicines and conventional medicines.**

IN RECENT YEARS, THERE HAS BEEN AN UPSURGE BY health-care professionals in the use of herbal medications for the treatment and prophylaxis of certain medical conditions. This chapter includes a few of the better-known and well-researched herbal supplements and identifies their uses, adverse effects and possible drug interactions. Considering that these preparations have pharmacological properties, including adverse effects, allergies and drug interactions, it is important that individuals consult a qualified health-care professional regarding their use and dosage. Herbal medicines consist of mixtures of many chemicals, and it is possible that some of these chemicals could interact adversely with conventional drugs and have adverse effects of their own. It is dangerous to say that because a medicine is natural, it is safe. Strychnine is natural but far from safe; rather, it is extremely poisonous, as are many other plant chemicals. In the USA in 1999, a young woman was prescribed a traditional Chinese medicine containing **ephedrine**, a naturally occurring adrenergic drug that can be used as a decongestant. The woman died shortly after its consumption from a hypertensive crisis induced by the drug.

There are many problems associated with the use of crude extracts of natural substances in therapeutics. For example, the active constituents of a plant product are not present in consistent amounts, and a change in the climate during a plant's growth may affect the plant's

production of a particular constituent. This aspect is now being controlled by some reputable manufacturers, which are trying to standardise their natural products. The Medicines and Healthcare Products Regulatory Agency (MHRA) is trying to improve product regulation. A registration scheme for herbal medicines was introduced in late 2005 following a European Community directive. Registered products will have to meet standards of safety, quality and consumer information. Simple remedies made up by herbalists themselves are not covered by this directive.

Contaminants from agricultural and manufacturing processes have been problematic with natural products. Indeed, there is evidence of unacceptable levels of metal contamination in some herbal preparations.

Drug interactions are becoming much more important as the number of patients taking herbal medicines increases. Warfarin is probably the most common drug involved in interactions. It may interact with boldo, cranberry, curbicin, genugreek, garlic, danshen, devil's claw, dong quai, ginkgo, papaya, lyceum and mango to cause possible over-anticoagulation. Warfarin may react with ginseng, green tea, soy and St John's wort to give a decreased anticoagulation effect.

This chapter in no way purports to be a comprehensive review of the area. Rather, it should be regarded as a very brief overview of 14 herbal substances that are all fairly well known and have gained some press in both popular magazines and professional medical journals. There are many others not explored in this text. The herbal substances covered are aloe vera, cranberry, chamomile, echinacea, evening primrose oil, feverfew, garlic, ginger, ginkgo, ginseng, red clover, St John's wort, saw palmetto and valerian.

ALOE VERA

Aloe vera is the botanical name of a wide-ranging succulent member of the lily family. An extract of the leaves has been used as a purgative. The juice of the leaves has become a very popular ingredient of skin applications. It is believed that Christ's body was embalmed with this juice. The sticky juice, fresh if possible, reportedly has healing properties on the skin and is used medicinally as a soothing and healing salve for radiation burns. The juice is also incorporated in many skin lotions and shampoos.

✚ CLINICAL CONSIDERATIONS

If used as an oral purgative, aloe vera may cause griping, and in large doses it is associated with nephritis. It can colour alkaline urine red when used as an oral purgative. The oral purgative should be avoided in pregnant women, breast-feeding women and patients with renal problems. Aloe vera is used in sunburn and other skin conditions. This use does not usually cause any allergic tendencies and is generally tolerated well in people with sensitive skin.

CRANBERRY

The **cranberry** or **guelder rose** (*Viburnum opulus*) bears red berries, which are compounded into a juice. This juice has long been popular as a refreshing beverage due to its tart taste. It is also commonly blended with other juices such as blackcurrant. Cranberry juice is known to have properties that help in urinary tract infections (UTIs). The mechanism of action was long thought to be due to its acidifying effect on the urine, but evidence now points to the fact that it prevents the adherence of bacteria to the bladder and urethral wall. As UTIs can cause serious kidney infections, cranberry juice is not usually recommended as a sole treatment. Artificially sweetened cranberry juice is not recommended.

✚ CLINICAL CONSIDERATIONS

Cranberry can be used in pregnancy and breast feeding without problems. It should, however, be avoided in people with a past history of renal calculi because it may make the condition worse. When consuming regular amounts, there are no known adverse effects of cranberry. Patients should be informed not to consume more than 3–4 l a day, however, because this may cause diarrhoea and other gastrointestinal problems.

Ingesting large amounts of cranberry juice may increase the formation of uric acid and oxalate renal stones, but it may decrease the formation of stones that develop in alkaline urine. There is a possibility that cranberry may interfere with the metabolism of some drugs including warfarin. The Commission on Human Medicines had received at least ten reports through the Yellow Card System reporting possible interactions between warfarin and cranberry by 2003. In October 2003, the CSM warned that patients taking warfarin should avoid drinking cranberry juice, which contains various antioxidants, including flavinoids, which are known to inhibit cytochrome P450 activity and may thus interfere with the metabolism of warfarin and other drugs.

CHAMOMILE

Chamomile usually refers to two species of *Chamaemelumas*, small, daisy-like plants found in Europe. The name 'chamomile' means 'earth apple', but we do not know why, as 'earth apple' is a term usually associated with potatoes, which are in no way botanically related to chamomile. The dried chamomile flower heads are the parts normally used in herbalism, although the oil can also be used. The oil is used in aromatherapy to help in asthma and bronchitis, but there is no convincing evidence that any medicinal effect is apparent from this use. As there

have been reports of anaphylactic shock with the use of this oil, it could be very dangerous to use in patients with any type of allergic disorder. The chemical composition of the oil varies dramatically depending on the source of the plant; this would almost certainly lead to differences in action. The oil is also an ingredient of some shampoos, promoted as an agent to lighten and condition the hair. Most studies show that it is mainly the detergents in shampoo that clean the hair of sebaceous gland secretions; other ingredients simply add to the cost, odour and consistency of the shampoo and do not affect the 'dead', relatively inactive keratin proteins of hair.

Chamomile is prepared as a relaxing tea by soaking the dried flowers, usually in teabags, in boiling water. Chamomile may also induce a deep sleep. When given in large amounts, it often causes gastrointestinal colic and sometimes severe allergic reactions, adverse effects that would not normally be accepted in an hypnotic. The gastrointestinal colic may be surprising to some, as chamomile contains the anticoagulant **coumarin**, which in itself is said to have antispasmodic properties. Apigenin, an active component found in some chamomile extracts, has been shown to bind to the benzodiazepine receptor in the gamma-aminobutyric acid (GABA) receptor complex of the brain (see Chapter 34). This action could explain the sedative effect of chamomile and why sources containing more apigenin are better sedatives. As well as having hypnotic activity, apigenin is an isoflavone, a group of compounds with well-known antioxidant properties. Chamomile may be useful as an antioxidant. Chamomile appears to have some antiseptic properties and when combined with apple pectin (itself an antidiarrhoeal) appears to have a beneficial effect on diarrhoea in children. Reports that chamomile mouth rinses, because of purported anti-inflammatory activity, help in oral mucositis have been disproved. Another use of chamomile is in wound healing, but its efficacy here remains unconfirmed. In Germany, chamomile is prescribed by general practitioners as a vaginal pessary to combat trichomoniasis and fungal conditions.

✚ CLINICAL CONSIDERATIONS

In view of its coumarin content, caution should be taken with the concomitant use of **warfarin**. The effects of chamomile on the benzodiazepine receptor may also preclude the use of chamomile with benzodiazepines or with other sedative or hypnotic drugs. Chamomile should be avoided by patients with a known hypersensitivity to members of the daisy family. It may also cause allergic reactions in some people with asthma.

ECHINACEA

This is one of the few commonly used herbal preparations that still bears the Greek name. The species' common name is coneflower. *Echinos* in Greek means hedgehog, and here it refers to the prickly cones in the centre of the flowers. The plant originates in the USA, and native Americans have traditionally used the roots and rhizomes of the plant as an anti-infective agent. **Echinacea** has been advocated for use in a conglomeration of infections and skin disorders, such as colds, influenza, fungal infections, venereal diseases (including herpes), psoriasis, septicaemia and gangrene. It can be used topically for skin disorders and orally for other infections. Evidence for its efficacy is sparse, and it would be imprudent to use it as the sole agent in many of these disorders. Some of these infections can be quickly fatal without conventional medical treatment – normally antibiotics, and sometimes surgery in cases of severe gangrene. It can be assumed that the term 'gangrene' here is used for the type caused by *Clostridium* species. Echinacea is one of the most popular herbs in countries with an interest in natural therapies, especially for the treatment of colds and influenza. Whether or not it helps in these conditions is still debatable, as there have been few properly controlled trials. Evidence suggests that it is of little use in the prevention of the common cold, but it may be of help in treating and shortening the length of the infection. Contradictory results arising from different trials could be due to the source and species of echinacea used.

There is some evidence that echinacea extract incorporated in a gel for topical use may suppress the itch and erythema associated with mosquito bites and other inflammatory skin reactions due to local anaphylactoid reactions.

There has been little human research on the mechanism of action of echinacea. Animal studies have shown that it may act as an immunostimulant on various parts of the immune system. In vitro studies have demonstrated some antibacterial (bacteriostatic) and antiviral properties. There has also been a report demonstrating an adverse effect of echinacea on spermatozoa and suggestions of it being used as a contraceptive in the future. In view of its apparent safety and lack of known interactions with other drugs, there is no real reason why it cannot be used in the hope of improving the symptoms of some common and relatively benign viral infections. Further research is still needed, however, before echinacea has a definite role to play in therapeutics.

✚ CLINICAL CONSIDERATIONS

Echinacea should be avoided in people with progressive systemic disease, such as tuberculosis, multiple sclerosis and acquired immunodeficiency syndrome (AIDS). It should also be avoided by individuals who have a known hypersensitivity to the daisy family and by pregnant women. Tolerance to echinacea develops when used continually.

EVENING PRIMROSE OIL

This plant is sometimes called king's-cure-all. The seeds of the evening primrose (*Oenothera biennis*) contain an oil that is high in both linoleic and gamma-linolenic acid, which are essential fatty acids, although gamma-linolenic acid can be made from linoleic acid. **Evening primrose oil** is promoted by healthfood manufacturers as beneficial for various ailments, including such diverse diseases as psoriasis, mastalgia (breast pain) and Parkinson's disease. Its role in helping some conditions is unproven, but there is good evidence of its efficacy in mastalgia and dermatitis. Evening primrose oil should be avoided in people with epilepsy or a past history of epileptic seizures. Linoleic and gamma-linolenic acids are needed for prostaglandin synthesis, and it has been shown that people who responded well to the action of evening primrose oil had increases in their blood of arachidonic acid the precursor of prostaglandins.

✚ CLINICAL CONSIDERATIONS

Generally, evening primose oil is tolerated well. The patient should be informed, however, that it may cause mild gastrointestinal effects, such as nausea, indigestion and softening of stools. It may also cause headaches due to its effect on cerebral blood vessels. The patient should be advised to ensure that recommended doses are consumed, as high intakes have been found to lead to haemorrhage. If a female patient is using evening primrose oil for premenstrual syndrome, it is advisable that she consumes the preparation a few days before menstruation in order to ensure maximum benefit.

FEVERFEW

Feverfew (*Tanacetum* spp.), like chamomile, belongs to the daisy family and is commonly known as tansy. The feverfew group of plants includes the pyrethrum, which contains pyrethrins. Pyrethrins are commonly used in insecticide sprays. Pyrethrins are reportedly non-toxic to humans, but there is no doubt that pyrethrins can be a strong irritant to the eyes and mucous membranes. Hypersensitivity reactions can also occur. The volatile oils obtained from the *Tanacetum* genus may be particularly toxic to arthropods.

The name suggests that feverfew leaf extract would be used to counteract fevers, and this was one of the original uses. Today, scientific interest has been aroused to investigate the use of feverfew as a migraine prophylactic and as an antiarthritic drug. The evidence points strongly towards its positive effect as a migraine prophylactic comparable to conventional therapies. It also appears to have antiplatelet activity. When used as such, feverfew is like all other drugs in that it is not completely free from side effects. These are mainly gastrointestinal in nature and include aphthous ulcers. Long-term use and sudden discontinuation cause rebound headaches. The active ingredients of feverfew are termed parthenolides, the concentration of which can vary tremendously from batch to batch. Parthenolides interfere with contractile and relaxant mechanisms of blood vessels and have also been shown to have cytotoxic activity under some circumstances. Feverfew's use as an antiarthritic is still under investigation, but laboratory studies have shown some anti-inflammatory properties on the immune system, which would be useful in autoimmune conditions. Feverfew has some inhibitory action on the enzyme phospholipase A_2, which facilitates the release of arachidonic acid from the phospholipid cell membrane.

✚ CLINICAL CONSIDERATIONS

In view of its potential as an antiplatelet drug, feverfew should not be used in individuals on anticoagulant therapy. It is contraindicated in pregnancy because of the possibility of miscarriage. It should also be avoided by individuals with a hypersensitivity to daisies. The patient should avoid sudden discontinuation of therapy following long-term use, as a rebound headache may occur; instead, the dose should be decreased gradually. To prevent gastrointestinal effects, feverfew may be taken with meals.

GARLIC

Garlic (*Allium sativum*) is a member of the onion family, and it is said that the best garlic for herbal therapy comes from Japan and Arizona in the USA. Garlic is much better known as a flavouring agent, and in some countries, such as Korea, Japan and Italy, it is consumed in large quantities. Most people are aware of garlic consumption by the strong smell it imparts to the breath. In addition, odiferous compounds are often excreted via the sweat, conferring on the person not only halitosis but also generalised body odour. Many people find this smell objectionable, but it is said that the odour disappears if the complainant ingests garlic, the theory being that continuous stimulation of smell receptors confers adaptation, leaving the smell almost unnoticeable. To overcome this problem, manufacturers have extracted some of the odiferous compounds from garlic preparations, selling them under the label of 'odour-free garlic'. It is possible that the therapeutic substances and desired effects are lost in this process. This seems highly likely, as the potentially pharmacological active compounds derived from the garlic clove (a segment of the bulb) are organic sulphur-containing compounds. It is these compounds that are responsible for the strong odours associated with most species of the *Allium* family. Some references suggest that the active ingredient is a prodrug activated in the ileum only by an enzyme present in garlic itself. If this is the case, then removal of the organic sulphides would remove the halitosis but not affect the

pharmacological properties. This would entail consuming garlic in the raw form or in an enteric-coated form, but as the organic sulphides are excreted in sweat and other body secretions, the problem of odour would not be eliminated completely. The cooking of garlic would, of course, denature the activating enzyme. The other garlic organic sulphides are considered by most authorities to be of therapeutic importance, and so if garlic has any potential therapeutic qualities it seems that one must tolerate the smell. The term 'alliaceous' has been coined to describe anything with this type of smell.

The principal use of garlic is in the treatment of cardiovascular disease, particularly atherosclerosis, where it is reported to lower plasma low-density lipoprotein (LDL) cholesterol levels and thus protect the arteries from atheroma formation (see Chapter 43). There is only scant evidence that garlic in any form has any beneficial effects on plasma cholesterol levels, but there is slight evidence that its use may help to decrease atheroma formation and prevent the deterioration of epithelial cells into arteriosclerotic lesions in the blood vessels. A diet high in members of the onion family has long been reputed to have cardioprotective properties.

Garlic is said to protect against viral infections such as the common cold and against some cancers, but there is no conclusive evidence for this. Some antibiotic-resistant bacteria are susceptible to garlic extracts in vitro. Perhaps people avoid some viral infections because the consumption of large amounts of garlic causes virally infected people to avoid them!

✚ CLINICAL CONSIDERATIONS

There is some evidence that garlic may increase the activity of warfarin; therefore, patients on anticoagulant therapy should be warned about this. In therapeutic doses, garlic should be avoided in patients on hypoglycaemic therapies and anti-inflammatory agents, such as **aspirin**. Garlic should be avoided by pregnant women at doses exceeding those used in foods, as it may cause miscarriage.

GINGER

Ginger is a spice derived from the rhizomes and stems of *Zingiber officinale* (some preparations use the term 'zingiber'), a common garden plant found in the tropics and subtropics. Ginger has long been used as a flavouring agent in many recipes, but only recently has it become of real interest to the medical profession as an antiemetic and antinauseant. Many trials have been carried out using powdered ginger as a prophylactic antiemetic in various situations that often result in nausea and vomiting. The results of trials using herbal medications are often contradictory, as is the case with the majority of chemically pure drugs, and ginger is no exception. There is evidence that ginger helps in the nausea of travel and motion sickness (kinetosis), whether caused by car, plane or ship, and in hyperemesis gravidarum (nausea of pregnancy). As ginger has no known teratogenic effects, its use in pregnancy should be tried rather than resorting to antiemetic drugs in the first instance, except perhaps for **pyridoxine** (see Chapter 61). It does not appear to be of any value in postoperative nausea or nausea caused by chemotherapy. Some research suggests that ginger extract helps prevent osteoarthritis of the knee joint. The only known adverse effect of ginger is an occasional gastric upset due to hyperacidity. Allergies have also been reported on rare occasions, which can occur with any meal spiced strongly with ginger root or powder. There is some evidence that ginger can lower thromboxane levels, and so its use in patients on warfarin should be carried out with caution. Its active constituent is still not known, but it could be either an aromatic alcohol called gingerol or another called shogaol. Other uses for ginger, such as in cancer and infections, are unsubstantiated.

✚ CLINICAL CONSIDERATIONS

Caution should be exercised when administering ginger to individuals on warfarin, due to its anticoagulant effect. Advise the patient that a common sign of ginger toxicity is diarrhoea. Therapy should cease if diarrhoea occurs. Inform the patient that powdered ginger is more effective than ginger ale and ginger tea.

GINKGO

Ginkgo comes from the leaves of the tree *Ginkgo biloba*, commonly called the maidenhair tree, which is indigenous to China. This tree is of great interest to botanists, who consider it a living fossil. It has been estimated that it existed in China more than 200 million years ago, long before humans made an appearance. Chinese medicine has included ginkgo in its pharmacopoeia for centuries as a treatment for brain disorders, for which it is still used by traditional Chinese practitioners. Extracts of ginkgo have antioxidant properties and are able to scavenge free radicals in the body; this is a possible mechanism for its action. Ginkgo contains several bioflavanoids, which are well-known antioxidants. Many studies have shown that ginkgo can prevent tissue damage due to this effect; it also appears to increase the blood flow to various organs, especially to the brain. There is evidence that ginkgo improves memory function in elderly people. Ginkgo is prepared in Germany as a standardised extract and is used widely in Europe to treat various dementias, including Alzheimer's disease, seemingly with considerable success. In view of its lack of serious adverse effects, perhaps it should be tried more often than it is in the dementias of old age, as the drugs available at present tend to have several adverse

effects (see Chapter 36). Another use is in plastic surgery, where it is used to help in skin grafting and to promote the healing of skin flaps. In fact, the use of ginkgo is potentially of value in many circulation problems, and ongoing research may yet prove the inherent medicinal properties of ginkgo.

The only adverse effects documented are mild gastrointestinal upsets and headaches, both of which are uncommon. There is, of course, always the possibility of an allergic reaction. It must be noted that seeds of the tree, extracts of which are sometimes used by herbalists to treat urinary incontinence, are considered to be quite toxic. The authors would consider any use of seed preparations to be inadvisable.

✚ CLINICAL CONSIDERATIONS

The patient should be informed that ginkgo is a good alternative to caffeine for promoting alertness without the adverse effects of sympathetic stimulation. Warn the patient that diarrhoea, nausea, vomiting, irritability and restlessness may occur with high doses.

GINSENG

Ginseng is one of the best known and widely used of all herbal preparations. It is available in a variety of preparations, from chewing gums to liquid elixirs. The origin of ginseng, like ginkgo, is in the Far East, mainly in China and Korea. The best types are thought to come from Korea and the USA; species grown elsewhere are said to have less potency. The active Korean preparation is prepared from the root of *Panax ginseng*, whereas the Siberian type is from the root of *Eleutherococcus senticosus*. Decreased potency is associated with Siberian ginseng, which, as the genus name suggests, should not be mistaken for true ginseng. A species of *Panax* also grows in the USA. The word 'ginseng' derives from the Chinese and means human. It is so-called because the thickly branched root is said to resemble the human form. The genus name, *Panax*, means panacea and gives some idea of the herb's value. Many Koreans consume vast quantities of this relatively expensive drug: the chewing one sees in the streets of Seoul is not usually of chewing gum but of ginseng root. Ginseng is said to have many beneficial properties. The proposed active ingredients of ginseng are the ginsenosides, a group of steroid substances (some reports have said that they have slight androgenic activity) bearing some structural relationship to **digoxin**, but not in their pharmacological profile. The principal use of ginseng is as an adaptogen, a substance that can increase stamina and wellbeing. It is also said to have aphrodisiac properties.

Many experts dispute the results of research into these effects of ginseng. This could be due to the difficulty in quantifying the changes that occur in the individual. The active ingredients are also said to have a slow onset of action, which again poses obstacles in its evaluation. At the moment, the case for ginseng as a physical and mental stimulant remains unproven, but most of the evidence to date points towards it having these effects. The preparations should not be taken at night, and the heavy use of caffeine-containing drinks should be avoided in case of insomnia. As with most of the herbs mentioned in this chapter, the concurrent use of warfarin may be contraindicated.

✚ CLINICAL CONSIDERATIONS

Ginseng should be avoided in patients with acute illness and hypertension. Individuals receiving stimulants, antipsychotic drugs and monoamine oxidase inhibitors should also avoid ginseng. A patient needs to be on a course of ginseng for only a few days for therapeutic benefit to occur, and a prolonged course of therapy is not recommended.

RED CLOVER

Clover is a very common weed found in most temperate and subtropical areas of the world. It is a plant that has a symbiotic relationship with nitrogen-fixing bacteria and, therefore, has value as forage for many herbivorous animals. There are several hundred different species, but the main one of interest to herbalists is the red or purple flowering variety, *Trifolium pratense*. Herbalists have long used the extracts of the flowers of **red clover** for a variety of miscellaneous conditions, including skin diseases, certain cancers and coughs. It has been shown that clover is a rich source of isoflavones, potent antioxidants and free-radical scavengers. It is these properties that are being examined closely at present. Red clover's isoflavones consist mainly of genistein, biochanin A, daidzein and formononetin. Isoflavones are found in many plant products, especially the legumes (the bean family), but clover has by far the most – almost ten times that of soybeans. All isoflavones have weak oestrogenic activity (most plants contain similar compounds, and these are generally referred to as phyto-oestrogens), which may contribute to their therapeutic action. Research shows an increase in bone density in postmenopausal women taking red clover isoflavones. The oestrogenic activity will not cause feminisation in men; nor will it replace oestrogen supplements used in hormone replacement therapy (HRT) (see Chapter 58). These compounds have been partially purified and are available in standardised preparations. Evidence points to their protective effect on the development of postmenopausal cardiovascular disease.

There do not appear to be any known drug interactions with red clover, but it is suggested that it should be avoided in pregnancy and in patients with breast cancer.

✚ CLINICAL CONSIDERATIONS

Red clover is used cautiously in individuals susceptible to bleeding problems or who are receiving anticoagulants. It is relatively safe to use in children with whooping cough, bronchiolitis and skin conditions.

ST JOHN'S WORT (HYPERICUM)

St John's wort is found as a weed in many countries. In European countries, where it originates, the flowers were thought to have magical properties for centuries and were used to ward off the devil when hung above doors. When the yellow flowers are cut or damaged, they exude a red fluorescent pigment thought by ancient peoples to be a form of blood. 'St John' refers to John the Baptist, and 'wort' is an Old English word for a herb used in medicine. Its Latin name is *Hypericum perforatum*, hence its other common name, **hypericum**. This herb has been used for all sorts of conditions, but its main claim to fame today is as an antidepressant, although a common herbal medicine text specifically states that it is not to be used in chronic depression. In Germany, hypericum is prescribed by medical professionals four times more often than standard tricyclics and selective serotonin reuptake inhibitors (SSRIs) for the treatment of depressive illnesses (see Chapter 35), the vast majority of which are chronic or endogenous. Many studies have been carried out on the effect of hypericum on depression, most of which are placebo-controlled and have compared the herb with standard antidepressants. It appears that hypericum is as good as the antidepressants mentioned in Chapter 35, without the adverse effects associated with them.

The only adverse effect reported with hypericum is photosensitivity, and care should be taken with its use in fair-skinned people. One active substance in hypericum is thought to be hypericin, which is found in all parts of the plant; preparations are standardised according to their hypericin content. The mechanism of action is not known but, as like other antidepressants, its onset of action is delayed by up to 3 weeks, the active constituent or constituents probably act by modifying the dopaminergic, noradrenergic or serotonergic receptor activity in parts of the higher brain centres. In view of this proposed mechanism of action, it is suggested that the drug is not used in combination with other antidepressants affecting these receptor sites. As hypericum has slight monoamine oxidase inhibitor (MAOI) activity, it should not be used with MAOI; diet is not a problem, as this effect has been demonstrated only in vitro. Hypericum should be avoided in pregnancy as it has abortifacient and teratogenic properties in high doses. As it has some central nervous system (CNS)-depressing properties, probably through some activity on the GABA receptor complex (see Chapter 34), concomitant use of sedatives and alcohol should be avoided. Studies have shown that hypericum increases the blood levels of several drugs, such as ciclosporin. Care should be taken and advice sought if other drugs are taken with hypericum.

Hypericum appears to be one of the most promising of the herbs, although research still produces as many negative as positive results.

✚ CLINICAL CONSIDERATIONS

High doses of St John's wort may potentiate existing MAOI or antidepressant drug therapy. Advise the patient that benefit may not be seen until 3–4 weeks following commencement of therapy. Sun precautions should be taken because St John's wort can cause photosensitivity.

SAW PALMETTO

This unusual name derives partly from the Spanish word for 'small palm', as the plant looks like a small palm tree whose leaves have serrated edges. It is common near the US coasts of Florida and Georgia. Its botanical name is *Serenoa repens* and it bears olive-shaped, sweet berries from which the proposed therapeutic active compound or compounds are derived. **Saw palmetto** has long been used for various urogenital conditions, from infections to impotence, but its main use relates to its effect on the enlarged prostate gland. The condition of benign prostatic hypertrophy (BPH) is very common in elderly men and can cause urinary retention due to increased pressure on the urethral exit point from the bladder. Saw palmetto supposedly causes a decrease in the size of the prostate gland, and many studies have shown that it is equivalent to **finasteride** (see Chapter 58) in action but without the adverse effects. Saw palmetto used clinically consists of a lipophilic extract of the berries and contains many fatty acids and sterols. Several of these compounds, mainly sitosterol, inhibit the conversion of testosterone into its active form, dihydrotestosterone. This is the mechanism of action of finasteride; however, sitosterol or some other lipid may block the dihydrotestosterone receptor sites. It may also be beneficial in baldness, acne and female hirsutism.

Adverse effects, if they occur, are mild and may include headaches and gastrointestinal upsets.

✚ CLINICAL CONSIDERATIONS

Drug interactions with saw palmetto are unknown so far, but it would be sensible not to use this drug with oestrogens such as the oral contraceptive pill or hormone replacement therapy. Administration of saw palmetto with food may decrease the incidence of gastrointestinal irritation.

VALERIAN

Valerian belongs to a large group of wild plants found worldwide. The species of particular interest to herbalists

is *Valeriana officinalis*. The term 'valerian' is derived from the Latin word for 'strength' and may refer to its strong smell (which is due mainly to the short-chain fatty acid valeric or pentanoic acid; interestingly, it is an odour that is loved by cats and, for that reason, is used as a bait to capture feral felines) or to its strong therapeutic effect. The term '*officinalis*' means 'coming from a monastery', and the herb was grown by monks for medicinal purposes and for flavouring liqueurs. It is also one of the flavourings used in the soft drink root beer. Active preparations are made from the roots and are said to have a sedative action that helps in insomnia. A few studies have shown that valerian decreases the time for the onset of sleep, improves the quality of sleep and has little or no hangover effect (hangover effects are common to most other hypnotics).

Habituation and tolerance do not usually appear to be a problem, but extended use should be avoided as a precaution. The active constituents are thought to be a group of compounds called valepotriates. As some of these valepotriates bear a slight structural resemblance to serotonin, which is physiologically important in sleep, there may be an association here. This may be an important concern for its mechanism of action. Others have suggested that the mechanism of action is mediated through the GABA receptor complex, and so valerian should not be used in conjunction with benzodiazepines (see Chapter 34). Valerian has also been shown to prolong the action of barbiturates; therefore, it should be avoided before **thiopentone**- and **methohexitone**-induced anaesthesia and in individuals using barbiturates for other reasons. Adverse effects are uncommon and consist of headache, restlessness and occasionally palpitations.

✚ CLINICAL CONSIDERATIONS

Valerian should be avoided in patients with hepatic dysfunction because high doses of the herb can cause hepatotoxicity. It is normally taken at night to prevent daytime drowsiness. The patient should be advised to avoid caffeine, nicotine and foods high in sugar and fat in the early evening, as they may affect the quality and amount of sleep.

CLINICAL MANAGEMENT

Herbal medicines

Aloe vera

Assessment

- Assess the patient's reason for administering aloe vera. If it is to be used as an oral purgative or laxative, the patient could be directed to milder preparations because of its tendency to cause severe griping.
- Assess the female patient if pregnant or breast feeding. Oral purgatives with aloe vera should be avoided in pregnant and breast-feeding patients, but skin preparations containing aloe vera are safe.
- Assess the patient for renal disease when considering the use of oral purgatives containing aloe vera. They should not be used in these individuals.

Planning

- For the patient with constipation, bowel motions will become more regular.
- For the patient with a skin condition, use of aloe vera will create a soothing effect on the skin.

Patient teaching

- Patients considering the use of aloe vera as an oral purgative should be advised to use milder formulations that do not cause griping.
- Oral formulations of aloe vera may colour alkaline urine red, but this is harmless.
- Skin preparations containing aloe vera provide soothing relief for the treatment of skin irritation, sunburn, radiation burns and insect bites.

Evaluation

- Determine the effectiveness of aloe vera as an oral purgative on bowel motion regularity and consistency.
- Determine the effect of an external application of aloe vera on skin irritations.

Cranberry

Assessment

- Cranberry can be used in pregnancy and breast feeding without problems.
- Cranberry should be avoided in patients with a past history of renal calculi, because it may make this condition worse.
- Assess the patient for concomitant use of warfarin. Caution should be exercised due to possible inhibition of cytochrome P450 drug-metabolising enzymes by cranberry juice.

Planning

- The patient is less likely to have a urinary tract infection when cranberry is used as a preventive agent.
- The patient will have a limited duration of a urinary tract infection when cranberry is used as a therapeutic agent.

Patient teaching

- When consuming regular amounts, there are no known adverse effects of cranberry.
- Patients should be informed not to consume more than 3–4 l a day because of the possibility of diarrhoea and other gastrointestinal problems.

Evaluation

- Evaluate the effectiveness of cranberry in preventing urinary tract infection.
- Evaluate the effectiveness of cranberry in treating urinary tract infection.

Chamomile

Assessment

- Determine the patient's complaint for administering chamomile, which may include anxiety, insomnia, nausea or vomiting.
- Assess the patient for concomitant use of warfarin. Caution should be exercised due to chamomile's anticoagulant effect.
- Determine whether the patient is taking benzodiazepines, such as diazepam and temazepam. Chamomile should not be administered concomitantly in view of the possibility of excess sedation.
- Assess the female patient if pregnant or breast feeding. Supplements should be avoided in pregnant and breastfeeding patients, but chamomile tea is acceptable.
- Assess the patient for a tendency towards allergic reactions. Avoid using chamomile oil in aromatherapy in such patients due to its ability to cause anaphylactic shock.

Planning

- The patient will have relief from anxiety and insomnia.
- For the patient with nausea and vomiting, the aim is to relax gut activity and provide relief from nausea and vomiting.

Patient teaching

- Advise the patient to consume chamomile tea whenever emotions may disturb digestion or sleep.
- Chamomile tea should not be taken during the morning or middle part of the day, in order to prevent a sedative effect. Instead, it should be consumed in the late afternoon or early evening.
- A chamomile teabag placed in bath water is effective as a relaxing soak. This method of administration is also soothing for the treatment of skin irritations, sunburn and insect bites.

Evaluation

- Evaluate the effectiveness of chamomile to reduce anxiety, promote relaxation and alleviate nausea and vomiting.
- Determine the effect of the external application of chamomile on skin irritations.

Echinacea

Assessment

- Assess the patient's specific complaint, which may involve infections such as the common cold.
- Assess the female patient for pregnancy. As the effects of echinacea during pregnancy are not known, it should not be taken at this time.
- Caution is advised in autoimmune disease and leukaemia until its effects are known fully.

Planning

- For the patient with a respiratory infection, the patient will have a reduced fever and reduced duration of the infection.

Patient teaching

- Advise the patient it is best not to self-administer echinacea. The dose should be tailored to suit the needs of the individual patient. As a result, it is best taken on the advice of a health professional appropriately trained in natural therapies.
- Indicate to the patient that the medication should be taken at the onset of a respiratory infection for maximum effectiveness.
- As a tolerance to echinacea develops when used continually, advise the patient to alternate the length of time taken. For instance, the medication can be taken for 2 weeks and then stopped for 2 weeks.

Evaluation

- Evaluate the medication's ability to provide relief of the symptoms of colds, flu and other infections of the upper respiratory tract.

Evening primrose oil

Assessment

- Assess the patient's reason for wishing to use evening primrose oil, which may include dermatitis, premenstrual syndrome, psoriasis, eczema and mastalgia.
- Assess the female patient for pregnancy. As the effects of evening primrose oil during pregnancy are not known, it should not be taken at this time. It may be taken during breast feeding.
- Evening primrose oil should not be used in patients with epilepsy, because it can increase the risk of an epileptic fit.
- Avoid use of evening primrose oil in patients with schizophrenia.

Planning

- For the patient taking the preparation for a dermatological condition, the goal is to decrease the incidence of redness, pain, oedema and itchiness.
- For the female patient taking the preparation for premenstrual syndrome, there will be improvement in the condition.
- For the patient taking the preparation for mastalgia, there will be a decreased incidence of pain associated with the condition.

Patient teaching

- The patient should be informed that evening primrose oil may cause mild gastrointestinal effects, such as nausea, indigestion and softening of stools. It may also cause headaches due to its effect on cerebral blood vessels.
- The patient should be advised to ensure that recommended doses are consumed, as high intakes have been found to lead to haemorrhages.
- If a female patient is using evening primrose oil for premenstrual syndrome, it is advisable that she consumes the preparation a few days before menstruation.

Evaluation

- Evaluate the effectiveness of the preparation in treating a dermatological condition.
- Evaluate the effectiveness of the preparation in reducing the incidence of premenstrual syndrome.
- Evaluate the effectiveness of the preparation in reducing the pain associated with mastalgia.

Feverfew

Assessment

- In view of feverfew's effect as an antiplatelet drug, it should not be used in patients on anticoagulant therapy.
- Assess the female patient for pregnancy and lactation. Feverfew should not be administered to pregnant and breast-feeding patients.

Planning

- For the patient with rheumatoid arthritis, the aim will be to improve joint function.
- For the patient taking this medication for migraine attacks, the goal will be to reduce the frequency and duration of attacks.

Patient teaching

- The patient should avoid sudden discontinuation following long-term use, as this may lead to rebound headaches. Instead, the dose should be reduced gradually.
- Feverfew is not a pain-relieving herb and will not help a migraine headache once it has begun. For maximum benefit, it should be taken as a preventive form of treatment.
- To prevent the incidence of adverse gastrointestinal effects, such as diarrhoea, flatulence and nausea, the medication should be taken with meals.
- Gargling mouthwashes may decrease the incidence of mouth ulcers and a dry, sore tongue.
- The patient should be encouraged to avoid foods that tend to aggravate or trigger migraine attacks. Foods that should be avoided include fried foods, hard cheese, chocolate, red wine and salt-containing foods.

Evaluation

- Evaluate the effectiveness of the medication in reducing the incidence and duration of migraines.
- The patient will experience relief from joint pain after taking feverfew.

Garlic

Assessment

- As garlic has anticoagulant properties, caution must be exercised in administering this medication to patients on warfarin.

- Investigate the patient's specific complaint, which may include artherosclerosis, viral respiratory infections such as the common cold, and hayfever.
- Assess the patient for any impending surgery. The patient should be cautioned not to take a medication containing garlic for several weeks before surgery in order to prevent any problems with bleeding.

Planning

- For the patient with artherosclerosis, the aim may be to lower the blood cholesterol level.
- For the patient with hayfever or a viral respiratory infection, the aim will be to reduce the duration of these conditions.

Patient teaching

- The patient should be advised that raw garlic is therapeutically active, but cooking garlic reduces its benefit.
- Eating raw parsley helps remove the aftertaste of eating uncooked garlic.
- The patient should be warned about the toxic effects of garlic consumption, which include faintness and a drop in blood pressure.

Evaluation

- Evaluate the potential benefits of garlic in atherosclerosis, which may include normal blood cholesterol levels, normal blood pressure and reduced chest pain.
- Determine whether the patient's hayfever or respiratory infection are improving after the consumption of garlic.

Ginger

Assessment

- Assess the type of nausea or vomiting experienced by the patient. Ginger may be helpful for nausea and vomiting associated with travel or pregnancy. It is not particularly useful in postoperative nausea or nausea caused by chemotherapy, however.
- Caution should be exercised in administering ginger to patients on warfarin due to its anticoagulant effect.

Planning

- The aim will be to reduce the severity of nausea or vomiting.

Patient teaching

- Advise the patient that powdered ginger is more effective than ginger ale and ginger tea.
- Ginger is an effective treatment of morning sickness during pregnancy, with no ill-effects sustained by the fetus.
- To make fresh ginger tea, instruct the patient to steep half a teaspoon of grated fresh ginger root in a cup of water for 15 minutes. This mixture is then strained and honey added if a sweetener is desired.
- Indicate to the patient that as ginger does not have the sedating properties of scheduled antiemetics, it is a valuable medication for travelling.
- Advise the patient that a common sign of ginger toxicity is diarrhoea.

Evaluation

- The severity of nausea or vomiting will be reduced.

Ginkgo

Assessment

- Assess the patient's brain function relating to mental alertness and memory skills.

Planning

- For the patient with dementia, the aim will be to improve memory.
- For an elderly patient who shows signs of forgetfulness, the aim will be to improve alertness and memory.

Patient teaching

- The patient needs to be cautioned that diarrhoea, nausea, vomiting, irritability and restlessness may occur with large doses of the medication.
- The patient should be informed that this medication is a good alternative to caffeine in promoting alertness, without the adverse effects of sympathetic stimulation.

Evaluation

- Patients with dementia may demonstrate greater alertness and socialisation skills.
- Elderly patients may demonstrate improved short- and long-term memory and vigour.

Ginseng

Assessment

- Assess the patient's stamina and ability to perform day-to-day activities.
- As ginseng has some anticoagulant properties, caution should be exercised when used by patients on warfarin.

- Caution should be exercised in patients with high blood pressure. Patients with blood pressure problems should consult a doctor before using ginseng.
- Ginseng is contraindicated in patients with hyperthyroidism, as it increases the metabolic activity of body organs.

Planning

- The patient will have an increased sense of wellbeing after taking ginseng, although this may be somewhat difficult to evaluate.

Patient teaching

- Advise the patient that the benefits of ginseng may take weeks or months to be seen.
- Investigate the patient's diet and the prevalence of stress in daily activities. The patient will also need to address these areas to promote a sense of wellbeing.
- Ginseng is a short-term booster of body functions. The patient does not need repeated doses beyond a course of a few days.
- Advise the patient to consult with a qualified health professional about the dose that may be consumed. Ginseng has highly individualised effects in different people.
- Advise the patient that signs of toxicity of ginseng include nausea and vomiting.
- If a patient is taking too much ginseng, either hyperactivity or a paradoxical tiredness may be experienced.

Evaluation

- From the patient's perspective, determine any improvement in physical or mental stamina.

Red clover

Assessment

- Assess the patient's specific complaint, which may include a skin condition, such as eczema or psoriasis, or a respiratory infection.
- As red clover contains isoflavones, it should not be taken during pregnancy.
- Assess the child patient who may have whooping cough, bronchiolitis or a skin condition. Red clover is a safe and effective form of therapy in young children.

Planning

- The patient will obtain relief from the skin condition or respiratory infection.

Patient teaching

- If an excessive dose is used, red clover may increase faecal elimination of waste material, leaving the patient feeling uncomfortable and exhausted.
- A qualified health-care professional should be consulted about the appropriate dose.

Evaluation

- The skin condition will begin to clear following administration of red clover.
- The symptoms of a respiratory infection, such as laboured breathing, coughing and fever, will begin to improve following administration.

St John's wort (hypericum)

Assessment

- Assess the patient for concomitant use of antidepressants such as tricyclic antidepressants and monoamine oxidase inhibitors. St John's wort should not be taken by patients on these drugs.
- Assess the patient for concomitant use of benzodiazepines. St John's wort should not be taken by patients on these drugs.
- Assess the patient for concomitant use of warfarin. St John's wort should not be taken by patients on warfarin as there may be a decreased anticoagulant action of warfarin.
- Assess female patients for pregnancy, and advise that St John's wort should not be taken during this time.
- Assess the patient's state of depression before and during the administration of St John's wort.

Planning

- The aim is to improve the patient's state of depression following administration of St John's wort.

Patient teaching

- Advise the patient that a benefit may not be seen for up to 3–4 weeks following commencement of therapy. This is a similar scenario to that seen with other antidepressant drugs.
- Direct the patient to various support networks to provide further assistance for depressive symptoms.
- The dose of St John's wort should be monitored carefully by a qualified health-care professional.
- Advise the patient to take precautions when going out in the sun, due to the medication's tendency to cause photosensitivity (see Table 11.19 in Chapter 11 for further information).

Evaluation

- Evaluate the patient's symptoms of depression following a course of St John's wort.

Saw palmetto

Assessment

- Ask the female patient whether she is taking the oral contraceptive pill or hormone replacement therapy. As saw palmetto contains sterols, its use is contraindicated in a patient taking these medications.
- Assess the male patient's symptoms of benign prostatic hypertrophy.
- Assess the patient for other specific complaints for which saw palmetto is useful, including baldness, acne and female hirsutism.

Planning

- The male patient will have relief from the discomfort of benign prostatic hypertrophy.
- For the patient with baldness, acne or female hirsutism, aim to improve the condition.

Patient teaching

- Advise the patient that adverse effects of saw palmetto include headaches, nausea and vomiting.
- Administration of the medication with food may reduce the incidence of gastrointestinal upsets.
- As the prostate gland is affected by diet, exercise and lifestyle, the male patient should examine these factors to reduce the severity of a prostate problem. A nutritious low-fat diet and reasonable exercise are helpful for this condition.

Evaluation

- The male patient with a prostate problem will demonstrate decreased urinary retention.
- The symptoms in the patient with baldness, acne or female hirsutism will improve.

Valerian

Assessment

- Assess the patient's ability to sleep and factors that may prevent the onset and duration of sleep.
- Determine whether the patient is likely to have an anaesthetic in the near future. This patient should not be taking valerian for the time leading up to the anaesthetic administration.

Planning

- The aim will be to improve the patient's ability to sleep.

Patient teaching

- Valerian should be taken only at night in order to prevent daytime drowsiness.
- Only a short course of valerian should be taken for sleeping problems in order to prevent the incidence of tolerance or dependence. It must be acknowledged that tolerance and dependence are not proven characteristics of this therapy; it is advisable to be cautious, however.
- Advise the patient to avoid caffeine, nicotine and foods high in sugar and fats in the early evening.

Evaluation

- The patient's ability to sleep will improve, as shown by a decreased onset and an increased duration of sleep.

SUMMARY

- Herbs and related products are used widely by society for the prevention and treatment of many ailments.
- Herbs and their extracts can have adverse effects similar to those with conventional medications.
- Many herbs can cause deleterious interactions with other drugs (see Appendix 6).
- Most herbal preparations have inconclusive activity in the treatment and prevention of disease.
- A few herbs have well-proven efficacy in the treatment of disease.
- Many of today's medicines are derived from herbs, and it is likely that this number will increase in the future.

1 What is the evidence that supports the value of St John's wort as an antidepressant?

2 Explain the therapeutic value of phyto-oestrogens.

3 Which is better and why – odourless garlic or pure garlic oil?

4 Marianna Rossito is a 28-year-old woman in the third trimester of her pregnancy. She has been experiencing difficulties with sleep due to the pressure of the fetus. Ms Rossito asks you about taking chamomile supplements to help with her problem. What would you advise?

5 Joel Smith, a 55-year-old patient, has experienced ongoing problems with migraine headaches since adolescence. His medical practitioner recommends that a course of feverfew may help his condition. What aspects of patient education relating to the administration of feverfew would you talk over with Mr Smith?

6 How would you evaluate the potential benefits of raw garlic in a patient who is taking it for atherosclerosis?

7 What herbal medication could you recommend to a patient who experiences morning sickness during pregancy?

8 Herb Elbs, a 78-year-old patient, is taking saw palmetto for benign prostate hypertrophy. How would you assess whether the therapy is producing some benefit?

CASE STUDY XIII.1

Mr MM, aged 55 years, is admitted to hospital with acute pancreatitis due to chronic alcoholism. Over the past few weeks, he has been losing weight rapidly and experiencing difficulty in breathing and has endured nausea and vomiting. On the treatment sheet, the doctor orders for Mr MM nil orally and the insertion of a nasogastric tube to decompress the bowel. The doctor then inserts a central venous catheter and prescribes total parenteral nutrition (TPN). In Mr MM's nursing care plan, the nurse documents that the central line should be changed every 48 hours and a daily dressing performed on the insertion site. Both procedures are to be performed using sterile gloves, gown and dressing. An Actrapid infusion is also commenced, running at 2 units per hour.

Seven days after admission, the nurse notices yellow ooze at the insertion site of the central catheter and notifies the doctor. Blood glucose analysis by finger-prick indicates a level of 16 mmol/l.

QUESTIONS

1. *Detail how you would evaluate whether Mr MM is receiving adequate TPN.*
2. *What should be done to treat a blood glucose level of 16 mmol/l?*
3. *What has caused the development of yellow ooze at the insertion site?*
4. *What treatment would be instigated for the condition associated with this ooze?*
5. *Why is the central line changed and daily dressing performed under sterile conditions?*
6. *Why is TPN administered for Mr MM instead of enteral nutrition?*
7. *Why is TPN administered through a large central vein rather than through a peripheral vein?*
8. *Following insertion of the central venous catheter, what procedure is performed before the commencement of TPN? Explain.*

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WEB RESOURCES

HerbMed www.herbmed.org

Herbal safety news www.mhra.gov.uk/home/idcplg?IdcService=SS_GET_PAGE&nodeID=96

Linus Pauling Institute (vitamins) http://lpi.oregonstate.edu/

Prescription Alternatives www.rxlist.com/alternative.htm

Research Council for Complementary Medicine www.rccm.org.uk

MODULATION OF CELLULAR GROWTH AND PROLIFERATION

Here we may speak of magic bullets which aim exclusively at the dangerous intruding . . . strangers to the organism, but do not touch the organism itself and its cells.

PAUL EHRLICH – IN *KRANTZ'S HISTORICAL MEDICAL CLASSICS INVOLVING NEW DRUGS*

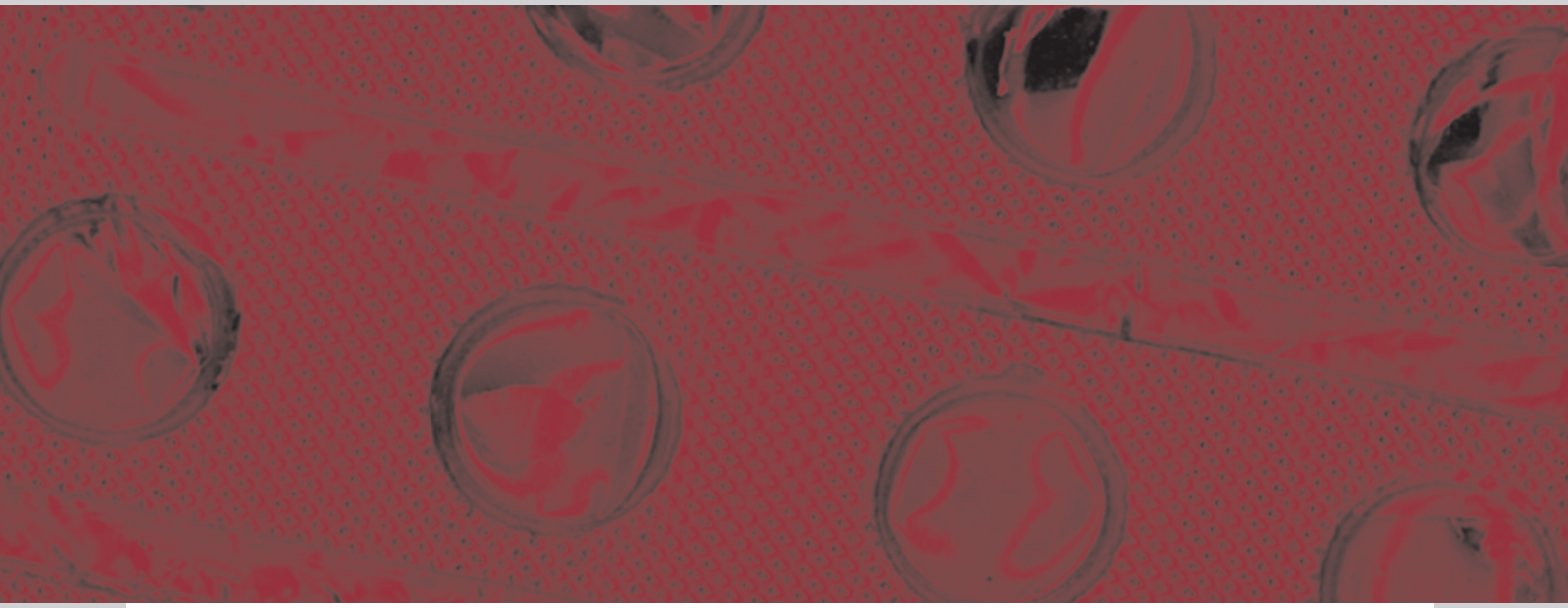
In the quote above, Paul Ehrlich identifies the fundamental principle of chemotherapy – that is, selective toxicity. Whether the dangerous stranger is a virus, a bacterium, a parasite or a cancerous cell is of no import: the aim of therapy is to destroy the foreign cell without damaging the normal body cells of the host organism.

In this section, we examine the drugs used in chemotherapy. Significantly, most of these agents were developed only in the twentieth century. Over a relatively short time, chemotherapy has established itself and become a prominent area of clinical pharmacology. Such is the pace of development that many agents have already become redundant, either because they have been replaced by safer and more potent compounds, or because drug resistance has emerged.

The chapters in this section explore the nature of the chemotherapeutic agents used to facilitate the eradication of pathogenic organisms from the body. The principles of chemotherapy (Chapter 66) apply not only to the treatment of bacterial infections (Chapters 67–69) but also to those caused by multicellular parasites (Chapters 71 and 72), viruses (Chapter 73) and fungi (Chapter 74). The actions of antiseptics and disinfectants are described in Chapter 70. In Chapter 76, we demonstrate how these chemotherapeutic principles also apply in the treatment of cancer.

Immune cells proliferate in response to the presence of 'dangerous strangers' in the body, e.g. microbes, transplanted cells and cancer cells. A number of drugs can stimulate or boost immunity, while others inhibit it, and in

XIV



Chapter 75 we examine the function of drugs that modify the function of the immune system.

Manipulation of gene expression may represent the future direction of chemotherapy. The principles, current procedures and limitations associated with gene therapy are explored in Chapter 77. Gene therapy may also have applications in immune, inflammatory cardiovascular and endocrine disorders.

INTRODUCTION TO CHEMOTHERAPY

66

CHAPTER SIXTY-SIX

OBJECTIVES

After completing this chapter, the reader should be able to:

- **describe the principal mechanisms of action of antimicrobial agents and suggest examples of classes of drugs that act in each way;**
- **contrast bactericidal and bacteriostatic actions;**
- **discriminate between narrow- and broad-spectrum antimicrobials;**
- **outline the main adverse effects of antimicrobial agents and explain why they occur;**
- **describe how microbes acquire resistance to the action of antimicrobial drugs, and state some factors that contribute to the development of resistance and how its incidence can be minimised.**

KEY TERMS

Antibiotic-associated colitis
Bactericidal action
Bacteriostatic action
Drug resistance
Infection
Selective toxicity
Spectrum of activity
Superinfection

INCREDIBLY, IT IS LITTLE MORE THAN A CENTURY SINCE the illuminating experiments of Pasteur and Koch linked specific infectious diseases to specific kinds of microorganism. By identifying and understanding the nature of the causative agent, scientists had an opportunity to develop a cure.

In the early part of the twentieth century, the search began for drugs that would be effective in treating the infectious diseases responsible for countless human fatalities

through the ages. This search has led to the development of many important antimicrobial agents, such as the sulphonamides and the antibiotics. More recently, research has led to the formulation of drugs with efficacy against viral infections.

In this chapter, we introduce some general chemotherapeutic principles relating to the actions and effects of antimicrobial drugs.

MECHANISM OF ACTION OF ANTIMICROBIAL AGENTS

The ideal antimicrobial agent will, after entering the body, move to the site of infection, destroy the pathogenic microbe (or facilitate its destruction), and then be eliminated from the body without affecting the structure or function of human body cells. To achieve this, we must attack and disable some microbial process or structure not present in humans. This is known as the principle of selective toxicity. Indeed, there are many differences between human cells and microbes to exploit (see Figure 66.1).

The mechanism of action of any antimicrobial drug can be classified according to the way in which it exploits these differences. The four categories by which antimicrobial drugs work are described here.

Inhibition of cell-wall synthesis

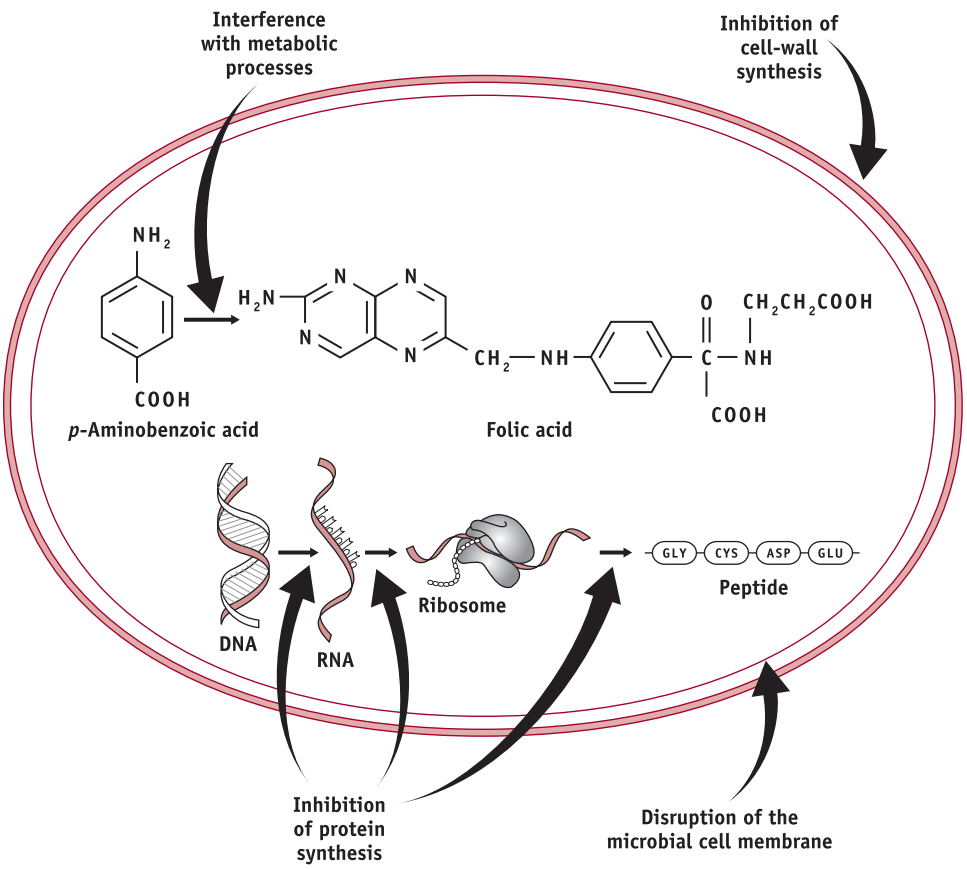
Most bacteria possess a cell wall to protect them from the osmotic influences of the external environment. As these microbes divide to produce progeny, new cell walls are synthesised. Certain antimicrobial agents interrupt the formation of the cell wall in these progeny, leaving them vulnerable to outside influences. As a result, the cell ruptures and the microbes perish. Penicillins, cephalosporins, **vancomycin** and **bacitracin** are examples of drugs that work in this way. These are relatively non-toxic antimicrobials, as human cells do not possess a cell wall.

Disruption of the microbial cell membrane

Antimicrobials that act through this mechanism affect membrane transport, both into and out of the microbe. This

FIGURE 66.1 MECHANISMS OF ACTION OF ANTIMICROBIAL DRUGS

Antimicrobial drugs act by one of four general mechanisms selectively toxic to prokaryotic cells.



change in cellular permeability is incompatible with survival. **Polymyxin B** and **colistin** are two examples of such drugs. These agents are more toxic systemically than the previous group, as some human cells (e.g. erythrocytes) are particularly vulnerable to their action.

Inhibition of protein synthesis

There are two locations at which these drugs can act: at the site of protein synthesis (the ribosome) or within the nucleus by preventing the synthesis of nucleic acids (inhibiting either DNA replication or RNA synthesis), thereby blocking transcription. Proteins are essential for repair and growth. As new proteins need to be manufactured before cell division, inhibition of this process halts microbial population growth. Examples of drugs that act in this way are the tetracyclines, aminoglycosides and macrolides (e.g. **erythromycin**). These agents exploit structural differences between human and bacterial ribosomes or enzymes involved in nucleic acid synthesis to achieve selective toxicity. At higher doses, however, they can be quite toxic to human cells.

Interference with metabolic processes

These agents are structurally similar to para-aminobenzoic acid (PABA), a component of folic acid. The latter substance is an essential participant in nucleic acid synthesis. Without folic acid, bacteria cannot produce the proteins necessary for growth and replication. Antimicrobials with this action inhibit the synthesis of folic acid by competition with PABA or incorporate into the structure of folic acid, thus interfering with the metabolic reactions in which it would normally participate. The selectivity of these drugs derives from the fact that many microbes must synthesise their own folic acid, whereas humans can utilise folic acid present in the diet. The sulphonamides and **trimethoprim** are examples of drugs with this mechanism of action.

BACTERICIDAL ACTION VERSUS BACTERIOSTATIC ACTION

When considering bacterial infections, the mechanism of action of antimicrobial agents can also be classified according to whether they lead to the death of the susceptible microbe (bactericidal action) or inhibit the growth and, therefore, spread of the microbial population (bacteriostatic action). A bacteriostatic action enables the host's immune system to rid the body of a static population of invading organisms. An unwanted effect of a bactericidal agent is that microbial cell death may result in the release of endotoxins into surrounding tissues or even the general circulation. This could lead to substantial damage to body organs and tissues.

As a general rule, drugs that inhibit the formation of a cell wall or disrupt the cell membrane are bactericidal agents, while drugs that inhibit protein synthesis or interfere with metabolic processes are bacteriostatic. Since some bacteriostatic agents are bactericidal at higher doses, however, such classification may not always be simple.

SPECTRUM OF ACTIVITY

The number of species of microbes that are sensitive to the action of the antimicrobial agent is defined as its spectrum of activity. Logically, an antimicrobial agent that is effective against only a few species is a narrow-spectrum agent. For instance, **penicillin G** is regarded as a narrow-spectrum antibiotic, as it is effective only against Gram-positive bacteria and a limited number of other microbes. In contrast, the tetracyclines are effective against both Gram-positive and Gram-negative bacteria, mycoplasma, chlamydiae and some protozoa and therefore are considered broad-spectrum antibiotics.

The terms 'narrow spectrum' and 'broad spectrum' should never be confused with drug potency and efficacy. Narrow- and broad-spectrum drugs do not equate to 'weak' and 'strong' antibiotics. In fact, a narrow-spectrum antimicrobial, effective against only a few species, may be more efficacious than a broad-spectrum drug in treating a particular infectious agent. The converse is also true.

UNWANTED EFFECTS

The side effects of antimicrobial usage vary from drug group to drug group. Therefore, the major specific problems associated with each group are discussed in the following chapters on chemotherapy. We often observe a number of adverse effects common to a variety of antimicrobial agents, such as gastrointestinal disturbances and allergic reactions.

To avoid repetition in the following chapters, some important general unwanted effects are described below. These include the gut-associated problems of superinfection and antibiotic-associated colitis, hypersensitivity and drug resistance.

Superinfection

Some of the microbes that live in the gastrointestinal tract as natural flora may be susceptible to the action of orally administered antimicrobial agents. As a result, the balance of pathogenic and non-pathogenic gut flora, maintained through competition for resources, is disturbed. Certain pathogenic organisms can then proliferate to a point where a serious secondary illness arises; this is a superinfection. Common protagonists are staphylococci, *Candida albicans* and Gram-negative bacteria. Fortunately, such a state occurs infrequently and is usually associated with prolonged therapy.

C. albicans infection is called candidiasis or candidosis. It usually affects the mucous membranes of the mouth and gastrointestinal tract, but it can also affect the vagina.

Common manifestations include rash, local itchiness and diarrhoea. Oral candidiasis is a painless condition, with whitish lesions that can involve the lips, tongue, throat and the buccal surface of the cheeks.

Hypersensitivity reactions

Hypersensitivity reactions are triggered by an interaction of preformed antibodies or immune cells with specific antigens. (The characteristics of the various hypersensitivity reactions are described in Chapter 17.) After administration of antibiotic drugs, specific antibodies form in our bodies. This is not surprising, as some of these substances are defensive secretions made by or derived from other living organisms. As such, they are antigenic to humans. In fact, we may possess antibodies to a particular antibiotic without ever having received it as clinical treatment. This can occur because of residual amounts of antibiotic drugs being present in the meat we eat. Similarly, inhalation of airborne particles of antibiotics while visiting a pharmacy or hospital could provide a route of exposure.

For the majority of people, this phenomenon does not cause problems. In some individuals, however, these antibodies can trigger a life-threatening type I (anaphylactic) hypersensitivity reaction if the person comes into contact with the antigenic substance a second time. Allergies to penicillins and other related drugs are relatively common.

Antibiotic-associated colitis

This adverse effect of antimicrobial drug treatment is characterised by an inflammation of the wall of the colon. Examination of the affected wall reveals diffuse pseudomembranous plaques – hence its former name, pseudomembranous colitis. The following drugs are noted for this effect: penicillins, tetracyclines, **chloramphenicol** and **cotrimoxazole**. Not surprisingly, the condition is observed more often after oral than parenteral administration of the drug. Every instance of antibiotic-associated colitis is accompanied by diarrhoea; however, these agents can also induce diarrhoea without necessarily causing colitis.

Studies of individuals with antibiotic-associated colitis have revealed the presence of toxic particles in the gut. These particles have been found to damage cells that line the gastrointestinal tract in vitro, but the source of the particles is yet to be established. The anaerobic bacterium *Clostridium difficile* is known to induce this condition, but it can be controlled by vancomycin therapy. The condition also responds well to treatment with either steroidal anti-inflammatory agents or **cholestyramine**, the latter binding to and causing the elimination of the toxic particles. On occasion, the condition has been fatal.

Antimicrobial resistance

Acquired resistance to the action of antimicrobial agents by a previously sensitive strain of microorganism is a major problem associated with the effectiveness of drug therapy of infectious diseases.

Resistance of a microbe to a specific antimicrobial drug can develop in a number of ways. Spontaneous genetic mutation in a single microbial organism may result in the organism gaining the ability to evade the function of the antimicrobial agent. For example, a mutation may result in the ability to produce a lytic enzyme capable of inactivating the therapeutic agent (as in penicillin and cephalosporin resistance) or may allow the microbe to bypass the metabolic block imposed by the antimicrobial agent (as in sulphonamide resistance). Another means by which antimicrobial resistance may be gained is through the spontaneous exchange of genetic material encoding resistance to specific antimicrobial drugs between microbes, not necessarily of the same strain. The vectors of this information are called plasmids – small packets of DNA that can be transferred from one microbial cell to another through conjugation. A pertinent example of such an exchange is that between vancomycin-resistant enterococci (VRE) and methicillin-resistant *Staphylococcus aureus* (MRSA). Vancomycin remains the most reliable and effective antimicrobial drug in the treatment of infections with MRSA (see Chapter 68). In clinical practice, vancomycin is used judiciously in order to avoid the spread of resistance. VRE are gut flora that have developed resistance to vancomycin and could easily pass this property to MRSA. The widespread development of vancomycin-resistant MRSA would be catastrophic for individuals with serious MRSA infections, and in some hospital settings patients are tested for the presence of VRE and subject to special infection-control procedures in order to minimise the risk of transfer of resistance to MRSA.

An additional problem is that organisms that have acquired resistance to a particular class of antimicrobials are also insensitive to the action of similarly structured drugs. Cross-resistance between antimicrobial classes is observed in microbes with resistance to penicillins, which may also be resistant to the action of the cephalosporins.

Improper use of antimicrobials over the years has caused the problems we are experiencing today with resistant strains. Excessive use of antibiotics on animals bred for human consumption has led to residual amounts of antibiotics in meat. The consequence of this is that our gut flora have been exposed to sublethal doses of these drugs, which have provided them with the opportunity to acquire resistance themselves and then transmit it via plasmids to other microbes. Research has revealed that *Escherichia coli* isolated from the gut flora of infants may have resistance to up to three antibiotics without the infant ever having received treatment with these agents. Spraying excess antibiotic into the air after drawing it up for injection allows exposure to airborne microbes. Failure to conform to an appropriate dosage regimen by not taking the full dose for the designated period leads to the proliferation of resistant organisms and makes

subsequent therapy more problematic. Using broad-spectrum antibiotics to treat infection when the causative microbe is sensitive to a narrow-spectrum drug is another example of a situation that may lead to the emergence of drug-resistance.

ANTIMICROBIAL DRUGS IN PREGNANCY

The actions of antimicrobial drugs are aimed at inhibiting the growth and metabolism of rapidly dividing pathogenic cells. Therefore, it is not surprising that these drugs can have deleterious effects on the developing human in utero.

The categories describing the relative risk of teratogenic damage of therapeutic agents are discussed in Chapter 17. As expected, very few antimicrobial agents feature in the low-risk category. Selected penicillins, cephalosporins, erythromycin, **clindamycin**, **lincomycin**, **natamycin**, **nitrofurantoin** and **nystatin** are the only antimicrobial drugs that appear not to harm the fetus.

TIME-DEPENDENT AND CONCENTRATION-DEPENDENT ACTIVITY

For some antimicrobial agents, their action on microorganisms has a time-dependent effect. These antimicrobials need time to produce their therapeutic effect. An increase in dose will therefore produce no increase in effect. Rather than the dose, the time above the minimum effective concentration (see Chapter 17) determines the effect. Examples of antimicrobial agents that have a time-dependent activity on microorganisms are the beta-lactams (e.g. penicillins), macrolides (e.g. erythromycin) and glycoproteins (e.g. vancomycin, **teicoplanin**). With such antimicrobial agents, it is not necessary therefore to measure peak and trough concentrations of time-dependent antibiotics, but it is important for the levels to be maintained above the minimum effective concentration for at least 60 per cent of the time in order to ensure efficacy.

For other antimicrobial agents, their effectiveness depends on the concentration or dose administered rather than the time in contact with the microorganism. For these antimicrobials, the higher the peak blood level of agent, the better the antibacterial effect achieved. Examples of antimicrobials that have a concentration-dependent activity on microorganisms are the quinolones (e.g. **norfloxacin**, **ciprofloxacin**) and aminoglycosides (e.g. **gentamicin**, **tobramycin**). The clinical significance of this characteristic is that for these types of agents, it is important to measure the peaks and troughs of plasma concentration in order to ensure that the peak concentration achieved is sufficient. Figures 66.2 and 66.3 illustrate schematically the activities of time-dependent and concentration-dependent antimicrobial agents.

FIGURE 66.2 ACTIVITY OF TIME-DEPENDENT ANTIMICROBIAL AGENTS

For time-dependent antibiotics, the time above the minimum effective concentration (MEC) determines the effectiveness of therapy against microorganisms.

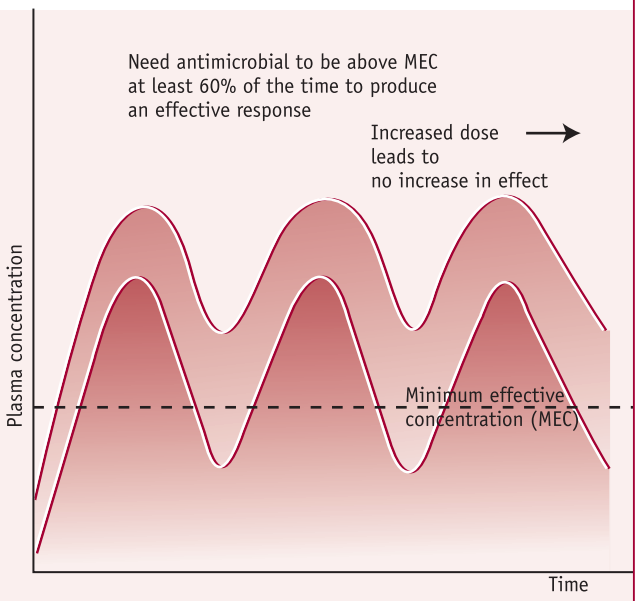
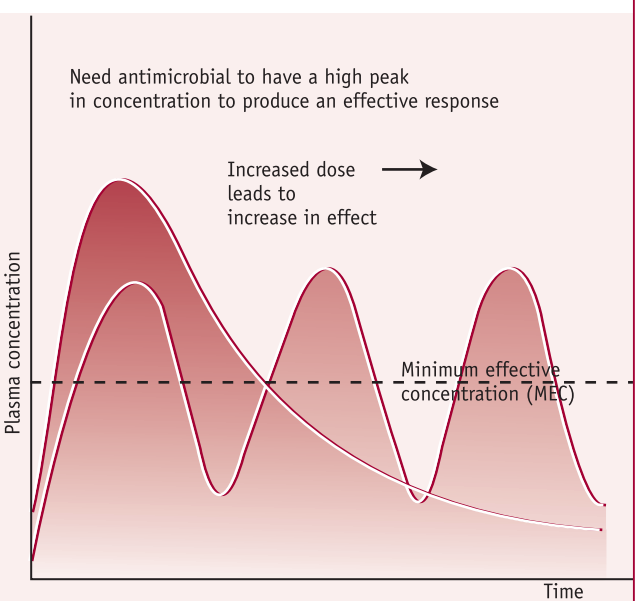


FIGURE 66.3 ACTIVITY OF CONCENTRATION-DEPENDENT ANTIMICROBIAL AGENTS

For concentration-dependent antibiotics, the height of the peak level determines the effectiveness of therapy against microorganisms.



SUMMARY

- Antimicrobial drug therapy is a form of chemotherapy that exploits structural and functional differences between human cells and microbial cells.
- Antimicrobial agents tend to act via one of four mechanisms: inhibition of cell-wall synthesis, disruption of the microbial cell membrane, inhibition of protein synthesis, and interference with microbial metabolic processes.
- The activity of antimicrobial agents can be classified as bacteriostatic, where microbial cell growth is inhibited, or bactericidal, where the treatment kills the microbe.
- A broad-spectrum antimicrobial agent is effective against a wide range of microbes, and a narrow-spectrum agent is effective against only a few microbes.
- The major unwanted effects commonly associated with antimicrobial therapy are superinfection, hypersensitivity, antibiotic-associated colitis and antimicrobial resistance.
- The effectiveness of some antimicrobial agents depends on the concentration of the drug in the blood (concentration-dependent), while for others the effectiveness depends on the time of exposure to the infective organisms (time-dependent).

1 State the four general mechanisms of action of antimicrobial agents.

2 Compare the following terms:
(a) bactericidal and bacteriostatic drugs;
(b) narrow- and broad-spectrum drugs.

3 Antibiotic sensitivity testing of a sputum culture from Audrey Hepspa, a 26-year-old with a persistent respiratory tract infection, has revealed that the bacteria are sensitive to both penicillin G and a tetracycline. Assuming that Audrey is not allergic to either drug, which antimicrobial drug should be used to treat the infection? Why?

4 Name three unwanted effects of antimicrobial therapy.

5 State three ways in which resistance to antibiotics can be conferred on microbes.

6 State the ways in which the spread of antimicrobial resistance in our community can be reduced.

7 Jacinta Cheflin, 26 years old, is in the second timester of pregnancy. She has developed a bacterial respiratory infection. A swab is taken and antibiotic sensitivity testing shows that the infectious bacterium is sensitive to the aminoglycoside gentamicin, the tetracycline doxycycline, the penicillins floxacillin and amoxicillin, and the quinolone ciprofloxacin. Refer to a suitable clinical reference and decide which antibacterial agent is most suitable and why.

8 In what way do vancomycin-resistant enterococci pose a threat to the management of methicillin-resistant *Staphylococcus aureus* (MRSA) infections?

SULPHONAMIDES AND TRIMETHOPRIM

67

CHAPTER SIXTY-SEVEN

OBJECTIVES

After completing this chapter, the reader should be able to:

- **describe the mechanism of action of the sulphonamides and trimethoprim;**
- **outline the adverse effects of the sulphonamides and trimethoprim;**
- **understand the clinical uses of the sulphonamides and trimethoprim.**

KEY TERMS

Crystalluria
Drug hypersensitivity
Folic acid metabolism

THE SULPHONAMIDES WERE THE FIRST SUCCESSFUL antibacterial drugs. The red dye prontosil was found to be effective against streptococcal infection. Its antimicrobial action was induced by conversion into sulphanilamide within the body. This discovery triggered the start of bacterial chemotherapy on a wider scale and led to the development of a number of related compounds known collectively as the sulphonamides.

Trimethoprim was originally introduced as an antimalarial, but it has a similar spectrum of bacteriostatic activity to that of the sulphonamides. In combination with a sulphonamide, it offers an advantage over the sulphonamide alone.

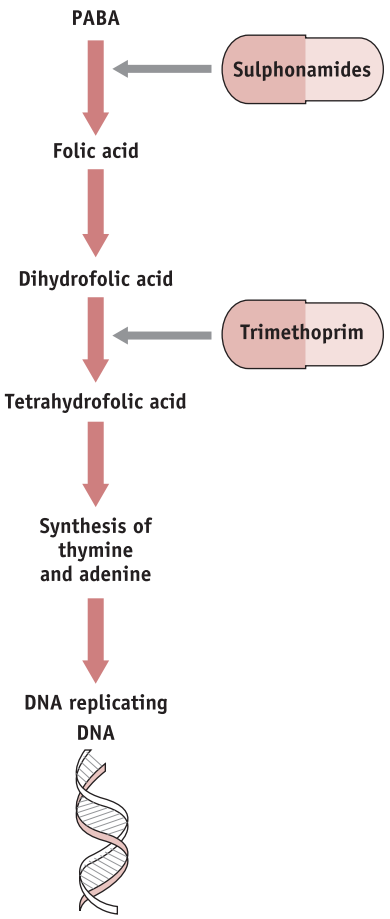
Additionally with the discovery of the sulphonamides, other useful applications became apparent. The important antileprotic agent dapsone was developed as a result of sulphonamide research and has a similar mechanism of action (see Chapter 69). The development of the oral hypoglycaemic agents (see Chapter 57) and the diuretic agents, carbonic anhydrase inhibitors (see Chapter 47), also came about through observations of side effects of the sulphonamides.

MECHANISM OF ACTION

The mechanism of action of both the sulphonamides and trimethoprim is through interference with an important metabolic pathway involving folic acid. Bacteria, unlike mammals, are unable to take up folic acid from the environment and thus are dependent on their own de novo synthesis form p-aminobenzoic acid. Folic acid in the form of tetrahydrofolic acid promotes the incorporation of thymidine and uridine into DNA. Thus, interference with the pathway of folic acid production prevents the synthesis of DNA. Trimethoprim and the sulphonamides act at different points within the pathway (see Figure 67.1). Such interference will result in the inhibition of microbial growth and is therefore considered bacteriostatic. In some instances, the effects of the drug are delayed for some days until all microbial stores of folic acid are depleted.

FIGURE 67.1 SITES OF ACTION OF THE SULPHONAMIDES AND TRIMETHOPRIM IN DNA SYNTHESIS

This figure shows the metabolic pathway for DNA synthesis. The sites at which the sulphonamides and trimethoprim interfere with this pathway differ. Sulphonamide antimicrobials interfere with the synthesis of folic acid from para-aminobenzoic acid (PABA). Trimethoprim interrupts the conversion of dihydrofolic acid into tetrahydrofolic acid.



ADVERSE EFFECTS

Serious adverse effects associated with the use of sulphonamides and related drugs are diarrhoea, related to a change in the balance in gut flora, crystalluria, as a consequence of these drugs becoming insoluble in the urine due to the acidity of this environment, and hypersensitivity, ranging from a mild rash and photosensitivity through to severe blood dyscrasias such as agranulocytosis and aplastic anaemia. The latter effects are due to the inhibition of differentiation of bone marrow cells into mature blood cells by blocking the nucleic acid synthesis necessary for cell division. One type of hypersensitivity reaction occasionally associated with sulphonamide therapy is Stevens–Johnson syndrome, which can be lethal.

USES AND CLINICAL CONSIDERATIONS

Current use of the sulphonamides is limited. There are two main reasons for this: the toxicity of these drugs compared with newer antimicrobials (hypersensitivity reactions, crystalluria and blood dyscrasias), and the problem of acquired resistance in previously sensitive organisms. **Sulfamethoxazole** (sulphamethoxazole) and trimethoprim are often used in combination (as **co-trimoxazole**) because of their synergistic activity.

The Commission on Human Medicines has produced the following advice on the use of co-trimoxazole:

> Co-trimoxazole should be limited to the role of drug of choice in *Pneumocystis carinii* (*Pneumocystis jiroveci*) pneumonia; it is also indicated for toxoplasmosis and nocardiasis. It should now only be considered for use in acute exacerbations of chronic bronchitis and infections of the urinary tract when there is good bacteriological evidence of sensitivity to co-trimoxazole and good reason to prefer this combination to a single antibacterial; similarly it should only be used in acute otitis media in children when there is good reason to prefer it.

Trimethoprim is often used alone for common infections in adults, such as urinary tract infections. For this indication, the trimethoprim–sulfamethoxazole combination does not offer any clinical advantage over trimethoprim and is associated with several adverse effects.

Sulfadiazine (sulphadiazine) is used in combination with **pyrimethamine**, a folate antagonist. Adverse reactions to this combination are relatively common, and folinic acid supplements and weekly blood counts are needed.

When using a high dose of a sulphonamide, it is important to ensure an adequate fluid intake of at least 2–3 l daily in order to prevent crystalluria. The use of a urinary alkaliniser will assist in reducing the risk of crystalluria.

During prolonged or high-dose treatment with sulphonamides, it is important to conduct a full blood examination and monitor folate status. For patients on prolonged treatment or who have pre-existing renal dysfunction, renal function should also be monitored.

To reduce the incidence of photosensitive rash, the patient is advised to use a sunscreen, avoid sun exposure and wear protective clothing when outside. Sulphonamides are best taken with food in order to minimise the incidence of gastrointestinal effects. Trimethoprim alone is best taken as single daily doses at bedtime in order to maximise the urinary concentration.

CLINICAL MANAGEMENT

Sulphonamides and trimethoprim

Assessment

- Assess the patient for hypersensitivity and allergic reaction to sulphonamides, including rash, skin eruptions and itching. Anaphylaxis may also occur.
- Question the patient about a history of allergy to other sulphonamides, thiazide diuretics, acetazolamide and oral hypoglycaemic agents.
- Assess female patients for pregnancy status. Use of sulphonamides in pregnant patients who are near full term causes displacement of bilirubin from serum proteins in the fetus.
- Avoid use of sulphonamides in infants less than 2 months old, as displaced bilirubin from serum proteins may lead to kernicterus.
- Consider another form of antibacterial agent in patients with renal or hepatic disease, as they are more prone to toxic reactions from impaired metabolism of the sulphonamide.
- Make an assessment of the manifestations of the infection process. If used for urinary tract infection, determine relief of pain on urination, frequency of urination and amount of urine produced. Obtain a urine sample for culture and sensitivity tests.
- Assess vital signs and compare with subsequent observations.
- Assess for other medications taken by the patient. Most sulphonamides are highly protein-bound and compete for protein sites. Medications such as non-steroidal anti-inflammatory drugs, digoxin, oral anticoagulants and phenytoin displace sulphonamides from the protein sites and therefore raise free sulphonamide concentration in the blood.

Planning

- The patient's infection will be alleviated.

Implementation

- Monitor the manifestations of infection during therapy.
- Monitor fluid balance, including fluid intake and urine output. Ensure that urinary output is more than 1200 ml daily in order to prevent the development of crystalluria and kidney stones. Administer oral sulphonamides with extra fluid to increase urinary output. Urinary alkalinisation may also lessen the risk of crystalluria associated with a high dose or increased use of sulphonamides.
- Monitor the patient for haematological reactions that may lead to life-threatening anaemias. Early manifestations include sore throat, purpura, unexplained bruising or bleeding, and lowered white blood cell and platelet counts.
- Monitor for manifestations of superinfection, including diarrhoea and oral and genital *Candida* infection.
- Note that intravenous sulfamethoxazole–trimethoprim preparations should be diluted in the ratio of a 5-ml ampoule to 125 ml 5% glucose. The diluted solution is then administered in a burette over 60–90 minutes.

Patient teaching

- Advise the patient to report the development of sore throat, fever, difficulty in breathing, unexplained bruising or bleeding, malaise, jaundice and skin changes.
- Advise the patient that sulphonamides can cause superinfections due to disturbance of normal flora. Examples include oral and genital thrush (see Tables 11.7 and 11.16 in Chapter 11 for further information).
- Instruct the patient to increase fluid intake to at least 2000 ml daily in order to prevent crystalluria and kidney stones.

- Advise the patient to avoid contact with direct sunlight to prevent photosensitivity (see Table 11.19 in Chapter 11 for further information).
- For sulphonamides used for ophthalmic purposes, ensure that the patient knows how to administer eye preparations (see Table 7.3 in Chapter 7 for further information).
- For patients receiving sulfamethoxazole or sulfasalazine, advise that these drugs may turn the urine or skin a yellow-orange colour. This is a harmless reaction.

Evaluation

- Evaluate the effectiveness of therapy in resolving the infection without producing adverse effects.

SUMMARY

- The sulphonamides and related drugs act by interfering with a metabolic pathway involving folic acid, which is necessary for nucleic acid synthesis. Microbial growth is inhibited as a result.
- A combination of sulfamethoxazole and trimethoprim is called co-trimoxazole.
- The adverse effects of treatment with these drugs can be serious. Drug hypersensitivity reactions and crystalluria can occur.
- For common infections, it is preferable to use trimethoprim alone.
- When using a sulphonamide, ensure an adequate fluid intake of at least 2 l daily in order to prevent crystalluria. The use of a urinary alkaliniser will also reduce this risk.
- Monitor the blood and folate status during prolonged or high-dose treatment with sulphonamides.
- Monitor renal function for patients on prolonged treatment with sulphonamides or who have pre-existing renal dysfunction.

1. Which one of the four general mechanisms of action best describes that of the sulphonamides and trimethoprim?
2. How do the specific mechanisms of action of trimethoprim and the sulphonamides differ?
3. In general, what adverse effects are expected when the sulphonamides are used?
4. State two reasons why the use of sulphonamides is limited today.
5. Devise a patient teaching plan for Maria Ringino, a 35-year-old patient who is taking a sulphonamide and trimethoprim preparation for a gonorrhoeal infection.
6. Sulphonamides are highly protein-bound medications. Warfarin, which is also highly protein-bound, competes with sulphonamides for protein-binding sites. What would you expect happens to the free drug concentration of a sulphonamide following the administration of warfarin?
7. Why do you need to ensure that a patient taking a sulphonamide has an adequate fluid intake? What other measure can be used to avoid this effect?
8. Russell Morrison, a 20-year-old student, tells you that he is allergic to penicillins. Is he able to take sulphonamides? Explain.
9. Olivia Boularis, a 35-year-old secretary, tells you that she has experienced a severe allergic reaction to sulphonamides. What manifestations would you expect in a severe allergic reaction?
10. Andy Metzer is 16 years old and is in hospital because of an acute flare-up of Crohn's disease. He has commenced sulfasalazine therapy. His mother assists Andy when he goes to the toilet. She calls for you while she is in the toilet with Andy, anxious that he is bleeding from the kidneys. You inspect the urine and note that it is orange. What is the most likely explanation for this? Is it harmful to Andy?

67 DRUG SUMMARY TABLE: SULPHONAMIDES AND TRIMETHOPRIM

FAMILY NAME	GENERIC NAME	TRADE NAME(S)
Sulphonamides	Sulfacetamide	
	Sulfadiazine	
	Sulfasalazine	Salazopyrin
Related drugs and combinations	Sulfamethoxazole + trimethoprim (co-trimoxazole)	Septrin
	Trimethoprim	Monotrim

ANTIBACTERIAL DRUGS

68

CHAPTER SIXTY-EIGHT

KEY TERMS

Antibacterials
Antibiotics
Bactericidal action
Bacteriostatic action
Drug allergy
Drug resistance
Methicillin-resistant *Staphylococcus aureus* (MRSA)
Spectrum of activity

OBJECTIVES

After completing this chapter, the reader should be able to:

- **match the major antibacterial classes with their corresponding mechanism of action;**
- **identify the major antibacterial drug groups used clinically, the nature of their action, their spectrum of activity and their adverse reactions.**

THE CLASSIC DEFINITION OF AN ANTIBIOTIC IS A SUBSTANCE produced by one microorganism that inhibits the growth of others. Although these agents were originally isolated from bacterial or fungal growths, however, many antibiotics are now partially or wholly synthesised in commercial laboratories. Included in this group are the penicillins, cephalosporins, tetracyclines, aminoglycosides and macrolides. There are also a number of important synthetic antibacterial agents that are used clinically. These include **nitrofurantoin**, the quinolones, the oxazolidinones and the nitroimidazoles.

Because the distinction between synthetic antibacterial and antibiotic agents is becoming less clear (a debate of greater significance for pharmacologists than for anyone else), both are discussed in this chapter. The major antibacterial drug classes are grouped here according to their principal mechanism of action and their major properties are then described. Local policies often limit the antibacterials that may be used in order to achieve reasonable economy consistent with adequate cover and to reduce the development of resistant organisms. A policy may indicate a range of drugs for general use and permit other drugs only on the advice of the microbiologist or physician responsible for the control of infectious diseases.

ANTIBACTERIALS THAT ATTACK CELL-WALL SYNTHESIS

Drugs in this category belong to a group of chemically related substances known as beta-lactams. The beta-lactams get their name from the characteristic ring structure that they all share. This group includes the penicillins, cephalosporins, monobactams and carbapenems.

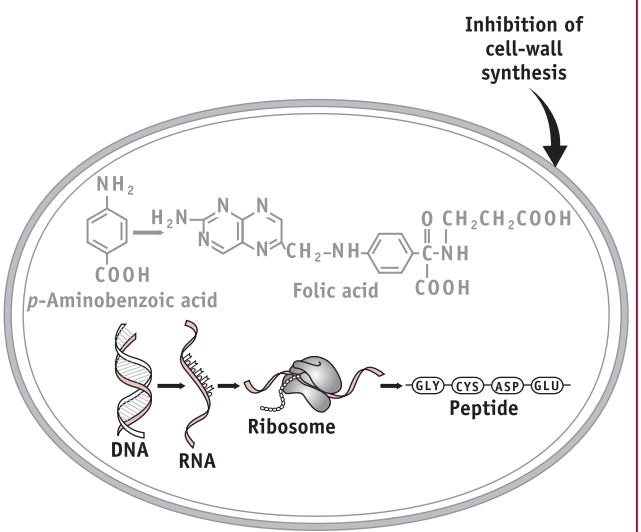
MECHANISM OF ACTION

These antibacterials are bactericidal agents that inhibit the formation of the rigid cell wall of dividing bacteria. The consequences are lethal for susceptible bacteria but relatively harmless for human cells, because the latter do not possess such a structure. This mechanism is highlighted in Figure 68.1.

CLINICAL CONSIDERATIONS

The major problems associated with the use of these antibacterials are the development of resistance in previously susceptible bacteria and serious allergic reactions. Resistance is due to the ability of bacteria to produce and release beta-lactamases or penicillinases, enzymes that catalyse the metabolism of, and therefore inactivate, these antibacterials. Penicillin and cephalosporin allergies arise from the fact that these substances are derived from non-human sources and precipitate an immune response on entering our bodies. Unfortunately, this reaction sometimes takes the form of life-threatening anaphylaxis (see Chapter 17). The best treatment for drug allergy is preventive – checking for allergy before administration. If there is a previous history of penicillin allergy, then an alternative antibacterial will be necessary. Cross-reactivity can also occur: if a patient is allergic to penicillins, he or she may be allergic to other beta-lactams.

FIGURE 68.1 MECHANISM OF ACTION OF ANTIBACTERIALS THAT INHIBIT CELL-WALL SYNTHESIS



Penicillins

The prototype of the penicillins is **benzylpenicillin** (penicillin G) and is naturally derived from a genus of moulds called *Penicillium*. The natural penicillins are designated by letters. The major properties characterising penicillin G are that it is an acid-labile substance, inactivated rapidly and absorbed erratically if taken orally (therefore, it is administered parenterally), with a narrow spectrum in activity (effective against most Gram-positive bacteria, a select few Gram-negative organisms and the spirochaetes). The other natural penicillin, **penicillin V** (phenoxymethylpenicillin), differs from the prototype in that it is acid-stable (suitable for oral use) and less potent than penicillin G. All other penicillins are either wholly or partially synthetic. This affords them certain properties, such as making them broader in spectrum, penicillinase-resistant or prolonging their duration of action.

LONGER-ACTING PENICILLINS

Procaine penicillin is a form of penicillin G that lasts longer in the body. The drug is administered in a depot form intramuscularly. The penicillin is released slowly into the circulation from the injection site and, because of this, cannot reach the same peak plasma levels of the prototype penicillin G. It is available on a named-patient basis and is used for the treatment of syphilis.

PENICILLINASE-RESISTANT PENICILLINS

Flucloxacillin, **dicloxacillin** and methicillin (the latter now discontinued) are chemical modifications of the prototype. These modifications provide protection against the degradative group of bacterial enzymes called penicillinases, which inactivate many of the penicillins. As a result, these agents have the advantage of being effective against staphylococci, which are now resistant to benzylpenicillin because they produce penicillinases. Flucloxacillin, however, is not inactivated by these enzymes and thus is effective in infections caused by penicillin-resistant staphylococci, which is the sole indication for its use. *Staphylococcus aureus* strains resistant to methicillin (methicillin-resistant *Staph. aureus*, MRSA) and to flucloxacillin have emerged. Common adverse reactions of this group include hypersensitivity reactions and gastrointestinal disturbances. An association has been found between flucloxacillin therapy and the development of a severe, life-threatening cholestatic hepatitis (see Commission on Human Medicines advice below). As a result, flucloxacillin is now recommended only for serious skin and soft-tissue infections.

The Commission on Human Medicines has advised that very rarely cholestatic jaundice and hepatitis may occur up to several weeks after treatment with flucloxacillin has been stopped. Administration for more than 2 weeks and increasing age are risk factors. The CSM has reminded that:

- flucloxacillin should not be used in patients with a history of hepatic dysfunction associated with flucloxacillin;
- flucloxacillin should be used with caution in patients with hepatic impairment;
- careful enquiry should be made about hypersensitivity reactions to beta-lactam antibacterials.

BROAD-SPECTRUM PENICILLINS

Amoxicillin and **ampicillin** have been developed as broader-spectrum agents to be effective against numerous species of Gram-negative bacteria. Like the natural penicillins, however, they are inactivated by penicillinases, including those produced by *Staph. aureus* and by common Gram-negative bacilli such as *Escherichia coli*. Amoxicillin is a derivative of ampicillin and has a similar antibacterial spectrum. It is better absorbed than ampicillin when given by mouth, producing higher plasma and tissue concentrations; unlike ampicillin, absorption of amoxicillin is not affected by the presence of food in the stomach.

Pivmecillinam is the prodrug of **mecillinam**. It is active against a range of Gram-negative bacteria but relatively inactive against *Pseudomonas aeruginosa* and *Streptococcus faecalis*. It is absorbed well from the oral route.

Ticarcillin and **piperacillin** are also broader-spectrum penicillins and the only ones effective against pseudomonal infections. They also appear to be sensitive to penicillinase-producing bacteria and, because of their acid lability, are not suitable for oral use.

ADJUNCTS FOR GREATER PROTECTION AGAINST BETA-LACTAMASES

Clavulanic acid and **tazobactam** have negligible intrinsic antibacterial activity but are inhibitors of many beta-lactamases. In combination with some penicillins, these substances protect the antibacterial from inactivation by microbes that produce beta-lactamases. In so doing, these substances extend the spectrum of activity of the penicillin to resistant strains of *Staph. aureus*, *E. coli* and *Haemophilus influenzae* and many *Bacteroides* and *Klebsiella* spp. Common combinations include clavulanic acid with amoxicillin (**co-amoxiclav**), the potassium salt of clavulanic acid (**potassium clavulanate**) with ticarcillin, and piperacillin with tazobactam.

◆ COMMON ADVERSE EFFECTS

Common adverse reactions associated with the penicillins include gastrointestinal disturbances (nausea, vomiting, diarrhoea, epigastric distress and a black, hairy tongue) and hypersensitivity reactions (skin eruptions, urticaria, fever, oedema, reductions in blood-cell subpopulations, nephritis, anaphylaxis). Convulsions can occur at high doses.

✚ CLINICAL CONSIDERATIONS

Allergies occur in about 10 per cent of individuals receiving penicillins, and anaphylaxis occurs in 0.01 per cent. Cross-sensitivity to cephalosporins and carbapenems may occur. Where a severe or immediate allergic reaction has happened, such as urticaria, anaphylaxis or interstitial nephritis, all penicillins, cephalosporins and carbapenems are contraindicated. Before giving a penicillin, it is important to ask the patient about allergic reactions to penicillin. Not having a history of penicillin allergy is no guarantee against a future reaction, however.

If prolonged high-dose treatment is required beyond 10 days, renal and hepatic function should be monitored. Large intravenous doses of penicillins should be administered slowly in order to prevent seizures. With large doses and during prolonged therapy, bacterial or fungal superinfection may occur, especially in older, debilitated and immunosuppressed patients.

Intravenous penicillin preparations are often physically incompatible with many drugs. It is better to avoid mixing a penicillin with other agents in a syringe or infusion solution. When administering a penicillin, it is advisable to use frequent doses in order to ensure the agent is maintained above the minimum effective concentration for maximal antibacterial effect.

Certain microorganisms have produced an extended spectrum of beta-lactamases from exposure to beta-lactam antibacterials (see Table 68.1). This group of microorganisms,

TABLE 68.1 EXTENDED-SPECTRUM BETA-LACTAMASES

Enterobacter spp. *Serratia* spp. *Citrobacter freundii* *Acinetobacter* spp. *Aeromonas* spp. *Proteus vulgaris*, *P. penneri* *Providencia* spp. *Morganella morganii*	Produce inducible chromosomally mediated beta-lactamases Occur from exposure to beta-lactams Inactivate third-generation cephalosporins; resistant to penicillins and cephalosporins Treat these bacteria with a carbapenem, aminoglycoside, fluoroquinolone or cotrimoxazole; combination of drugs may be needed

which includes species from *Enterobacter*, *Serratia*, *Citrobacter*, *Acinetobacter*, *Aeromonas*, *Proteus vulgaris* and *P. penneri*, *Providencia* and *Morganella morganii* (known by the acronym ESCAAPPM) should not be treated with a penicillin or cephalosporin because they are resistant.

Cephalosporins

The clinical drugs from this class are all semisynthetic derivatives of the antibiotic produced by the mould *Cephalosporium*, called **cephalosporin C**. The major advantages of these agents over penicillins are that, in general, they possess a wider spectrum of activity against Gram-negative bacteria, are active against some microbes capable of producing penicillin-degrading enzymes, and have longer half-lives.

The cephalosporins are classified into four generations based on progressive modifications of the prototype for greater effectiveness. In general, the first-generation cephalosporins (**cefalothin**, **cefalexin**, **cefazolin**, **cefradine**, **cefaclor**) are useful against infections caused by staphylococci, *E. coli*, *H. influenzae* and *Klebsiella*. The second-generation cephalosporins (**cefoxitin**, **cefotetan**, **cefuroxime**, **cefamandole**) are more protected from bacteria that produce beta-lactamases than the first-generation drugs, and their spectrum extends to include *Citrobacter*, *Enterobacter* and *Proteus* species.

The third-generation cephalosporins (**cefpodoxime** **cefotaxime**, **ceftriaxone**, **ceftazidime**) are also beta-lactamase-resistant, have the widest spectrum, effective against all the Enterobacteriaceae, and are most effective against *Pseudomonas* species.

The fourth-generation cephalosporins (**cefpirome**, **cefepime**) have a broad spectrum of activity and penetrate the cell walls of Gram-negative bacteria rapidly. Like most of the third-generation cephalosporins, the fourth-generation cephalosporins are parenteral medicines that are not susceptible to most beta-lactamase-producing species. Cefepime has an efficacy against *Pseudomonas aeruginosa* comparable to that of ceftazidime. Cefepime has a better coverage of Gram-positive bacteria than the latter, however, and is effective against a number of species that are resistant to the aminoglycosides and other cephalosporins. It is recommended that cefepime is not regarded as the drug of first choice in the treatment of sensitive microbial infections, in order to slow the development of antibacterial resistance.

Very few of the cephalosporins are available in oral formulations. The majority have to be administered parenterally as intravenous or intramuscular injections. This restricts the range available for convenient self-administration of medicines by the lay community. Cefalexin, cefradine and cefaclor (first-generation), cefuroxime (second-generation) and cefpodoxime (third-generation) are the exceptions.

◆ COMMON ADVERSE EFFECTS

Common adverse reactions associated with cephalosporin therapy include gastrointestinal disturbances (diarrhoea, nausea, antibiotic-associated colitis), hypersensitivity reactions and pain on intramuscular injection. Haematological abnormalities and a rise in serum hepatic enzyme levels have also been reported. Be aware that the use of cephalosporins produces hypersensitivity reactions in about 6 per cent of people who are allergic to penicillins. These individuals are allergic to the beta-lactam structure common to both drug groups.

✚ CLINICAL CONSIDERATIONS

Patients with a history of an urticarial or anaphylactic reaction should avoid taking penicillins, cephalosporins and carbapenems. Microorganisms from the ESCAAPPM group should not be treated with a cephalosporin as they are resistant to these agents (see Table 68.1).

For high-dose treatment and during prolonged therapy, monitor renal function and complete a full blood examination. Rapid intravenous infusions may lead to seizures, especially in patients on high doses or who have renal impairment. Superinfection may occur with prolonged treatment or when the broader-spectrum cephalosporins are used.

Intravenous preparations of cephalosporins are often incompatible with many drugs. It is best to infuse cephalosporins separately from other drugs.

Other beta-lactams

The major advantages of these miscellaneous beta-lactams is that they have activity against bacteria that have become resistant to penicillins and the potent aminoglycoside antibacterials and are effective against a number of Gram-negative bacteria. They are available only for parenteral use as they are inactivated in the gastrointestinal tract.

The miscellaneous beta-lactams fall into two groups according to their chemical structure: the carbapenems and monobactams. The carbapenems include **imipenem**, **ertapenem** and **meropenem**. This group has a very broad spectrum of activity against most Gram-positive and Gram-negative bacteria (aerobic and anaerobic) compared with other beta-lactams. They are, however, ineffective against MRSA and some *Pseudomonas* species. Imipenem is inactivated by a renal proteolytic enzyme and must be administered in combination with **cilastatin**, which inhibits the responsible enzyme.

The main monobactam is **aztreonam**. This is effective only against Gram-negative bacteria, including those that produce beta-lactamases.

◆ COMMON ADVERSE EFFECTS

Common adverse effects associated with these drugs are nausea and vomiting. All of these agents tend to produce

local reactions at the injection site, including phlebitis, pain and redness.

✚ CLINICAL CONSIDERATIONS

Monitor renal and hepatic function, and complete a full blood examination for patients on prolonged therapy with a carbapenem. The risk of seizures with these drugs is increased in individuals who have a history of central nervous system (CNS) dysfunction or renal impairment. Caution should be exercised in administering carbapenems to these individuals. If seizures occur, treatment should be discontinued.

The monobactam aztreonam may increase bleeding time with patients on anticoagulation therapy. Use with caution in these patients and monitor clotting times closely. Individuals who are allergic to penicillins or cephalosporins may not be allergic to aztreonam. Close monitoring of patients who have had an immediate hypersensitivity reaction to these antibacterials is still advisable, however.

Polypeptide and glycopeptide antibacterial agents

■ MECHANISM OF ACTION

The glycopeptides (**vancomycin**, **teicoplanin**) and the polypeptide **bacitracin** also inhibit the synthesis of cell walls in susceptible microbes, but due to the toxicity of these drugs their uses are restricted to critically ill patients and those who have demonstrated hypersensitivity to the beta-lactams. They are relatively narrow-spectrum agents effective against Gram-positive cocci. Vancomycin and teicoplanin are glycopeptide antibacterials important in the treatment of MRSA resistant to other antibacterial agents. Teicoplanin acts longer than vancomycin and can be given intramuscularly or intravenously. Bacitracin is useful for MRSA infections and also has activity against *Neisseria* and *Clostridium* species, *Corynebacterium diphtheriae* and *Treponema pallidum*.

◆ COMMON ADVERSE EFFECTS

Bacitracin is nephrotoxic and is, therefore, restricted to use as a topical antibacterial for skin, eye and ear infections in combination with polymyxin B and neomycin. Vancomycin is usually administered intravenously, although it is given orally for antibiotic-associated colitis produced by *Clostridium difficile*. Careless technique can cause necrosis and phlebitis at the injection site when infused too quickly. Vancomycin and teicoplanin are known to irritate the tissues surrounding the injection site, leading to pain.

✚ CLINICAL CONSIDERATIONS

As these drugs represent part of the last line of effective defence against MRSA, it is not surprising that the identification of enterococci that are vancomycin-resistant has met with alarm from the medical community. This apprehension is based on the possibility that the vancomycin-resistant enterococci (VRE) will transfer their resistance to MRSA.

During parenteral therapy, it is advisable to monitor renal function and complete a full blood examination at least weekly. Monitor these parameters more frequently in patients with impaired renal function, older patients, during prolonged therapy and during treatment with high doses of treatment. As these agents may cause nephrotoxicity and ototoxicity, avoid other antibacterials that have a similar predisposition, such as the aminoglycosides.

Measurement of drug concentration is not usually needed in most individuals. For certain conditions, however, such as endocarditis, cellulitis and meningitis, the trough concentration is measured. With increased resistance in VRE, vancomycin use should be restricted and great care taken to maintain infection-control precautions.

ANTIBACTERIALS THAT INHIBIT PROTEIN SYNTHESIS

■ MECHANISM OF ACTION

Most of the antibacterials that act by inhibiting protein synthesis are derived from products secreted by *Streptomyces* moulds. Specifically, the site of action is usually (but not always) one of the ribosomal subunits, where proteins are actually manufactured. The selective toxicity of these drugs against microbial cells arises out of differences between the structure of prokaryote (microbial) and eukaryote (mammalian) ribosomes. At higher doses, however, these antibacterials also inhibit mammalian ribosomal processes. Protein synthesis inhibitors tend to have bacteriostatic properties at standard therapeutic doses. This mechanism of action is highlighted in Figure 68.2.

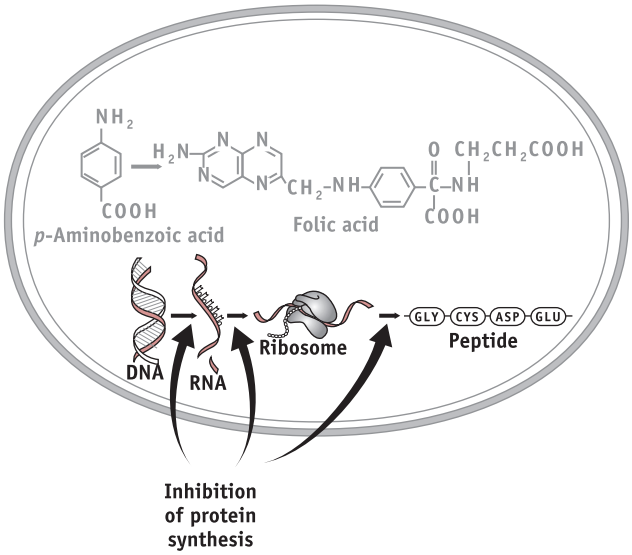
Aminoglycosides

The prototype aminoglycoside was **streptomycin**, which was the next major antibacterial identified after penicillins and the first isolated from a *Streptomyces* mould. The clinically important aminoglycosides are **framycetin**, **netilmicin**, **gentamicin**, **tobramycin**, **neomycin** and **amikacin**. Streptomycin is sometimes used as an alternative where there is resistance to gentamicin.

■ MECHANISM OF ACTION

Even though the aminoglycosides act by inhibiting protein synthesis (affecting the smaller ribosomal subunit) and therefore microbial growth, their potency at therapeutic dose levels affords them bactericidal properties. The spectrum of activity of most of these drugs is broad, effective against a wide range of Gram-negative bacteria (making them important agents in the treatment of serious Gram-negative

FIGURE 68.2 MECHANISM OF ACTION OF ANTIBACTERIALS THAT INHIBIT PROTEIN SYNTHESIS



sepsis), staphylococci and, to a lesser degree, streptococci. The aminoglycosides are often used when microbes are found to be resistant to cheaper, less toxic antibacterials.

◆ COMMON ADVERSE EFFECTS

The toxicity of these drugs is well noted. The three body sites seriously affected by the aminoglycosides and the toxic effects observed are the kidneys (nephrotoxicity), the eighth cranial nerve (ototoxicity) and the neuromuscular junction (neuromuscular paralysis). These effects can be minimised by measuring peak and trough serum drug levels in order to ensure that they conform to the desired range, as well as monitoring the patient for altered renal and vestibular function. The neuromuscular effects can be avoided through slow intravenous administration.

✚ CLINICAL CONSIDERATIONS

The absorption of aminoglycoside antibacterials from the gastrointestinal tract is negligible, and so for systemic effectiveness these drugs must be administered parenterally. The exception is neomycin, which is usually administered orally for bowel sterilisation before surgery. The use of amikacin is usually reserved for situations in which resistance to the other aminoglycosides is apparent. Framycetin is used topically for skin infections and infections of the eye and ear.

Once-daily dosing of aminoglycosides is currently thought to be as effective as more frequent dosing and is generally recommended for individuals with normal renal function. If treatment is likely to continue for less than 72 hours, drug concentration monitoring is not required. For treatment for more than 72 hours, drug concentration and creatinine clearance should be checked every 3–5 days in clinically stable patients and daily in patients with some form of clinical instability. Baseline creatinine clearance is determined for all patients before treatment.

There are a number of strategies that could be implemented to prevent aminoglycoside toxicity. Dosage frequency should be once-daily and certainly no more than 12-hourly, except in specified conditions such as infective endocarditis and osteomyelitis. Duration of therapy should be relatively short and, generally, not more than 7–10 days. Cochlear toxicity can be monitored using audiometry testing every 1–2 weeks during prolonged treatment. Ensuring adequate hydration can help to prevent nephrotoxicity. If the renal function deteriorates, the aminoglycoside dosage may need to be adjusted or an alternative antibacterial considered.

Tetracyclines

■ MECHANISM OF ACTION

Tetracyclines are broad-spectrum bacteriostatic antibacterials. As with the aminoglycosides, the mechanism of action is directed at the smaller ribosomal subunit. **Demeclocycline** is the only natural antibacterial used clinically; all the others – **tetracycline**, **doxycycline**, **lymecycline**, **minocycline**, **oxytetracycline** – are either semisynthetic or synthetic derivatives. They all have a similar spectrum of activity and are effective against the *Plasmodium* species that cause malaria (see Chapter 72), many *Mycoplasma*, *Chlamydia*, rickettsiae, spirochaetes and some amoebae. Minocycline has a broader spectrum of activity than the other tetracyclines. In terms of Gram-negative and Gram-positive bacteria, many strains have become resistant to the action of the tetracyclines and therefore culture and sensitivity testing are recommended.

◆ COMMON ADVERSE EFFECTS

The most commonly observed adverse effects associated with the tetracyclines are gastrointestinal disturbances (nausea, vomiting, diarrhoea, anorexia, abdominal pain), hypersensitivity reactions (rash, discoloration of nails, photosensitivity) and superinfection. This latter effect is usually associated with prolonged treatment with tetracyclines and can be avoided by administering the antifungal agent **nystatin** in combination with tetracycline. Gastric irritation, oesophagitis and, more rarely, oesophageal ulceration have been reported during doxycycline therapy.

✚ CLINICAL CONSIDERATIONS

Many of the tetracyclines are absorbed poorly from the gastrointestinal tract after oral administration; however, the resultant blood levels are still therapeutically effective. One of the major problems associated with the tetracyclines is

their ability to bind to free divalent and trivalent ions, especially calcium (Ca^{2+}), in the gut and blood. In the gut, this property results in less of the drug being absorbed. This is especially problematic when tetracyclines are administered with food or non-systemic antacids containing salts of aluminium, calcium and magnesium. The only exceptions are doxycycline and minocycline, which are very lipid-soluble tetracyclines and whose absorption is not impaired by the presence of food in the gut. Antacids and preparations containing iron decrease the absorption of all tetracyclines.

The effect of binding calcium ions in the blood is that less calcium is stored in bones and teeth. This is the main reason why tetracyclines are not recommended for children under the age of 8 years and for women in the latter half of pregnancy. Newly forming teeth become permanently discoloured and poorly enamelled. In children with discoloured teeth as a result of exposure to tetracycline, one can see the borderline separating affected and normal growth. If this line is close to the gums, then the exposure was later in tooth development; if it is closer to the crown, then exposure was early in development. Bone growth may also be affected.

In order to reduce the risk of gastric and oesophageal reactions, it is recommended that doxycycline be administered with food or milk and that the patient does not lie down for 2 hours after taking the drug. The latter recommendation minimises drug contact with the oesophageal region. Ingestion just before bedtime should therefore be avoided.

As tetracyclines may cause photosensitivity, patients are advised to wear protective clothing when outside and to use sunscreen. Tetracycline is absorbed poorly from the gastrointestinal tract and therefore needs to be given away from food and in high doses to obtain an adequate response. Unfortunately, these actions tend to increase the gastric irritation produced by tetracycline.

Macrolides

Erythromycin, **clarithromycin**, and **spiramycin** are macrolide antibacterials. The ketolide **telithromycin** is a derivative of erythromycin with a similar spectrum of activity to the macrolides.

■ MECHANISM OF ACTION

The macrolides specifically affect the function of the larger microbial ribosomal subunit without reacting with the human ribosome. This accounts for their relatively low human toxicity.

The spectrum of activity of this group resembles that of penicillin G; however, culture and sensitivity testing are recommended, as resistance to previously sensitive strains has been demonstrated. Compared with erythromycin, the newer drugs are less active against Gram-positive bacteria but more effective against Gram-negative bacteria, especially *H. influenzae*. **Azithromycin** is very effective in the treatment of toxoplasmosis and may be more effective against *Legionella* and *Chlamydia*. The newer drugs also have a lower potential for hepatotoxicity than orally administered erythromycin. Because of their spectrum of activity, the macrolides are an important alternative for patients with allergy to penicillins and other related antibacterials.

◆ COMMON ADVERSE EFFECTS

Unpleasant gastrointestinal disturbances and superinfection are common adverse reactions. The frequency of these adverse reactions is reduced with the newer agents.

✚ CLINICAL CONSIDERATIONS

The macrolides can be administered orally or parenterally. The newer drugs are more acid-stable than erythromycin. Some forms of erythromycin must be enterically coated for oral administration, due to its acid-lability. Erythromycin has a bitter taste, which is somewhat reduced by the enteric coating; however, paediatric forms (granules, dulcets, suspensions) are flavoured in order to make them more palatable.

Macrolides are useful alternatives to penicillins and cephalosporins for individuals who are allergic to these agents. Erythromycin is best absorbed when taken about an hour before or 2 hours after meals. If nausea occurs, however, it must be taken with food.

Rapid intravenous infusion of erythromycin may cause prolongation of the QT interval and development of serious ventricular dysrhythmias. It is also important to monitor for hepatic dysfunction during long-term and high-dose erythromycin therapy. Discontinue erythromycin therapy if severe hepatic dysfunction occurs.

Streptogramins

A combination of the streptogramin antibacterials, **quinupristin** and **dalfopristin**, is used for infections due to Gram-positive bacteria.

■ MECHANISM OF ACTION

The streptogramins target protein synthesis at the ribsome. Each of these agents induces a bacteriostatic action, but when used together the effect becomes a bactericidal action. They are indicated for intravenous administration in MRSA infections when other antimicrobial drugs are inappropriate. These drugs should be used in combination with other antibacterials for mixed infections that also involve Gram-negative organisms.

◆ COMMON ADVERSE EFFECTS

Common adverse effects include reactions at the injection site, such as inflammation, pain and oedema. Systemic adverse reactions include nausea, vomiting, diarrhoea and rashes.

✚ CLINICAL CONSIDERATIONS

This combined preparation is prone to causing peripheral vein irritation. This effect can be reduced by using large infusion volumes of at least 250 ml. Monitor the blood count periodically in order to determine whether thrombocytopenia or anaemia occurs.

Oxazolidinones

Linezolid is an oxazolidinone. Like the streptogramins, it is active against Gram-positive bacteria and can be used for MRSA infection. Linezolid is formulated for both oral and parenteral administration.

■ MECHANISM OF ACTION

Linezolid acts to inhibit protein synthesis at the ribosome. Its mechanism of action is different from that of other antibacterial drugs, however. It binds to one of the subunits and prevents the two subunits from joining together. Subunit joining is essential in order for translation to occur.

◆ COMMON ADVERSE EFFECTS

Common adverse reactions include nausea, vomiting, diarrhoea, headache, altered taste, abnormal liver function tests and superinfection with *Candida albicans*. Myelosuppression has also been observed.

✚ CLINICAL CONSIDERATIONS

Linezolid reversibly inhibits monoamine oxidase. Patients should avoid consuming foods that are rich in tyramine (e.g. mature cheese, yeast extracts) when taking linezolid as they may experience a rise in blood pressure. Similarly, linezolid should not be administered concurrently with monoamine oxidase inhibitors.

Long-term treatment of more than 21 days should be avoided in order to prevent the development of linezolid-resistant enterococci. This drug is considered only if other antibacterial agents have failed or are inappropriate due to allergy or resistance.

Inactivators of the larger ribosomal subunit

The lincosamides, **chloramphenicol** and **fusidic acid** inhibit protein synthesis by inactivating the larger ribosomal unit. The lincosamides and chloramphenicol are all naturally occurring antibacterials derived from *Streptomyces*. Fusidic acid, derived from a species of *Fusidium* mould, is chemically related to the cephalosporins.

LINCOSAMIDES

The lincosamides **lincomycin** and **clindamycin** are narrow-spectrum antibacterial agents not unlike erythromycin, effective against Gram-positive but not Gram-negative bacteria. Lincomycin is no longer used in the UK. Clindamycin, a derivative of lincomycin, is a more potent agent and is better absorbed from the gastrointestinal tract.

◆ COMMON ADVERSE EFFECTS

The most common adverse reactions are gastrointestinal disturbances such as antibiotic-associated colitis, hypersensitivity reactions and blood dyscrasias.

✚ CLINICAL CONSIDERATIONS

Treatment with a lincosamide should stop immediately if significant diarrhoea or antibiotic-associated colitis occurs. If diarrhoea or colitis occurs, antidiarrhoeal preparations should be avoided due to the possible retention of the toxin and worsening of the condition. Undertake a complete blood examination and assess the hepatic and renal function during prolonged treatment with clindamycin or lincomycin.

CHLORAMPHENICOL

Chloramphenicol has a broader spectrum of activity and is effective against both Gram-positive and Gram-negative bacteria, rickettsiae, *Chlamydia* and *Coxiella*.

◆ COMMON ADVERSE EFFECTS

Chloramphenicol is particularly toxic to mammalian cells, especially bone marrow cells, and as a result its use can induce aplastic anaemia. Its systemic use is restricted to the treatment of severe infections unresponsive to other antimicrobial agents, e.g. typhoid fever, bacterial meningitis and rickettsial infections. Toxic side effects are minimised when chloramphenicol is used topically as eye/ear drops or ointment (see Chapter 79).

✚ CLINICAL CONSIDERATIONS

When using systemic chloramphenicol, monitor the full blood count, platelets, serum iron and reticulocyte levels before and during therapy. Stop the drug immediately if anaemia, granulocytopenia or thrombocytopenia develops. Advise the patient to report if sore throat, vomiting, nausea, fever or mouth sores develop during therapy.

FUSIDIC ACID

Although fusidic acid is related chemically to the cephalosporins, the mechanism of its action is not prevention of cell-wall synthesis but inhibition of protein synthesis. Fusidic acid is a narrow-spectrum agent effective against Gram-positive bacteria. Its use is restricted to the treatment of staphylococci infections such as osteomyelitis, particularly as it becomes concentrated in bone. Clinically, it is available as the sodium salt (**sodium fusidate**), which is absorbed better from the gut.

◆ COMMON ADVERSE EFFECTS

Common side effects observed after fusidic acid treatment are allergic reactions and mild gastrointestinal disturbances.

✚ CLINICAL CONSIDERATIONS

Resistance develops rapidly if fusidic acid is used alone. It is best used in combination with another antimicrobial, such as rifampicin, in order to reduce the risk of resistance. Liver function should be monitored when using high doses of fusidic acid and during prolonged treatment.

Miscellaneous antibacterials

SPECTINOMYCIN

■ MECHANISM OF ACTION

Spectinomycin is a bacteriostatic antibacterial that inhibits protein synthesis by affecting the function of the smaller ribosomal subunit. It is active against a number of Gram-positive and Gram-negative bacteria, but its principal use is as an alternative to penicillin in the treatment of gonorrhoea when resistance or hypersensitivity is a problem. It is no longer used in the UK.

◆ COMMON ADVERSE EFFECTS

Spectinomycin is administered intramuscularly and is generally tolerated well. The most commonly observed adverse effects are pain at the injection site, nausea, urticaria and fever.

✚ CLINICAL CONSIDERATIONS

Spectinomycin is useful for individuals who are allergic to cephalosporins or quinolones.

MUPIROCIN

Mupirocin is a topical antibacterial agent recommended for use in infected skin lesions.

■ MECHANISM OF ACTION

Mupirocin blocks protein synthesis by inhibiting the enzyme that makes transfer-RNA molecules. It is effective against selected Gram-positive bacteria, including MRSA.

◆ COMMON ADVERSE EFFECTS

Local reactions are the most common adverse effects associated with this drug. Such reactions include itching, stinging, redness and pain. If absorbed from the site into the systemic circulation, this drug can cause nausea.

✚ CLINICAL CONSIDERATIONS

When applying mupirocin, avoid contact with mucous membranes, the eyes and the nose. Mupirocin is formulated as a cream and an ointment. The ointment contains the additive **polyethylene glycol**, which may cause renal impairment if absorbed systemically.

SYNTHETIC ANTIBACTERIALS AFFECTING METABOLISM

NITROFURANTOIN

Nitrofurantoin is a bactericidal antibacterial agent effective against a range of both Gram-positive and Gram-negative bacteria. Its principal use is in the treatment of urinary tract infections.

■ MECHANISM OF ACTION

The bactericidal action is afforded by blocking enzymes involved in the metabolism of sugars. This mechanism of action is highlighted in Figure 68.3. Nitrofurantoin is absorbed well from the gastrointestinal tract, but it becomes inactive in excessively acidic urine.

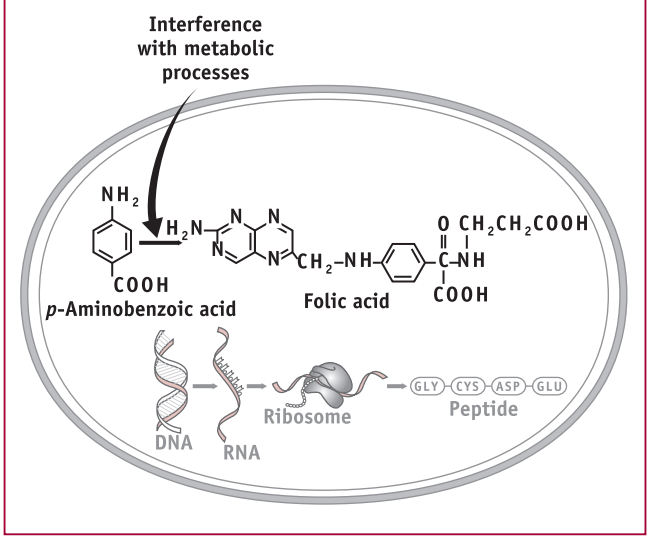
◆ COMMON ADVERSE EFFECTS

The most commonly observed side effects of nitrofurantoin are gastrointestinal (nausea and vomiting), central (drowsiness and headache) and allergic. It also has a tendency to produce an iridescent yellow urine, but this is a harmless side effect of treatment.

✚ CLINICAL CONSIDERATIONS

The antibacterial effectiveness of nitrofurantoin is diminished if urinary pH is greater than 8. During long-term treatment, monitor liver function every month for 3 months and then every 3 months. Nitrofurantoin should be taken

FIGURE 68.3 MECHANISM OF ACTION OF THE SYNTHETIC ANTIBACTERIALS AFFECTING METABOLISM



with food and milk in order to improve absorption and reduce the incidence of nausea.

ANTIBACTERIALS AFFECTING PLASMA MEMBRANE PERMEABILITY

Polymyxins

These antibacterials are derived from the *Streptomyces* moulds. The two best-known agents in this category are **colistin** and **polymyxin B**. The current use of polymyxin B is limited, however.

■ MECHANISM OF ACTION

Their action is to make the cell membrane of the microbe more permeable to the external environment. The microbe is then vulnerable to the osmotic pressures of its environment and eventually ruptures. This is a bactericidal action. This mechanism of action is highlighted in Figure 68.4.

The polymyxins are effective against Gram-negative bacteria, particularly *Pseudomonas* species. The development of resistance to these drugs is rare.

◆ COMMON ADVERSE EFFECTS

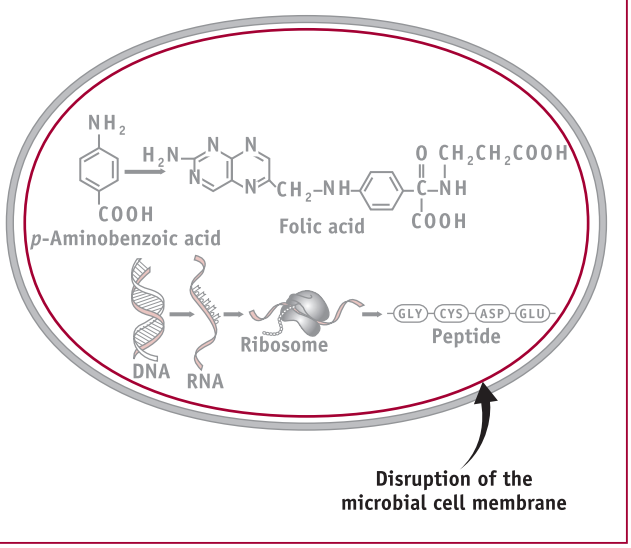
The major adverse effects appear to be those on the kidneys (nephrotoxicity) and the nervous system (altered sensation, dizziness and, at higher doses, neuromuscular paralysis).

✚ CLINICAL CONSIDERATIONS

Polymyxins are not absorbed well from the gut and generally are administered to adults intramuscularly (or intrathecally if the infection involves the CNS). Colistin, however, is indicated for oral administration in intestinal infestation and in paediatric therapy, where sufficient levels of drug are absorbed systemically to be effective against susceptible bacteria. Colistin can also be used topically where necessary.

During systemic colistin therapy, monitor for renal function. Colistin should not be given with non-depolarising neuromuscular agents because of its ability to cause neurotoxicity and because of the enhanced neuromuscular blockade produced. Assess for neurotoxicity as shown by numbness, tingling of extremities and dizziness. Ensure that respiratory emergency equipment is close by and readily available in case of respiratory paralysis.

FIGURE 68.4 MECHANISM OF ACTION OF ANTIBACTERIALS AFFECTING PLASMA MEMBRANE PERMEABILITY



SYNTHETIC ANTIBACTERIALS THAT INHIBIT DNA REPLICATION

Quinolones

Antibacterial agents from this group are synthetic derivatives of **quinolone**. The prototype is the semisynthetic quinolone **nalidixic acid**, effective against a limited number of species of Gram-negative bacteria involved in urinary tract infections. Its use is no longer recommended and it has been superseded by the broader-spectrum, less toxic, fluorinated quinolones **norfloxacin** and **ciprofloxacin**. Other quinolones have been introduced, including **levofloxacin**, **moxifloxacin** and **ofloxacin**.

■ MECHANISM OF ACTION

The quinolones inhibit bacterial growth by preventing DNA synthesis before mitosis. They are considered bactericidal at therapeutic doses. They are active against a range of Gram-negative and some Gram-positive bacteria and are used in the treatment of urinary and gastrointestinal tract infections caused by susceptible microbes. The spectrum of activity of the newer agents is broader than that of the others and so they may be useful in pneumonia, pelvic inflammatory disease, gonorrhoea and chlamydial cervicitis. Many staphylococci are resistant to the quinolones, and so these drugs should be avoided in MRSA infection.

◆ COMMON ADVERSE EFFECTS

Commonly observed adverse effects are mainly neurological (headache, dizziness), gastrointestinal (nausea, vomiting, dyspepsia, abdominal pain) and allergic (rash, hypersensitivity). These drugs are contraindicated in children and pregnant women because of the risk of permanent damage to developing joints.

✚ CLINICAL CONSIDERATIONS

Most are available in parenteral and oral forms; norfloxacin and levofloxacin are available only in oral form. Ciprofloxacin is available as eye drops.

Quinolone treatment should be ceased at the first sign of tendon pain or inflammation. Advise the patient to drink plenty of fluids during therapy due to the risk of crystalluria. Quinolone agents may cause dizziness and faintness, which could affect the ability to drive and operate machinery. Due to these drugs' photosensitivity tendency, sun precautions should be adopted. Instruct the patient to wear protective clothing, use a sunscreen and avoid sun exposure whenever possible.

Nitroimidazoles

The nitroimidazoles (**metronidazole**, **tinidazole**) are used principally in the treatment of protozoan infestations (see Chapter 71), but they have been found to be effective in the treatment of certain types of bacterial infection. They exhibit a unique specificity against obligate Gram-negative anaerobes. Tinidazole has a longer duration of action than metronidazole.

■ MECHANISM OF ACTION

The mechanism of action of these drugs is not understood well. They are believed to attack DNA directly, preventing its replication. They are bactericidal at therapeutic doses. Metronidazole is available in parenteral, topical, oral and suppository forms. Tinidazole and **ornidazole** are available only in tablet form.

◆ COMMON ADVERSE EFFECTS

Frequently observed side effects involve the gastrointestinal tract (nausea, vomiting, diarrhoea) and CNS (headache, vertigo, paraesthesias). Patients who receive therapy with these drugs for longer than 10 days should be monitored for signs of leucopenia and peripheral neuropathy. The drugs must be discontinued if these reactions occur. They can also interact with alcohol to induce a disulfiram-like reaction (see Chapter 23).

✚ CLINICAL CONSIDERATIONS

Alcohol should be avoided during therapy and for 48 hours afterwards to prevent nausea, vomiting, flushing and palpitations. Advise the patient to stop taking the drug immediately if they experience numbness, tingling, pain or weakness in the hands or feet.

CLINICAL MANAGEMENT

Antibiotic and synthetic antibacterial agents

For clinical management of the nitroimidazoles, see also Chapter 71.

Assessment

- Assess whether the patient has previously taken an antibacterial. If the patient has taken an antibacterial before, determine whether a hypersensitivity reaction occurred. If this is the first time an antibacterial has been taken, observe the patient for about 30 minutes after administration. Note that a hypersensitivity reaction occurs in up to 10 per cent of the population receiving penicillins. Anaphylaxis occurs in 0.01 per cent of individuals receiving penicillins. Cross-sensitivity between drugs in the penicillin, cephalosporin and carbapenem groups occurs in 5–10 per cent of individuals. Thus, in individuals with a hypersensitivity reaction to a penicillin-type medication, drugs in the cephalosporin or carbapenem group are also contraindicated.
- Tetracyclines should not be administered to children under 8 years old as they cause irreversible staining of permanent teeth. Women who are breast feeding are also most sensitive to their hepatotoxicity effect and should not take tetracyclines. Binding of tetracyclines to bones may cause a slowing of bone growth in infants. Tetracyclines may also raise the intracranial pressure in infants, leading to bulging fontanelles.
- Assess vital signs and compare with subsequent observations.
- Assess the organ where infection is present. Obtain a specimen of the affected site for microbiology and culture studies. Possible sites of infection include wounds, sputum, urine and blood.
- Assess whether the patient has a viral infection. Viral infections should never be treated with an antibacterial agent. There is no evidence to suggest that antibacterials reduce the duration of a viral infection or prevent the onset of a secondary bacterial infection.
- For patients on aminoglycosides, assess for ototoxicity (e.g. tinnitus, loss of balance, hearing changes) and nephrotoxicity (decreased urine output, elevated urea and creatinine levels).
- For patients on tetracyclines, assess laboratory values for liver function and renal function tests, including liver enzymes, urea, creatinine and potassium levels. As tetracyclines can decrease vitamin K synthesis in the intestine, a full blood examination and platelet count should also be completed.

- Note that tetracycline absorption is affected adversely by antidiarrhoeals, dairy products and antacids.
- For patients on high-dose macrolides or who are prescribed macrolides over a prolonged period, assess for signs of liver damage, such as elevated liver enzyme levels and jaundice.
- For patients on lincomycin and clindamycin, assess the patient for a history of gastrointestinal disease, as antibiotic-associated colitis may occur with these drugs. Assess the patient for diarrhoea, weight loss, weakness and abdominal cramps, which are indicative of the condition.
- Note that systemic chloramphenicol should not be administered in patients with bone-marrow depression or who have had cytotoxic therapy or radiation therapy, as the drug can cause bone-marrow depression, aplastic anaemia and other blood dyscrasias.
- For patients on spectinomycin for the treatment of gonorrhoea, assess for syphilis at the time of diagnosis of gonorrhoea and 3 months afterwards. Spectinomycin may mask the symptoms of syphilis.
- Assess patients on quinolones for a history of central nervous system disorders such as epilepsy. Caution should be exercised in these conditions because of the increased risk of central toxicity.
- Patients with inflammatory intestinal disorders may have increased absorption of vancomycin and, therefore, a higher risk of toxicity. These patients should be assessed carefully, and caution should be exercised in administering vancomycin in the presence of these conditions.
- Exercise caution when using nitrofurantoin in patients with peripheral neuropathy and respiratory disease, as these conditions may worsen.

Planning

- The patient's infection will be eliminated.

Implementation

- Monitor the patient for allergic reactions to the drug. Allergic reactions may include rash, urticaria and anaphylaxis.
- Ensure that emergency equipment and drugs are available in case of anaphylaxis, especially for penicillin and cephalosporin therapy. Observe the patient closely for about 20–30 minutes after administration of medication (see Table 11.2 in Chapter 11 for further information on measures to take if anaphylaxis occurs).
- Monitor the patient's urinary output to determine adequacy. Urinary output should be at least 600 ml/day. Most antibacterials are excreted by the kidneys. Impaired renal function can lead to drug accumulation and eventual toxicity.
- Administer antibacterials at equal intervals over the day in order to maintain blood levels.
- Monitor the white blood cell count, which tends to increase during infection and decrease as infection resolves.
- Monitor serum electrolytes. Note that antibacterials can cause electrolyte and fluid disturbances from the type of preparation and from adverse effects such as diarrhoea. More common electrolyte imbalances include hypernatraemia (from antibacterials made with a sodium base) and hypokalaemia (from severe diarrhoea or the administration of an antibacterial containing a large amount of sodium). An extracellular volume excess can occur from administering multiple antibacterials (and intravenous drugs) in a diluted form. Monitor for dependent oedema, pulmonary oedema, shortness of breath, increase in body weight and positive fluid balance.
- Monitor for manifestations of superinfection, especially if the patient is taking high doses over a prolonged period. Manifestations may include anal and genital discharge, anal and genital itching, and stomatitis (see Tables 11.7, 11.14 and 11.16 in Chapter 11 on measures to take if oral candidiasis, stomatitis or genital candidiasis occurs).
- Send a specimen of the affected area for culture and sensitivity tests. A broad-spectrum antibacterial can be administered initially. Once results of tests are known, a more specific antibacterial may be administered. Note that cultures taken after antibacterials or paracetamol have been commenced are not very reliable.
- Dilute antibacterials for intravenous use in a suitable volume for administration according to product information. Ensure that intravenous antibacterials are administered alone and not in the presence of other drugs or infusions, in order to prevent incompatibilities.
- Intramuscular injections should be administered into large muscle masses (e.g. gluteal muscle) and rotated to prevent irritation.
- Note whether the health-care institution has a policy for the administration of antibacterials. Such policies contain guidelines that restrict the administration of antibacterials to a specific time period in order to prevent antibacterial resistance.
- Prophylactic treatment with antibacterials should be restricted to certain clinical conditions and surgical procedures with a high risk of infection, such as post-splenectomy, prevention of recurrent rheumatic fever, abdominal surgery, coronary bypass surgery and amputation of a gangrenous limb.

- Topical antibacterials should be avoided, as they can increase sensitisation and resistance. Treatment with ophthalmic antibacterial preparations, and with topical preparations not generally available for systemic administration (e.g. mupirocin), are exceptions to this consideration.

Penicillins

- Some oral penicillins, including ampicillin and cloxacillin, should be administered on an empty stomach as they are affected by gastric acid. Administer 1 hour before or 2 hours after meals to decrease destruction by gastric acid.
- Certain oral penicillins are not affected by gastric acid and can be taken without concern about meals. These include amoxicillin, clavulanic acid and phenoxymethylpenicillin.
- Do not administer intravenous penicillins too quickly, as rapid administration has been associated with seizures. Follow product information about administration carefully.
- Monitor the patient for bleeding if high doses of penicillin are given. A decrease in platelet count has been associated with high doses.
- Be aware that preparations containing benzathine and procaine are never given intravenously. These preparations are long-acting and administered intramuscularly.
- Generally, intravenous penicillins are physically incompatible with other medications and should be administered separately.
- The patient's hepatic and renal function and full blood profile should be monitored carefully during prolonged (> 10 days) and during high-dose treatment.

Cephalosporins

- Administer intravenous cephalosporins over 30–45 minutes to prevent venous irritation.
- Perioperative cephalosporins for prophylaxis are discontinued about 24–48 hours after surgery.
- The patient's hepatic and renal function and full blood profile should be monitored carefully during prolonged (> 10 days) and during high-dose treatment.

Monobactams

- Aztreonam is used mainly to treat Gram-negative aerobic infections in patients who are allergic to beta-lactam antibacterial agents, such as penicillins.

Carbapenems

- Monitor hepatic and renal function and full blood profile during prolonged treatment.

Polypetides and glycopeptides

- Ensure that the eye is clear of exudate before administering bacitracin eye ointment (see Table 7.3 in Chapter 7 for further information on the technique of application).
- For patients using bacitracin eye ointment, monitor for pain, redness, swelling and discharge from the infected eye.
- If the intravenous form of vancomycin has been ordered for oral use, then the contents of the vial are dissolved in about 30 ml water or juice. Administer straight or through a nasogastric tube to minimise the unpleasant taste.
- Monitor pre- and post-administration levels of vancomycin to ensure maximum effectiveness and minimal toxicity. Pre-administration levels should be less than 10 mg/l and post-administration levels between 20 and 40 mg/l. Take pre- (trough) levels about 5 minutes before administration and post- (peak) levels 1 hour after administration. Report levels to the doctor.
- Teicoplanin can be given once daily and does not usually require monitoring of serum levels.
- Monitor patients on teicoplanin or vancomycin for hearing loss. Teicoplanin or vancomycin treatment alone rarely causes ototoxity. Hearing loss may be enhanced when these medications are combined with other ototoxic therapies, such as aminoglycosides.
- Monitor renal function and full blood profile at least weekly in patients receiving teicoplanin or vancomycin. More frequent monitoring is required during prolonged or high-dose treatment.
- For patients receiving teicoplanin or vancomycin, avoid administering other potentially nephrotoxic or ototoxic medications, such as aminoglycosides.

Aminoglycosides

- Encourage the patient to increase fluid intake while taking aminoglycoside. This measure assists in preventing renal failure from nephrotoxicity.
- Monitor pre- and post-aminoglycoside serum levels to ensure maximum effectiveness and minimal toxicity. Pre-gentamicin levels should be less than 2 mg/l and post-gentamicin levels between 5 and 10 mg/l. Take pre- (trough) levels about 5 minutes before administration and post- (peak) levels 1 hour after administration. Report levels to the doctor. Note that monitoring of serum levels is unnecessary in patients with normal renal function who are treated for 72 hours or less.
- To minimise toxicity problems, short treatment periods (7–10 days) and once-daily administration

should be used. The patient should not receive a dose more often than every 12 hours, except in specific circumstances, such as bacterial endocarditis and burns.

Tetracyclines

- Administer tetracyclines on an empty stomach (e.g. 1 hour before or 2 hours after meals) in order to facilitate absorption. The absorption of tetracyclines is influenced strongly by the presence of food and other drugs. Note that doxycycline and minocycline can be taken on a full or empty stomach.

Macrolides

- Administer oral macrolides with a full glass of water on an empty stomach (1 hour before or 2 hours after meals) to create a maximum effect.
- Enteric-coated, sustained-release preparations can be administered with food and are often prescribed for patients with gastrointestinal intolerance.
- When administering oral suspensions, ensure that they are shaken well and refrigerated after opening.

Streptogramins

- Peripheral vein irritation may be reduced if the preparation is administered through a large central vein or if larger infusion volumes are used.

Oxazolidinones

- Monitor the full blood count periodically to determine the incidence of anaemia and thrombocytopenia.

Other inactivators of the larger ribosomal subunit (lincosamides, chloramphenicol, sodium fusidate)

- Monitor serum chloramphenicol levels, which should be in the range of 10–20 mg/ml. Concentrations greater than 30 mg/ml increase the risk of side effects.
- Monitor the patient on systemic chloramphenicol for pale skin, sore throat, fever, unexplained bruising or bleeding, leucopenia and thrombocytopenia.
- Administer oral sodium fusidate after meals to prevent gastric irritation.
- Sodium fusidate should be administered with other antibacterials, as resistance develops quickly when given as a sole antibacterial.
- Cease treatment immediately if diarrhoea or antibiotic-induced colitis occurs during clindamycin treatment. Do not administer antidiarrhoeal medications to treat diarrhoea due to the possible retention of toxins and worsening of the condition.

Spectinomycin

- This drug is for intramuscular use only. It is administered by deep intramuscular injection into the vastus lateralis or ventrogluteal site. Warn the patient that the injection is painful. Obtain cultures of gonococcal infection sites.

Nitrofurantoin

- Administer the antibacterial after meals to prevent gastric irritation.
- Monitor for renal and liver function.
- The antibacterial activity is reduced if the urinary pH is above 8. It is important, therefore, to avoid alkalinisation of the urine.

Polymyxins

- Administer intravenous polymyxins by slow intravenous infusion, as rapid administration can produce respiratory paralysis.
- Monitor patients for nephrotoxicity as shown by increased serum potassium, creatinine and urea levels, and decreased urinary output. Assess also for neurotoxicity, as shown by numbness, tingling of extremities and dizziness.
- Ensure that respiratory emergency equipment is close by and readily available in case of respiratory paralysis.

Quinolones

- Monitor for urinary pH, as ciprofloxacin becomes insoluble in an alkaline medium, resulting in crystalluria.
- Administer norfloxacin on an empty stomach. Other quinolones can be administered with or without food.
- Monitor urinary output and ensure that the patient maintains a urine output of more than 1200 ml per day in order to minimise the incidence of crystalluria.
- Treatment should cease at the first sign of tendon or joint pain and inflammation. Quinolones may lead to symptoms of tendonitis, arthritis and myalgia.

Nitroimidazoles

- Monitor for leucopenia, seizures and peripheral neuropathy during prolonged or high-dose treatment.

Patient teaching

- Instruct the patient to complete the prescribed course of treatment over the required period. Discontinuing the drug prematurely may mean the infection is not treated fully and may lead to antibacterial resistance. Completing the course is important even if symptoms of infection subside.

- Advise on the importance of maintaining equal time intervals for administration to ensure sustained blood levels.
- Advise the patient of manifestations of allergy. If an allergic reaction occurs, the antibacterial should be discontinued immediately and the doctor notified.
- Advise the patient to refrigerate an oral suspension and to discard the unused portion after 7–10 days, as indicated on the container. The preparation should not be frozen, and the patient must shake the container thoroughly before administration.

Penicillins

- Advise patients to take penicillins on an empty stomach (1 hour before or 2 hours after meals) in order to facilitate absorption. Note that amoxicillin may be taken with meals in order to decrease gastric upsets.

Cephalosporins

- Advise patients to take cephalosporins on an empty stomach, although they may be taken with food if gastric irritation occurs.

Bacitracin

- Instruct the patient on the method for administering bacitracin eye ointment (see Table 7.3 in Chapter 7 for further information).

Tetracyclines

- Advise the patient to avoid taking tetracyclines within 1–2 hours of consuming dairy products, antacids or antidiarrhoeals.
- Instruct the patient that tetracyclines can cause photosensitivity reactions, and to avoid the sun during the warmest time of day (10 a.m. to 2 p.m.), use a sunblock and wear a hat and protective clothing (see Table 11.19 in Chapter 11 for further information).
- Be especially wary of tetracycline preparations beyond their expiry date. These have been associated with toxic reactions from the breakdown products of tetracycline.
- Instruct the patient to store tetracyclines away from light and extreme heat. Tetracyclines decompose in light and heat, producing toxic breakdown products.
- Warn patients taking minocycline to avoid driving and operating heavy machinery if they experience dizziness.
- Female patients using the contraceptive pill should use additional barrier methods of contraception, as tetracyclines have been associated with decreased effectiveness of the pill.
- Advise patients to take tetracyclines on an empty stomach. Note that doxycycline and minocycline can be taken on a full or empty stomach.
- Inform the patient that capsules and tablets should be taken with a large glass of water. The patient should then be advised not to lie down within 1 hour of taking the preparation in order to prevent it from becoming lodged in the oesophagus.

Macrolides

- Advise the patient to take enteric-coated tablets whole and not to crush them. These can be taken with meals. Other, non-enteric-coated tablets should be taken with a glass of water and on an empty stomach. Suspensions should be shaken well before administration and kept in the refrigerator once opened.

Oxazolidinone

- Advise the patient to avoid foods containing tyramine.

Other inactivators of the larger ribosomal subunit (lincosamides, chloramphenicol, sodium fusidate)

- Advise patients on lincomycin and clindamycin to report the development of diarrhoea. The patient should immediately cease taking the medication if diarrhoea occurs.
- Advise the patient to take oral clindamycin with a full glass of water, with or without meals. Take oral lincomycin with a full glass of water on an empty stomach.
- Advise the patient to take oral chloramphenicol with a full glass of water on an empty stomach.
- Advise patients on chloramphenicol to avoid driving and operating heavy machinery if confusion or visual disturbances occur.
- Advise the patient on chloramphenicol to report any manifestations of blood dyscrasias, such as sore throat, weakness, unexplained bruising or bleeding, and fever.
- Instruct the patient on chloramphenicol to delay all dental work until the blood count is verified as normal. Teach the patient about the importance of oral hygiene, with cautious use of toothbrushes (use a soft brush), dental floss and toothpicks.
- Advise the patient on sodium fusidate to take the antibacterial after meals to reduce the incidence of gastric irritation.

Nitrofurantoin

- Acidification of the urine inhibits the growth of urinary tract microorganisms and therefore increases the effectiveness of nitrofurantoin. Encourage the patient to consume large quantities of fluid to wash out the

microorganisms more easily and to consume fluids with a high vitamin C content, such as orange juice.
- Advise the patient to avoid driving and operating heavy machinery, as dizziness and drowsiness may occur.
- Instruct the patient to take the antibacterial after meals in order to prevent gastric irritation.

Quinolones

- Advise the patient that norfloxacin should be taken on an empty stomach. Other quinolones can be taken with or without food.
- Advise the patient to ensure that adequate fluids are consumed in order to maintain a high urinary output, therefore preventing crystalluria.
- Advise the patient to report visual disturbances, dizziness, lightheadedness and depression, as these antibacterials can cause central nervous system toxicity. If these manifestations occur, the patient should avoid driving and operating heavy machinery. Alcohol may worsen these effects and should be avoided.
- Warn the patient that photosensitivity may occur, and to avoid sun exposure (see Table 11.19 in Chapter 11 for further information).
- Inform the patient that quinolone preparations may increase the stimulatory effects of caffeine. Caffeine intake may need to be reduced.

Nitroimidazoles

- Advise the patient to avoid alcohol consumption during treatment and for 48 hours after the course in order to prevent nausea, vomiting, flushing, headache and palpitations (i.e. disulfiram-like reaction).
- Inform the patient to take the preparation with or immediately after meals.
- Advise the patient to stop taking metronidazole and to see the doctor immediately if numbness, tingling, pain or weakness occurs in the hands or feet.

Evaluation

- For local infections, evaluate the alleviation of redness, oedema, heat and pain.
- For systemic infection, evaluate the return to normal of the temperature, pulse rate, respiratory rate and white blood cell count. Evaluate an improvement in appetite and a sense of wellbeing.
- If purulent discharge is present, evaluate the presence of a decreased amount and a more normal appearance and consistency.
- In the critically ill patient, evaluate an improvement in organ function.

SUMMARY

- Antibacterial drug groups that act by attacking microbial cell-wall synthesis include the penicillins, the cephalosporins, the carbapenems, the monobactams and the glycopeptides.
- Allergies occur in about 10 per cent of individuals receiving penicillins, and anaphylaxis occurs in 0.01 per cent. Cross-sensitivity to cephalosporins and carbapenems may also occur.
- Renal and hepatic function should be monitored during prolonged high-dose therapy.
- With large doses and during prolonged therapy, bacterial or fungal superinfection may occur, especially in older, debilitated and immunosuppressed patients.
- Antibacterial drug groups that act by inhibiting protein synthesis include the aminoglycosides, the tetracyclines, the macrolides, the streptogramins, the oxazolidinones and the lincosamides.
- For aminoglycoside therapy longer than 72 hours in duration, drug concentration and creatinine clearance should be checked.
- Avoid tetracycline antibacterial use in children younger than 8 years and in pregnant women due to the risks associated with calcium deposition in bone and teeth.
- Macrolides and monobactams are useful alternatives for individuals allergic to penicillins and cephalosporins.
- The quinolones prevent bacterial growth by inhibiting DNA synthesis before mitosis.

1. State the four general mechanisms of action of antimicrobials.
2. Give the mechanism of action for the following groups of antimicrobials:
   (a) macrolides;
   (b) penicillins;
   (c) oxazolidinones;
   (d) tetracyclines;
   (e) aminoglycosides;
   (f) cephalosporins;
   (g) lincosamides.
3. For the drug groups listed in question 2, indicate the most important specific clinical uses.
4. Name two antimicrobial groups that you regard as the most toxic, and two you regard as the least toxic. Explain your answers.
5. (a) Hypersensitivity reactions are common adverse drug effects during antibacterial therapy. List examples of the specific reactions that may be seen and, if possible, indicate the seriousness of each one, e.g. mild, severe, life-threatening.
   (b) Once a hypersensitivity reaction manifests in a person without a history of such a reaction, what should be done?
6. (a) The aminoglycoside antibacterials can produce ototoxicity during therapy. What is an early sign of possible hearing loss?
   (b) Name another major drug group known for its ototoxicity.
7. Why should the patient take the full course of prescribed antibacterial until it is finished?
8. What types of toxicity are associated with aminoglycosides? What clinical manifestations should the nurse assess to determine whether these types of toxicity are apparent?
9. Andrea May, 6 years old, has otitis media. The doctor prescribes amoxicillin syrup. As her nurse, you ask Andrea's mother whether she is allergic to anything. Her mother replies that Andrea is allergic to penicillin. Is amoxicillin similar to penicillin? Explain. What action should you take?
10. Why are serum blood levels regularly taken for a patient on the aminoglycoside gentamicin?

68 DRUG SUMMARY TABLE: ANTIBACTERIAL DRUGS

FAMILY NAME	GENERIC NAME	TRADE NAME(S)
Penicillins	Amoxicillin sodium/trihydrate	Amix
		Amoram
		Amoxident
		Amoxil
		Galenamox
		Rimoxallin
	+ Clavulanic acid (co-amoxiclav)	Augmentin preparations
	Ampicillin	Penbritin
		Rimacillin
	Benzylpenicillin (penicillin G)	Crystapen
	Flucloxacillin	Floxapen
		Fluclomix
		Galfloxin
		Ladropen
	+ Ampicillin (co-fluampicil)	Magnapen
	Phenoxymethylpenicillin (penicillin V)	
	Piperacillin	
	+ Tazobactam	Tazocin
	Pivmecillinam	Selexid
	Procaine benz penicillin	
	Ticarcillin + potassium clavulanate	Timentin
Cephalosporins and related	Cefaclor	Distaclor
		Keftid
	Cefadroxil	Baxan
	Cefalexin	Ceporex
	Cefotaxime	Claforan
	Cefpirome	Cefrom
	Cefpodoxime	Orelox
	Cefprozil	Cefzil
	Cefradine	Velosef
	Cefuroxime	Zinacef
		Zinnat
	Ceftazidime	Fortum
		Kefadim
	Ceftriaxone	Rocephin
Other beta-lactams	Aztreonam	Azactam
	Ertapenem	Invanz
	Imipenem + cilastatin	Primaxin
	Meropenem	Meronem
Polypeptides and glycopeptides	Bacitracin	
	Teicoplanin	Targocid
	Vancomycin	Vancocin

FAMILY NAME	GENERIC NAME	TRADE NAME(S)
Aminoglycosides	Amikacin	Amikin
	Framycetin	Soframycin Eye/Ear
	Gentamicin	Genticin
		Minims Gentamicin
	Neomycin + Gramicidin	Neosporin
	Netilmicin	Netillin
	Tobramycin	Tobi
Tetracyclines	Demeclocycline	Ledermycin
	Doxycycline	Vibramycin
	Lymecycline	Terralysal 300
	Minocycline	Minocin MR
		Sebomin MR
	Tetracycline	Deteclo
	oxytetracycline	oxymycin
		oxytetramix
Macrolides and related drugs	Azithromycin	Clarosip
		Zithromax
	Clarithromycin	Klaricid XL
	Erythromycin	Erymax
		Erythrocin
		Erythroped
	telithromycin	ketek
Streptogramins	Dalfopristin + quinupristin	Synercid
Oxazolidinone	Linezolid	Zyvox
Lincosamides	Clindamycin	Dalacin C
Other antimicrobials	Bacitracin + neomycin	Cicatrin
	Neomycin + polymyxin B + gramicidin	Neosporin topical ointment
	Chloramphenicol	Chloromycetin
		Kemicetine
		Minims Chloramphenicol
	Colistin	Colomycin
		Promixin
	Fusidate/fusidic acid	Fucidin
	Mupirocin	Bactroban
	Nitrofurantoin	Furadantin
		Macrobid
		Macrodantin
Quinolones	Ciprofloxacin	Ciproxin
	Levofloxacin	Tavanic
	Moxifloxacin	Avelox
	Norfloxacin	Utinor
	Ofloxacin	Tarivid
Nitroimidazoles	Metronidazole	Flagyl
		Metrolyl
	Tinidazole	Fasigyn

ANTITUBERCULOTIC AND ANTILEPROTIC DRUGS

69

CHAPTER SIXTY-NINE

OBJECTIVES

After completing this chapter, the reader should be able to:

- **discuss the aetiology of tuberculosis;**
- **discuss the uses, mechanisms of action and problems associated with the use of antituberculotic drugs;**
- **discuss the aetiology of leprosy;**
- **discuss the uses, mechanisms of action and problems associated with the use of antileprotic drugs.**

KEY TERMS

Tuberculosis
Leprosy

THIS CHAPTER DEALS WITH DRUGS USED IN THE TREATMENT of tuberculosis and leprosy.

TUBERCULOSIS

Tuberculosis (TB) is a worldwide disease caused by the acid-fast bacterium *Mycobacterium tuberculosis*. Other mycobacteria can also cause a type of tuberculosis, especially in immunocompromised people. The statistics on TB are horrifying, with a third of the world's population infected with the bacterium and more than 2 million people per year dying from this infection. Particular risk groups appear to be elderly people, immigrants, alcoholics, intravenous drug users, homeless people, people infected with human immunodeficiency virus (HIV), immunocompromised people and certain occupational groups, such as health-care workers. The organism can infect various organs of the human body, such as the spleen, kidneys, bone and central nervous system (CNS), but it is the lungs that are most often infected. This is because the spread of the infection is by inhalation of infectious aerosols. The organism is very slow-growing, which makes treatment with antibiotics difficult. Antibiotics, because they affect metabolic processes, cause more damage to a cell metabolising at a fast rate than to one metabolising at a slow rate. (This is analogous to a car speeding and hitting a brick wall versus a car going very slowly and hitting the same wall. Consider that the brick wall is the antibiotic and the car is the organism; under which circumstances will the most damage be done?) Another problem in the treatment of TB is the ability of the organism to develop resistance to antituberculotic drugs. This makes the use of drug combinations the norm in the treatment of this infection.

The twentieth century was characterised by a decline in the incidence of TB in most developed countries. This was due largely to antibiotic drugs, active immunisation, screening of people and livestock, and better living conditions. More recently, we have seen a disturbing rise in TB infections. This appears to be due to immigration patterns, emergence of drug-resistant strains of TB and prevalence of conditions that impair immunity, e.g. HIV, acquired immunodeficiency virus (AIDS) and organ-transplant therapy.

The various other mycobacteria responsible for human diseases, common in the environment, do not often cause infections. When they do, the disease produced is usually less serious than TB, as the organisms are less virulent. Similar drugs are used in the treatment of these infections. A textbook on medical microbiology should be consulted for more details.

Antituberculotics

Drugs used in the treatment of TB are divided into two groups – first- and second-line antituberculotics – on the basis of their efficacy, activity and adverse effects. In fully sensitive cases, there are two phases of treatment. The initial phase uses at least three drugs and the continuation phase uses two drugs. The Joint Tuberculosis Committee of the British Thoracic Society (BTS) has produced guidelines for the treatment of TB in the UK, and these are available from the BTS website. Treatment regimens vary in other countries. Therapy is usually started with **ethambutol**, **isoniazid**, **rifampicin** and **pyrazinamide** for the first 2 months followed by isoniazid and rifampicin for a further minimum period of 4 months. These drugs are usually given as a combined preparation. This regimen is suitable if bacteriology shows fully sensitive acid-fast bacilli on culture. Longer treatment is necessary for meningitis and for resistant organisms. In the initial phase, ethambutol can be omitted if there is little risk of resistance to isoniazid (first treatment for TB, no immunosuppression, no contact with drug-resistant organisms). Occasionally, **streptomycin** is still used in the UK if there is resistance to isoniazid before treatment commences. The EHRZ regimen may be used in pregnancy and during breast feeding, but streptomycin is not given in pregnancy.

If the patient is unlikely to take their drugs without supervision, a different regimen is used for directly observed therapy (DOT). This is explained in full in the *British National Formulary* (BNF).

In immunocompromised patients, multi-resistant organisms are more common and stringent monitoring is needed after treatment is completed to ensure the infection has been eradicated. In HIV-positive patients, specialist advice is needed in order to avoid potential drug interactions.

FIRST-LINE ANTITUBERCULOTICS

ISONIAZID

■ MECHANISM OF ACTION

Isoniazid, or isonicotinic hydrazide (INH), is an enzyme inhibitor that interferes with the synthesis of mycolic acids. These acids are constituents of the mycobacterial cell wall. The drug is similar in structure to nicotinic acid and one of its metabolites may interfere with nicotinamide adenine dinucleotide (NAD) synthesis. It is bactericidal in actively dividing cells but only bacteriostatic to resting cells. As with all antituberculotics, resistance develops easily because the bacterial cell becomes impervious to the drug.

Being a fairly small molecule, isoniazid can penetrate caseous lesions associated with the infection and in which the bacterium resides. This property is also useful in cases of tuberculotic meningitis, when penetration into the cerebrospinal fluid is important.

◆ COMMON ADVERSE EFFECTS

Isoniazid, although generally a well-tolerated drug, is associated with some problems. One of the major problems is

due to its interference with pyridoxine (vitamin B_6) metabolism. This renders the vitamin incapable of carrying out its normal function, especially in the peripheral nervous system. This can be a real problem in the fairly high proportion of the population described as slow acetylators (see Chapter 18). One of the processes of drug metabolism is acetylation (see Chapters 14 and 18), and approximately 40 per cent of Americans, for example, are lacking normal amounts of the enzyme involved. This increases the half-life of isoniazid and thus the chances of a peripheral neuropathy developing. Fortunately, this condition is usually easily avoided by supplementing with pyridoxine tablets. It is usual to treat all patients on isoniazid with pyridoxine rather than to carry out tests to see whether or not they are slow acetylators.

The other problem with isoniazid is that one of its metabolites is hepatotoxic, which can lead to fatal hepatitis in rare instances. Slow acetylators are at an advantage here, as the metabolite, being produced at a slower rate, causes less hepatotoxicity.

Isoniazid has been known to precipitate seizures.

✚ CLINICAL CONSIDERATIONS

Concurrent administration with pyridoxine is recommended in order to reduce the risk of peripheral neuropathy. Monitor liver function tests during therapy. If transaminase or bilirubin levels increase, treatment should be suspended. Advise the patient to stop treatment if they develop persistent nausea, vomiting, malaise or jaundice, and to see their doctor.

RIFAMPICIN

Rifampicin has revolutionised the treatment of tuberculosis. Although it is derived from a similar species of bacterium to that of the first antituberculotic, streptomycin (see later in this chapter), it bears no structural relationship to it and its mechanism of action is different. Rifampicin is absorbed well following oral administration.

■ MECHANISM OF ACTION

Rifampicin acts by binding to DNA-dependent RNA polymerase and inhibiting RNA synthesis. It is bactericidal and is effective against dormant cells. Rifampicin is also useful in the treatment of other bacterial infections, such as leprosy (see later in this chapter) and Legionnaire's disease, and in the chemoprophylaxis of meningococcal meningitis. It can also be used to treat methicillin-resistant *Staphylococcus aureus* (MRSA) infection, usually in combination with other antibiotics. Rifampicin is lipophilic and penetrates most tissues rapidly, including macrophages, where the organism can reside. This property makes the drug suitable for killing both intracellular and extracellular bacteria.

◆ COMMON ADVERSE EFFECTS

Rifampicin is relatively free of serious adverse effects. The intermittent use of rifampicin is associated with the highest incidence of adverse effects, most of which probably have an immunological basis. Effects include general malaise, haemolytic anaemia and renal failure, the latter contraindicating subsequent use of the drug. These effects may be avoided by making sure patients take their doses regularly and do not skip doses.

Rifampicin is occasionally hepatotoxic, and care should be taken with patients who may have liver damage. Thrombocytopenia can occur and this, like renal failure, precludes the further use of rifampicin.

Like many drugs, rifampicin is a powerful hepatic enzyme inducer and can speed up the inactivation of many drugs that are given concurrently, including the contraceptive pill.

RIFABUTIN

Rifabutin has, for the most part, similar uses and problems to those of rifampicin. Rifabutin is particularly useful in cases where *Mycobacterium* are resistant to rifampicin, as cross-resistance is not usually a problem. Apart from its use as an alternative to rifampicin in the treatment of TB, rifabutin can be used as a prophylactic against TB in cases when exposure to the disease has occurred, particularly in young children (< 4 years) and HIV-positive individuals. Post-exposure prophylaxis is recommended (although not necessarily with rifabutin) regardless of whether the person is tuberculin-positive or -negative. There is evidence that rifabutin has an antiviral action against HIV type 1 and may be useful for patients with uncomplicated AIDS.

◆ COMMON ADVERSE EFFECTS

Arthralgia is more prevalent (particularly in high doses) with rifabutin than with rifampicin, and uveitis occurs occasionally. Rifabutin, like rifampicin, is a highly coloured compound (reddish-violet) and often causes an orange-tan discoloration of the skin and of bodily excretions, a harmless effect of which patients should be warned.

✚ CLINICAL CONSIDERATIONS OF RIFAMPICIN AND RIFABUTIN

Rifampicin and rifabutin have a red-orange colour and are excreted via body fluids, including tears, sweat and urine, which could prove distressing to the patient if they have not been warned. Patients who wear soft contact lenses should be warned that the lenses may become discoloured. Advise females using a hormonal contraceptive that they should use an alternative means of contraception during the course and for 4 weeks following the cessation of therapy. Monitor full blood count and liver function during the

course of therapy, and for clinical manifestations of liver toxicity, including fatigue, jaundice, anorexia, nausea, vomiting and dark urine.

ETHAMBUTOL

Ethambutol is an unusual synthetic antimicrobial drug in that it is active only against mycobacteria. In combination with isoniazid and rifampicin, ethambutol is one of the first-line drugs used in the chemotherapy of tuberculosis.

■ MECHANISM OF ACTION

The action of ethambutol is unclear. It may act by inhibiting RNA synthesis or by inhibiting the synthesis of polyamines. Polyamines are microbial substances derived from amino acids that are necessary for normal DNA function. Ethambutol is bacteriostatic.

◆ COMMON ADVERSE EFFECTS

The major problem associated with ethambutol is optic neuritis, which has been known to lead to permanent blindness. In most cases, the neuritis is reversible on discontinuation of the drug. It is recommended that patients who are about to commence ethambutol therapy have an ophthalmological examination. They should also be told to try regularly to read fine print and then to report any difficulties with this as soon as possible. Ethambutol may impair renal clearance of uric acid, which can lead to hyperuricaemia and gout. This impairment is responsive to **probenecid** and **allopurinol**.

✚ CLINICAL CONSIDERATIONS

If the patient develops sight difficulties, the drug should be stopped immediately and medical advice sought. Measure renal function, visual acuity and colour vision before and during treatment.

PYRAZINAMIDE

Pyrazinamide is a synthetic drug, similar in structure to nicotinamide. It is possible that, like isoniazid, pyrazinamide interferes with NAD synthesis. Like isoniazid, pyrazinamide is a small molecule and has the ability to penetrate caseous lesions and macrophages.

◆ COMMON ADVERSE EFFECTS

Hepatotoxicity with pyrazinamide is common with high doses, and so the tendency is to give small doses. As with other antituberculotic drugs, combination therapy is the norm. This enables smaller doses to be given and helps to prevent the development of resistant bacterial strains.

Patients on pyrazinamide should be told to report any incidences of anorexia and nausea, as these may be indicative of hepatitis. Hyperuricaemia occurs occasionally with pyrazinamide, but, unlike that associated with ethambutol, this is unresponsive to the usual antigout drugs. The resulting arthralgia can usually be treated with **aspirin**.

✚ CLINICAL CONSIDERATIONS

Before treatment, measure the full blood count, serum urea, creatinine, uric acid and liver transaminase concentrations. Advise the patient to inform the doctor if nausea, vomiting, fatigue, yellowing of the skin, dark urine or pale faeces occur. These may be manifestations of liver impairment.

SECOND-LINE ANTITUBERCULOTICS

CAPREOMYCIN

Capreomycin is an aminoglycoside antibiotic (see Chapter 68) reserved exclusively for the specialised treatment of cases of TB resistant to the more commonly used drugs mentioned above. Capreomycin, like the other aminoglycosides, is absorbed poorly from the gut and therefore is given by deep intramuscular injection. Adverse effects are similar to those of the other aminoglycosides, notably renal damage and eighth cranial nerve damage.

✚ CLINICAL CONSIDERATIONS

Before and during capreomycin therapy, monitor serum creatinine and potassium levels to determine its effect on kidney function. Assess audiometric and vestibular function before and during treatment to determine hearing and balance problems.

CYCLOSERINE

Cycloserine is a simple derivative of the amino acid serine, but it is a true antibiotic, as it is isolated from a species of *Streptomyces*. Like capreomycin, cycloserine is used only in cases where the use of the more common drugs has failed.

■ MECHANISM OF ACTION

Cycloserine is related to the amino acid serine and its structure resembles that of another amino acid, alanine. Its action is by inhibiting two enzymes involved in the incorporation of alanine in the cell wall of the bacteria; thus, it is bactericidal. In some respects, it is similar in action to the penicillins and cephalosporins. The drug is not very potent and has a low therapeutic index and is therefore used only in cases of resistance to other drugs.

◆ COMMON ADVERSE EFFECTS

Cycloserine is given orally. It often causes headaches (sometimes severe) and other neurological symptoms (hallucinations, paranoia, aggression), which may necessitate psychiatric intervention. The consumption of alcoholic

beverages during cycloserine therapy may lead to epileptiform seizures; thus, alcohol is contraindicated during therapy. In view of the drug's toxicity, blood levels should be monitored. Cycloserine should be avoided if possible in patients with psychiatric, neurological, hepatic and renal disorders.

✚ CLINICAL CONSIDERATIONS

Before and during cycloserine treatment, measure renal and hepatic function, and perform complete blood counts. As this drug may cause photosensitivity, advise the patient to wear protective clothing, use a sunscreen and wear a hat when outdoors.

STREPTOMYCIN

Streptomycin is now mainly of historical interest, being the first aminoglycoside discovered. For many years it was one of the standard drugs used in the treatment of TB. Owing to its inherent toxicity, the need for parenteral administration and the availability of more potent drugs, its use has declined greatly worldwide. As streptomycin is very cheap, it may still be used in developing countries, but it is used only very occasionally in Britain. Nevertheless, some patients might be placed on streptomycin through a special access scheme in situations where other antitubercular drugs are contraindicated.

✚ CLINICAL CONSIDERATIONS

Monitor renal function in patients receiving streptomycin. Measure urea, creatinine and potassium serum levels regularly, and monitor auditory and vestibular function before and during treatment. Treatment should be ceased if signs of ototoxicity or renal impairment occur.

CIPROFLOXACIN

The antimicrobial drug **ciprofloxacin** is also effective against the mycobacteria and can be used as a second-line drug. (See Chapter 68 for a discussion of its actions.)

LEPROSY

Leprosy, or Hansen's disease, is a bacterial disease of the skin, mucous membranes and peripheral nerves caused by *Mycobacterium leprae*. The clinical presentation of the disease is subdivided into at least six different categories, lepromatous and tuberculoid being the types found at either end of the spectrum. The differentiation between the types is based mainly on the appearance of the skin lesions and immunological tests. The lepromatous type is the most severe, with extensive tissue destruction that can eventually include cartilage and bone. This is also the most contagious type.

Contrary to popular belief, leprosy is not a very contagious disease. It is transmitted by aerosols and by mucus from the respiratory tract. Continuous exposure for a number of years is often needed to become infected. Arthropods, such as fleas and mites, have not been ruled out as vectors. The organism itself cannot be cultured in the laboratory on ordinary microbiological media, but it can be cultured in tissue culture. This makes the study and diagnosis according to Koch's principles difficult. Diagnosis is made by finding acid-fast organisms in the lesions.

Leprosy is mainly of tropical origin and was first recognised in the ancient civilisations of China, Egypt and India. Treatment with multidrug therapy (MDT) is highly effective, and since 1995 the World Health Organization (WHO) has provided free MDT for all patients with leprosy worldwide. The WHO elimination project for leprosy (www.who.int/lep/en) has been highly successful, and approximately 410 000 new cases of leprosy were detected in 2004 compared with 804 000 in 1998. The number of new cases detected has been falling by about 20 per cent each year since 2003, and since 1993 the global prevalence of leprosy has fallen by almost 90 per cent. The countries where leprosy is still a problem include Brazil, India, Madagascar, Mozambique, Nepal and Tanzania.

Antileprotic drugs

Treatment of leprosy is very successful if the disease is caught in its early stages, before there has been severe tissue damage. Sometimes tissue damage leads indirectly to infection, as the peripheral pain receptors are destroyed, rendering injuries painless and therefore unnoticed; some people with leprosy have even had their fingers and toes nibbled at by rats while they are asleep. The drugs used in the treatment of leprosy are termed antileprotics and usually cure the disease completely if resistance has not developed. Fortunately, there are several antimicrobial agents and other drugs useful in the treatment of the disease. Multibacillary leprosy should be treated for at least 2 years. The WHO has made recommendations to overcome the problem of **dapsone** resistance and to prevent resistance developing to other drugs. Drugs recommended are dapsone, rifampicin and **clofazimine**. Other drugs that are less effective than rifampicin, including **ofloxacin**, **minocycline** and **clarithromycin**, are reserved for second-line treatment.

DAPSONE

Dapsone is the mainstay of leprosy treatment and has been for several decades, owing to its cheapness and its high activity against the bacteria. As resistance is now a problem, dapsone is combined with one of the other antileprotics. A three-drug regimen is recommended for multibacillary leprosy and a two-drug regimen for pancibacillary leprosy.

Advice from a member of the Panel of Leprosy Opinion is essential for treatment and details can be obtained from the Department of Health. Dapsone is also useful to treat *Pneumocystis carinii* pneumonia (PCP) and toxoplasmosis.

■ MECHANISM OF ACTION

Dapsone is related structurally to the sulphonamides (it belongs to a group of drugs known as sulphones) and, as one would expect, is antagonistic to folic acid biosynthesis in the bacteria (see Chapter 67). It is mainly bacteriostatic, but it may have slight bactericidal properties. Treatment with dapsone is usually long-term and sometimes lifelong, to avoid remission.

◆ COMMON ADVERSE EFFECTS

Adverse effects are rare with dapsone, but they may include gastrointestinal upsets, such as nausea and vomiting, headache and a blue discoloration of the lips and fingertips.

Treatment of leprosy with dapsone occasionally results in an allergic skin reaction called erythema nodosum leprosum. If this happens, treatment with clofazimine is indicated (see below). Mild haemolytic anaemia is common during long-term treatment with dapsone. Other serious adverse effects are uncommon.

✚ CLINICAL CONSIDERATIONS

Before starting treatment with dapsone, measure full blood count and liver function. Monitor blood count weekly during the first month and then monthly during therapy. Dapsone syndrome may occur during the first 6 weeks of therapy; this manifests as fever, jaundice and eosinophilia. The sydrome resolves usually after stopping dapsone therapy.

CLOFAZIMINE

Clofazimine is a reddish phenazine dye whose mechanism of action is unknown. The drug is bactericidal. Being a dye, it can cause discoloration of the urine and the skin. This skin discoloration may persist for several months after discontinuation of treatment and is particularly noticeable in pale-skinned people. Clofazimine also possesses anti-inflammatory properties, which makes it very useful in the treatment of erythema nodosum leprosum.

RIFAMPICIN

Rifampicin is discussed in detail earlier in this chapter. This antibiotic is the most active antilepromatous drug available. The WHO recommends that rifampicin be given only once a month to patients being treated daily with dapsone.

THALIDOMIDE

Thalidomide, being immunosuppressive, like clofazimine, has anti-inflammatory properties and has proven useful in the treatment of erythema nodosum leprosum (unlicensed use). This action of thalidomide has no relation to its original use as a sedative. It is contraindicated in pregnancy. Thalidomide is extremely teratogenic and should be used only in men and in postmenopausal women. Male patients, including those who have had a vasectomy, should wear a condom during sexual intercourse for 1 month before, during and 1 month after treatment because semen may contain the drug, which could exert its teratogenicity by an indirect route. To prevent sedation and dizziness, thalidomide should be taken at night. Severe erythema nodosum leprosum may need treatment with prednisilone.

CLINICAL MANAGEMENT

Antituberculotics

Assessment

- Obtain a history of any past instances of tuberculosis. Determine when the last tuberculin test was performed and the reaction this test produced.
- Assess vital signs and perform respiratory assessment. Compare with subsequent observations.

Planning

- The result of the patient's sputum test for acid-fast bacilli will be negative following the course of therapy.

Implementation

- Monitor the findings on chest X-ray. Perform regular respiratory assessments.
- Monitor liver enzyme levels, especially if the patient is taking rifampicin, pyrazinamide and isoniazid. Also assess for symptoms of hepatotoxicity, including fever, malaise and liver tenderness.
- Monitor full blood examination and platelet count.
- Monitor patients on isoniazid and ethambutol for manifestations of neuropathy, such as numbness and tingling of the extremities.

- For patients taking aminoglycosides, monitor for hearing changes.
- Monitor sputum culture for acid-fast bacilli. Acid-fast bacilli is the term given to bacteria such as *Mycobacterium tuberculosis* that are not readily decolourised by acids after microbiological staining. Usually three consecutive morning sputum specimens are required. This routine is repeated a few weeks following treatment and recovery.
- For patients receiving streptomycin, monitor renal function. Measure serum levels regularly, and monitor auditory and vestibular function if there is renal impairment.
- Monitor patients on isoniazid and ethambutol for visual changes. Organise regular eye examinations for patients on these drugs.
- Administer isoniazid, rifampicin and rifabutin on an empty stomach if possible, as food slows the absorption rate.
- Pyridoxine can be administered with isoniazid to prevent peripheral neuropathy.
- Avoid administering aluminium-containing antacids with isoniazid. Isoniazid should be administered at least 1 hour before these antacids.
- For patients on isoniazid, check liver function before commencing treatment and monitor subsequently only if symptoms of liver disease develop or if the patient is over 50 years old.
- Ethambutol is best administered as a single daily dose to prevent visual problems. Divided doses are more likely to cause visual disturbances.
- For capreomycin therapy, serum creatinine and potassium levels should be taken before commencing treatment and at weekly intervals during the course of therapy.
- Monitor the patient's audiometric and vestibular function before, and at 2- to 3-monthly intervals during capreomycin treatment.
- For patients receiving cycloserine, monitor renal and hepatic function and full blood profile before and during treatment.

Patient teaching

- Advise the patient to take the drug regimen as prescribed. Ineffective treatment may occur if the patient takes the drugs intermittently or the drug is discontinued when manifestations decrease. Treatment has to continue over a long period of time, usually for several months.
- Instruct the patient to avoid alcohol, as it may increase the risk of hepatotoxicity.

Isoniazid

- Stress to the patient the importance of taking pyridoxine, if ordered. Also advise the patient on dietary sources of pyridoxine. See Chapter 61 for further information.
- Advise the patient to avoid taking aluminium-containing antacids with isoniazid. Isoniazid should be administered at least 1 hour before these antacids.
- Advise the patient that the drug absorbs better on an empty stomach.
- Advise the patient to avoid driving and operating heavy machinery if dizziness or drowsiness occurs.
- Instruct the patient to contact the doctor if tinnitus, visual changes, dizziness or ataxia occur.
- Instruct the patient to notify the doctor if manifestations of hepatotoxicity occur, including fever, liver tenderness, loss of appetite, malaise and jaundice.

Rifampicin and rifabutin

- Inform the patient taking rifampicin or rifabutin that urine, faeces, saliva, sputum, sweat and tears may develop a red-orange coloration. This effect is harmless. Soft contact lenses should not be worn, as they may become stained permanently.
- Advise the patient to take the drug on an empty stomach.
- Instruct the patient to avoid driving and operating heavy machinery if drowsiness or dizziness occurs.
- The contraceptive pill may be rendered ineffective in female taking rifampicin or rufabutin. An alternative means of contraception should be considered.
- Instruct the patient to notify the doctor if manifestations of hepatotoxicity occur, including fever, liver tenderness, loss of appetite, malaise and jaundice.

Ethambutol

- Advise the patient on the importance of regular eye examinations. If the patient experiences problems with vision, the drug should be stopped immediately.
- Ethambutol may be taken with meals to lessen gastric irritation.
- Instruct the patient to avoid driving and operating heavy machinery if drowsiness or dizziness occurs.

Pyrazinamide

- Instruct the patient to notify the doctor if manifestations of hepatotoxicity occur, including fever, liver tenderness, loss of appetite, malaise and jaundice.

Cycloserine

- Advise the patient that cycloserine may cause photosensitivity. Sun precautions should be taken, as indicated in Table 11.19 in Chapter 11.

Evaluation

- Evaluate the effectiveness of the drug regimen as shown by the negative result of the sputum test for acid-fast bacilli.

Antileprotic drugs

Assessment

- Assess the patient for respiratory, cardiac, renal and hepatic disease. Exercise caution when using antileprotic drugs in these conditions.

Planning

- The patient's condition will be alleviated as shown by negative tissue cultures.

Implementation

- Monitor tissue cultures of the organism regularly until the leprosy is treated.
- Monitor the patient for a full blood examination, platelet count, and serum creatinine and urea levels.
- Treatment of leprosy usually requires the administration of at least two antileprotic drugs. Standard treatment for leprosy involves a combination of dapsone, clofazimine and rifampicin.
- Administer oral doses with meals to lessen the incidence of gastric irritation.

Patient teaching

- Advise patients to take the drugs with meals to lessen the incidence of gastric irritation.
- Patients on dapsone who develop erythema nodosum leprosum may be placed on a gluten-free diet to alleviate this skin condition. Foods that contain gluten, including wheat, barley, oats, bran, brewer's yeast, malt and pizza, should be avoided.
- Warn patients on clofazimine that it is a dye that can discolour skin, eyes and body secretions. Secretions affected include faeces, urine, sputum, sweat and tears. This reaction is harmless.
- Advise patients that if drowsiness or dizziness occurs, they should avoid driving and operating heavy machinery.
- Provide emotional support for the patient. Treatment is usually required for a prolonged period.

Evaluation

- Evaluate the effectiveness of drug therapy as shown by the disappearance of skin lesions and negative tissue cultures.

SUMMARY

- Tuberculosis is one of the major diseases of the world and has considerable morbidity and mortality.
- Drug resistance is common in *Mycobacterium tuberculosis*.
- The successful treatment of tuberculosis relies on multiple drug use and prolonged therapy.
- Drugs used to treat tuberculosis are termed first-line or second-line, the second-line drugs being used in cases of non-effectiveness of the first-line drugs.
- Leprosy is caused by *Mycobacterium leprae* and is still a common disease in developing countries.
- The treatment of leprosy is similar to that of tuberculosis.

1 Why is multiple drug therapy the norm in the treatment of tuberculosis?

2 Why are pyridoxine supplements given to patients on isoniazid?

3 What could be an advantage of being a slow acetylator while on isoniazid?

4 What is a disadvantage of being a slow acetylator while on isoniazid?

5 Why should routine ophthalmoscopy be performed on patients undergoing treatment with ethambutol?

6 What clinical laboratory test should be performed on patients using pyrazinamide?

7 Why is the determination of antibiotic sensitivity difficult with *Mycobacterium leprae*?

8 What are the causes of tissue damage in leprosy?

9 What are the other uses for dapsone and rifampicin?

10 What is a potential adverse reaction to the administration of isoniazid? Is this reaction likely to be worsened in a patient with liver disease or diabetes mellitus? Explain.

11 Why should a patient drink copious fluids while receiving ethambutol?

12 Would you advise a patient to continue wearing soft contact lenses while taking rifampicin? Explain.

13 What procedure would you use to evaluate the effectiveness of antituberculotics?

14 What blood test is conducted while a patient takes isoniazid and rifampicin?

69 DRUG SUMMARY TABLE: ANTITUBERCULOTIC AND ANTILEPROTIC DRUGS

FAMILY NAME	GENERIC NAME	TRADE NAME(S)
Antileprotic agents	Clofazimine	
	Dapsone	
Antituberculotics	Capreomycin	Capastat
	Ciprofloxacin	
	Cycloserine	
	Ethambutol	
	Isoniazid	
	Pyrazinamide	
	Rifabutin	Mycobutin
	Rifampicin	Rifadin Rimactane
	+ Isoniazid	Rifinah Rimactazid
	+ Isoniazid and pyrazinamide	Rifater

ANTISEPTICS AND DISINFECTANTS

70

CHAPTER SEVENTY

OBJECTIVES

After completing this chapter, the reader should be able to:

- **discuss the difference between antiseptics and disinfectants;**
- **discuss the mechanisms of action of:**
  - **oxidising agents;**
  - **alkylating agents;**
  - **detergents;**
  - **phenols;**
  - **alcohols;**
  - **heavy metals;**
  - **dyes used as antimicrobials;**
  - **tea tree oil;**
  - **honey;**
- **list representative examples of each type of antiseptic and disinfectant;**
- **give the indications for use of the various types of antiseptic and disinfectant;**
- **discuss the problems associated with the various types of antiseptic and disinfectant.**

KEY TERMS

Antiseptics
Disinfectants
Detergents
Phenol coefficient
Alkylating agents
Oxidising agents

A DISINFECTANT IS A CHEMICAL AGENT THAT DESTROYS OR INHIBITS THE GROWTH of pathogenic microorganisms. Disinfectants do not kill all microorganisms but reduce them to a safe level. Disinfectants may also be able to denature viruses. The term 'disinfectant' is applicable to agents used to treat inanimate objects and materials and may also be applied to agents used to treat the skin and other body membranes and cavities. In this latter case, they are then called antiseptics.

Agents that can sterilise surfaces are more correctly called sterilants. Most disinfectants are only partially successful in killing or denaturing microorganisms. Antiseptics are never able to sterilise completely and cannot be relied on to produce asepsis. Nevertheless, antiseptics play an important role in medicine and help prevent many nosocomial infections, as do disinfectants.

Disinfectants that are used on inanimate objects are generally more toxic than those used as antiseptics. Sometimes similar chemicals are used in both circumstances, but as disinfectants they are utilised at a much higher concentration, which would be irritant to living tissue. The efficacy of antiseptics and disinfectants is measured by comparing them with the original antiseptic used by Lister, phenol. Each compound is evaluated by comparing its killing effect on a bacterium, usually *Salmonella* spp. or *Staphylococcus* spp., with a standard concentration of phenol. The coefficient is calculated by dividing the concentration of the test compound at which it kills the test organism in 10 minutes, but not in 5 minutes, by the concentration of phenol that kills the organism under the same conditions.

If the coefficient is calculated to be less than 1, then the agent is superior to phenol; the lower the coefficient, the better. Unfortunately, the results obtained from this test are not always applicable to the clinical setting because very often nosocomial infections are caused by bacteria not used in the test. Many of the chemicals used as antiseptics and disinfectants are inactivated by substances such as proteins, which are often present on areas to be treated. The test can be done in the presence of a standard amount of organic matter.

Antiseptics and disinfectants are classified according to their mode of action, which is usually chemical in nature. Some disinfectants are commonly found in households and are similar to those employed in hospitals and clinics. Here, reference will be made only to those agents commonly used in the clinical setting.

OXIDISING AGENTS

Many enzymes contain in their active centre a sulfhydryl group, which is represented by the –SH radical. This group is very susceptible to being oxidised to what is known as a disulphide bridge, –S–S–. If this happens, the enzyme is inactivated and the organism dies, or at least is immobilised. (This type of reaction occurs in the opposite direction with various other drugs; see the action of acetylcysteine in Chapters 40 and 52.)

The commonly used oxidising agents belong to the halogen group of elements, namely **chlorine** and **iodine**. Both of these substances are strong oxidising agents in the elemental form. Chlorine, being much stronger than iodine, is used mainly as a disinfectant, while iodine is used as an antiseptic.

Chlorine in gaseous form is used to disinfect water supplies. Because chlorine is so toxic, chlorine-containing compounds that release the element slowly are usually employed as antiseptics. A very common disinfectant is **sodium hypochlorite**, which is sold under the trade name of Milton™. This is commonly used to disinfect items, from babies' feeding bottles to hospital equipment and surfaces. In view of the corrosiveness of chlorine, chlorine-containing mixtures are not often used as antiseptics, but occasionally one meets Eusol (Edinburgh University solution), which is a dilute solution of chlorinated lime and is still used in wound dressings and in ear, nose and throat (ENT) surgery. The use of this agent on wounds has shown that capillary damage can occur, which delays the healing process, and its future use may be in doubt.

Iodine is known widely as a solution in alcohol, called tincture of iodine, which is still used occasionally. As anyone who has had this applied to a graze or cut knows, its initial stinging effect can be painful. Iodine nevertheless is still one of the most commonly used antiseptics in a form known as an iodophor, the most common iodophor being **povidone–iodine**. Povidone is a polyvinylpyrrolidone that complexes loosely with iodine. Povidone–iodine appears to be like an iodine solution; the only difference is that the iodine is at a much lower concentration than in its tincture. This makes it much less irritating to tissues. When iodine oxidises an enzyme, the iodine is reduced to the iodide ion, which is inactive as an antiseptic. Povidone–iodine in solution is in an equilibrium, as shown in the following equation. If iodine is removed by being reduced to iodide, more povidone–iodine converts to free iodine in order to maintain the equilibrium:

$$\text{Povidone–iodine} \rightleftharpoons \text{povidine} + \text{iodine}$$

As mentioned in Chapter 74, povidone–iodine has antifungal properties and may also have some antiviral properties. A wide variety of formulations are available, including a mouthwash for oral infections such as candidiasis and topical powders for the treatment and prevention of wound

infection. For vaginal application, povidone–iodine has also been formulated as pessaries. The application of povidone–iodine to large areas may produce the systemic adverse effects of iodine. Regular and prolonged use should be avoided in patients with thyroid disorders and in patients receiving lithium therapy.

The other oxidising agents in common use are the peroxides. Of these, **hydrogen peroxide** is still used fairly widely – if not as an antiseptic, then as a bleach for hair. It is also a very suitable oxidising agent for dealing with severe algal overgrowth in swimming pools.

The active part of hydrogen peroxide is the hydroxide radical. This is released from the peroxide in a manner similar to that of chlorine from the hypochlorites and iodine from povidone–iodine. When hydrogen peroxide breaks down, oxygen bubbles are produced, which may contribute to its cleansing action. Unfortunately, many organisms and human cells produce an enzyme called catalase, which breaks down hydrogen peroxide rapidly, causing it to lose its effectiveness. Hydrogen peroxide is used as a 3% solution to disinfect contact lenses; it is particularly useful for this use, since it is effective against *Acanthamoeba* spp. Because it is irritant to the eye, however, the peroxide must be inactivated with sodium pyruvate, catalase or sodium thiosulfate before the lenses are used. Occasionally, a dilute solution is used as a mouthwash for gingivitis and other oral infections. Hydrogen peroxide is often available in dilutions named after the amount of free oxygen they can release. For example, 100-volume hydrogen peroxide releases 100 times its own volume of oxygen. A 100-volume solution of hydrogen peroxide is about a 30 per cent solution. The concentration used for disinfecting inanimate objects varies between 3 and 6 per cent, and the concentration used for an antiseptic is 1.5 per cent. Hydrogen peroxide is a very reactive chemical (very strong preparations are actually used as rocket fuel), and care must be taken with its use as, for example, 100-volume is corrosive to skin. Bottles of hydrogen peroxide should be made of dark glass and should be stored at a cool temperature, because the release of oxygen on exposure to light or heat may cause the bottle to explode.

The other peroxide in common use is **benzoyl peroxide**, an ingredient of many formulations used to treat acne. These are discussed in more detail in Chapter 78.

Another oxidising agent in relatively common use is **potassium permanganate** (Condy's crystals). Although this is bactericidal when used on inanimate objects, it is inactivated rapidly in the presence of body fluids. Solutions are used to clean wounds, ulcers and abscesses and are added to baths for certain skin conditions where there is secondary infection.

✚ CLINICAL CONSIDERATIONS

Iodine solutions and powders should be shaken well before use, as the various components have a tendency to separate. Although hydrogen peroxide solution is placed on sloughy skin that requires debridement, its use should be avoided on healthy skin. When using a benzoyl peroxide preparation, wash the affected area first with mild soap and warm water, and pat dry. The benzoyl peroxide preparation is then applied gently to the affected area. With all of these preparations, avoid contact with the eyes, mouth and mucous membranes. It is also important to avoid contact with hair and coloured fabrics because discoloration may occur.

ALKYLATING AGENTS

Alkylating agents, when used as antimicrobial substances, act by combining with various reactive groups on either structural or cytoplasmic compounds in an organism, thus inactivating the compound (see Chapter 76 for the use of alkylating agents in neoplasia). Most of the alkylating agents are very toxic to all living organisms and thus are reserved for the decontamination of inanimate materials. Compounds such as the gas **ethylene oxide** are so efficient that they are useful for sterilising objects such as endoscopes, which heat would damage. Ethylene oxide has been used to sterilise spacecraft. When surgical instruments are sterilised using this gas, care must be taken to ensure that all the gas has dispersed from the instruments before use. Ethylene oxide is a suspected carcinogen, and traces left on materials have resulted in thrombophlebitis and tracheitis. Ethylene oxide acts on the nucleic acids.

The other two alkylating agents in common use are **formaldehyde** solution and **glutaraldehyde**. Because formaldehyde is a noxious chemical and very harmful to living tissues, its use is reserved for sterilising laboratory materials and for the decontamination of infected glassware. **Glutaraldehyde** is less noxious and less damaging to living tissue than formaldehyde. Nevertheless, glutaraldehyde has been reported to induce asthma attacks, conjunctivitis and rhinitis in people exposed to it frequently. Glutaraldehyde can be used to sterilise items such as surgical and dental equipment. It is also available as a solution for the treatment of warts owing to its virucidal properties.

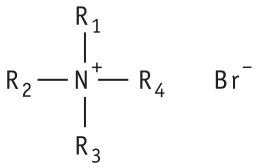
✚ CLINICAL CONSIDERATIONS

When using ethylene oxide, ensure that the gas has dispersed from surgical instruments in order to prevent tissue toxicity. Gloves should be worn when handling formaldehyde and glutaraldehyde in order to prevent skin contact.

SUBSTANCES AFFECTING CELL PERMEABILITY

These substances can be divided into three groups of detergents and the phenols. They are among the most widely used antiseptics and detergents. The simplest of these are

FIGURE 70.1 BASIC STRUCTURE OF A QUATERNARY COMPOUND



the anionic detergents (the negative ion is the detergent part and they are normally sodium or potassium salts of long-chain fatty acids), or simple soaps, which are only weakly antiseptic. Sometimes other antiseptics are added to soaps. The cationic detergents are much more effective. Most are quaternary ammonium compounds and can be represented by the structure shown in Figure 70.1. The ammonium ion has the formula NH_4^+ and the hydrogen atoms have the ability to be replaced with either lipophilic or lipophobic groups. When all four hydrogens are replaced with other groups, the result is a quaternary ammonium compound. If only three are replaced, the compound is a tertiary amine.

In **cetrimide**, the R_1, R_2 and R_3 groups stand for the methyl groups CH_3. The R_4 group is the cetyl or hexadecanyl-C_{16} group. This is a long chain of 16 carbon atoms and is very lipophilic. It is represented in Figure 70.2.

The anion associated with the cation is usually a halide – in the case of cetrimide, a bromide. The cationic detergents have good penetrating power and cause disruption to the cell membranes of bacteria and other microorganisms in the same way that dishwashing detergents dissolve or emulsify fats. All the cationic compounds are relatively free of adverse reactions; skin sensitivities and allergies are rare. The other common cationic detergents used as antiseptics and/or disinfectants are **benzalkonium chloride**, **cetalkonium chloride**, **cetylpyridinium chloride** and **benzethonium chloride**. All of these are found in a multitude of external preparations. Table 70.1 lists some cationic detergents and their uses.

Some detergents have antimicrobial properties and are non-ionic. They are of interest not because they are used to kill bacteria but because they are used to kill spermatozoa. Spermicidal contraceptives containing **nonoxynol** or **octoxinol** have been used. Both of these are non-ionic alcohols with detergent properties. Nonoxynol appears to be the more effective. Nonoxynol has antimicrobial

FIGURE 70.2 HEXADECANYL GROUP

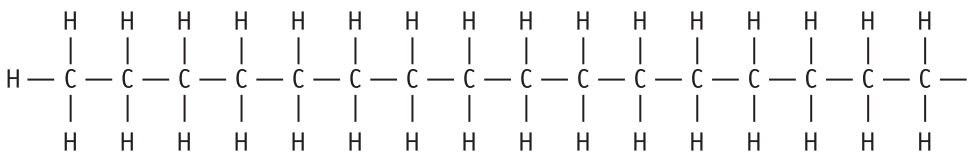


TABLE 70.1 CATIONIC DETERGENTS

Cationic detergent	Use
Cetrimide	Infected skin conditions Scalp infections
+ Chlorhexidine + Lidocaine + Salicylic acid	Insect bites Minor burns and cuts
Benzalkonium chloride	Abrasion, minor wounds Acne Seborrhoea
Cetalkonium chloride (+ choline salicylate)	Oral irritation
Cetylpyridinium chloride	Sore throat
Benzethonium chloride	Minor wounds Otitis externa

activity against a number of bacteria and viruses, and it was hoped that the use of spermicidal contraceptives would provide some protection against sexually transmitted diseases. This has not proved to be the case, however, and nonoxynol's irritant action may even increase the risk of genital ulceration and, thereby, the risk of HIV infection. The United Nations and the WHO have advised against its use by women at high risk of infection.

Chlorhexidine belongs to a group of chemicals known as the biguanides. It acts on bacterial cell membranes, causing their disruption. It is one of the most widely used antiseptics today, as it has a very high therapeutic index. The advantages of chlorhexidine are that it can be used over a wide range of pH values and it is not inhibited greatly by the presence of organic material, such as pus. Its uses as an antiseptic are legion, and there are even more chlorhexidine-containing preparations available than there are cationic antiseptics. As either the gluconate or hydrochloride, chlorhexidine is present in many cleansing soaps and scrubs, skin antiseptic creams, mouthwashes, gargles and throat lozenges. When used often as a mouthwash, staining of the teeth and gingival bleeding can occur.

✚ CLINICAL CONSIDERATIONS

Antiseptic liquids containing cetrimide should be diluted before use according to the manufacturer's directions. Contact with the eyes, middle ear and brain meninges must be avoided, as cetrimide may cause tissue irritation. For the same reason, cetrimide should not be used as an enema or in body cavities. Diluted solutions of cetrimide must be discarded after use.

When using a nonoxynol preparation, additional applications are required each time intercourse is repeated. If a diaphragm is used with a nonoxynol preparation, the diaphragm should remain in place for 6–8 hours after intercourse to allow for the full spermicidal effect. Several of these topical contraceptive treatments are applied using a vaginal applicator. Refer to Table 7.13 in Chapter 7 for further information about administering medications by the vaginal route.

Chlorhexidine may be diluted or used undiluted before application, depending on the type of preparation and reasons for use. Chlorhexidine may cause skin and hypersensitivity reactions, which warrants discontinued use. When applying chlorhexidine solutions to wounds, discard any remaining solution after use.

PHENOLS

Phenol (carbolic acid) was the original antiseptic used by Lister in his pioneering work on surgical antisepsis. Today phenol is considered too toxic for general use as an antiseptic, owing to its central nervous system (CNS) toxicity. Many substituted phenols are still in general use, such as cresols, **thymol**, **resorcinol**, **chloroxylenol** and **triclosan**. One phenol derivative that was very popular in the 1960s and 1970s was **hexachlorophene**, which was accepted almost universally as one of the better antiseptics. It was used in many situations in hospitals. It took several years, however, to discover that this substance sometimes caused CNS damage in infants following skin absorption and in adults following application to mucous membranes. Nowadays, hexachlorophene is used mainly in soaps and creams in low concentrations and is an ingredient of various preparations for skin disorders. A reported outbreak of methicillin-resistant *Staphylococcal aureus* (MRSA) infection in a neonatal intensive care unit was controlled by the use of hexachlorophene soap for hand washing by staff. It should be used with caution on infants and, as it may be teratogenic, it should also be avoided during pregnancy. Phenols exert their action by disrupting cell membranes, and they are protein denaturants.

The cresols are used mainly as disinfectants because they are quite irritating to skin. Thymol is viewed by some as having a pleasant taste and smell and is therefore incorporated in many mouthwashes, but probably at too low a concentration to be of much value.

Resorcinol is an ingredient of some acne and other skin preparations; it is mildly keratolytic as well as antiseptic. Triclosan has a spectrum of efficacy similar to that of chlorhexidine, except that it is not very effective against *Pseudomonas aeruginosa*, a common cause of nosocomial infections; therefore, its use in hospitals is not advised. As a general antiseptic, triclosan is incorporated in many soaps, facial washes, shampoos and acne preparations. It has only occasionally been reported to cause dermatitis. Chloroxylenol is one of the active ingredients of Dettol™ preparations.

Another group of phenolic compounds have an important part to play in pharmaceutical preparations. These are the parabens, derivatives of para-hydroxybenzoic acid. They are effective at very low concentrations and appear to be devoid of systemic toxic effects at a concentration of about 0.2 per cent. They are used as preservatives in many ointments, creams and oral liquid preparations. One severe problem associated with the parabens is that in atopic individuals they can cause severe dermatitis.

✚ CLINICAL CONSIDERATIONS

Prolonged application of chloroxylenol and triclosan preparations, especially in the form of undiluted solutions, should be avoided as they can cause skin irritation. In the case of eye contact, the eye should be irrigated with copious amounts of cold water. Diluted solutions should be applied within 24 hours and discarded immediately after use in order to prevent bacterial growth in these environments. Preparations containing paraben compounds should be avoided by individuals who are susceptible to allergic reactions.

ALCOHOLS

Two alcohols are commonly used as antiseptics – **ethanol** (ethyl alcohol) and **2-propanol** (isopropyl alcohol, IPA). Their mechanism of action is by denaturing proteins in cells. They do this by a dehydrating process and essentially upset tertiary structures of protoplasmic proteins, rendering them non-functional. They can also dissolve membrane lipids. To be effective, these alcohols are best used at a concentration of 70 per cent in water. The water helps the alcohol penetrate the cell walls. 2-Propanol is slightly more efficacious than ethanol in its germicidal properties; when used on the skin, the slower rate of evaporation of 2-propanol maintains a longer contact time with the surface organisms. 2-Propanol has the disadvantages of having a slightly unpleasant smell and being a vasodilator. This latter property can result in increased bleeding from needle punctures. Both of these alcohols are slow in acting when applied to skin surfaces, with a 2-minute contact time being needed for only a 75 per cent reduction in bacterial count. Ethanol will evaporate during this time and, when used in a swab, its main action is most probably the cleansing of the skin surface made by the wiping motion. The same is true to a lesser extent with 2-propanol swabs. Neither alcohol has any effect on bacterial spores, even after prolonged contact. The activity of other antiseptics is enhanced when they are dissolved in alcohol, usually ethanol. Ethanol, being less toxic than 2-propanol, is incorporated in many mouthwashes.

Glycerol (glycerine) is a non-toxic alcohol with some antibacterial properties and is used occasionally as a preservative in injectable medications.

✚ CLINICAL CONSIDERATIONS

Health-care professionals are advised to use alcohol wipes to disinfect equipment, even though there is not a full elimination of bacteria during this process. Before administering injections, it is also important that the site is cleaned with an alcohol swab. It is also recommended that equipment (e.g. thermometers) is scrutinised and cleaned thoroughly before use. Preparations containing glycerol should be shaken vigorously because it is a viscous substance that can cause separation of medication components.

HEAVY METALS

The two main heavy metals that occur in antiseptics are mercury and silver. They are always used as compounds rather than as the elemental forms. Their action is to combine with sulfhydryl groups and thus denature proteins. Mercury is still available as an organic derivative in **merbromin** and **thiomersal**. Merbromin is a fairly obvious antiseptic as it is bright red and is still used as an antiseptic in some parts of the world. In view of its CNS toxicity and the availability of superior compounds, it is amazing that it is still used at all. Thiomersal is still found as a preservative, mainly in eye drops.

Silver nitrate is used in some countries as an eye instillation in neonates. It is used to prevent gonococcal infections of the eye that may have been picked up in the birth canal. **Silver sulfadiazine**, a sulphonamide salt of silver, is very useful as a burn antiseptic cream. The presence of silver ions and a sulphonamide make this a fairly powerful antibacterial substance active against *P. aeruginosa*, a common nosocomial pathogen likely to lead to sepsis in burns. The compound does not cause any pain when applied to burns and, unlike most other silver compounds, does not stain dressings and bed linen black.

Another metal with slight antiseptic properties is zinc, used mainly as the sulphate and the oxide. **Zinc sulphate** is present as a mild antiseptic in some eye drops. **Zinc oxide** is found in many preparations for haemorrhoids and sunburn and in nappy rash pastes. Its inclusion in these preparations is for its astringent and antiseptic properties.

✚ CLINICAL CONSIDERATIONS

Silver sulfadiazine preparations should be applied with a sterile spatula or with a hand covered with a sterile glove, to a layer of about 3–5 mm thick. Each jar or tube should be reserved for one person in order to prevent the transfer of infection. Containers should be stored in a cool place and discarded after completion of treatment. Patients should be observed carefully for any signs of sensitivity relating to a sulphonamide allergy.

DYES

The use of dyes in antisepsis is considered rather old-fashioned today, but some are still available. They tend to be popular with children, who like to 'advertise' injuries and infections. Dyes are rather messy and stain the skin and clothing. **Acriflavinium** and **aminoacridine** belong to a group of dyes called the acridines, which bind to DNA in the nucleus of bacteria to inhibit growth. **Magenta** acts in a similar fashion in fungal infections.

Gentian violet reacts well with the cell wall of Gram-positive organisms and is bacteriostatic.

✚ CLINICAL CONSIDERATIONS

Hypersensitivity to dyes is a contraindication to their use. It is important to monitor for allergic reactions, such as itchiness and teary eyes during their first use. As these preparations may delay wound healing, prolonged use is inadvisable.

TEA TREE OIL

Tea tree oil, otherwise known as **melaleuca oil**, is obtained from the Australian tea tree (*Melaleuca alternifolia* and related species) and is now used widely. The oil is reported to

have bactericidal and fungicidal properties and it is used for the topical treatment of various skin disorders. Reports have suggested that the oil may be active against MRSA. Natural therapists promote the use of this oil for a multitude of disorders, from bunions to vaginitis. Numerous topical pharmaceuticals are available that contain tea tree oil, including soaps, shampoos and mouthwashes.

✚ CLINICAL CONSIDERATIONS

Avoid contact with the eyes when using tea tree oil on the hair and face. If eye contact does occur, wash with copious amounts of cold water.

HONEY

Honey has been subjected to many trials as an antiseptic, with promising results. Honey is hostile to bacteria because it has a low pH and high sugar content, but there may be other bactericidal/bacteriostatic ingredients that are yet to be discovered. Bandages soaked in honey are used in some hospitals on suppurative wounds, with some success. At least two preparations containing honey are available in the UK for use in the management of skin ulcers, wounds and burns.

CLINICAL MANAGEMENT

Antiseptics and disinfectants

Assessment

- Assess the nature of the tissue or object to which the antiseptic or disinfectant will be applied.
- Determine whether the patient has an allergy to any antiseptics.

Planning

- The goal depends on the intended purpose of use. For an antiseptic, it is anticipated that the patient's wound will be effectively cleaned and no infection introduced or the health-care professional's hands will be effectively cleansed. For a disinfectant, it is anticipated that equipment will be effectively sterilised.

Implementation/patient teaching

- Use these preparations in the recommended dilutions.
- Always wear protective gloves when handling disinfectants.
- Handle solutions carefully in order to avoid contamination.
- Do not store solutions in warm, moist areas as this may promote the growth of microorganisms.
- Note that dried organic material such as oil, milk, blood and other body secretions form a protective layer on equipment and therefore negate the effect of disinfectants. All instruments for sterilisation should be cleaned thoroughly before submersion in the disinfectant.
- Remove all traces of soap on skin and equipment before using antiseptics and disinfectants.
- Antiseptics with an alcohol base should not be used near sensitive tissues, such as the eyes and the urethra.

Evaluation

- Evaluate the effectiveness of the antiseptic or disinfectant in cleaning the patient's wound, cleansing the health-care professional's hands or sterilising equipment.

SUMMARY

- Antiseptics are bactericidal/bacteriostatic compounds used to treat minor topical infections.
- Disinfectant is a term normally used for a bactericidal/bacteriostatic compound when it is used to sterilise or disinfect inanimate objects and surfaces.
- Antiseptics and disinfectants work either by chemically altering substances essential for life or by a physical mechanism of action, for example disruption of cell membranes.

1. Why are alcohols diluted with water when used as antiseptics?
2. What is the difference between an antiseptic and a disinfectant?
3. What precautions should be taken before using a laparoscope sterilised with ethylene oxide?
4. Explain the advantages of povidone–iodine over tincture of iodine.
5. What is the danger of antiseptics such as merbromin?
6. What non-ionic detergent is used as a spermicide? What is its mechanism of action?
7. What antiseptic used therapeutically has virucidal properties? What is its mechanism of action?
8. Should a povidone–iodine preparation be used as an antiseptic to irrigate non-infective, granulating tissue? Explain.
9. Discuss the use of honey in therapeutics.
10. Louis Vitagio, a 50-year-old nursery owner with diabetes mellitus, uses gentian violet for a tinea infection. As secondary bacterial infections are common in patients with diabetes mellitus, how could the use of this preparation be a problem? Explain.
11. What advantages do you perceive for the use of silver sulfadiazine cream for a patient with a burn?

ANTIPARASITIC DRUGS

71

CHAPTER SEVENTY-ONE

KEY TERMS

Amoebiasis
Trichomoniasis
Giardiasis
Ascariasis
Enterobiasis
Encylostomiasis
Trichuriasis
Strongyloidiasis
Trichinosis
Wuchereriasis
Taeniasis

OBJECTIVES

After completing this chapter, the reader should be able to:

- **discuss the aetiology of common protozoan infections;**
- **discuss the use, mechanism of action and problems associated with antiprotozoal drugs;**
- **discuss the use, mechanism of action and problems associated with anthelmintic drugs.**

PARASITIC DISEASES CAN BE DEFINED AS INFECTIONS CAUSED by a member of the animal kingdom. They include such diverse infections as malaria, amoebiasis, worm infections and arthropod infestations. As malaria is one of the major diseases of the world, Chapter 72 is devoted exclusively to malaria and includes the substances used to combat it. Arthropod infestations, because they are restricted to superficial infections of the skin, are dealt with in Chapter 78. Before we discuss the drugs used to combat protozoan infections, the infections are described briefly.

PROTOZOAN INFECTIONS

Amoebiasis

The amoebae are a class of protozoans that move by amoeboid movement and eat by phagocytosis. They can simply be termed 'blobs' of protoplasm. They are very common organisms, found free in nature in damp and wet habitats. Only one is associated commonly with human disease – *Entamoeba histolytica*. This organism usually causes amoebic dysentery and remains in the intestine for the duration of the infection. It can remain even after the symptoms of diarrhoea have gone. The patient is then a carrier and can transmit the amoebae via the faecal/oral route to infect other individuals. It has been estimated that the carrier rate could be more than 50 per cent in poorly sanitised areas of the world. From carriers, the amoeba is excreted in an encysted form, which is infective. In acute diarrhoea, however, the organism is excreted as a motile trophozoite, which causes infections only rarely owing to its short life outside the gastrointestinal tract. Occasionally, the organism causes perforation of the muscular coat of the intestine. The organism can then gain access to the hepatic portal system and spread throughout the body, causing abscesses, principally in the liver and lungs. Various other amoebae can cause gastrointestinal infections and some occur as commensals in the intestines.

Naegleria fowleri is another amoeba of clinical importance. This amoeba occasionally causes a meningoencephalitis. The organism seems to grow in water above a temperature of 28 °C and can penetrate the nasal mucosa and travel along the olfactory nerve to the brain, where it can cause death in a few days. This amoeba can be found in domestic and public swimming pools. Divers can be at particular risk if water is forced up the nose during diving.

Infections caused by flagellates

The flagellates are a group of single-celled animals characterised by having one or more flagellae. Several flagellates are implicated in human disease. Those that cause sleeping sickness and leishmaniasis are found mainly in South America, Africa and central Asian countries and are not dealt with here. Two common flagellates in the UK are *Trichomonas vaginalis* and *Giardia lamblia*.

T. vaginalis is sometimes found naturally in the gastrointestinal tract and vagina. It can proliferate in the vagina and cause vaginal erythema, with a malodorous greenish-yellow discharge. It can be transmitted sexually to the male, where it can cause urethritis and epididymitis. Even though infection with *T. vaginalis* is classed as a venereal disease, other, non-sexual modes of transmission (often by unknown mechanisms) are common.

G. lamblia causes giardiasis, a common form of travellers' diarrhoea. Worldwide, this is the most frequently isolated intestinal protozoa. There are 4000–6000 cases annually in the UK. Worldwide, predominantly young children are affected.

Ciliates

Only one ciliate is connected occasionally with human disease – *Balantidium coli*, which can cause diarrhoea.

Sporozoans

This group of protozoans includes the plasmodia, the malaria-causing organisms (see Chapter 72). Two other organisms in this group are also of clinical importance: *Toxoplasma gondii* and *Pneumocystis carinii*.

T. gondii is of importance mainly because of its severe effects on the fetus if the infection is present during pregnancy. The organism is associated (but not exclusively) with cats.

P. carinii has gained notoriety in recent years as being the cause of death in immunocompromised patients with acquired immunodeficiency syndrome (AIDS). The infection can be considered opportunistic, the protozoan commonly being found in healthy individuals.

ANTIPROTOZOAL DRUGS

Nitroimidazoles

Metronidazole belongs to a group of drugs known as the nitroimidazoles, of which there are several. They have many different uses, such as in fungal infections and worm infestations. **Tinidazole** also belongs to this group.

■ MECHANISM OF ACTION

After being metabolised intracellularly, the metabolites of metronidazole bind to DNA, preventing transcription and replication. Metronidazole does not penetrate mammalian cells and so does not cause cell death in the host. Metabolism of metronidazole takes place only in organisms that are either anaerobic or microaerophilic. It was developed as an antiprotozoal and was not recognised as being antibacterial to anaerobic organisms until an observant dentist noticed that an anaerobic gingival infection cleared up in a patient being treated with metronidazole for trichomoniasis.

◆ COMMON ADVERSE EFFECTS

Adverse effects of metronidazole are usually minor and related to the gastrointestinal tract. Patients should be warned that urine may be dark brown during treatment if higher than usual doses are being used. Occasionally, neurological side effects and blood dyscrasias are seen. These are usually reversible on cessation of therapy. One important problem to warn patients about is its effect when combined with alcohol consumption. Many people who take metronidazole and alcohol concurrently experience extreme nausea, vomiting and general malaise; this is similar to the disulfiram reaction discussed in Chapter 23.

Metronidazole is suitable for most forms of amoebiasis, except when encystation has occurred. It can be used to treat trichomoniasis, giardiasis, balantiditis and many anaerobic bacterial infections. It is commonly given by suppository preoperatively in abdominal surgery in order to help prevent postoperative infections.

✚ CLINICAL CONSIDERATIONS

Tinidazole is very similar to metronidazole but has the advantage of having a longer half-life and causing fewer problems when taken with alcohol.

Oral preparations of nitroimidazoles should be given with meals to prevent gastric irritation. Inform patients that sexual partners should be treated simultaneously in order to avoid reinfection. Alcohol and alcohol-containing medications should be avoided during therapy and for at least 3 days following therapy in order to prevent a disulfiram-like reaction.

Other antiprotozoal drugs

DI-IODOHYDROXYQUINOLINE

Di-iodohydroxyquinoline, or iodoquinol, probably acts by inhibiting several microbial enzymes. It is available in some countries as an antidiarrhoeal, but due to its toxicity in some patients its use is not generally recommended. Its side effects are related to its iodine content and are usually in the form of rashes and interference with normal thyroid function. More seriously, it is occasionally neurotoxic. Although no longer available in Britain, it is still available in South-East Asia.

PENTAMIDINE

Pentamidine acts by binding to DNA, preventing replication and translation.

Pentamidine is associated with many common adverse effects, including pain on intramuscular injection, tachycardia, vomiting, headache and hypotension. As it can cause changes in blood glucose levels, care should be exercised if it is used in a patient with diabetes.

This drug is particularly useful in the treatment of *P. carinii* infections in patients with AIDS, where it is sometimes administered by aerosol inhalation.

✚ CLINICAL CONSIDERATIONS

Use cautiously in patients with blood pressure problems, hepatic or renal dysfunction, anaemia or diabetes. It is important to monitor serum creatinine and urea levels daily to determine any effects on the kidneys. Blood pressure is measured at 5-minute intervals for the first 15 minutes of intravenous administration, and then every 15 minutes for the remaining part of the infusion. Blood glucose levels, complete blood counts and serum calcium and potassium levels are also monitored.

OTHER DRUGS

The other drugs used in the infections discussed above are only summarised here, as they are considered elsewhere in this book. **Chloroquine** (see Chapter 72) can be used for amoebiasis, especially if the liver is infected. **Pyrimethamine** (see Chapter 72) and **sulfadiazine** (sulphadiazine) (see Chapter 67) can be used in toxoplasmosis. **Cotrimoxazole** (see Chapter 67) can be used in *P. carinii* infections.

WORM INFESTATIONS

Worm infestations, or helminthiases, occur in all societies. The worms, or helminths, can be divided into three groups according to their zoological classification. The nematodes are roundworms, which commonly infect the gastrointestinal tract, blood and tissues. Some diseases caused by roundworms are fairly benign, but some can lead to hideous disfigurement, as in elephantiasis. The other groups both belong to the larger group of the platyhelminths, or flatworms. The trematodes, or flukes, have leaf-shaped bodies. These organisms cause various diseases that can involve most systems of the body and often cause death. The cestodes are the tapeworms and are usually associated with the gastrointestinal tract but can invade the body and sometimes cause fatalities. Most of the parasitic worms, except for some of the nematodes, have complex lifecycles involving intermediate hosts.

Nematode infestations

These can be intestinal or extraintestinal, depending on the site they usually inhabit. The infections they cause are usually called after their Latin names, as described below.

Ascariasis is caused by the giant roundworm *Ascaris lumbricoides*. This organism causes infestations by the faecal/oral route. The mature worm may be as thick as a pencil and occasionally wanders about the gastrointestinal tract; it may even appear through a nostril. The organisms have been known to proliferate so widely that an intestinal blockage occurs. Treatment is usually with **mebendazole** or **pyrantel**.

Enterobiasis, or pinworm infestation, is caused by *Enterobius vermicularis* and is one of the most common worm infestations. Note that this worm is called threadworm in Britain. It is particularly common in temperate areas such as western Europe and North America, but it is not so common in the tropics. Worldwide annual incidence has been estimated at over 200 million. Levels in white children in Europe range from 30 to 80 per cent. Fortunately, it does not usually cause serious complications.

The main sign of threadworm infestation is intense perianal itching caused by the worm descending through the anus and laying its eggs on the perianal skin. This happens mainly at night and in children, who invariably scratch. The eggs get under the fingernails and are quickly spread throughout the household to infect the whole family. It is therefore important that all family members are treated. The drugs of choice are mebendazole and pyrantel.

Ancylostomiasis, or hookworm infestation, is caused by *Ancylostoma duodenale*, an organism that gains entry to the body through the skin of the feet and so is more common in areas where people walk bare foot. The organism migrates to the intestine, where it attaches to the intestinal wall and sucks blood. In severe infestations, anaemia may result. Treatment is with mebendazole.

Trichuriasis, or whipworm infestation, is caused by *Trichuris trichiura*. This is one of the most common parasitic worms. Infestation is often asymptomatic. If the infestation is severe, as it can be in poverty-stricken areas of the tropics, fatal anaemia can develop. Infestation has also been known to produce rectal prolapse. Treatment is with mebendazole.

Strongyloidiasis, or threadworm (zoologically speaking) infestation, is caused by *Strongyloides stercoralis*. Like the hookworm, this organism gains entry through the skin, usually the feet. It migrates by a complicated route to the intestine. As part of this route involves the lungs, pulmonary problems may occur. Severe intestinal infestations can result in diarrhoea and a colitis, which can lead to bowel perforation. Treatment is with **ivermectin**, available on a named-patient basis.

Trichinosis, or pork roundworm infestation, is caused by *Trichinella spiralis* and is obtained by eating undercooked, infected pig or bear meat. The organism, after being ingested, eventually finds its way into skeletal or cardiac muscle tissue, where it encysts and waits for a carnivore to eat the subject. In many cases, the infection goes unnoticed, but if the eyelid muscle is involved oedematous eyelids may result. If respiratory or cardiac muscle is grossly affected, the consequences can be severe. Treatment is with **albendazole**; prophylaxis is by avoidance of undercooked pork and bear meat.

Wuchereriasis and brugiasis are caused by *Wuchereria bancrofti* and *Brugia malariae*, respectively, and can cause elephantiasis. These filarial worms are transmitted to humans by infected mosquitoes. The organisms live in the lymphatic system, which can be obstructed, resulting in massive oedema of the legs, scrotum and vulva. Treatment is with **diethylcarbamazine** (not available in the UK).

Onchocerciasis is caused by another filarial worm common in Africa and South and Central America and is transmitted by the black fly. The filaria tend to remain in the subcutaneous tissue, from where they migrate throughout the body, including the eye, where they can cause blindness (river blindness). In the tissues, they cause an intense itch. Elephantiasis is a rare complication. Treatment is with diethylcarbamazine or ivermectin.

Cestode infections

Taeniasis, or pork and beef tapeworm infection, is caused by various species of cestodes, most of which have complex lifecycles. *Taenia solium* is the pork tapeworm. It normally lives part of its lifecycle as an intestinal parasite in humans and as a muscle parasite in pigs. Occasionally, it lives in human muscle tissue or in brain tissue. This condition is termed cysticercosis; it can cause epileptiform seizures and death can ensue. The beef tapeworm, *Taenia saginata*, is similar to the pork tapeworm but does not cause cysticercosis. The most common tapeworm is *Hymenolepsis nana*, which is mainly parasitic in humans, although rodents can act as carriers. Symptoms of tapeworm infestation are often minimal but loss of weight can occur. (One enterprising charlatan tried to sell tapeworm eggs in capsules as a dietary aid. This is not an advisable method of dieting!) Treatment is with **praziquantel**, available on a named-patient basis.

Echinococcus granulosus and *E. multilocuraris* are accidental parasites in humans. Their normal lifecycle involves herbivores alternating with canines or felines. When they do infect humans, they encyst in various parts of the body and can cause severe damage, especially if the brain is involved. Treatment is usually by surgery to excise the cyst. Long-term treatment with mebendazole may give some benefit.

Trematode infections

Trematode infections are not common in the UK, but in some parts of the world, where forms are endemic, close to 100 per cent of the population can be infected. Such is the case with schistosomiasis in parts of Africa. As almost every body of water in Africa is infested with the snails that form part of the parasite's lifecycle, this infection is easily obtained by swimming. It is likely that this infection, often called bilharzia, will be seen more and more.

The other trematode infections are the various fluke infections of the lungs, intestine and liver. Treatment is with praziquantel.

ANTHELMINTICS

Drugs used to treat worm infestations are termed anthelmintics. Some of the drugs mentioned here may not be in general use in the UK because the infectious organism is not endemic in this country. In situations where infested travellers return from countries where endemic infections occur, these drugs can be obtained in the UK.

MEBENDAZOLE

■ MECHANISM OF ACTION

Mebendazole kills helminths by inhibiting their uptake of glucose, thus starving the organism of an essential nutrient. This causes the worm's slow death. It can take up to 3 days for complete clearance of the worms from the gastrointestinal tract. It does not have a similar effect on human intestinal cells.

◆ COMMON ADVERSE EFFECTS

As relatively little of this drug is absorbed, systemic side effects are uncommon, although headache and dizziness have been reported. Abdominal cramps and diarrhoea can occur, and it has been suggested that these may be due to the death throes of the worms.

✚ CLINICAL CONSIDERATIONS

Long-term treatment may be required. Families should be treated when pinworm infestations are diagnosed. The use of monthly doses of mebendazole as a worm prophylactic in children is to be discouraged.

Mebendazole tablets may be chewed, swallowed whole, or crushed and mixed with food. It is safe to use in children older than 6 months.

NICLOSAMIDE

Niclosamide, available on a named-patient basis, is used principally for cestode infections, but it also has some activity against *Echinococcus vermicularis*.

■ MECHANISM OF ACTION

Its mechanism of action is to inhibit various processes related to respiration, mainly at the mitochondrial level.

◆ COMMON ADVERSE EFFECTS

As niclosamide is hardly absorbed, the incidence of adverse effects is insignificant, except for occasional gastrointestinal discomfort.

✚ CLINICAL CONSIDERATIONS

As a taeniacide, niclosamide is effective only against the mature tapeworm and not the eggs. Some eggs may be left behind in the gastrointestinal tract, act as though they are in a pig and migrate to the muscles or the brain. This can be dangerous, as cysticercosis can then result. This can be avoided by giving a laxative after the dose of niclosamide in order to cause expulsion of the gastrointestinal contents, including the eggs. It is important to examine the faeces after niclosamide treatment to ensure that the scolex (the head of the worm) has not been left behind, as the head may regrow into a worm.

THIABENDAZOLE

■ MECHANISM OF ACTION

Thiabendazole (not generaly available) is one of the most potent chemotherapeutic agents available. It is very specific in its action on some helminths and some fungi, but it is not used in fungal infections, due to its toxicity. Its mechanism of action is directed towards interfering with several biochemical pathways in some worms. Thiabendazole has some anti-inflammatory activity, which is useful in many systemic helminth infections. It is absorbed rapidly from the gut and is the preferred anthelmintic for many tissue helminths.

■ COMMON ADVERSE EFFECTS

Adverse effects are common, especially anorexia, nausea, vomiting and dizziness. These adverse effects may incapacitate the patient for several hours after dosing, so the patient must be forewarned. Many other adverse effects have been reported with thiabendazole, but these are less frequent and usually reversible on withdrawal of the drug. There is no absolute contraindication to the use of thiabendazole but, as it can be hepatotoxic, care must be given when it is administered to patients with hepatic disease.

ALBENDAZOLE

Albendazole can be used in small doses to treat intestinal taeniasis and other worm infestations, but it is normally used in higher doses to treat tissue hydatid disease – that is, when the tapeworms encyst in tissues, either long-term or before surgical excision. Adverse effects are usually gastrointestinal, and an increase in liver enzymes is common. The main problem is that albendazole is probably highly teratogenic (category D; see Chapter 17).

✚ CLINICAL CONSIDERATIONS

For intestinal parasites, this medication is taken before food in order to minimise absorption. When treating systemic infections, however, it is taken with food in order to increase absorption. Liver function and blood counts should be monitored during prolonged treatment. Albendazole is safe to use in children older than 6 months.

PYRANTEL

■ MECHANISM OF ACTION

The mechanism of action of pyrantel is as a depolarising neuromuscular blocking agent. It also shows anticholinesterase activity (see Chapter 27). Helminth neurons are more sensitive than mammalian neurons to these effects.

◆ COMMON ADVERSE EFFECTS

Like mebendazole, pyrantel is absorbed relatively poorly and so is useful only for intestinal infestations. Side effects are minimal and similar to those of mebendazole. Large doses may produce neuromuscular blockade.

✚ CLINICAL CONSIDERATIONS

Tablets may be crushed or mixed with jam for better palatability. Pyrantel should be used cautiously in patients with severe malnutrition or anaemia, and in patients with hepatic dysfunction. This medication is safe to use in children of all ages.

IVERMECTIN

■ MECHANISM OF ACTION

Ivermectin could be classed as an antibiotic, being derived from a species of *Streptococcus*. It inhibits the gamma-aminobutyric acid (GABA) receptor in the worm; as GABA is an important neurotransmitter in some helminths, worm death ensues.

◆ COMMON ADVERSE EFFECTS

As ivermectin does not cross the blood–brain barrier, it does not cause any significant central nervous system (CNS) effects in humans. It is tolerated well and has adverse reactions similar to those of placebo. It must not be taken concurrently with hypericum (St John's wort).

✚ CLINICAL CONSIDERATIONS

Ivermectin is safe to use in children older than 5 years and in children weighing more than 15 kg. Additional doses may be required in patients who are immunosuppressed and in cases of complicated or disseminated infection.

PRAZIQUANTEL

Praziquantel is effective on a wide range of cestodes and trematodes. It is the drug of choice in the treatment of bilharzia. Its mechanism of action is to paralyse the worm; it can affect the worm's integument, making it unstable. Eventually the worm lyses. Praziquantel is not a pleasant drug to take, but it is less toxic than earlier drugs used to treat schistosomal infections. Most patients suffer from dizziness, headaches, abdominal pain, nausea and malaise shortly after dosing with praziquantel. In cerebral schistosomiasis, seizures may occur. These may be due more to an inflammatory response to the damaged worms than to the drug itself. There are usually no serious consequences with this drug. Schistosomes can be treated with one or two doses, but other flukes often require prolonged treatment.

◆ CLINICAL CONSIDERATIONS

Praziquantel is safe to use in children older than 2 years. By taking the medication with food, the palatability is increased. Instruct the patient to swallow the drug with plenty of water to prevent gagging and vomiting because of the bitter taste. Tablets may be cut in half, but they should not be chewed.

DIETHYLCARBAMAZINE

◆ MECHANISM OF ACTION

Diethylcarbamazine (not on the UK market) is related to **piperazine**, one of the older remedies for several worm infestations. Unlike piperazine, diethylcarbamazine is useful only as a filaricide and is the only drug commonly available for the treatment of such infections. It causes paralysis of the worms and alters their surface, making them more susceptible to the host's immune system.

As some adult forms of the filarial worms are not killed by diethylcarbamazine, cyclical therapy may be needed to rid the patient completely of the parasites.

◆ COMMON ADVERSE EFFECTS

Adverse effects of this drug are usually mild and include headache, malaise, arthralgia and gastrointestinal upsets. More serious adverse effects such as encephalitis and hyperpyrexia can occur, especially if the infestation is heavy. These effects are not due to the drug directly but due to a hyperimmune response mounted against the dead or dying organisms. The use of corticosteroids may be necessary for such reactions.

CLINICAL MANAGEMENT

Antiprotozoal drugs and anthelmintics

Assessment

- Assess the patient's history regarding recent travel, exposure to new food and water supplies, exposure through family members and school contacts, and any previous contact with parasitic infestation.
- Most of these drugs are not recommended for use in pregnant and breast feeding women. Assess female patients for these conditions.
- Assess for the manifestations common to the particular infestation. For instance, worm infestations commonly cause perianal itching, inability to sleep and loss of appetite.
- Assess the patient ordered topical anthelmintic preparations for acne, skin infections and eczema. These preparations should not be used in such conditions.
- Assess the patient's weight to determine the dose for anthelmintic oral preparations.

Planning

- The patient's infestation will be treated following a course of antiparasitic drugs.

Implementation

- For patients with a protozoal gut infestation, monitor faeces for character and frequency. Obtain a faecal specimen for microbiology and culture.
- Monitor fluid balance by recording input and output. Observe for manifestations of dehydration.
- For protozoal gut infestation, ensure that patients consume adequate fluids to prevent dehydration.
- Shake suspensions well before administration, and store in the refrigerator after opening.

Antiprotozoal drugs

- For the patient receiving intravenous pentamidine, monitor blood pressure and pulse at 5-minute intervals for the first 15 minutes of intravenous administration, and then every 15 minutes during the remainder of the infusion. This preparation is prone to causing acute hypotension and cardiac dysrhythmias.
- Monitor renal and hepatic function regularly during administration of pentamidine. Blood glucose levels and serum calcium and potassium levels should also be checked regularly.
- Nebuliser treatment with pentamidine requires a specialised mask to control the particle size and should be administered in a well-ventilated area.
- Prior use of a bronchodilator may prevent bronchospasm, which is a possible adverse effect of parenteral and inhalational use of pentamidine.
- When administering intravenous pentamidine, supervise the patient closely. Ensure that emergency drugs and equipment are available if the patient experiences an allergic reaction or severe hypotension.
- Monitor the character and frequency of faeces of patients on metronidazole, ornidazole and tinidazole. Perform microbiology and culture tests on faecal specimens to monitor the effectiveness of therapy.
- Administer oral preparations after meals to prevent gastric irritation. Note that metronidazole oral suspension is given 1 hour before meals.
- If these drugs are used to treat a trichomonal infection, sexual partners must be treated simultaneously in order for the treatment to be effective.

Anthelmintics

- Albendazole is used in the treatment of hydatid cysts where surgery is not considered feasible due to difficulty in accessing the site and for multiple cysts.
- Fasting or purging before administering the medication is not required.

Patient teaching

- Emphasise to the patient and family the need to take the course until it is completed and not to discontinue therapy.
- Review with the patient and family activities such as handwashing after attending the lavatory and before meals, and taking care of infected bed linen and clothing. Advise the patient not to walk barefoot in areas endemic for hookworm. Be non-judgemental and supportive.
- Instruct the patient and family on ways to avoid infestation through food. Advise on the importance of cooking pork and beef thoroughly, and of careful cleaning and cooking of fruit and vegetables.
- Advise the patient of the importance of washing hands carefully after using the lavatory and before eating.
- Several of these drugs can cause drowsiness and dizziness. Advise the patient to exercise caution when driving and operating heavy machinery.

- Remind parents of young children to keep preparations out of their reach. Many of these preparations are available as pleasant-tasting syrups and chewable tablets, which are very tempting to young children.
- Patients with *Trichomonas vaginalis* should ensure sexual partners are also treated.

Antiprotozoal drugs

- Advise the patient that metronidazole, ornidazole and tinidazole may cause a metallic taste in the mouth, nausea, loss of appetite, stomach pain and headache. The use of a mouthwash before meals may help remove the metallic taste and improve appetite.
- Warn the patient that metronidazole and tinidazole may temporarily stain the urine red-brown. This is a harmless reaction.
- Advise the patient to avoid alcohol during treatment with metronidazole and tinidazole as a disulfiram-like reaction may occur, as shown by flushing, abdominal cramps, nausea and vomiting.
- Advise the patient to take metronidazole, ornidazole and tinidazole after meals to prevent gastric irritation.
- Note that metronidazole suspension is given 1 hour before meals, shaken before use and stored in the refrigerator.

Anthelmintics

- Advise the patient on mebendazole tablets that these should be chewed thoroughly, swallowed whole, or crushed and mixed with food.
- Advise patients on mebendazole and pyrantel that these drugs may be taken with food. Praziquantel is usually taken after meals to reduce gastric irritation.
- Instruct the patient on praziquantel that tablets should be taken with plenty of water to prevent gagging and vomiting due to the bitter taste. Tablets may be divided into halves or quarters but should not be chewed.
- Advise patients taking pyrantel granules that these should be reconstituted with water or milk before administration.
- Advise patients on albendazole that the appropriate time for administering the preparation depends on the infestation process. For intestinal parasites, albendazole should be taken before food in order to minimise absorption. For systemic infestations, it should be taken with food in order to increase absorption.

Evaluation

- Evaluate the effectiveness of therapy as demonstrated by a reduction in the manifestations of infestation.

SUMMARY

- Parasitic diseases include malaria, amoebiasis, worm infestations and arthropod infestations.
- Most protozoal and worm infections can be treated successfully with drugs.
- Accurate diagnosis is needed in order to determine the correct drug.

1. What are two important advantages of mebendazole over many other types of anthelmintic?
2. When using pyrantel preparations, what must be done before administering the dose?
3. When treating a child for a threadworm infestation, why should the whole household be treated?
4. What can cause the severe allergic reactions that occur during the use of some systemic anthelmintics?
5. What are the major differences between cestodes, nematodes and trematodes?
6. Why is the consumption of alcoholic drinks contraindicated during metronidazole therapy?
7. Name possible vectors for tapeworm, filarial worms and schistosomes.
8. Tapeworms have been known to cause epileptiform seizures, which can lead to death. What causes this?
9. Pentamidine can cause pain on intramuscular injection, but this route is preferred to the intravenous route. Why?

10 Abdalla Bucarum, 5 years old, is ordered metronidazole mixture for a protozoal infection. What patient education would you provide for his parents?

11 Mary and John Browne visit the community health centre with their two young children. Ms Browne comments that the children have been bothered with severe perianal itching, especially at night. The community doctor diagnoses a pinworm infestation and orders mebendazole as the treatment of choice. What patient information would you provide for the family?

12 What non-pharmacological measures would you advise for a patient on antiparasitic therapy?

13 Jan McRobbin, a 30-year-old childcare worker, is placed on a course of metronidazole tablets to treat giardiasis. With what patient education would you provide Ms McRobbin?

71 DRUG SUMMARY TABLE: ANTIPARASITIC DRUGS

FAMILY NAME	GENERIC NAME	TRADE NAME(S)
Antiparasitic agents	Albendazole	Zentel
	Ivermectin	
	Mebendazole	Boots Threadworm Tablets
		Ovex
		Pripsen Mebendazole
		Vermox
	Metronidazole	Flagyl
		Metrolyl
	Niclosamide	
	Pentamidine	Pentacarinat
	Praziquantel	Cysticide
	Tinidazole	Fasigyn

ANTIMALARIAL DRUGS

72

CHAPTER SEVENTY-TWO

KEY TERMS

Blood schizontocides
Drug resistance
Gametocytocides
Hypnozoites
Malaria prophylaxis
Malaria treatment
Plasmodium organisms
Sporontocides
Tissue schizontocides

OBJECTIVES

After completing this chapter, the reader should be able to:

- **discuss the aetiology of malaria;**
- **discuss methods of malaria prophylaxis;**
- **discuss the use, mechanism of action and problems associated with antimalarial drugs.**

MALARIA IS A PROTOZOAL DISEASE THAT OCCURS IN MOST tropical and subtropical countries and causes up to three million deaths per year, making it one of the world's most serious infections. In much of the developing world, malaria is a major cause of death. Malaria does not occur naturally in Britain, but it is not uncommon for people to present with symptoms of this infection following tropical travel. Although most travellers to malarious countries use drugs for malarial prophylaxis, malarial parasites are becoming increasingly resistant to these drugs. Also, a significant number of travellers do not take any prophylactic measures. The UK has one of the highest incidences of imported malaria in developed countries, and about 2000 cases are reported annually to the national Malaria Reference Laboratory (MRL). Malaria is a notifiable disease. The incidence of paediatric malaria in the UK has tripled over the past 30 years. A prospective surveillance study on children with malaria in the UK began in January 2006 for 13 months and is being conducted through the British Paediatric Surveillance Unit (BPSU) of the Royal College of Paediatrics and Child Health in collaboration with the several centres in the UK and run by the University of London (details at http://bpsu.inopsu.com/studies/malaria).

The word 'malaria' comes from the French for 'bad air' because its incidence was noted to occur near swampy areas, which often had a malodorous aroma. It was thought that this miasma caused the disease. This theory is spurious, and it is now known that malaria is transmitted to humans when bitten by a female mosquito of the genus *Anopheles* that is carrying the organism in its salivary glands.

TRANSMISSION OF THE DISEASE

Before looking at the drugs that can be used in the treatment of malaria, it is necessary to look at the lifecycle of the organism, as different drugs affect different stages of this cycle.

The organisms that cause malaria belong to the genus *Plasmodium*. Four species can cause the disease, namely *P. falciparum*, *P. vivax*, *P. malaria* and *P. ovale*. Of these, *P. falciparum* (causing malignant malaria) is probably the most dangerous to humans and causes the most fatalities. Untreated, infection with *P. falciparum* can lead to fatal cerebral malaria. The incidence of fatalities is about 20 per cent. The lifecycle of all these parasites is similar and is shown in Figure 72.1.

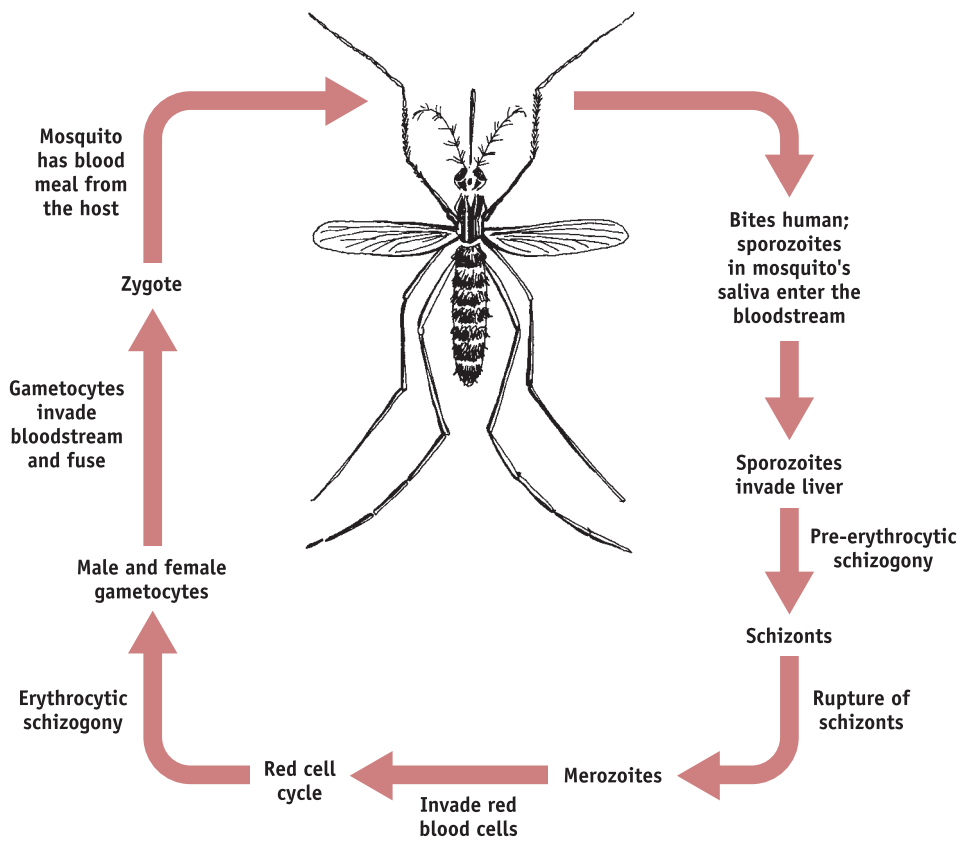
When the female mosquito injects its saliva into the human bloodstream, the protozoan (known as a sporozoite at this stage) enters a liver parenchymal cell and undergoes one mitotic division, which is called pre-erythrocytic schizogony. The resulting cells are called merozoites and they emerge into the circulation and enter an erythrocyte, where they undergo other stages of schizogony (erythrocytic schizogony). This schizogonal stage produces two types of cell, which can be either male or female gametocytes. When these gametocytes are developed, the erythrocyte ruptures; it is the release of these gametocytes into the bloodstream that causes the characteristic symptoms of malaria. These gametocytes can then fuse to form a zygote. This zygote can be taken up by a feeding mosquito and it undergoes a continuation of its cycle in the insect.

Different species of the parasite have varying cycle lengths in humans, and this can help in the diagnosis. With strains of *P. ovale* and *P. vivax*, the sporozoites that enter the liver cells sometimes delay their development, remaining dormant for several months before continuing as described above. This form is known as a hypnozoite and is responsible for the typical relapses that can occur with infection with these parasites. The relapse that can occur with *P. falciparum* is thought to be due to persistent erythrocytic forms of the parasite.

TREATMENT AND PROPHYLAXIS

The drugs used to treat malaria can be divided into five groups according to which stage of the cycle they affect. The nomenclature is logical and is as follows:

FIGURE 72.1 LIFECYCLE OF *PLASMODIUM*



- *Tissue schizontocides*: As these drugs inhibit the growth of the pre-erythrocytic stage of the organism, they are particularly valuable as prophylactics. Examples are **pyrimethamine**, **proguanil** and **doxycycline**.
- *Hypnozoites*: As these drugs kill the parasite in its dormant liver stage, they are useful in preventing relapses. An example is **primaquine**.
- *Blood schizontocides*: In general, drugs that act on this stage are used in therapy. The main drugs used are **chloroquine**, **mefloquine** and **quinine**, although probably all antimalarials have some effect on this stage of the disease.
- *Gametocytocides*: The only common drugs that can deal with this stage of the cycle are primaquine and mefloquine. Mefloquine may have no gametocytocidal effect on mature gametocytes of *P. falciparum* or on persistent hepatic forms of *P. vivax*.
- *Sporontocides*: Strictly speaking, a sporontocide is a drug that kills sporozoites in the mosquito itself, a process that is used occasionally in malaria control. This term can also be used to describe drugs that inhibit the zygote or oocyte in its transfer from the human to the mosquito when a blood meal is being taken. Pyrimethamine and proguanil are the drugs that act as sporontocides.

Malaria is one of the few diseases in which drugs are used more often as a preventive measure than in treatment. This is particularly true for travellers and short-term residents in areas endemic for malaria. Natives of malarious countries are usually immune to the parasites if they manage to survive infancy.

Prophylaxis does not involve only drugs taken internally. Other methods can also be used to combat the disease. Mosquitoes and their larvae can be destroyed by using insecticides or limiting the number of breeding spots available in certain areas. In regions where malaria is endemic, the use of mosquito nets, some impregnated with insecticides, is advisable. The use of personal insect repellents on areas of exposed skin is also advisable, as is exposure of as little bare skin as possible. This latter effort can be futile if only a thin fabric is used, however, as the proboscis of a mosquito easily pierces many materials. Lastly, people at risk should avoid being outdoors around dusk, when mosquitoes are at their most active.

Malaria in pregnancy carries very high risks for both the mother and the fetus, and travel to malarious regions during pregnancy should be avoided if possible. If such travel is unavoidable, extra precautions should be taken by the pregnant woman to avoid mosquito bites by remaining inside at dusk and night and coating mosquito nets with insecticide. The use of insect deterrents in pregnancy is probably safe in moderation, but risks to the fetus have not been eliminated completely. The use of most prophylactics, especially chloroquine and proguanil, is considered to be relatively safe in pregnancy. Doxycycline should not be used during pregnancy, and mefloquine should not be used in the first trimester. It is wise to supplement these drugs with **folic acid** if treatment or prophylaxis must be used during pregnancy.

The treatment and prophylaxis of malaria is changing continuously due to the development of resistance, which varies between countries. The latest information on malaria can be obtained from www.cdc.gov/malaria/ and this site should be considered a useful reference. The recommendations for prophylaxis for travellers from the UK are given in the *British National Formulary* (BNF) and reflect guidelines agreed by UK malaria specialists. There are specific recommendations by country, and the reader is referred to the BNF for this detail.

ANTIMALARIAL AGENTS

PYRIMETHAMINE

Pyrimethamine should not be used on its own today and is combined with a sulphonamide (sulfadoxine). The combination is sold under the name Fansidar™. It is not recommended for the prevention of malaria, but it is used for the treatment of *P. falciparum* malaria and can be used with or after quinine. It is not suitable for *P. vivax* infection.

■ MECHANISM OF ACTION

Pyrimethamine, like the sulphonamides, antagonises folic acid synthesis (see Chapter 67). When pyrimethamine is used in conjunction with a sulphonamide, such as sulfadoxine, a synergistic effect is achieved. Pyrimethamine, being strongly bound to tissues, has a long half-life. Currently a pyrimethamine–sulfadoxine combination should be used only for the treatment of chloroquine-resistant malaria because of its potential toxicity. **Dapsone** is also a folate antagonist (see Chapter 69) and may be used in combination with pyrimethamine. Previously a pyrimethamine–dapsone combination was used for malaria prophylaxis, but this combination is no longer recommended in the UK.

◆ COMMON ADVERSE EFFECTS

With Fansidar, a drug eruption called Stevens–Johnson syndrome may arise in 1 per 11 000–25 000 patients. This is a potentially fatal cutaneous reaction and is one of the reasons why Fansidar is not used as a prophylactic. Other common side effects of pyrimethamine are headache, gastrointestinal disturbances and methaemoglobinaemia. Occasionally, agranulocytosis has been reported, and it may be judicious to perform blood counts at intervals during use of this drug. Depression of haemopoiesis can occur due to the antifolate activity. This can be reversed by giving folic acid, which does not interfere with the action of the drug.

✚ CLINICAL CONSIDERATIONS

In many parts of the world, antifolate resistance has developed to pyrimethamine. It is thus often combined with other antimalarials, usually a schizontocide to assist with antifolate resistance. Pyrimethamine is not recommended for malaria prophylaxis because of toxicity. It is taken with or after food.

CHLOROQUINE AND HYDROXYCHLOROQUINE

Chloroquine is one of the most commonly used drugs for both prophylaxis and treatment of acute attacks of malaria. It is used where the risk of chloroquine-resistant falciparum malaria is still low. It is also used with proguanil when chloroquine-resistant falciparum malaria is present, but this regimen may not give optimal protection. Chloroquine is no longer recommended for the treatment of falciparum malaria or if the infecting species is unknown, because of widespread resistance. It is still recommended for the treatment of benign malarias. **Hydroxychloroquine** is similar to chloroquine in its action.

■ MECHANISM OF ACTION

The mechanism of action is to suppress DNA replication and transcription in the parasite, an action like that of many chemotherapeutic agents. Plasmodial parasites depend on the breakdown products of the haemoglobin molecule for most of their energy. Thus, any drug that suppresses the production of enzymes that do this will be particularly effective.

◆ COMMON ADVERSE EFFECTS

For short-term use, chloroquine has few associated problems. With long-term therapy, a serious problem is neuroretinitis, which can lead to blindness. (Chloroquine has an affinity for retinal and corneal cells.)

✚ CLINICAL CONSIDERATIONS

Chloroquine treatment is usually continued for only 2 days. This is a short period of treatment compared with that of most other antimicrobial substances.

Chloroquine has an anti-inflammatory action. This can create problems when used as a prophylactic and the patient also becomes infected with a chloroquine-resistant strain of the parasite. Because of the drug's anti-inflammatory action, suppression of the symptoms may occur. This can have dire consequences, as active treatment may not be sought quickly enough.

Because of its anti-inflammatory action, chloroquine and its derivatives are sometimes used to treat rheumatoid arthritis.

Preventive chloroquine is taken at the same time on the same day each week. It is started 1 week before entering and continued for 1 week after leaving a malaria-affected area. Visual acuity should be assessed before and following a course of therapy.

PRIMAQUINE

■ MECHANISM OF ACTION

Although primaquine is structurally very similar to chloroquine (primaquine is an 8-aminoquinoline whereas chloroquine is a 4-aminoquinoline), its mechanism of action is quite different. The major site of action of primaquine appears to be on the mitochondria, where it suppresses their normal role in cell metabolism. Primaquine's action is best against the hypnozoites, although it can affect the schizonts and gametocytes as well. It has no action on the asexual erythrocytic forms. As it preferentially kills the hypnozoites, it is useful in preventing relapses in *P. vivax* and *P. ovale* infections. It can also suppress *P. falciparum* infections. It is used to eliminate the liver stages of *P. vivax* and *P. ovale* following chloroquine treatment.

◆ COMMON ADVERSE EFFECTS

The adverse effects of primaquine are similar to those of chloroquine, as one would expect owing to their similar chemical structure. One important adverse effect of primaquine is that it can cause haemolytic anaemia in patients with erythrocyte glucose-6-phosphate dehydrogenase deficiency. It was noted in the Vietnam war that when primaquine–chloroquine combination therapy was used in soldiers, they often felt quite ill. Thus, perhaps this combination should not be used unless it is considered essential for either treatment or prophylaxis.

✚ CLINICAL CONSIDERATIONS

Primaquine should be taken with food to avoid gastric irritation. A complete blood count is required before primaquine therapy in order to ensure the patient does not have methaemoglobinaemia or haemolytic anaemia.

PROGUANIL

■ MECHANISM OF ACTION

Proguanil is a prodrug, but it also has intrinsic plasmodicidal properties of its own, inhibiting pyrimidine synthesis and thus nucleic acid synthesis in the parasites. Proguanil, like pyrimethamine, is also a folate inhibitor. Because of its short half-life, proguanil must be given daily. It is usually used with chloroquine, and occasionally alone, for the prohylaxis os malaria.

◆ COMMON ADVERSE EFFECTS

Proguanil has a remarkably low incidence of adverse effects and is safe in pregnancy, but there is a high rate of *P. falciparum* resistance to proguanil in Africa and South-East Asia. The most common, but still rare, adverse effects

of proguanil are gastrointestinal disturbances, headache, vertigo, rash and hair loss.

✚ CLINICAL CONSIDERATIONS

Proguanil is commenced 1 week before entering and continued for 4 weeks after leaving a malaria-affected area. It is taken after food to prevent gastric irritation.

ATOVAQUONE

In combination with proguanil, atovaquone is excellent in the treatment of acute malaria, due to their synergism of action (see Chapter 15).

■ MECHANISM OF ACTION

Atovaquone inhibits the electron-transfer chain in the parasite's energy-producing reactions, which are required for all biosynthetic pathways, hence the synergism. Several trials of this combination have shown 94–100 per cent cure rates in different tropical countries – this is vastly superior to all other current malaria treatments.

◆ COMMON ADVERSE EFFECTS

When used in combination, the individual dose of each drug is low and adverse effects are uncommon. They may include gastrointestinal upset, rash, headache, fever and cough, however.

✚ CLINICAL CONSIDERATIONS

Atovaquone is very fat-soluble. As dietary fat increases its absorption, the drug is taken with food to enhance its bioavailability. Tablets should not be crushed. Atovaquone is available as a suspension for paediatric use.

MEFLOQUINE

When mefloquine was introduced in the early 1990s, the malarial parasites had not developed any appreciable resistance to it. It was advised that mefloquine be used only in areas where both chloroquine and antifolate resistance had been demonstrated, especially as a prophylactic. Resistance to this drug is fast becoming widespread, however, especially in South-East Asia. Mefloquine should not be used for treatment if it has been used for prophylaxis.

■ MECHANISM OF ACTION

The mechanism of action of mefloquine is unclear. Unlike the related drugs of the chloroquine group, it does not bind to DNA. There are two possibilities for its mode of action. It binds to the erythrocyte membrane and so it may prevent the parasite from gaining access to the cell. It also binds to haematin, a breakdown product of haemoglobin that accumulates in the plasmodial cell, and in doing so may cause lethal membrane damage. The drug is effective against blood schizonts and the sexual blood forms of *P. vivax*, *P. malariae* and *P. ovale*, but not against the mature gametocytes of *P. falciparum*. The exo-erythrocytic hepatic forms and the sporozoites are unaffected. The drug is useful for both prophylaxis and treatment and, like pyrimethamine, can be given weekly.

◆ COMMON ADVERSE EFFECTS

Adverse effects of mefloquine are usually mild, including dizziness, nausea, diarrhoea and headache. As it is structurally related to quinine, it should not be used in patients with cardiac disease or in pregnant women, unless there is no alternative. There is a slight risk of major psychiatric illnesses developing with mefloquine use, and doctors, nurses, patients and their relatives should be on guard to note any developing mental health problems. The patient information leaflet should always be provided when the drug is dispensed. Mefloquine should not be used in pregnancy.

✚ CLINICAL CONSIDERATIONS

When using mefloquine as a prophylactic, administer it at the same time and on the same day of the week. Preferably start mefloquine 2.5 weeks before entering and continue for 4 weeks after leaving a malaria-affected area. As this medication can cause neurological adverse effects, such as paraesthesia, delirium and stupor, patients may experience difficulties in performing daily activities for up to 3 weeks after a dose. The drug should not be used in anyone with known neuropsychiatric problems, including depression.

QUININE

Quinine is the oldest of all antimalarial drugs. It is obtained from the bark of the cinchona tree. Quinine is an ingredient of tonic water, leading to the myth of gin-and-tonic being prophylactic against malaria and explaining its popularity in tropical countries. (There is far too little quinine in tonic water, however, to have any therapeutic effect.)

Quinine has also been used as an abortefacient by backstreet abortionists, but not always successfully: even with lethal doses, the uterus may not respond as desired.

The optical isomer of quinine, quinidine, is an antidysrhythmic (see Chapter 48). Quinine also has this property in high doses, although it is not used as such. Because of this antidysrhythmic effect, care must be taken when quinine is administered to patients with abnormal cardiac rhythm. Quinine has a mechanism of action similar to that of chloroquine, to which it is related. Quinine is not used much today in the treatment of malaria, except perhaps parenterally in cases of cerebral falciparum malaria. Cerebral malaria occurs when the parasitaemia is so severe that the brain capillaries become blocked, causing agonising headache, convulsions and death. The convulsions can be prevented with **phenobarbitone** and treated with **diazepam**. Occasionally, oral quinine is combined with other antimalarials to suppress attacks of malaria.

◆ COMMON ADVERSE EFFECTS

Quinine has some adverse effects that have been given specific names. One is cinchonism, which has among its symptoms tinnitus and visual disturbances. Quinidine can also cause these effects. The other adverse effect is blackwater fever, in which haemolysis occurs, causing pyrexia and blood pigments to appear in the urine (hence the name).

✚ CLINICAL CONSIDERATIONS

During quinine therapy, it is important to monitor blood glucose levels, blood pressure, visual acuity and cardiac rate and rhythm. Quinine is not used for prophylaxis because of the high incidence of adverse effects. Overdose of quinine may cause sudden blindness and fatal cardiac dysrhythmias.

DOXYCYCLINE

Doxycycline is discussed in Chapter 68. Unlike most other antibiotics, it is effective in malaria prophylaxis. Its mechanism of action in plasmodia is very different from that in bacteria. It acts in a similar way to primaquine, inhibiting normal mitochondrial function. The tetracyclines are active only against the pre-erythrocytic and asexual blood stages of *P. falciparum*. They have less activity against those stages of *P. vivax*.

One advantage of doxycycline over all other antimalarial drugs is that it has been advocated as a prophylactic against some forms of travellers' diarrhoea, an illness common in malarious countries.

✚ CLINICAL CONSIDERATIONS

Doxycycline is taken 2 days before entering and continued for 4 weeks after leaving a malaria-affected area. It is consumed with a meal and a large glass of fluid. The patient should be advised not to lie down immediately afterwards. As doxycycline may cause photosensitivity, instruct the patient to use a sun screen and wear protective clothing.

ARTEMETHER AND LUMEFANTRINE

A promising pharmacognostic Chinese discovery is a compound called artemisinin (an ingredient of sweet wormwood, *Artemisia annua*), and its derivatives. The derivative **artemether** is available in the UK on a named-patient basis. It is used in combination with **lumefantrine** for the treatment of acute uncomplicated falciform malaria.

■ MECHANISM OF ACTION

The artemether–lumefantrine combination acts as a blood schizontocide. The preparation prevents the breakdown of haem into a non-toxic pigment within the malarial parasite. The toxic intermediate is deadly to the parasite. The drugs also inhibit nucleic acid synthesis. The combination is more effective than either agent alone.

◆ COMMON ADVERSE EFFECTS

Common adverse effects include headache, fever, dizziness and asthenia. Serious adverse effects that have been reported include haemolytic anaemia, hepatitis and cardiac dysrhythmia associated with QT prolongation.

✚ CLINICAL CONSIDERATIONS

Patients should be monitored for signs of anaemia and liver impairment. Electrocardiographic (ECG) monitoring is recommended for patients with pre-existing symptomatic dysrhythmias and patients taking other drugs that prolong the QT interval, e.g. certain antidysrhythmic agents and antibacterials. This preparation should not be given concurrently with other antimalarial drugs.

CLINICAL MANAGEMENT

Antimalarial drugs

For the clinical management of tetracyclines, see Chapter 68.

Assessment

- Assess the patient for history of liver disease, blood disorders, neurological conditions and severe gastrointestinal disease. Exercise caution when using antimalarial drugs in these conditions.

Planning

- The patient will be free of the manifestations of malaria.

Implementation

- Monitor the patient's hearing, especially if taking quinine or chloroquine. These drugs may affect the eighth cranial nerve.
- Monitor the patient on chloroquine for visual changes.
- Monitor the patient for manifestations associated with cinchonism that occur with regular quinine use. Manifestations include tinnitus, dizziness, visual problems, gastrointestinal irritation and headache.
- Monitor for haematological effects that may occur in patients on quinine, including thrombocytopenia, agranulocytosis and haemolytic anaemia.
- Patients on long-term therapy should have regular full blood examinations and liver function tests.
- Monitor urinary output and liver enzyme levels to determine the patient's ability to metabolise and excrete the drugs.
- Monitor the patient for manifestations of toxicity, including convulsions, drowsiness, visual disturbances, headaches, and cardiac or respiratory arrest.
- Administer oral doses after meals to prevent gastric irritation.
- If using a pyrimethamine–dapsone combination, undertake regular full blood examinations during prophylaxis. This combination may cause severe granulocytopenia and immune suppression and should not be used for malaria prophylaxis unless other agents have been contraindicated.
- If using a pyrimethamine–sulfadoxine combination, monitor for Stevens–Johnson syndrome and toxic epidermal necrolysis during treatment of chloroquine-resistant malaria.

Patient teaching

- Advise patients travelling to malaria-infested countries to take prophylactic doses of antimalarial therapy before leaving, during the trip and after their return. Usually prophylaxis commences about 1 week before entering and continues for approximately 4 weeks after leaving a malarious area. Prophylaxis should be taken regularly at the same time and on the same day each week.
- Advise the patient to see a doctor if a febrile illness develops within 12 months of possible exposure.
- Advise the patient to avoid mosquito bites by using insect repellants and wearing protective clothing.
- Advise the patient to avoid alcohol while taking these drugs.
- Caution the patient to avoid driving and operating heavy machinery, and to notify the doctor, if visual changes occur.
- Teach the patient to watch out for manifestations of blood dyscrasias, including malaise, fever, sore throat, pallor, and unexplained bruising or bleeding.
- Advise the patient to take oral antimalarial drugs after meals to prevent gastric irritation.
- Advise patients on chloroquine to have regular eye examinations and to report visual changes immediately.
- Inform the patient that an additional dose of antimalarial is required if an oral dose is vomited within 1 hour of administration.

Evaluation

- Evaluate the effectiveness of drug therapy in preventing or treating malaria, without producing adverse effects.

SUMMARY

- Malaria is caused by various parasites of the *Plasmodium* genus and is transmitted to humans by the *Anopheles* mosquito.
- Malaria is a major cause of death in the developing world.
- There are a number of antimalarial drugs available that affect the parasites' viability or progression through the lifecycle.
- Prophylaxis against malaria is advised when entering an area endemic with malaria.
- Treatment and prophylaxis of malaria are becoming increasingly problematic because of resistance to most of the currently used drugs.

1. What is another use of chloroquine, apart from the prophylaxis and treatment of malaria?
2. What might be a problem of long-term treatment with chloroquine?
3. What is blackwater fever?
4. What precautions should one take on a visit to a malarious area?
5. What antimalarials should be avoided in pregnancy?
6. What type or types of malaria can cause recurrences?
7. What is a hypnozoite, and what drug or drugs are effective against it?
8. What is the perennial problem that occurs with the use of antimalarial drugs in general?
9. What is the schedule for the administration of chloroquine when used for prophylactic purposes?
10. What short-term adverse effects are commonly observed with antimalarial drugs?
11. What long-term adverse effects are observed with antimalarial drugs?
12. Why are ophthalmic examinations required at regular intervals during long-term therapy with chloroquine or hydroxychloroquine?
13. Before commencing a patient on quinine, what aspects of assessment are important? Explain.

72 DRUG SUMMARY TABLE: ANTIMALARIAL DRUGS

FAMILY NAME	GENERIC NAME	TRADE NAME(S)
Antimalarial agents	Artemether + lumefantrine	Riamet
	Atovaquone	Wellvone
	Chloroquine	Avloclor
		Nivaquine
	+ Proguanil	Paludrine/Avlocor
	Doxycycline	Vibramycin
		Vibramycin-D
	Mefloquine	Lariam
	Primaquine	
	Proguanil	Paludrine
	+ Atovaquone	Malarone
	Pyrimethamine	Daraprim
	+ Sulfadoxine	Fansidar
	Quinine	

ANTIVIRAL DRUGS

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CHAPTER SEVENTY-THREE

OBJECTIVES

After completing this chapter, the reader should be able to:

- **discuss the nature of viruses and viral infections;**
- **discuss the use, mechanism of action and problems associated with each of the drugs used to treat or prevent the following viral diseases:**
  - **influenza;**
  - **herpes;**
  - **HIV/AIDS and associated infections;**
  - **miscellaneous viral infections.**

KEY TERMS

Epstein–Barr virus
Hepatitis
Herpes infections
HIV/AIDS infections
Influenza
Respiratory syncytial virus

VIRUSES ARE INTRACELLULAR, OBLIGATE, PARASITIC microorganisms – if indeed they can be termed organisms, as they do not fit the normal description of life. Perhaps it is better to think of viruses as infectious agents that enter cells and interfere with their normal function. A virus is not a cell but a strand of either DNA or RNA, which has a protein coat and sometimes a lipid envelope. There is no cell membrane or cytoplasm. When a virus particle, or virion, enters a cell, it uses the host cell's enzymes to synthesise more of the viral nucleic acid and the components of its extranucleic structures. The viral nucleic acid can code for specific viral enzymes. A virus employs at least some of the existing metabolic machinery in the host cell for its own use. It is, therefore, very difficult to synthesise a drug that can destroy the virus without affecting the host cell. This is the principal reason for the existence of so few antiviral substances. Most antiviral agents exploit the differences that exist between viral nucleic acids or enzymes and the nucleic acids and enzymes of the host.

ANTIVIRAL AGENTS

Influenza

Influenza is often mistakenly confused with the common cold. Unlike the common cold, influenza can be treated with antiviral drugs and can be immunised against. Influenza is a much more serious viral infection than the common cold and epidemics of influenza frequently result in deaths, mainly in infants and elderly people. The virus that causes influenza mutates rapidly, and drug manufacturers continually develop new vaccines to deal with this. Influenza, like the common cold, is a respiratory infection, and although there are some common symptoms such as cough and headache, it is symptoms such as fever, myalgia and prostration that help to clinch the diagnosis. Symptomatic treatment of influenza is similar to that for the common cold (see Chapter 52). There are two types of influenza virus – A and B. The classification is based on which human membrane glycoprotein the virus uses to infect host cells. The National Institute of Health and Clinical Excellence (NICE) has recommended that currently available drugs are not a substitute for vaccination, which remains the most effective way of preventing illness from influenza.

AMANTADINE

■ MECHANISM OF ACTION

Amantadine is dealt with in Chapter 36 in the discussion of anti-parkinsonian drugs. Amantadine was used as an antiviral before the serendipitous find that a patient with Parkinson's disease being treated for influenza had a noticeable improvement in tremors.

Amantadine is a very specific antiviral, as it is active only against the Asian variety of the influenza virus. It is successful mainly as a prophylactic rather than as a cure. When a virus enters a cell, and before it can proceed with its multiplication, it must first uncoat itself. Amantadine appears to prevent the uncoating procedure, and this mechanism of action helps to show why it acts mainly as a prophylactic. It is also suggested that amantadine may prevent viral penetration. The success rate can be in the order of 90 per cent in preventing influenza infections.

◆ COMMON ADVERSE EFFECTS

As discussed in Chapter 36, amantadine has many adverse effects, and therefore it is not used routinely in the prevention of influenza. When used in elderly people, the dose is normally half that needed by a younger person because the drug is excreted mainly unchanged by the kidneys; if renal output is impaired, blood concentrations rise rapidly to toxic levels.

✚ CLINICAL CONSIDERATIONS

Amantadine should be used cautiously in older patients, and in patients with seizure disorders, heart disease, peripheral oedema, hepatic disease and renal impairment. If postural hypotension occurs, instruct the patient not to stand suddenly from a lying position or to change positions too quickly. Amantadine is not recommended in current NICE guidelines for post-exposure prophylaxis, seasonal prophylaxis or treatment of influenza.

ZANAMIVIR

Zanamivir is an antiviral drug useful in the treatment of influenza A and B. It should be administered within 48 hours of the initial symptoms. The earlier the administration, the better the results.

■ MECHANISM OF ACTION

The influenza virus affects only the superficial cells of the respiratory tract. Like all virus particles, it has to enter the cells in order to induce an infection. The influenza virus uses a viral enzyme, neuraminidase, to penetrate the cells. Zanamivir is a specific inhibitor of neuraminidase and thus prevents viral penetration. In order to reach the superficial cells of the respiratory tract, zanamivir must be given as an aerosol, using a specifically designed diskhaler. This can be life-saving in susceptible individuals.

◆ COMMON ADVERSE EFFECTS

Inhaled zanamivir has generally been tolerated well, with acute bronchospasm being reported only rarely. Other reported effects may be caused by the infection rather than the drug and include nasal symptoms, gastrointestinal symptoms, headache and cough. Hypersensitivity reactions, including oropharyngeal oedema and severe rashes, occur rarely.

✚ CLINICAL CONSIDERATIONS

Zanamivir is usually given twice a day for 5 days. It significantly reduces the term of the infection by up to 3 days. The patient must be advised to read the instructions for the diskhaler inhalation device carefully. If the patient has a respiratory disorder that requires a bronchodilator, the bronchodilator should be used before zanamivir. The full 5-day course of treatment should be completed, even if the patient is starting to feel better and symptoms have improved. Treatment should be commenced no later than 48 hours after the onset of infection in order to obtain maximum benefit. This preparation is not recommended for routine prophylaxis against influenza.

OSELTAMIVIR

Oseltamivir is similar in action to zanamivir but can be given orally. Oseltamivir is slightly better than zanamivir in warding off an attack of influenza, but the former has a greater potential for adverse effects, with transient vomiting and diarrhoea being relatively common.

✚ CLINICAL CONSIDERATIONS

Oseltamivir should be taken no later than 48 hours after the onset of infection for maximum benefit. NICE recommends that this drug should not be used for prophylaxis against influenza. Instead, it is used for post-exposure prophylaxis in at-risk adults and adolescents over age 13 years who are not protected effectively by influenza vaccine. Prophylaxis is also recommended for residents of care establishments, regardless of whether they have been vaccinated against influenza, who should commence oseltamivir within 48 hours if influenza-like illness is present in the establishment.

HIV infections

The human immunodeficiency virus (HIV), which results in acquired immunodeficiency syndrome (AIDS), is caused mainly by two viruses, HIV-1 and HIV-2. HIV-1 is found worldwide, whereas HIV-2 infections are most common in parts of Africa and India. The antiviral drugs used in the suppression of HIV are effective mostly against the HIV-1 strain. The virus infects the CD4 cells (a group of helper T-lymphocytes), thus decreasing the effectiveness of the cell-mediated immune systems. This makes the patient with AIDS more susceptible to other infections, caused mainly by protozoans, fungi and other viruses; it is these secondary infections that usually result in death. It is important to note that not all individuals infected with HIV develop AIDS, but they do remain carriers of the virus.

Most drugs used to suppress HIV are of two types: reverse transcriptase inhibitors and HIV protease inhibitors. The viral enzymes reverse transcriptase and protease are more susceptible than human enzymes to AIDS drugs. Humans do not have the reverse transcriptase enzyme; however, the enzyme inhibitors can affect other enzymes involved in human nucleic acid metabolism. A more recent type of drug that inhibits HIV from fusing to the host cell has been licensed for managing infection that has failed to respond to a regimen of other antiretroviral drugs.

REVERSE TRANSCRIPTASE INHIBITORS

Most reverse transcriptase inhibitors are nucleoside analogues, i.e. synthetic precursors of nucleic acids.

ZIDOVUDINE

Zidovudine is often known by the abbreviation AZT, which stands for azidothymidine (its simplified chemical name). Zidovudine was originally synthesised in the 1960s as a cytotoxic drug for use in tumour chemotherapy, but it was never used as such. When the AIDS epidemic occurred in the 1980s, zidovudine was reinvestigated and found to be effective in controlling the disease to some extent. But, like all antivirals, it is not curative.

■ MECHANISM OF ACTION

Zidovudine is a prodrug and is converted by a series of kinase reactions into a triphosphate metabolite. Its mechanism of action is fairly specific to the group of viruses known as retroviruses (hence, the proprietary name of the drug – Retrovir™). The retroviruses use an enzyme called reverse transcriptase, which causes transcription from RNA to DNA instead of the usual DNA to RNA. It appears that this enzyme can incorporate zidovudine triphosphate in the DNA. The DNA is then rendered defective and non-functional. Host DNA polymerase enzymes are affected only by very large amounts of this drug, in the order of 100-fold higher concentrations. A problem with zidovudine is its very short half-life, of approximately 1 hour. This means that the drug must be given every 4 hours, day and night, for the rest of the patient's life. Zidovudine is also very expensive.

◆ COMMON ADVERSE EFFECTS

Zidovudine has some severe adverse effects, including bone-marrow suppression. Blood transfusions are needed in a fair proportion of treated individuals. Considering the nature of the disease being treated, bone-marrow suppression is not a desirable consequence, but remission from the disease is usually preferential. Even though AIDS cannot be cured, zidovudine prolongs and improves the quality of life of people with AIDS. Combined with **aciclovir**, zidovudine has proven even more effective in the suppression of HIV.

The long-term survival rates of people with AIDS has become so good with newer treatment regimens that the development of the associated symptoms is no longer the death sentence it once was.

✚ CLINICAL CONSIDERATIONS

Zidovudine commonly causes headache, which can be controlled with paracetamol. Neutropenia commonly occurs about 2–4 weeks after starting treatment, and anaemia commonly occurs 6–8 weeks after starting treatment. It is important therefore to monitor these effects and avoid giving concomitant myelosuppressive medications. Blood transfusions may be required, depending on the severity of anaemia and the low blood count. Zidovudine should be used cautiously in individuals with hepatic and renal problems. The drug should be taken on an empty stomach. The patient should be advised to take the drug when sitting upright in order to avoid oesophageal irritation.

STAVUDINE

Stavudine, like zidovudine, is a thymidine derivative, and, after similar metabolic processes, inhibits viral reverse transcriptase. The adverse effects, of which patients should be warned, are similar to those of zidovudine.

✚ CLINICAL CONSIDERATIONS

Peripheral neuropathy experienced with stavudine usually responds to prompt withdrawal of the drug. It may be possible to recommence stavudine at a lower dose without recurrence of neuropathy. Elevated liver transaminase levels usually resolve a few weeks after stopping treatment. Patients should be monitored for the elevated enzyme levels that occur in pancreatitis. Stavudine may be taken with or without food.

DIDANOSINE AND TENOFOVIR

■ MECHANISM OF ACTION

Didanosine, a derivative of the purine inosine, can inhibit the replication of the HIV virus that has become resistant to zidovudine. Its mechanism of action is similar to that of zidovudine. Didanosine has a comparatively long half-life, which enables once- or twice-daily dosing. **Tenofovir** also has a similar mechanism of action to zidovudine and is used in combination with other antiviral agents.

◆ COMMON ADVERSE EFFECTS

The major adverse effects of these drugs are peripheral neuropathies and pancreatitis, which may be fatal. These effects are more likely at high doses. Didanosine is minimally toxic to bone marrow. Clinical trials indicate that tenofovir treatment is tolerated well. There is a risk of neutropenia and elevated liver enzymes during therapy.

✚ CLINICAL CONSIDERATIONS

Didanosine buffered tablets and enteric-coated capsules should be taken on an empty stomach about 30 minutes before food. Administering didanosine with food can decrease absorption by 50 per cent. Enteric-coated capsules should not be opened. Chewable tablets may be crushed and dispersed in water. The paediatric powder must be prepared by a pharmacist beforehand; then needs to be constituted with purified water and diluted with an antacid to a final concentration of 10 mg/ml. This mixture is stable for up to 30 days in a refrigerator. Patients should be monitored regularly for peripheral neuropathy, as shown by numbness and burning in the hands and feet, and investigated for pancreatitis, as shown by a rise in serum amylase levels. Patients should be observed for visual changes during didanosine therapy. There is evidence that tenofovir may increase the blood levels of other antivirals by interfering with their renal excretion. Liver enzyme levels and neutrophil levels should be monitored during treatment.

LAMIVUDINE

Lamivudine, as well as controlling the replication of HIV, helps to control the replication of the hepatitis B virus at a lower dosage, thus minimising adverse effects. Lamivudine is a prodrug preferentially activated in viral-infected cells, where it inhibits DNA polymerase, thus controlling the infection.

✚ CLINICAL CONSIDERATIONS

When using lamivudine, liver enzymes should be monitored for at least 4 months after discontinuation of therapy in patients with chronic hepatitis B. Platelet count and full blood count should be monitored during therapy. This drug should not be used in children with a history of pancreatitis or with risk factors for developing pancreatitis.

ZALCITABINE

■ MECHANISM OF ACTION

Zalcitabine is a synthetic analogue of cytidine that is incorporated into the viral RNA. By introducing a false base into the nucleic acid chain, zalcitabine causes the reverse transcriptase to be inhibited. This drug has proven to be a potent inhibitor of HIV replication in human T-cells in vitro. In vivo, zalcitabine has not proven as beneficial as zidovudine in terms of patient survival or in the suppression of opportunistic infections. Zalcitabine may be of use in patients who are unresponsive to or unable to take zidovudine. It may be combined with zidovudine, but little is known about the effectiveness of this combination yet.

◆ COMMON ADVERSE EFFECTS

Zalcitabine causes a high incidence of peripheral neuropathies but, as it is unable to cross the blood–brain barrier, central effects are unlikely.

✚ CLINICAL CONSIDERATIONS

Zalcitabine may produce peripheral neuropathy. The patient should be advised to contact their doctor if they experience numbness and burning in the hands and feet. If neuropathy occurs, treatment may be stopped and then recommenced at half the dose. This drug should be taken on an empty stomach. Zalcitabine should be used cautiously in patients with liver failure and in those with a history of pancreatitis or heart disease.

ABACAVIR

Abacavir, another reverse transcriptase inhibitor, works synergistically with lamivudine and zidovudine. The adverse-effects profile is similar to that of other reverse transcriptase inhibitors, but it has the tendency to cause serious hypersensitivity reactions.

✚ CLINICAL CONSIDERATIONS

Hypersensitivity reactions occur in about 4 per cent of patients taking abacavir. If these reactions occur, treatment

should be stopped immediately. Therapy should not be recommenced after a hypersensitivy reaction because life-threatening hypotension can occur. Symptoms of hypersensitivity include fever, rash, diarrhoea and abdominal pain.

NEVIRAPINE

■ MECHANISM OF ACTION

Nevirapine is a non-nucleoside inhibitor that non-competitively binds to the reverse transcriptase enzyme to inactivate it completely.

◆ COMMON ADVERSE EFFECTS

The main adverse effect is a rash that, if severe, warrants withdrawal of the drug, as fatal skin reactions may occur.

✚ CLINICAL CONSIDERATIONS

Nevirapine commonly produces a rash, which tends to disappear after continuous treatment. If the rash becomes more severe, or is associated with facial oedema, renal dysfunction, elevation in liver enzymes or muscle aches, nevirapine treatment should be stopped. Liver function should be monitored regularly during therapy. Use of nevirapine should be avoided in patients with impaired liver function.

EFAVIRENZ

■ MECHANISM OF ACTION

Efavirenz is another non-nucleoside reverse transcriptase inhibitor, active against the subtype HIV-1 but not HIV-2. It is generally given concurrently with other anti-HIV drugs.

◆ COMMON ADVERSE EFFECTS

Rash, central nervous system (CNS) disturbances, including dizziness, insomnia, somnolence, psychiatric symptoms and fits, gastrointestinal upsets, headache and hepatic effects have all been noted.

✚ CLINICAL CONSIDERATIONS

Efavirenz produces CNS effects, such as lethargy, tiredness and impaired concentration, which tend to resolve after 2–4 weeks of treatment. Alcohol should be avoided. The daily dose can be given at bedtime if central symptoms persist. A rash that commonly appears at the start of treatment generally resolves after a few weeks. Efavirenz treatment has been associated with an increased plasma cholesterol concentration.

PROTEASE INHIBITORS

■ MECHANISM OF ACTION

The viral RNA codes for a polyprotein that is cleaved by the viral protease into the active enzymes that the virus needs for complete replication. Inhibition of this protease therefore renders the virus inactive. The protease inhibitors are **saquinavir**, **amprenavir**, **atazanavir**, **fosamprenavir** (a prodrug of amprenavir), **indinavir**, **lopinavir**, **nelfinavir**, **ritonavir** and **tipranavir**.

◆ COMMON ADVERSE EFFECTS

The main adverse effects are gastrointestinal, and include nausea, vomiting and diarrhoea. Indinavir may also cause renal calculi. All inhibit the cytochrome P450 hepatic enzymes, and so drug interactions are common. As many of the reverse transcriptase inhibitors have short half-lives, combining them with a potent cytochrome P450 inhibitor can prolong the half-life and lead to better dosage compliance. Some drug regimens are designed with this in mind. Long-term use may lead to the unusual state of dysmorphic adiposity (abnormal fat disposition). This lipodystrophy can be quite disfiguring, for example hump back or abdominal distension due to abdominal adiposity but lack of subcutaneous fat elsewhere, giving the patient the appearance of a person with kwashiorkor, a form of malnutrition. Some instances of lipodystrophy have led patients to discontinue treatment, resulting in a rapid, and perhaps irreversible, drop in CD4 cells.

✚ CLINICAL CONSIDERATIONS

It is normal to use combination therapy in AIDS, even in asymptomatic patients, in order to reduce the plasma viral concentration as much as possible and to keep the CD4 count as high as possible. The normal regimen is two reverse transcriptase inhibitors and one protease inhibitor. The drug combination may be changed according to the patient's response and the plasma viral concentration. All of these drugs used in the treatment of AIDS are not curative. The virus can become resistant to the drugs used, or another infection may become overwhelming, meaning that the individual does not respond to treatment. Either alone or in combination, however, these drugs help to prolong and improve the quality of life of people with AIDS.

Patients on protease inhibitors may experience a redistribution of body fat, including a buffalo hump, peripheral wasting and central obesity. This effect is similar to that found during long-term corticosteroid therapy. Protease inhibitors may also cause spontaneous bleeding in some patients with haemophilia.

During amprenavir treatment, patients should avoid a high-fat diet, because it may decrease the absorption of the drug. Patients taking amprenavir should be advised that it contains a large amount of vitamin E. Any further supplementation with vitamin E may affect the blood coagulation process. This drug should be used cautiously in patients with liver impairment, diabetes, known sulphonamide allergy or haemophilia.

Nephrolithiasis (kidney stones) may occur during indinavir therapy, which generally resolves with temporary discontinuation of treatment and adequate hydration. This effect is not usually associated with kidney dysfunction. Indinavir is taken with water on an empty stomach. The patient should be advised to drink plenty of fluids during indinavir therapy in order to prevent nephrolithiasis.

Lopinavir is available in combination with ritonavir and should be taken with food for maximal absorption. If the oral solution is used, then it must be stored in a refrigerator.

Nelfinavir is taken with a meal or light snack for optimal absorption. The powdered dose is mixed with water or milk and consumed within 6 hours of reconstitution. If the patient has difficulty swallowing tablets, these may be dispersed in water. Ensure an adequate fluid intake in order to avoid nephrolithiasis.

Ritonavir is taken with meals to prevent gastric irritation. The oral liquid preparation may be mixed with milk or nutritional drinks to improve the taste. The oral solution and capsule preparations may be stored at room temperature. Ritonavir should be used cautiously in patients with hepatic dysfunction.

Combination therapy is recommended with saquinavir to prevent resistance. Saquinavir is taken with or after food to prevent gastric irritation. Before commencing and during therapy, full blood count, platelet count, electrolyte, uric acid, liver enzyme and bilirubin levels should be evaluated. Grapefruit juice should be avoided with saquinavir, because it can intensify the drug's effects.

HIV FUSION INHIBITORS

■ MECHANISM OF ACTION

The HIV fusion inhibitor **enfuvirtide** may be the first of a new class of drugs that act by blocking fusion of HIV with cells, thereby blocking viral entry into the cell.

◆ COMMON ADVERSE EFFECTS

Local injection-site reactions occur in 98 per cent of patients, but therapy needs to be discontinued in only a few. Other common adverse effects include nausea, diarrhoea, constipation, abdominal pain, anorexia, taste disturbances and fatigue. An increased incidence of some bacterial infections, particularly pneumonia, has also been reported. Hypersensitivity reactions have occurred in some patients.

✚ CLINICAL CONSIDERATIONS

Good injection technique may help to reduce the occurrence of injection-site reactions. Patients with risk factors for pneumonia should be monitored closely. The drug should be discontinued if a systemic hypersensitivity reaction is observed that is clearly linked to enfuvirtide therapy.

Other antiviral agents

DNA POLYMERASE INHIBITORS

■ MECHANISM OF ACTION

Aciclovir (acyclovir) is a guanine derivative that acts as a prodrug. It must be phosphorylated before it becomes active. It is this property that makes aciclovir such a useful antiviral in the treatment of infections of herpes virus type I. If a cell is infected with this virus, the viral enzyme thymidine kinase is present in the cell. This enzyme converts aciclovir into aciclovir monophosphate. Other enzymes in turn convert this into aciclovir triphosphate, which is the active form of the drug. It then acts to inhibit the enzyme DNA polymerase, which is needed for DNA replication. This occurs only in infected cells, and much higher concentrations of the drug are needed to affect host DNA polymerase. The drug therefore selectively prevents viral replication without adversely affecting uninfected cells.

Aciclovir is most effective against the herpes simplex type I virus, but it does have deleterious effects on other viruses, such as herpes simplex type II, varicella, herpes zoster (shingles) and the Epstein–Barr viruses. As with many viral infections, the virus can cause a latent or dormant infection, which can recur at a later date. It appears that the virus 'goes into hiding', away from the body's immune system; when circumstances permit, the virus reappears, causing a clinical infection. **Famciclovir**, like aciclovir, is a prodrug and is converted into the active form, **peniciclovir**, within the body. The action of peniciclovir is identical to that of aciclovir, but the former has certain advantages as it is better absorbed from the gut and has a longer half-life than the active form of aciclovir. Together, these qualities mean less frequent dosing by the patient, resulting in better compliance, especially during long-term treatment. Famciclovir has less activity on the herpes simplex type II virus than on the type I virus. This may lessen its usefulness in the treatment of genital herpes, which is more commonly associated with the type II virus.

Famciclovir is particularly useful in the treatment of shingles. Treatment must be given within 72 hours of the appearance of the rash.

Valaciclovir is a derivative of the amino acid valine and aciclovir. Valaciclovir is, therefore, a pro-prodrug. It has a very high bioavailability and a high hepatic first pass and is converted into aciclovir. Thus, this drug can attain blood concentrations of aciclovir equivalent to those attained when aciclovir is administered parenterally, which is useful. As aciclovir probably has fewer adverse effects and drug interactions, valaciclovir may prove to be one of the best antiviral drugs for the treatment of herpes zoster, for the treatment and suppression of genital herpes, and for prophylaxis of cytomegalovirus (CMV) infection and disease in immunocompromised patients.

Like aciclovir, **ganciclovir** is a guanine derivative that can be used to treat CMV infections in immunocompromised individuals, such as people with AIDS. **Valganciclovir** is a valine derivative of ganciclovir that acts as a prodrug. **Cidofovir** is a cytidine derivative, which is also used for CMV infections in immunocompromised patients. These drugs are inhibitors of DNA polymerase, but they are 600–800 times more effective in inhibiting CMV DNA polymerase than the human enzyme.

◆ COMMON ADVERSE EFFECTS

As might be expected from the mode of action, famciclovir, valaciclovir and aciclovir have minimal adverse effects. Commonly observed side effects are headache, nausea and vomiting.

Ganciclovir and cidofovir often cause neutropenia and are potentially carcinogenic. Ganciclovir can induce aplastic anaemia. Hence, these drugs are used only in life-threatening infections. Cidofovir is nephrotoxic and should not be used in renal impairment or in combination with or after the use of nephrotoxic drugs. The concomitant use of **probenecid** helps to prevent nephrotoxic reactions.

✚ CLINICAL CONSIDERATIONS

In genital herpes, aciclovir increases the healing rate of the lesions and decreases the associated pain. It can be given orally or applied as an ointment. Topical aciclovir is useful for treating herpes infections of the eye and lips. It also can be given parenterally to treat herpes simplex encephalitis and in immunocompromised patients. As oral aciclovir has a comparatively low bioavailability, parenteral administration is often needed in severe viral infections.

During aciclovir therapy, it is important to ensure the patient drinks adequate fluids (at least 2.5 l/day) in order to prevent renal impairment. Tablets can be dispersed in water or swallowed whole. Use cautiously in patients with neurological disorders, renal disease and dehydration.

Aciclovir is on sale to the public for the treatment of cold sores.

Famciclovir also requires adequate fluid consumption to prevent renal impairment. It should be used cautiously in patients with renal and hepatic impairment. Both famciclovir and peniciclovir can be used in the treatment and prophylaxis of genital herpes. In the treatment of acute attacks, the quicker the therapy is initiated, the more successful the results; occasionally, the condition may be completely healed and the incidence of recurrences lessened. In patients with frequent recurrences, suppression can be obtained by continued treatment for several months. Failure of these drugs to produce a therapeutic effect can occur. With oral aciclovir, which is not absorbed well, missed tablets may lead to blood levels less than the minimum effective concentration. This can lead to ineffectiveness of the treatment, as can any cause of intestinal hurry. Resistance to aciclovir is an emergent cause of concern; this may also eventuate with famciclovir. Resistant cases can be treated with **foscarnet** (see below).

Oral ganciclovir must be taken with or after food to maximise absorption. This drug should be handled using cytotoxic precautions, as it is considered carcinogenic. Neutropenia and adverse renal effects can occur during the first few weeks of treatment; these effects are dose-dependent and reversible. Complete blood count, electrolyte levels and renal function should be monitored at baseline and during therapy.

Valaciclovir must be consumed with plenty of fluids to prevent renal impairment and should be used cautiously in patients with renal impairment. It is not recommended for use in patients with HIV infection or in recipients of bone-marrow or organ transplants.

Patients using cidofovir should be advised to drink plenty of fluids in order to prevent renal failure. Serum creatinine and urine protein concentrations should be measured within 48 hours before each dose. **Probenecid** is given before and following a cidofovir infusion to minimise the possibility of nephrotoxicity. Neutropenia should be monitored during therapy.

FOSCARNET

■ MECHANISM OF ACTION

Foscarnet has similar actions to aciclovir in that it directly inhibits the viral enzyme DNA polymerase and reverse transcriptase. This action occurs at concentrations lower than those required to inhibit normal cell growth. The compound is a broad-spectrum antiviral drug and is especially toxic towards the viruses of the herpes group, the Epstein–Barr virus and CMV. Administration is by intravenous infusion. The only recognised use for foscarnet is in the treatment of CMV infections in people with HIV infection and for aciclovir-resistant mucocutaneous herpes simplex virus infections in immunocompromised patients. Foscarnet is used as the trisodium salt.

◆ COMMON ADVERSE EFFECTS

Adverse effects often seen are convulsions, penile and vulval ulcerations (on excretion it has irritant properties), impaired renal function, disturbances in blood electrolyte levels and anaemia.

✚ CLINICAL CONSIDERATIONS

Ensure the patient drinks adequate fluids daily (at least 1.5 l) to prevent the onset of renal failure. Supplementation with calcium and magnesium may be needed to avoid electrolyte disturbances. Complete blood counts and electrolyte levels should be monitored regularly. The patient should be advised to wash well around the genital area after urinating and to notify the doctor if sores appear.

IDOXURIDINE

■ MECHANISM OF ACTION

Idoxuridine has an action similar to that of zidovudine: after being converted to the triphosphate, it is incorporated in the viral DNA to produce a defective strand. Unfortunately, this also happens with the host DNA, and so idoxuridine cannot be used in systemic infections. Its main use is in treating ocular viral infections, such as herpes simplex infections of the conjunctiva, cornea and eyelids. As the drug is unable to penetrate the tissues of the eye, it is of use only in very superficial lesions. Several proprietary preparations of this drug have been formulated, including ointment for the treatment of herpes simplex infections of the lips (cold sores). It is doubtful whether idoxuridine can penetrate the lip mucosa deeply enough to effect a remission from the infection, but it may help if the infection is treated in its very early stages, before a lesion is present but when a tingling sensation is felt in the lip area.

◆ COMMON ADVERSE EFFECTS

When applied to the eye, idoxuridine has been reported to produce corneal opacities occasionally. Local irritation, photophobia and itching can also occur.

✚ CLINICAL CONSIDERATIONS

Idoxuridine ointment should be applied at the first sign of tingling around the lips. A thin layer is applied to the affected area every hour on the first day and then every 4 hours until the lesion disappears. Avoid contact with mucous membranes during administration.

RIBAVIRIN

■ MECHANISM OF ACTION

Ribavirin is a synthetic nucleoside resembling guanosine. Like other such drugs, it is phosphorylated rapidly on entering living cells. One of these phosphorylated metabolites, the triphosphate, inhibits the influenza virus RNA polymerase without affecting various host cell polymerases. This derivative, as well as the monophosphate and the diphosphate, are remarkably inhibitory to the initiation and elongation of viral RNA molecules, and these actions greatly disrupt the formation of complete viral particles. Ribavirin is used clinically to treat respiratory infections in children caused by the respiratory syncytial virus (RSV). This is an extremely common infection in infants and young children; in most circumstances, symptoms not unlike those of the common cold and influenza result. In some children, however, especially those who are immunocompromised, RSV infection can be fatal. Ribavirin administered as an aerosol is an effective treatment for high-risk infants and children with RSV infections.

◆ COMMON ADVERSE EFFECTS

As this drug is administered by an aerosol method, there has been some concern regarding the risk of staff and visitors inhaling the drug and suffering from delayed adverse effects. There is no evidence that this is the case; however, the drug is teratogenic in rabbits, and pregnant women should be kept well away from patients undergoing active treatment with ribavirin. Many of the adverse effects of ribavirin involve both the respiratory and cardiovascular systems. These effects are almost certainly due to the infection itself or related to the individual's concurrent condition.

✚ CLINICAL CONSIDERATIONS

Thus far, there appear to be no problems with resistance of any virus to ribavirin. There have been studies showing that this drug given by either the oral or intravenous route is of some use in AIDS, hepatitis A and B, herpes infections, viral haemorrhagic fever, influenza, measles and varicella. Ribavirin in combination with **interferon alfa-2b** (see below) can be used to prevent relapses of chronic hepatitis C. In view of its apparent safety, its use may increase dramatically in the future.

Complete blood counts, electrolyte levels, serum creatinine and liver function should be monitored before starting oral treatment and then regularly during treatment. The rate and depth of breathing, and equality of entry into both sides of the lungs during inhalation therapy, should be assessed to determine lung function.

INTERFERONS

■ MECHANISM OF ACTION

Interferons are naturally occurring glycoproteins, produced by a wide variety of cells in the body in response to viral infections. When the interferons are released from virus-infected cells, they affect neighbouring cells and prevent the virus from entering these cells. Interferons also have macrophage-stimulating properties, which can help macrophages destroy virus-infected cells. This mechanism of action is useful in the treatment of certain cancers and as an immunostimulant (see Chapter 75). Several interferons have been isolated, and with the advent of recombinant DNA techniques their availability has improved. Interferon alfa has been used successfully in a nasal spray to prevent the common cold, and topically or intralesionally to treat genital warts. Interferon alfa-2b is available for the treatment of some malignancies and is also approved for the treatment of chronic hepatitis B and C (see ribavirin). **Interferon** beta-1b has been introduced in the treatment of multiple sclerosis and may modify the progression of the disease. **Interferon** delta-1b is used as

an adjunct in the reduction of infection in patients with chronic granulomatous disease. In these latter two cases, the drug may be acting as an immunomodulating agent rather than as an antiviral.

◆ COMMON ADVERSE EFFECTS

The interferons when used therapeutically have many adverse effects, such as severe influenza-like symptoms, CNS disturbances leading to depression and suicidal thoughts, and hepatic toxicity.

✚ CLINICAL CONSIDERATIONS

Flu-like symptoms can be minimised by administering interferon at bedtime and taking **paracetamol** beforehand. Complete blood counts and liver function should be monitored at baseline and every 3 months during therapy.

PALIVIZUMAB

The lower respiratory tract infection caused by RSV is potentially fatal in infants. **Palivizumab** is a monoclonal antibody against the causative virus and is used as a prophylactic in high-risk infants. It is ineffective once the symptoms of the infection appear.

◆ COMMON ADVERSE EFFECTS

Adverse effects are rare with palivizumab. Hypersensitivity has not been reported.

✚ CLINICAL CONSIDERATIONS

Palivizumab is given to high-risk infants born at 32–35 weeks' gestation and infants with bronchopulmonary dysplasia. If the infant is febrile, palivizumab administration should be delayed until the infant becomes afebrile.

CLINICAL MANAGEMENT

Antiviral drugs

Assessment

- Assess the patient for pregnancy and epilepsy. Use of antiviral drugs in these conditions is contraindicated.
- Assess elderly and debilitated patients for heart disease and renal disease. Exercise caution when using antiviral drugs in these conditions.
- Assess the patient's vital signs, including lying and standing blood pressures. Compare with subsequent observations.
- Assess patients prescribed didanosine for a history of pancreatitis.

Planning

- The patient will experience diminished or no manifestations of the viral infection, depending on the virus.

Implementation

- Monitor the patient for manifestations of blood dyscrasias arising from the use of the antiviral drugs, including unexplained bleeding and bruising, sore throat, fever, malaise and weakness.
- Monitor blood status by performing regular blood tests such as haemoglobin, platelet count and white blood cell count. These tests give some indication of whether the drugs have caused blood dyscrasias. Report abnormal results such as thrombocytopenia, leukopenia and low haemoglobin levels.
- Take lying and standing blood pressures. Note that amantadine and aciclovir may cause postural orthostatic hypotension.
- In general, administer oral drugs after meals to prevent gastric irritation. Administer oral didanosine, however, at least 30 minutes before meals to prevent decreased absorption.
- Advise the patient not to rise from a sitting or lying position too quickly, in order to prevent dizziness from postural hypotension. Assist the patient with ambulation (see Table 11.20 in Chapter 11 for other measures that can be implemented for postural hypotension).

Amantadine

- Monitor for antimuscarinic side effects in patients on amantadine, such as urinary retention, dry mouth, blurred vision and constipation (see Tables 11.4 and 11.9 in Chapter 11 for further information on measures to take for constipation or dry mouth).

Zanamivir

- For maximum effectiveness, zanamivir should be administered within 48 hours of the onset of influenza symptoms.

Nucleoside reverse transcriptase inhibitors

- Monitor patients taking didanosine, stavudine or zalcitabine for peripheral neuropathy, as indicated by numbness and tingling extremities. Peripheral neuropathy usually responds to a reduction in dose.
- For the patient taking didanosine or stavudine, monitor for signs of pancreatitis. Common signs include abdominal pain, vomiting, nausea and decreased bowel sounds. Pancreatitis usually resolves within 1–3 weeks after cessation of treatment.
- Avoid combining didanosine with zalcitabine, due to an increased risk of peripheral neuropathy.

Non-nucleoside reverse transcriptase inhibitors

- Monotherapy with these drugs rapidly promotes viral resistance. A regimen involving a combination of two or three drugs is recommended.
- If severe liver function abnormality develops during nevirapine therapy, treatment should cease. Wait until the liver enzyme levels are back to normal and recommence the nevirapine regimen at half the initial dose.
- Nevirapine induces its own metabolism and therefore requires a dosage increment after 2 weeks of treatment.

Protease inhibitors

- Monotherapy with protease inhibitors is not recommended, due to the increased incidence of viral resistance. Treatment should be part of a regimen involving two or three medications.

HIV fusion inhibitors

- Good injection technique may reduce the occurrence of injection-site reactions.
- Monitor patients with risk factors for pneumonia.
- If a systemic hypersensitivity reaction is observed, discontinue the drug.

DNA polymerase inhibitors

- Monitor patients on aciclovir and ganciclovir for renal status, including urinary output, and serum potassium, urea and creatinine levels.
- Administer intravenous aciclovir by infusion rather than as a bolus in order to prevent nephrotoxicity.
- For patients receiving ganciclovir, monitor for the incidence of neutropenia and impaired renal function.
- Administer adequate fluids to prevent nephrotoxicity. Oral probenecid should be given before and following cidofovir therapy.

Foscarnet

- Monitor renal function, serum electrolyte levels and full blood profile in patients on foscarnet. Nephrotoxicity may be prevented by maintaining a high fluid intake (at least 1.5 l daily) during treatment. Supplementation with calcium, magnesium and other electrolytes may be required.

Idoxuridine

- Avoid contact with mucous membranes during administration.

Interferons

- Monitor patients on interferon for alterations in cardiac, renal, hepatic and bone-marrow function. Also monitor neuropsychiatric status during therapy.
- Ensure that the patient obtains adequate hydration while on interferon in order to prevent nephrotoxicity.

Palvizumab

- Do not administer to febrile infants.

Patient teaching

- Instruct the patient to report adverse effects of therapy, including decrease in voiding, central nervous system changes such as confusion, anxiety and depression, and gastric irritation.
- Advise the patient experiencing dizziness from postural hypotension to arise slowly from a sitting or lying position (see Table 11.20 in Chapter 11 for further information).
- Advise the patient to maintain an adequate fluid intake in order to increase urinary output and prevent renal problems.
- Instruct the patient with genital herpes to avoid spreading the infection by exercising sexual abstinence or using a condom. Advise female patients with genital herpes to have a regular Pap smear test, as indicated by the doctor or other health-care professional.

Zanamivir

- Ensure that the patient is aware of the correct way to administer a zanamivir inhaler (see Table 7.17 in Chapter 7 for further information).

Nucleoside reverse transcriptase inhibitors

- Advise the patient to take didanosine on an empty stomach, at least 30 minutes before meals. Doses should be separated by 12 hours. The tablets may be chewed or crushed in 30 ml water before administration.

- For the patient taking stavudine or zalcitabine, any abdominal pain, numbness, burning and tingling should be reported to the doctor.

Non-nucleoside reverse transcriptase inhibitors

- Advise the patient on zidovudine to avoid taking paracetamol and non-steroidal anti-inflammatory drugs, such as aspirin and indometacin, as they may inhibit the metabolism of zidovudine, there by increasing the possibility of toxicity.
- The patient should inform the doctor if a rash develops while on delaviridine or nevirapine.

Protease inhibitors

- Advise the patient on indinavir to drink at least 1.5 l daily in order to prevent the incidence of nephrolithiasis (renal calculi).
- Advise the patient on nelfinavir, ritonavir or saquinavir to take the preparation with a light meal or snack.
- Inform the patient on indinavir that the preparation should be consumed with water, on an empty stomach, either 1 hour before or 2 hours after meals.

Idoxuridine

- Advise patients using idoxuridine ointment for herpes simplex keratitis that the preparation is not active if a scab has formed over the lesion. The ointment should be used for at least 5 days after the lesion has apparently healed.
- Advise the patient using idoxuridine ointment to apply a thin layer to the affected area every hour on the first day and then every 4 hours until the lesion disappears.
- Advise patients using an idoxuridine eye preparation for herpes simplex keratoconjunctivitis to wear sunglasses in order to prevent a blurring effect from a visual haze.

Oseltamivir

- Advise the patient to take oseltamivir as early as possible after flu symptoms occur.

Evaluation

- Evaluate the effectiveness of therapy in eliminating or lessening the manifestations of the viral infection.

SUMMARY

- Viral infections are difficult to treat because viruses are essentially non-living infectious agents that use the host's cellular machinery for replication.
- Many antiviral drugs are prodrugs that are activated in virally infected cells. This lessens their toxicity.
- In the treatment of human immunodeficiency virus (HIV) infection, it is normal to use a combination of antiviral therapies.

1. Why are viral infections difficult to cure with drugs? Give two reasons.
2. Why is aciclovir relatively non-toxic to uninfected cells?
3. Why is zidovudine relatively non-toxic to uninfected cells?
4. Why is idoxuridine suitable only for topical application?
5. Why has amantadine been used in the prevention rather than the treatment of influenza?
6. Why should a patient on zidovudine avoid taking paracetamol?
7. Differentiate between the protease and reverse transcriptase inhibitors used in human immunodeficiency virus (HIV) infections.
8. Discuss the use of multiple antivirals in the treatment of HIV infections.
9. John Dove, a 25-year-old carpenter diagnosed HIV-positive 4 years ago, has just commenced zidovudine therapy. What patient education would you offer Mr Dove?
10. Why would you perform a full blood examination before starting antiviral therapy?

11 What patient education would you offer a patient with genital herpes?

12 Lay Mun Yew, a 20-year-old student, is often bothered by cold sores during times of stress. She commences an idoxuridine ointment to combat the condition. What advice would you offer her?

13 Intravenous aciclovir can cause renal tubular damage as a result of crystallisation in the renal tubules. How can this damage be minimised? What renal tests should be performed during intravenous aciclovir therapy?

73 DRUG SUMMARY TABLE: ANTIVIRAL DRUGS

FAMILY NAME	GENERIC NAME	TRADE NAME(S)
Miscellaneous agents	Aciclovir	Zovirax
	Adefovir	Hepsera
	Amantadine	Symmetrel
	Cidofovir	Vistide
	Famciclovir	Famvir
	Foscarnet	Foscavir
	Ganciclovir	Cymevene
	Idoxuridine	
	Oseltamivir	Tamiflu
	Zanamivir	Relenza
	Interferon alfa	IntronA
		Roferon-A
		Viraferon
	Palivizumab	Synagis
	Penciclovir	Vectavir
	Ribavirin	Virazole
	Valaciclovir	Valtrex
	Valganciclovir	
Protease inhibitors	Amprenavir	Agenerase
	Atazanavir	Reyataz
	Fosamprenavir	Telzir
	Indinavir	Crixivan
	Lopinavir + ritonavir	Kaletra
	Nelfinavir	Viracept
	Ritonavir	Norvir
	Saquinavir	Invirase
	Tipranavir	Aptivus
Reverse transcriptase inhibitors	Abacavir	Ziagen
	Didanosine	Videx
	Efavirenz	Sustiva
	Emtricitabine	Emtriva
	Lamivudine (3TC)	Epivir
		Zeffix
	+ Zidovudine	Combivir
	+ Zidovudine, abacavir	Trizivir
	Nevirapine	Viramune
	Stavudine (d4T)	Zerit
	Tenofovir	Viread
	Zalcitabine (ddC, DDC)	Hivid
	Zidovudine (AZT)	Retrovir
Other antiretrovirals	Enfuvirtide	Fuzeon

ANTIFUNGAL DRUGS

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CHAPTER SEVENTY-FOUR

OBJECTIVES

After completing this chapter, the reader should be able to:

- **discuss the aetiology of fungal diseases;**
- **discuss the use, mechanism of action and problems associated with each of the following antifungal drugs;**
  - **griseofulvin;**
  - **terbinafine;**
  - **amphotericin;**
  - **nystatin;**
  - **flucytosine;**
  - **imidazoles.**

KEY TERMS

Mycoses
Tinea infections
Yeasts

THE FUNGI ARE A DIVERSE GROUP OF ORGANISMS. PREVIOUSLY they were classified as belonging to the plant kingdom, but today they are included in their own discrete groups of yeasts and moulds. Over one million species of fungi have been identified. Of these, only about 20 are associated with systemic infections and about a dozen with superficial infections in humans. Many fungi can also cause opportunistic infections. The normal, healthy individual is resistant to most fungal infections and is infected only when faced with overwhelming challenge. Many pathogenic fungi exhibit a phenomenon known as dimorphism, in which two different types of growth form exist. The most common type of growth, and the one with which most people are familiar, is the mycelial or hyphal growth. This is the type of growth typically seen on a mouldy piece of bread. The other type of growth occurs when the fungal cells exist separately, somewhat like bacteria but much bigger. This form occurs in the yeasts. Depending on environmental conditions, some fungi can exist in either of these forms. This is sometimes of clinical importance because in infected tissues the form is usually a yeast, but when grown in culture the form is a typical mould.

A fungal infection is termed a mycosis. The mycoses are divided into three main groups, depending on the type of infection:

- *Systemic or deep mycoses*: These occur when the internal systems are infected. They can be disseminated widely throughout the body. The causative agents are normally soil saprophytes, which gain access to the body through the respiratory tract. Before the availability of effective antifungal drugs, these infections were invariably fatal.
- *Subcutaneous mycoses*: These occur when skin, fascia and bone are infected. This type of infection is most common in tropical countries. It occurs when the fungi, usually saprophytes, gain entry to the body through a wound caused by, for example, a thorn. This type of infection is often grossly disfiguring and, without treatment, can be fatal.
- *Cutaneous mycoses*: These occur when the epidermis, hair and nails are involved. Fungi that cause these lesions are known as dermatophytes. Many of these organisms are obligate parasites of mammalian skin and are transmitted by direct contact or by desquamated epidermal cells. A good example of this is athlete's foot. This infection is commonly picked up from infected desquamated cells on the floors of communal showers and swimming baths. There are several different dermatophytes, which all cause similar infections, and the nomenclature of the infection is based on the area of the body that is infected. These dermatophytic infections look like small worms burrowing beneath the skin: the general term tinea (Latin *tinea*: worm) is used, followed by the area of the body affected:
  - tinea capitis – the head;
  - tinea corporis – the body;
  - tinea cruris – the groin (often called jockstrap itch);
  - tinea pedis – the foot;
  - tinea unguium – the nails;
  - tinea barbae – the beard.

There are numerous other tineal infections, but these are the most common. When only the very outermost layers of the epidermis and hair are involved, this is sometimes refered to as superficial mycoses.

A common opportunistic infection is candidiasis (also called candidosis, moniliasis and thrush). This is caused by *Candida albicans*, a normal resident of the gastrointestinal tract and vagina. Infection can occur during the use of broad-spectrum antibiotics (see Chapter 68) and by alteration of the environmental conditions in the female reproductive tract due to pregnancy or the use of oral contraceptives.

ANTIFUNGAL AGENTS

Drugs used to treat fungal infections are often termed antimycotics.

GRISEOFULVIN AND TERBINAFINE

■ MECHANISM OF ACTION

Griseofulvin is an antibiotic obtained from a similar organism to the one that produces penicillin. Griseofulvin was originally used to control moulds on vegetables grown in greenhouses. It acts as a fungistatic drug and inhibits fungal cell division by disruption of the mitotic spindle structure. It prevents the infection from spreading. The drug has an affinity for keratin, in which it is incorporated when given systemically; it is therefore concentrated in keratin. Keratin is the major protein component of the superficial structures of the body likely to be infected by dermatophytes, and griseofulvin is ideal for such infections.

Terbinafine inhibits fungal cell-wall synthesis and is fungicidal against dermatophytes when taken orally. There is substantial evidence that it is better than griseofulvin at treating onychomycosis (fungal infection of the nails), sometimes curing the condition in as little as 12 weeks, although it usually takes twice this long.

◆ COMMON ADVERSE EFFECTS

Griseofulvin is tolerated well. Apart from minor gastrointestinal upsets and headaches, adverse effects are not common with this drug. Patients should be instructed to avoid alcohol when taking griseofulvin, as tachycardia and flushing may result. Griseofulvin is a liver enzyme inducer (see Chapter 14), which may affect other drugs given concurrently. Care should be taken with its use in patients with liver disease and porphyrias. Gastrointestinal effects can be reduced by administering two divided doses with the morning and evening meals.

✚ CLINICAL CONSIDERATIONS

When griseofulvin is administered orally, absorption is enhanced by the presence of fats. It is thus more effective when given with a fatty meal. As keratinised tissue such as hair and nail is very slow-growing, griseofulvin therapy must be maintained for a long period, sometimes more than a year, in order to eradicate the infection completely.

Renal and hepatic function and complete blood counts are monitored during prolonged therapy with griseofulvin. This drug has a narrow spectrum of activity, which is largely confined to dermatophytes. An accurate diagnosis is therefore important before starting a long course of therapy.

Terbinafine cures nail infection, but the nail needs to grow out completely in order to appear normal. Liver enzyme levels and blood count are monitored if treatment exceeds 6 weeks. The patient should inform their doctor if they feel unusually tired, have pale faeces or notice yellowing of the eyes and skin, as these could be manifestations of liver problems.

AMPHOTERICIN B

■ MECHANISM OF ACTION

Amphotericin B is, like griseofulvin, an antibiotic produced from an organism related to one that produces streptomycin. It belongs to a class of antibiotics known as the polyenes because of the high number of double bonds in their structure. Mammalian cell membranes contain cholesterol as a major component; fungi contain a sterol related to cholesterol, ergosterol. Amphotericin B and other polyenes interact with ergosterol and disrupt fungal cell membranes, upsetting the normal membrane permeability. They thus cause death of the fungus when given in large doses; smaller doses are fungistatic. The polyenes can also bind to cholesterol but not as strongly, and hence usually less harm is done to the host's cell membranes. Amphotericin B also has antiprotozoal activity and is used for leishmaniasis.

◆ COMMON ADVERSE EFFECTS

Amphotericin B is a toxic drug, but in life-threatening situations large doses may have to be given. Even though amphotericin has many adverse effects, it is often the only alternative available in potentially fatal fungal infections. A large dose invariably causes severe renal impairment, which may take some months to return to normal. Other adverse effects include anorexia, malaise and fever. Intrathecal use may result in central nervous system (CNS) disturbances, such as paraesthesias.

When used topically, the only problem appears to be occasional sensitivity.

✚ CLINICAL CONSIDERATIONS

Amphotericin is absorbed poorly from the gastrointestinal tract. For systemic infections, it must therefore be given parenterally, although it can be used to treat oral and/or gastrointestinal candidiasis in the form of lozenges. It is also available as a topical preparation for cutaneous and mucocutaneous infections. When used for CNS infections, it may have to be given intrathecally.

The lipid complex form of parenteral amphotericin B reduces the chances of nephrotoxicity compared with the conventional form of parenteral therapy. Monitor serum creatinine, potassium, magnesium and blood urea levels, blood count and liver function during parenteral treatment. The high cost of the lipid complex limits its use to individuals with existing renal impairment and patients at risk of developing nephrotoxicity.

NYSTATIN

Nystatin (which, interestingly, derives its name from New York state) is another polyene antimycotic that interferes with the permeability of the fungal cell membrane. It is used principally for candida infections of the skin and mucous membranes. It is much more toxic when given systemically.

◆ COMMON ADVERSE EFFECTS

Usually, no adverse effects are associated with nystatin when used topically.

✚ CLINICAL CONSIDERATIONS

Like amphotericin B, nystatin is not absorbed when given orally. It is thus useful for treating intestinal candidiasis. It is available as pessaries and vaginal creams to treat fungal vaginitis.

Resistance to nystatin does not generally occur. It can be useful, if taken orally, as a prophylactic against candidiasis in people being treated with broad-spectrum antibiotics for prolonged periods of time. Nystatin is available combined with other agents such as **oxytetracycline** in creams for bacterial and fungal skin infections.

Nystatin liquid and lozenges are best taken after a meal or drink. The liquid should be washed around the mouth for as long as possible before swallowing.

CASPOFUNGIN

■ MECHANISM OF ACTION

Caspofungin is referred to as an echinocandin antifungal. It is a semisynthetic lipopeptide that inhibits the synthesis of glucans, a polysaccharide, in the cell walls of fungi.

This drug is effective against *Aspergillus* and *Candida* infections produced by strains not susceptible to other antimycotic drugs. At present, caspofungin has been approved for use in invasive aspergillosis that is unresponsive to amphotericin B and **itraconazole** and in patients who cannot tolerate these drugs. *Aspergillus* species are common fungi and usually cause fungal infections only in immunocompromised patients and in some cases where large amounts of the fungus gain access to the body, usually by inhalation. For example, farmer's lung and aspergillosis may develop in people working with mouldy hay and inhaling the spores. Invasive fungal infections are often rapidly fatal and need aggressive treatment.

◆ COMMON ADVERSE EFFECTS

Caspofungin is given only intravenously. When used for invasive aspergillosis, its adverse effects – fever and chills being the most commonest – are acceptable. When used for candidiasis, although it is effective, adverse effects are unacceptably high, hence it is only used in patients with neutropenia for this indication.

✚ CLINICAL CONSIDERATIONS

As this parenteral preparation may cause a reduction in potassium levels, monitor potassium levels during

therapy. The dose should be reduced in patients with liver impairment.

FLUCYTOSINE

■ MECHANISM OF ACTION

Flucytosine, like some of the antivirals, is a prodrug. It is converted in fungal cells into its active form, **5-fluorouracil** (a substituted pyrimidine), which is incorporated in RNA, making it defective. Mammalian cells cannot activate flucytosine. The drug is fungistatic. Flucytosine is usually given by intravenous infusion. It is distributed well in all body compartments.

◆ COMMON ADVERSE EFFECTS

As flucytosine is specific towards fungi, adverse effects are few. Nausea, vomiting and diarrhoea are seen occasionally. Flucytosine is excreted unchanged by the kidneys; care must be taken in patients with renal insufficiency, as blood levels may reach toxic levels due to an effective increase in half-life.

✚ CLINICAL CONSIDERATIONS

The drug is used to treat various systemic fungal infections, including those involving *Candida albicans*. Some fungi are more susceptible than others, and resistance has been reported.

As resistance to flucytosine may develop rapidly, it is used in combination with another antifungal. Monitor hepatic and renal function before and during treatment.

CICLOPIROX

Ciclopirox is available as a shampoo for scalp infections.

■ MECHANISM OF ACTION

Ciclopirox is a synthetic antimycotic that is chemically classed as a hydroxypyridone. Its mechanism of action is poorly understood. It has a broad spectrum of activity.

◆ COMMON ADVERSE EFFECTS

As a topical agent, ciclopirox is well tolerated. Common adverse reactions include itchiness and a burning sensation at the site of administration.

✚ CLINICAL CONSIDERATIONS

Ciclopirox is available in some countries as a cream or solution to be applied to the affected area. It should not be applied as an occlusive dressing.

Azole derivatives

This group of drugs also includes anthelmintics, antiprotozoals and antibacterials, which are dealt with in other chapters. Several azole derivative antifungals are in common use, all of which act by similar mechanisms. Some are used only to treat superficial mycoses.

The commonly used imidazoles are **ketoconazole**, **miconazole**, **clotrimazole** and **econazole**. **Fluconazole**, **itraconazole** and **voriconazole** are triazoles.

■ MECHANISM OF ACTION

The mechanism of action of these drugs is two-fold. First, they inhibit the formation of ergosterol and therefore the permeability of the cell membrane. They also interfere with the enzymes involved in the metabolism of hydrogen peroxide, which builds up intracellularly and kills the cell.

The imidazole drugs are formulated as creams and pessaries for vaginal candidiasis. They are applied for 3–14 days. It is important that all sexual partners of the patient are also treated with an antimycotic preparation, as the infection can be transmitted venereally. The imidazoles have a broad spectrum of activity; clotrimazole has some trichomonicidal activity. They are all available for topical use. Miconazole has been combined with hydrocortisone in a cream to relieve the pruritus and inflammation associated with fungal infections.

Oral treatment of vaginal fungal infection with fluconazole and itraconazole is also effective. For more details regarding the use of these drugs and the choice of drug in fungal infections, more specialised textbooks should be consulted.

◆ COMMON ADVERSE EFFECTS

When applied topically, there is minimal absorption of these drugs. Systemic adverse effects are uncommon but may include abdominal cramps and diuresis. Local irritation is uncommon.

Only three of the azole derivatives are used in systemic therapy – fluconazole, itraconazole and miconazole. Ketoconazole and itraconazole can be given orally to treat superficial mycoses not responsive to topical treatment and some systemic fungal infections. All have a similar adverse-effects profile, with gastrointestinal disturbances such as dyspepsia, nausea, abdominal pain and diarrhoea being the most common. These gastrointestinal effects are more common if the drug is taken on an empty stomach. Itraconazole and fluconazole have both been implicated in the development of Stevens–Johnson syndrome. All of these drugs have been reported to be hepatotoxic on occasion. This hepatotoxicity is normally reversible, but in rare instances it may prove to be fatal. This necessitates routine liver function tests in patients undergoing therapy.

Ketoconazole is not absorbed well in patients with achlorhydria. Gynaecomastia, associated with antiandrogenic activity, is another side effect reported.

Fluconazole does not seem to be as clinically effective as amphotericin B, but the former has a lower incidence of adverse effects. Other adverse effects are relatively trivial and include headache and rash. Rarely, more serious, sometimes fatal, effects occur, including hepatic damage and exfoliative skin disorders.

✚ CLINICAL CONSIDERATIONS

Fluconazole is mainly of use in patients unresponsive to amphotericin B therapy. Fluconazole is of particular use in cryptococcal meningitis and in patients with serious *Candida* infections. The drug can be given by mouth or parenterally by intravenous injection. Fluconazole is more reliably absorbed from the gastrointestinal tract compared with the other azole derivatives. A common use for fluconazole is in chronic anal and vaginal candidiasis derived from gastrointestinal *Candida*, where one capsule taken orally eradicates the yeast. With this dosage, there are normally no adverse effects.

Ketoconazole has been superseded by fluconazole and itraconazole, which have less toxicity. The risk of hepatitis during ketoconazole therapy is increased in individuals who are treated for more than 14 days, in patients aged over 50 years and in patients who have been treated recently with griseofulvin. During ketoconazole therapy, liver function is monitored before and during therapy. Ketoconazole is available as a cream and shampoo (see Chapter 78) for topical treatment and appears to be useful in the treatment of seborrhoeic dermatitis. An unusual use of ketoconazole is in the treatment of bone pain due to metastatic prostate cancer. This effect is due to its ability to inhibit steroid hormone biosynthesis.

When using miconazole gel, the patient should keep the gel in the mouth for as long as possible before swallowing. Miconazole treatment is continued for a week after symptoms clear. With fluconazole treatment, the patient should inform their doctor if they develop dark urine, pale faeces, unusual tiredness, or yellowing around the eyes or skin. Hepatic and renal function are checked at baseline and during fluconazole therapy. Itraconazole capsules are taken with food to achieve maximum absorption. The oral solution of itraconazole is taken on an empty stomach. Liver function and serum potassium levels are checked regularly if itraconazole treatment continues for more than 1 month.

Other antifungal drugs

AMOROLFINE

Amorolfine is a morpholine derivative with a long half-life in the skin. Amorolfine is available as a nail lacquer for the treatment of many fungal nail infections. It acts in a similar way to the azole drivatives.

✚ CLINICAL CONSIDERATIONS

Amorolfine is applied once or twice weekly to infected nails that have been cut or filed down as thoroughly as possible. Before each application, the nails should also be cleansed using 2-propanol swab sticks, supplied with the lacquer. Filing the nails with disposable files is better than using scissors, which need to be sterilised before further use. It is important not to use cosmetic lacquers, artificial nails and occlusive dressings during treatment. Treatment is continued without interruption until the nail regrows.

Several other preparations are available for the treatment and prophylaxis of fungal infections.

Tolnaftate is a synthetic drug for topical use. It can be used to treat a few of the common skin infections, but not candidiasis. Its mechanism of action is unknown. Adverse effects are rare. In powder form, tolnaftate is useful as a prophylactic when added to the insides of socks of sports people who may be at high risk of athlete's foot.

Whitfield's ointment, which consists of **benzoic acid** and **salicylic acid**, is a traditional treatment for ringworm that is still used occasionally. Salicylic acid is keratolytic, thus helping the benzoic acid, which is fungistatic, to penetrate to the infected tissue. **Undecenoic acid** and its zinc salt are fungistatic and applied topically in the prophylaxis and treatment of superficial dermatophytoses.

Dyes such as **gentian violet** and **magenta** are still used but cause severe skin staining.

Povidone–iodine (see Chapter 70) is a very effective fungicidal drug, although, like the dyes, it is messy. It is available as a vaginal douche and as pessaries for vaginitis. It is useful for treating mixed vaginal infections.

In candidal vaginitis, the cause may be environmental. In cases of recurrent infection, restoration of a normal environment may be necessary. This can be done by restoring the acidity of the vagina. A mild acid mixture such as Aci-Jel™, which contains acetic acid, can be used. As normal vaginal acidity is partially maintained by the presence of the *Lactobacillus* species of bacteria (Döderlein's bacilli), a vaginal douche containing vinegar and lactobacilli can be used. Some women apply a vaginal douche of yogurt or related product containing lactobacilli for the same purpose. The avoidance of yeast-containing foods does not have any basis in the treatment of yeast infections.

Tolciclate is used to treat common skin infections. It is available as a cream and a powder. It has limited value because of its poor penetration of tissue, but it has few adverse effects.

Tioconazole is a broad-spectrum antifungal agent indicated for topical treatment of skin infections by susceptible dermatophytes and yeasts. It also has antibacterial activity against some Gram-positive bacteria. Adverse effects involve mild skin irritation and are usually associated with the commencement of therapy.

CLINICAL MANAGEMENT

Antifungal drugs

Assessment

- Assess the source of fungal infection, including chemotherapy, immunotherapy, antibiotics, nutritional support through the intravenous route, the presence of invasive devices such as an endotracheal tube, and high-dose steroids.
- Assess the patient prescribed flucytosine for a history of receiving radiation therapy and antineoplastic drugs. Flucytosine may worsen the bone-marrow depression caused by these agents.
- Assess the manifestations of the fungal infection, depending on the condition. Determine whether the patient has tried measures to eradicate the infection.
- Assess patients who are to receive systemic antifungal agents for a history of hepatic and renal disease. Exercise great caution with the use of the drugs in such patients.

Planning

- The patient's fungal infection will be resolved.

Implementation

- If possible, remove the causative agent, which may include discontinuing drugs predisposing the patient to infection.
- For patients on intravenous antifungal agents, monitor for vital signs, fluid input and output.
- Monitor patients on intravenous antifungal agents for renal function, such as urinary output, serum creatinine, and potassium and urea levels. Ensure adequate fluid intake. Intravenous antifungal agents may cause nephrotoxicity.
- Monitor patients on intravenous antifungal agents for liver function, such as liver enzyme levels.
- Monitor patients on intravenous antifungal agents for adverse effects such as fever, nausea, vomiting, headaches, phlebitis and electrolyte imbalances (hypokalaemia may occur with intravenous amphotericin B).
- Patients on intravenous antifungal agents may be premedicated with other drugs in order to curb the incidence of various side effects. Premedication with aspirin, paracetamol, an antiemetic or an antihistamine may be helpful.
- Give oral antifungal agents after food to prevent gastric irritation.
- If treatment with terbinafine continues for more than 6 weeks, periodic liver function tests and complete blood profiles should be taken.
- For a patient on intravenous amphotericin B, ensure that the fluid bag is protected from light and stored in the refrigerator until required for infusion. The drug should be made up using glucose or water but not saline, as precipitation may result otherwise.
- Nephrotoxicity with intravenous amphotericin B may be reduced by hydrating the patient before amphotericin therapy.
- Liposomal amphotericin B may be used to reduce the incidence of nephrotoxicity, fever, chills and nausea compared with conventional amphotericin B; however, the liposomal form is more expensive.
- Monitor for hypokalaemia during intravenous amphotericin B infusion. Manifestations may include muscle weakness, tingling extremities and nausea. Hypokalaemia may also cause cardiac dysrhythmias. Monitor the pulse for rate and rhythm regularly. Take serum potassium levels to determine effect.

Patient teaching

- Advise the patient to take oral antifungal agents after food.
- Instruct the patient to take the drug as ordered. Discontinuing the drug before the course is completed may result in a relapse of infection. Advise the patient to avoid driving and operating heavy machinery when taking amphotericin B, ketoconazole or flucytosine because these drugs may cause dizziness, visual changes and drowsiness.
- Advise the patient to obtain liver function tests as required for oral fluconazole, flucytosine, itraconazole, ketoconazole and terbinafine.
- Advise patients on ketoconazole, fluconazole and itraconazole to report any symptoms of liver toxicity, including fatigue, anorexia, nausea, vomiting, jaundice, dark urine and pale faeces.
- Ketoconazole should not be taken with medications that decrease stomach acid, including antacids, H_2-receptor antagonists and proton pump inhibitors. Fluconazole and itraconazole absorption are not reduced by medications that alter the gastric pH.
- Miconazole oral gel should be dropped on the tongue and kept in the mouth for as long as possible before swallowing.

- Instruct patients on the correct mode of administration of oral and topical antifungal agents (see Table 7.13 in Chapter 7 for methods of administration of vaginal pessaries and creams). Instruct the patient taking amphotericin B lozenges to allow the lozenge to dissolve slowly in the mouth. When treating toes and feet, make sure that the agent gets between the toes and on the soles of the feet. Sprinkle or spray the agent on socks. With ointments and creams, the preparation is gently rubbed into the area. With aerosols or sprays, shake well before using and hold the spray about 10–20 cm away from the area to be treated. Avoid inhaling the solution or powder and getting the preparation into the eyes.
- For female patients with vaginal infection, provide the following advice: Do not wear tampons during therapy (use sanitary towels instead). Continue therapy through the menstrual period. Avoid sexual intercourse during therapy, or ensure the partner wears a condom. Wipe from front to back following defaecation and voiding. Do not douche between doses of medication. Wear cotton rather than synthetic underwear. Avoid tight trousers and use tights with a built-in cotton gusset. Avoid the use of soaps and fragrant lotions on the vaginal mucosa during washing. Take showers instead of baths. If patients develop photophobia with oral agents, advise on the use of sunglasses and to avoid bright lights and sunlight (see Table 11.13 in Chapter 11 for further information).
- Instruct patients on griseofulvin and ketoconazole to avoid taking alcohol concurrently, as a disulfiram-like reaction may occur.
- Warn female patients on griseofulvin that the effectiveness of oral contraceptives may be reduced by this drug. Alternative measures of contraception should be used during therapy.
- Remind female patients that antifungal agents (even topical preparations) should be avoided during pregnancy and breast feeding. Refer such patients to the doctor.
- Warn patients on griseofulvin that photosensitivity may occur. Instruct patients to use a sunblock and avoid sunlight during the warmest part of the day (see Table 11.19 in Chapter 11 for further information).
- Advise patients on terbinafine that maximum effectiveness occurs several months after completion of treatment, at the time when the healthy nail growth occurs.

Evaluation

- Evaluate the effectiveness of the antifungal agent in resolving the infection.
- Evaluate the patient's knowledge of the use of non-pharmacological measures to treat and prevent fungal infections.

SUMMARY

- Fungal diseases of humans are usually topical and rather benign.
- Systemic fungal infections are very often fatal, even with modern chemotherapy.
- Fungal infections are contagious.
- Some fungal infections are opportunistic.
- Fungal infections of the skin are named after the areas affected rather than the name of the fungus.
- Fungi can become resistant to antimycotics.

1. Why are many fungal skin infections named after the part of the body infected rather than the causative agent?
2. Why is vaginal candidiasis more common in pregnancy and when the patient is taking the oral contraceptive pill?
3. Is candidiasis a venereal disease?
4. Why can people on broad-spectrum antibiotics acquire oral candidiasis?
5. What is the main reason for griseofulvin's use in fungal nail infections? Why is treatment prolonged?
6. What tests should be made on patients taking ketoconazole?

7 Why is flucytosine, an inhibitor of DNA synthesis, relatively safe in humans?

8 Why is amphotericin B available as lozenges for sucking? Why are side effects rare with this mode of administration?

9 What precautions should be taken in a patient on cimetidine when ketoconazole is administered?

10 Why is oral nystatin often prescribed as well as a topical preparation in vaginal candidiasis?

11 Jane Ridge, aged 30 years, is prescribed nystatin oral suspension for oral candidiasis. How would you instruct Ms Ridge to use the oral suspension?

12 What blood test should be checked regularly while a patient is taking griseofulvin?

13 Mary Ricard, a 28-year-old patient, visits the sexual health clinic complaining of intense itching around her vaginal area. The doctor diagnoses genital candidiasis and prescribes a course of clotrimazole vaginal cream. What patient education would the doctor offer Ms Ricard? What assessment would the doctor make during Ms Ricard's visit? (See Table 7.13 in Chapter 7 for assistance.)

14 What non-pharmacological measures would you suggest for a patient with genital candidiasis? (See Table 11.16 in Chapter 11 for assistance.)

15 Parenteral amphotericin B therapy is associated with renal impairment as an adverse effect. What blood tests should be performed regularly during therapy in order to determine effects on renal function?

74 DRUG SUMMARY TABLE: ANTIFUNGAL DRUGS

FAMILY NAME	GENERIC NAME	TRADE NAME(S)
Imidazoles	Clotrimazole	Canesten clotrimazole
	Econazole	Ecostatin
		Pevaryl
	Fluconazole	Diflucan
	Itraconazole	Sporanox
	Ketoconazole	Nizoral
	Miconazole	Daktarin
	Sulconazole	Exelderm
	Tioconazole	Trosyl
	Voriconazole	Vfend
Miscellaneous antifungals	Amorolfine	Loceryl
	Amphotericin	Abelcet
		Fungilin
		Fungizone
		AmBisome
		Amphocil
	Caspofungin	Cancidas
	Flucytosine	Ancotil
	Griseofulvin	Grisovin
	Nystatin	Nystan
	Terbinafine	Lamisil
	Tolnaftate	Tinaderm-M
	Undecanoate	Monphytol
		Mycota

VACCINES AND IMMUNOMODULATING DRUGS

75

CHAPTER SEVENTY-FIVE

KEY TERMS

Active immunity
Antibodies
Autoimmune disease
Cytokines
Hypersensitivity reaction
Immunisation
Immunity
Immunosuppression
Leucocytes
Organ transplantation
Passive immunity
Recombinant DNA technology
Vaccination

OBJECTIVES

After completing this chapter, the reader should be able to:

- **outline the categories of immunomodulating agents and state their general uses;**
- **state the names and functions of blood cells involved in immunity;**
- **give a broad overview of an immune response;**
- **describe the actions and major adverse effects associated with drugs that stimulate immunity;**
- **describe the actions and major adverse effects associated with drugs that suppress immunity.**

IMMUNOMODULATING AGENTS ARE DRUGS THAT MODIFY the body's immune responsiveness. Upon entering the body, immunomodulators affect the function of leucocytes and/or alter the levels of cytokines (the secretions produced by leucocytes, such as interferon and interleukins) and immunoglobulins.

Immunomodulating agents fall into two categories: (i) immunostimulants, which act to enhance immune responsiveness in order to fight cancer or infection; and (ii) immunosuppressants, which suppress immune reactions associated with tissue rejection and autoimmune disease.

OVERVIEW OF IMMUNE CELLS AND FUNCTIONS

Immunity and immune reactions are facilitated mostly through the actions and secretions of leucocytes, both granular and agranular. Monocytes and neutrophils are phagocytic cells that engulf damaged body cells and foreign matter. When a monocyte leaves the bloodstream and enters the tissue, it is called a wandering macrophage. Monocytes and macrophages often participate in antigen recognition, making the initial contact with the antigen and presenting it to other leucocytes, such as lymphocytes, in order to trigger a full immune reaction. This reaction involves the rapid proliferation of leucocyte subpopulations.

Lymphocytes play an integral role in immunity and are subdivided into B-cell and T-cell types, responsible for humoral and cellular immunity, respectively. When exposed to an antigen, B-cells differentiate into plasma cells, which secrete antibodies. After exposure to an antigen, T-cells differentiate into a number of subpopulations. 'Cytotoxic' T-cells appear to directly destroy cells or co-opt other immune cells through the release of cytokines. Modulation of the immune response can be facilitated by other subpopulations of T-cells called 'helper' and 'suppressor' cells. As their names suggest, these act, respectively, either to stimulate the proliferation of lymphocytes (T- and B-cells) to participate in the immune response or to suppress the activity of lymphocytes. The subpopulations of T- and B-cells called 'memory cells' 'remember' the contact with the antigen in case the same antigen enters the body again. If the antigen does invade again, the memory cells elicit a full immune response more quickly. This process of cell proliferation following antigen presentation is summarised in Figure 75.1.

Basophils and eosinophils participate in inflammation and allergic reactions. Basophils contain chemicals such as histamine and serotonin, which, when released, intensify the inflammatory reaction. Mast cells are derivatives of basophils that have lodged in body tissues, particularly the skin, lungs and gastrointestinal tract, and are often involved in allergy. Eosinophils release substances that neutralise those released by basophils and mast cells and thus act to regulate allergic reactions. They also have some capacity for phagocytosis.

A number of specific cytokines are produced by leucocytes and other body cells, such as interferons, interleukins and leucocyte colony-stimulating factors (CSF), and their properties have been identified (see Table 75.1).

At least three types of interferon have been isolated: α, β and δ. All act to improve a cell's defences against viral infection and cancer. There are many different interleukins, which variously stimulate the proliferation and differentiation of bone-marrow cells, B-cells, T-cells, plasma cells and eosinophils. CSF stimulate the proliferation of specific subpopulations of leucocytes, such as monocyte–macrophages, neutrophils, eosinophils and granulocytes in general).

IMMUNOMODULATING AGENTS THAT STIMULATE IMMUNITY

Antisera and vaccines are considered immunomodulators because they enhance immune protection. As you will see, however, the nature of the immunostimulation varies somewhat.

Antisera

■ MECHANISM OF ACTION

Injection of antiserum leads to a form of passive immunity, which provides immediate and short-term protection against harmful agents. Antiserum provides the humoral products of immunity (i.e. antibodies) transferred from either a human or animal source with pre-existing natural immunity. This immunity is instant but it is only transient, because there has been no presentation of antigens to the recipient's immune cells and no memory has formed of exposure.

Antisera provide instant immunity for travellers in areas of high risk for viral or bacterial infection and who have no pre-existing immunity. A preparation labelled 'immunoglobulin' usually consists of specific human antibodies, while antivenoms and antitoxins contain antibodies derived from non-human sera. An antivenom is made up of antibodies directed against the venom of a poisonous animal, whereas an antitoxin comprises antibodies directed against potentially lethal toxins produced by a specific bacterium.

◆ COMMON ADVERSE EFFECTS

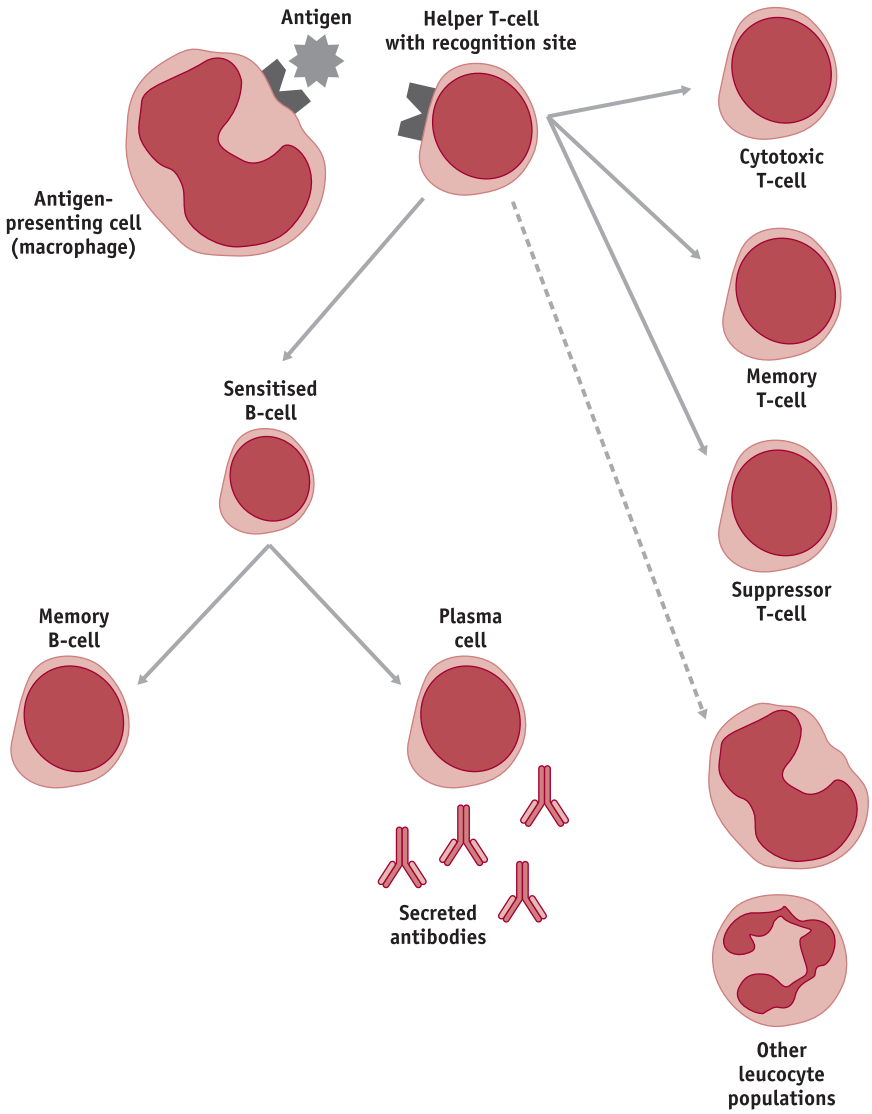
Common adverse effects of non-human antisera comprise allergic reactions to serum contaminants, such as fever, chills, rashes and serious anaphylactoid reaction. Adverse reactions to human immunoglobulin are rare; if they do occur, they are usually allergic in nature. Hypersensitivity to blood products is a contraindication for use. The major concern in the administration of blood products is the transmission of bloodborne viruses such as hepatitis and human immunodeficiency virus (HIV).

✚ CLINICAL CONSIDERATIONS

Currently, there are immunoglobulins or antitoxins available against diphtheria, cytomegalovirus (CMV), rabies, hepatitis B, antibody deficiency, tetanus and herpes zoster. An immunoglobulin to the rhesus (Rh) factor is also available in order to prevent Rh incompatibility between a pregnant woman and her fetus when applicable (see Table 75.2).

FIGURE 75.1 PROLIFERATION OF IMMUNE CELLS IN AN IMMUNE RESPONSE

The presentation of an antigen to a helper T-cell, in this case by a macrophage, stimulates the proliferation of a variety of T-cell, B-cell and leucocyte subpopulations, which embody the immune response.



In regions with indigenous populations of poisonous animals, such as jellyfish, spiders, ticks, stonefish and snakes, antivenom is widely available. Acute envenomation is rare in the UK, where the only indigenous venomous snake is the adder; the European viper venom antiserum is available for injection. Patients should be observed for allergic reactions to non-human antisera, and **adrenaline** should be available to treat any anaphylatic reaction to the antivenom. Envenomation and its clinical management are covered in Chapter 21.

Vaccines

MECHANISM OF ACTION

The principle underlying vaccination is that exposure to an antigen or antigens derived from a virus or bacterium in a relatively harmless form sensitises immune cells for a possible subsequent exposure to the organism. On re-exposure, the memory of the previous challenge triggers an immune response more quickly. As the individual's own immune processes are stimulated by this agent, this is a form of active immunity.

TABLE 75.1 IMPORTANT CYTOKINES

Cytokine	Functions	Secreting cell
Colony-stimulating factors (CSF)		T-cells, endothelium, fibroblasts
Granulocyte CSF	Stimulates proliferation and differentiation of granulocyte subpopulations	
Macrophage CSF	Stimulates proliferation and differentiation of macrophages and monocytes	Bone-marrow fibroblasts
Stem cell factor (SCF)	Synergises with other cytokines and erythropoietin to stimulate proliferation of blood cell lines	
Interferon α and β	Inhibits viral replication, stimulates T-cell proliferation	Macrophages, viral infected cells
Interferon δ	Enhances cellular and humoral immunity	T_H- and T_C-cells
Interleukin 1	Induces fever, stimulates B- and T-cell proliferation	Monocytes, macrophages
Interleukin 2	Stimulates lymphocyte proliferation, activates cellular immunity, stimulates cytokine production	T_H-cells
Interleukin 3	CSF that stimulates production of many leucocyte populations	T-cells
Interleukin 4	Stimulates B-cells, enhances antibody production	T-cell
Migration inhibiting factor	Inhibits macrophage migration away from site of inflammation/infection	T-cells
Tumour necrosis factors (TNF)	Chemotactic factor, proinflammatory, stimulate cytokine secretion, stimulate B-cells, induce fever, cause calcium mobilisation, activate neutrophil, anti-tumour activity	Macrophages, T-cells

TABLE 75.2 ANTISERA PREPARATIONS AND THEIR SOURCES

Condition	Trade name(s)	Source
Antitoxins		
Diphtheria	Diptheria antitoxin	Horse
Imunoglobulins		
Antibody deficiency	Human normal immunoglobulin	Human
Cytomegalovirus	Cytomegalovirus immunoglobulin	Human
Hepatitis B	HBIG	Human
Rabies	Rabies vaccine	Human
Rhesus incompatibility	Anti-D(RH_0) immunoglobulin	Human
Tetanus	Tetanus Immunoglobulin	Human
Varicella zoster	Varicella-Zoster Immunoglobulin	Human

The valency of a vaccine is often included in the information supplied by the manufacturer. Valency refers to the combining power of the preparation. In this context, it indicates the number of strains of microbe with which the vaccine can combine. A vaccine may be bivalent, trivalent or polyvalent, indicating that it is effective against two, three or more than three strains, respectively. If valency is not noted, then we assume that the vaccine is effective against only one strain. Valency is also pertinent to snake antivenoms. A polyvalent antivenom is usually given when the snake has not been positively identified (see Chapter 21).

In some cases, an efficacious vaccine can be prepared from the killed microbe or a toxin produced by a bacterium. In other cases, it is necessary to use live microbes that have been attenuated and inactivated in order for long-term immunity to result. It is theoretically possible that a vaccine of the latter type will trigger the illness in the recipient, but this is not regarded as a significant risk. Vaccines created from the microbe itself are known as cellular vaccines. Usually, vaccines made from inactivated microbes or their toxins require more than one dose of the vaccine in order to trigger a rapid, full immune response. The number of doses reflects the potency of the vaccine. Examples of vaccines comprising inactivated organisms are the injectable typhoid, hepatitis A and poliomyelitis vaccines. Vaccines made from toxoids include those for diphtheria and tetanus. Live attenuated vaccines trigger both antibody production and cell-mediated responses, and usually only one dose of vaccine is sufficient to induce a full, rapid immune response. Examples of vaccines made from live attenuated organisms are those for measles, mumps and rubella and the oral poliomyelitis and typhoid preparations.

Recombinant DNA technology has proven useful in the area of vaccine development. Highly pure preparations of microbial surface antigens can now be produced by culture of *Saccharomyces cerevisiae*, the yeast used in beer-making. The yeast cells have been genetically manipulated to carry the genes that programme for expression of pathogenic surface antigens. The vaccine is a suspension of the antigens adsorbed on to aluminium hydroxide. These are known as acellular vaccines. The advantages of this approach are that the antigens alone are sufficient to induce immunity, the preparation is relatively free of protein contaminants that might trigger allergic reactions, and there is no chance of inducing the illness in the recipient. Examples of acellular vaccines include the pneumococcal, *Haemophilus influenzae* type b (Hib) influenza and new-generation pertussis vaccines.

Bacille Calmette–Guérin (BCG) vaccine, used for the prevention of tuberculosis, has the distinction of also being used as an adjunct in the treatment of some solid and superficial skin neoplasms. Its antigenic properties act to stimulate immune cell responsiveness and therefore heighten activity against tumour cells.

◆ COMMON ADVERSE EFFECTS

The most common adverse effects associated with vaccination include localised inflammation at the site of injection and transient febrile state characterised by mild fever, headache, dizziness, malaise and nausea. Nowadays, a pre-vaccination dose of **paracetamol** is recommended in order to minimise the sensitivity of the recipient to these common reactions. This can be followed by further doses of paracetamol every 3–4 hours as required, up to the maximum daily dosage. Convulsions resulting in permanent brain damage have been reported after immunisation with some cellular vaccines, e.g. pertussis vaccine, but these reactions are rare and idiosyncratic. As with all biological products, there is a risk of severe allergic reaction in some people immediately after vaccination. The recipient should be observed for a short time after administration of the vaccine, and adrenaline should always be available in case anaphylaxis occurs. Contraindications for vaccination include pregnancy, lactation, acute febrile illness and known hypersensitivity. An antimicrobial agent is often incorporated in a vaccine in order to minimise the risk of infection at the injection site.

✚ CLINICAL CONSIDERATIONS

Vaccines are available against a range of bacterial infections, including diphtheria, pneumonia, tuberculosis, typhoid, tetanus, pertussis, meningitis, plague, Q fever and cholera, and a range of viral infections, including measles, mumps, poliomyelitis, influenza, hepatitis A and B, rabies, rubella and yellow fever. The current recommended childhood immunisation schedules are available in clinical references such as the BNF for Children.

Cytokines

Newer agents being used to stimulate immunity are purified extracts of natural cytokines. Agents currently available for clinical use are a number of interferons and the colony-stimulating factors **lenograstim**, **filgrastim** and **molgramostim**.

INTERFERONS

Interferons that have been approved for use are **interferon alfa-2a**, **interferon alfa-2b**, **interferon beta-1a**, **interferon beta-1b** and **interferon gamma-1b**. Interferons are used in the treatment of the viral infection that causes genital warts, selected leukaemias (see Chapter 76), Kaposi's sarcoma (often associated with the later stages of acquired immunodeficiency syndrome (AIDS)) and chronic hepatitis B and C.

■ MECHANISM OF ACTION

Interferons act to protect uninfected cells from viral infection, suppress viral replication in infected cells, and heighten the activity of macrophages and cytotoxic T-cells

against a virus or neoplastic cells. Their general effects are outlined in Table 75.1.

Interferons alfa-2a and alfa-2b are used in the treatment of viral hepatitis; in addition, interferon alfa-2b is used in chronic myelogenous leukaemias. **Peginterferon** is a combination of interferon alfa-2b and polyethylene glycol, which prolongs the activity of the former in the body. Clinical trials have shown that this treatment is more effective than interferon alfa-2b alone in the management of chronic hepatitis C in adults who have not received previous treatment with interferons. A preparation combining interferon alfa-2b with the nucleoside analogue **ribavirin** is available for the treatment of hepatitis C. Ribavirin has been shown to inhibit hepatitis C viral replication (see Chapter 73). The preparation has been shown to be quite efficacious in interferon-relapsed patients and in patients who have not received interferon treatment before.

Interferons beta-1a and beta-1b are used selectively in cases of relapsing–remitting multiple sclerosis (MS) (see Chapter 36). Their mechanism of action in MS is yet to be established, but they have been shown to have antiviral and immunoregulatory activity. An advantage of interferon beta-1a is its long duration of action, and the patient has to have only a single weekly injection rather than an injection every 2 days.

Interferon gamma-1b is used in the treatment of chronic granulomatous disease (CGD). The specific action of interferon gamma-1b in CGD is not known, but it may involve stimulating macrophage cytotoxicity and antibody-dependent cell-mediated cytotoxicity.

◆ COMMON ADVERSE EFFECTS

Influenza-type symptoms (fever, malaise, joint/muscle pain, anorexia) are commonly associated with interferon treatment. These effects may be lessened by paracetamol administration before interferon injection. Less frequently observed are cardiovascular and neurological effects, such as hypotension, headache, confusion and dizziness.

In combined therapy with interferon alfa-2b and ribavirin, haemolysis and anaemia have been observed.

✚ CLINICAL CONSIDERATIONS

The flu-like reactions of interferons can be reduced by dosing at bedtime and by administering paracetamol beforehand. Complete blood count and liver function should be monitored at baseline and during interferon therapy.

COLONY-STIMULATING FACTORS

Filgrastim and **lenograstim** are human granulocyte colony-stimulating factors (G-CSF), produced using recombinant DNA technology. They are used to treat the neutropenia that occurs during some types of anticancer therapy (see Chapter 76) and after bone-marrow transplantation.

◆ MECHANISM OF ACTION

Colony-stimulating factors are glycoproteins that act as growth factors. They bind to receptors on the surface of selected precursor blood cells and stimulate proliferation, differentiation and activation of these cell lines. G-CSF is produced by monocytes, endothelial cells and fibroblasts (see Table 75.1) and stimulates neutrophil production. Granulocyte/macrophage colony-stimulating factor (GM-CSF) is secreted by many body cells and stimulates most precursor blood cells types. These agents must be administered parenterally by the subcutaneous or intravenous route.

Another growth factor used clinically is stem-cell factor (SCF), which is produced by bone-marrow cells. This is produced using recombinant DNA technology and, in this form, is called **ancestim**. When ancestim is administered subcutaneously with filgrastim, it induces a synergistic effect to stimulate neutrophil production.

◆ COMMON ADVERSE EFFECTS

A common adverse reaction to CSF is bone pain. They may also cause an alteration in blood cell levels, gastrointestinal disturbances, fever and rash. They are contraindicated in myeloid cancers, as they may enhance neoplastic development.

Common reactions associated with ancestim administration include local reactions, such as redness, pruritus and urticaria. Mild respiratory symptoms (pharygitis, cough) have been observed during ancestim and filgrastim treatment.

✚ CLINICAL CONSIDERATIONS

With filgrastim and lenograstim, complete blood count should be moitored before giving cytotoxic therapy. For all CSF drugs, monitor kidney and liver function twice a week during treatment; monitor cardiac function in patients with pre-existing cardiac conditions.

Before ancestim treatment, the patient is premedicated with H_1-receptor and H_2-receptor antihistamines (e.g. **promethazine** and **ranitidine**), and an inhaled β_2 agonist (e.g. **salbutamol**) in order to prevent the onset of an allergic reaction.

INTERLEUKIN-2

Another cytokine used clinically is interleukin-2. This is available in the form of **aldesleukin** and is recommended in the management of adults with metastatic renal cell carcinoma.

■ MECHANISM OF ACTION

Aldesleukin is produced using recombinant DNA techniques. It mimics the immunomodulating effects of endogenous interleukin-2 (see Table 75.1). The immune responses induced include the activation of cell-mediated immunity and the secretion of a number of cytokines,

including tissue necrosis factor, gamma interferon and interleukin-1. Inhibition of tumour growth has been demonstrated in animal models.

◆ COMMON ADVERSE EFFECTS

Common adverse reactions include fever, chills, anaemia, diarrhoea, nausea, vomiting and reactions at the local injection site. When administered intravenously, the treatment can induce capillary leak syndrome, characterised by hypotension, pulmonary oedema, oliguria and weight gain. This condition can be severe and result in death.

✚ CLINICAL CONSIDERATIONS

Baseline assessments of respiratory and cardiac function should be performed before commencing therapy with aldesleukin. Thyroid, renal and hepatic function and blood glucose levels should be monitored at baseline and during therapy. Paracetamol and corticosteroids may be used to manage symptoms of adverse effects.

IMMUNOMODULATING AGENTS THAT SUPPRESS IMMUNITY

This is an important group of drugs used to prevent the rejection of transplanted tissues and organs. These agents can also be used in autoimmune diseases characterised by aberrant immune surveillance, such as systemic lupus erythematosus (SLE), MS and Hashimoto's thyroiditis. In autoimmune conditions, immune cells not only react against cells bearing foreign antigens but also destroy normal body cells not recognised as bearing markers of 'self'. Anti-inflammatory agents should be considered immunosuppressants because they suppress overexuberant inflammatory responses, which lead to pain, immobility and deformity. The non-steroidal anti-inflammatory agents have been discussed (Chapter 40), as have the corticosteroids (Chapter 58). As the corticosteroids are used in the prevention of graft rejection, however, some discussion of them in the context of immune function is appropriate here.

Significantly, immunosuppression can lead to increased susceptibility to infection and the development of malignancies. From a therapeutic point of view, the desired result in transplantation medicine is to attain immunological tolerance of the grafted tissue or organ without producing excessive immunosuppression. This state of tolerance is difficult to achieve with the current drugs available.

Corticosteroids

◆ MECHANISM OF ACTION

The corticosteroids greatly affect the immune system, but they tend to have specific effects on certain components rather than non-specifically altering all aspects. They reduce the size and substance of the lymph nodes and spleen without suppressing bone-marrow cells, thus reducing the risk of bone marrow toxicity. The corticosteroids are particularly toxic to the helper and suppressor subpopulations of T-cells, greatly affecting the modulation of the immune response and, in particular, cellular immunity. Plasma cells and humoral immunity in general are relatively unaffected, however. Although plasma cells are resistant, the inhibition of new protein synthesis by corticosteroid agents results in lower levels of antibodies in the blood (diminishing previously well-established antibody responses) and reduced cytokine production. Macrophage responsiveness is also suppressed.

◆ COMMON ADVERSE EFFECTS

As a consequence of these actions, the patient may become more susceptible to infection and may need to be monitored closely for early symptoms. Other common acute adverse effects include fluid retention, electrolyte imbalances (especially hypokalaemia), increased blood pressure, elevated blood glucose levels and euphoria.

✚ CLINICAL CONSIDERATIONS

The corticosteroids **prednisone** and **dexamethasone** are used to prevent the rejection of transplanted tissues in preference to **cortisone** because they produce less sodium retention (see Chapter 58). They may be used alone or in combination with another immunosuppressant in order to minimise adverse effects.

Patients should be monitored for clinical manifestations of infection. If the corticosteroid has been administered for more than 3 weeks, the dose should be reduced gradually if it is time to stop taking the drug. Blood glucose levels, weight, blood pressure and electrolyte levels should be measured at baseline and during therapy. Bone mineral density should also be assessed at baseline for patients needing repeat courses and those on chronic therapy.

Anti-T-lymphocyte immunoglobulin

Two forms of immunoglobulin are available that selectively depress the number or function of human T-cells: **antithymocyte immunoglobulin** and **muromonab-CD3**. T-cells play a significant role in cell-mediated and delayed-type hypersensitivity reactions, which result in the rejection of tissue transplants. These drugs are indicated for patients experiencing acute graft rejection after renal transplant.

■ MECHANISM OF ACTION

Antithymocyte immunoglobulin is horse sera containing antibodies directed against human T-cells. Its administration results in depleted blood levels of T-cells; humoral immunity remains intact. Muromonab-CD3 is mouse sera

containing monoclonal antibodies directed against a protein, CD3, located on the surface of T-cells and involved in antigen recognition. All T-cell functions are blocked as a result.

◆ COMMON ADVERSE EFFECTS

The principal adverse effect associated with these preparations is due to the fact that they are obtained from non-human sources and may trigger immune reactions of an allergic type after administration. Reactions ranging from rash to anaphylaxis and serum sickness can occur. The antithymocyte immunoglobulin can contain antibodies to other formed elements in human blood, which may lead to thrombocytopenia and leucocytopenia.

✚ CLINICAL CONSIDERATIONS

Perform skin testing for allergy reactions before administering the antithymocyte immunoglobulin. Complete blood count should be monitored daily until stable during immunoglobulin therapy. Muromonab-CD3 therapy also requires monitoring of the complete blood count on a daily basis. The patient should inform the doctor immediately if they experience chest pain, shortness of breath or signs of allergy during muromonab-CD3 administration.

Calcineurin inhibitors

Ciclosporin and **tacrolimus** belong to a group of immunosuppressants known as calcineurin inhibitors. Ciclosporin is an antibiotic substance derived from the fungus *Tolypocladium*. Ciclosporin is an important immunosuppressant that has revolutionised transplant surgery. It is used to prevent the rejection of transplanted organs such as kidney, liver and heart. Tacrolimus is a macrolide antibiotic (see Chapter 68). Structurally it is quite different from ciclosporin and is related more closely to erythromycin, but the effects of ciclosporin and tacrolimus are similar. Tacrolimus has been approved for the prevention of tissue rejection in liver and kidney transplantation.

■ MECHANISM OF ACTION

The calcineurin inhibitors disrupt the intracellular signalling pathways associated with T-cell surface-receptor activation. These receptors are activated by the presentation of an antigen (see Figure 75.1). Calcineurin is a phosphatase, an enzyme responsible for dephosphorylating (removing a phosphate molecule from) a nuclear factor. This factor activates genes associated with cytokine production. One of these cytokines is interleukin-2, responsible for T-cell proliferation and differentiation.

Calcineurin inhibitors act to block the production of specific cytokines that stimulate T-cell proliferation, such as interleukin-2, interleukin-3 and gamma interferon, and consequently prevent the proliferation of T-cells after antigen presentation, without affecting phagocytosis, sensitising T-cell function or suppressing bone-marrow cells.

◆ COMMON ADVERSE EFFECTS

Commonly observed adverse reactions associated with ciclosporin treatment include hirsutism, liver and kidney dysfunction and gastrointestinal disturbances.

The common adverse effects of tacrolimus include diarrhoea, headache, tremor and nausea. Renal function, glucose metabolism and blood pressure should be monitored during therapy.

✚ CLINICAL CONSIDERATIONS

The nephrotoxicity of ciclosporin is significant and is measured by plasma creatinine levels, which will rise. During graft rejection, plasma creatinine levels may rise, thus masking the toxicity of ciclosporin. Patients must be monitored carefully during this time, and a reduction in ciclosporin dosage may be appropriate.

The ciclosporin dose can be reduced using a therapeutic combination with **diltiazem** or **ketoconazole**. Patients must be informed about the reasons underlying the use of the other agent. Trough ciclosporin concentration levels should be measured every 2–3 months. Renal and hepatic function tests should be monitored regularly.

Clinical studies using tacrolimus and low-dose corticosteroids have indicated that this regimen is at least as effective as ciclosporin therapy. Tacrolimus is marketed as a drug that is less toxic than cyclosporin. Tacrolimus tablets are taken 12 hours apart at the same time each day, and on an empty stomach. Renal and hepatic function and trough levels should be monitored every 2–3 months during therapy.

Antiproliferative agents

Sirolimus, **azathioprine**, **mycophenolate** and **leflunomide** can be grouped together for the purpose of this discussion as antiproliferative agents that inhibit the proliferation of immune cells required in an immune response.

SIROLIMUS

Sirolimus, like tacrolimus, is a macrolide antibiotic. Their mechanisms of action are different, however.

■ MECHANISM OF ACTION

Sirolimus inhibits T-cell function involved in graft rejection. In contrast to the calcineurin inhibitors, which achieve this by blocking interleukin-2 production, sirolimus acts downstream to block transmission of the intracellular signal produced by interleukin-2 acting on T-cells. Sirolimus inhibits the mTOR (mammalian target of rapamycin) intracellular pathway, which is triggered by interleukin-2 and is important for lymphocyte proliferation (see Chapter 76).

◆ COMMON ADVERSE EFFECTS

Common adverse reactions of sirolimus include abdominal pain, diarrhoea, urinary tract infection, altered blood lipid profile, blood dyscrasias and arthralgia.

✚ CLINICAL CONSIDERATIONS

Sirolimus should be used, at least initially, in combination with ciclosporin and corticosteroids. Sirolimus should be taken at the same time every day, with the same type of food. Drug trough monitoring is valuable for determining compliance. Complete blood count and triglyceride and cholesterol levels should be monitored regularly during therapy. Sirolimus-releasing coronary artery stents have been developed to reduce restenosis.

AZATHIOPRINE

Azathioprine is a cytotoxic drug used in the treatment of neoplastic disease (see Chapter 76). It also has applications as an immunosuppressant.

■ MECHANISM OF ACTION

Azathioprine damages the structure of DNA by inserting its metabolite mercaptopurine into the DNA molecule. This disables the process of cellular reproduction. As a consequence, cell populations undergoing rapid proliferation are selectively destroyed while non-dividing tissues are spared. The proliferation of immune cells following antigen presentation and recognition is blocked after azathioprine administration. Azathioprine is indicated in the treatment of organ transplant rejection and in a number of autoimmune diseases, such as rheumatoid arthritis and SLE.

Unlike the previously described immunosuppressants, azathioprine does not discriminate between T-cells and other immune cell subpopulations; instead, it suppresses all types of T-cell.

◆ COMMON ADVERSE EFFECTS

Toxic side effects associated with azathioprine therapy manifest as thrombocytopenia, anaemia and leucopenia. Susceptibility to infection is a major concern while taking this drug. Higher doses can result in liver and kidney dysfunction and gastrointestinal disturbances.

✚ CLINICAL CONSIDERATIONS

The patient should inform their doctor if they experience bleeding, increased bruising or infection. Complete blood count (including platelet and differential count) and liver function tests must be monitored regularly.

Health-care professionals are advised to handle uncoated azathioprine tablets with gloves and in accordance with cytotoxic precautions. The dose should be withheld if the white blood cell count is less than 3×10^9/l.

MYCOPHENOLATE

Mycophenolate is used to prevent rejection of kidney transplants. The drug is administered orally and can be used in combination with other immunosuppressants, such as ciclosporin and corticosteroids.

■ MECHANISM OF ACTION

Mycophenolic acid is an immunosuppressant derived from *Penicillium stoloniferum*. It has potent cytostatic effects on both T- and B-lymphocytes. It is given with other immunosuppressants for the prevention of graft rejection, and it has also been tried in various diseases with autoimmune and immune-mediated inflammatory components. The action of mycophenolate is to selectively inhibit the T- and B-lymphocyte proliferation that follows antigen presentation. It does this by being a reversible inhibitor of inosine monophosphate dehydrogenase and thus inhibiting purine synthesis, an important component in the mitotic process. Lymphocytes are more dependent on this pathway for proliferation than other immune cells. As a consequence, an immune response against the transplanted tissue cannot be effectively mounted.

◆ COMMON ADVERSE EFFECTS

Common adverse effects are diarrhoea, sepsis, vomiting and a tendency to develop certain infections.

✚ CLINICAL CONSIDERATIONS

Patients should be advised to take the preparation with food in order to prevent gastric irritation. Complete blood counts (including neutrophil count) should be monitored during therapy. The patient should tell their doctor if they develop diarrhoea or experience signs of infection.

LEFLUNOMIDE

Leflunomide has immunosuppressant and antiproliferative properties and is used in the treatment of active rheumatoid arthritis. It is also used in the treatment of active psoriatic arthritis and is being investigated in the management of various solid neoplasms.

■ MECHANISM OF ACTION

Leflunomide is a synthetic agent that modulates immune function by inhibiting the proliferation of lymphocytes. It achieves this by interfering with the synthesis of pyrimidines, which are essential components of nucleic acids. In clinical trials, it has demonstrated a similar efficacy to **methotrexate**.

◆ COMMON ADVERSE EFFECTS

Common adverse effects of leflunomide treatment include diarrhoea, rash, hair loss and elevated liver enzyme levels.

Immunosuppression may lead to increased susceptibility to infection and an increased risk of a malignancy developing.

✚ CLINICAL CONSIDERATIONS

Before the commencement of therapy, blood pressure, liver function and full blood cell count should be taken. Blood cell counts and liver function need to be monitored regularly during treatment. Alcohol ingestion during therapy can increase the risk of liver impairment.

The patient should be advised to contact their doctor if jaundice, persistent fever, sore throat, bleeding or skin problems develop.

Monoclonal antibodies

A number of drugs that are monoclonal antibodies are available. This term means that the drug consists of antibodies that are identical because they were produced by one type of immune cell. They can be produced against specific target body cells and structures and against organisms that may enter the body. These drugs can be identified easily by the suffix '-mab' (an abbreviation of monoclonal antibody). They are used in a wide range of conditions. There has been widespread debate in the UK regarding the availability of a humanised monoclonal antibody trastuzumab (Herceptin™; see Chapter 76) for breast cancer. The use of humanised monoclonal antibodies is not without problems, as evidenced by a clinical trial in human volunteers in whom an extreme, unexpected reaction occurred. Not surprisingly, this trial generated a great deal of media concern about this class of drug and the conduct of clinical trials.

Four monoclonal antibody preparations that are linked to immune function are described here: **basiliximab**, **daclizumab**, **infliximab** and **palivizumab**.

✚ CLINICAL CONSIDERATIONS

Patients should be monitored for signs of allergy, including shortness of breath and chest tightness. Emergency equipment such as adrenaline, antihistamines and corticosteroids should be easily accessible when using these agents. Pretreatment with paracetamol and an antihistamine may help to reduce possible hypersensitivity.

BASILIXIMAB AND DACLIZUMAB

Basiliximab and daclizumab are indicated for the prevention of acute graft rejection in kidney transplantation.

■ MECHANISM OF ACTION

These agents comprise monoclonal antibodies directed against the interleukin-2 receptor on the surface of T-lymphocytes. Normally, interleukin-2 stimulates this receptor and triggers T-cell proliferation and the activated T-cells induce an immune reaction against transplanted organs when the lymphocytes interact with tissue antigens that indicate 'foreignness'. These monoclonal antibodies function as interleukin-2 receptor antagonists by binding to the alpha chain (CD25 antigen) of the interleukin-2 receptor on the surface of activated T-lymphocytes. As a result, they suppress the T-cell proliferative response, leading to immunosuppression.

◆ COMMON ADVERSE EFFECTS

Common adverse reactions of basiliximab include nausea, constipation and urinary tract infection. As the antibodies are, in part, raised against mice tissues, some patients develop antibodies to this agent.

Daclizumab treatment induces gastrointestinal disturbances, hypersensitivity reactions and dyspnoea.

✚ CLINICAL CONSIDERATIONS

Treatment with basiliximab starts before transplant surgery and continues up to 4 days post-operation. This provides immunosuppression for up to 6 weeks. Treatment with daclizumab commences 24 hours before surgery and continues for a subsequent five doses, 14 days apart.

INFLIXIMAB

Infliximab is used in the management of moderate to severe active rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, Crohn's disease and ulcerative colitis.

■ MECHANISM OF ACTION

Like basiliximab, infliximab is a monoclonal antibody but is raised against the cytokine tumour necrosis factor alpha (TNF-α). TNF-α (see Table 75.1) is a proinflammatory cytokine that plays a significant role in the pathophysiology of the chronic inflammatory conditions rheumatoid arthritis and Crohn's disease. Infliximab binds to TNF-α and blocks its actions.

◆ COMMON ADVERSE EFFECTS

Adverse effects associated with infliximab include increased susceptibility to infection, respiratory distress, alterations in blood pressure (hypotension or hypertension) and gastrointestinal disturbances.

PALIVIZUMAB

Palivizumab is recommended for the prevention of respiratory syncytial virus (RSV) in children at high risk during the RSV season.

■ MECHANISM OF ACTION

Palivizumab is directed against RSV. It binds to and neutralises RSV, preventing viral replication. It is administered intravenously at monthly intervals throughout the RSV season.

◆ COMMON ADVERSE EFFECTS

The most common adverse effects associated with this treatment are upper respiratory tract infection, fever, runny nose and cough.

Other immunosuppressants

ETANERCEPT

Like infliximab, **etanercept** is a parenteral agent used in the treatment of rheumatoid arthritis.

■ MECHANISM OF ACTION

Etanercept is a protein principally consisting of a combination of the binding site of a TNF receptor and a fragment of immunoglobulin G (IgG). It is not a monoclonal antibody, but, like infliximab, it binds to TNF-α, effectively neutralising the cytokine.

◆ COMMON ADVERSE EFFECTS

An increased susceptibility to infection may develop, which can lead to sepsis. Common adverse effects include local reactions around the subcutaneous injection site (redness, itching, pain, swelling). Systemic effects include suppression of blood cell levels, central nervous system demyelination and hypersensitivity.

✚ CLINICAL CONSIDERATIONS

Local injection-site reactions can be minimised by pretreatment with paracetamol or an antihistamine. Blood cell counts and neurological function should be monitored during therapy. As these patients have an increased susceptibility to infection, a clean environment must be maintained and patients should be kept away from other individuals with infections. All procedures must be performed using aseptic techniques.

GLATIRAMER

Glatiramer is used as an immunomodulating agent in the management of the relapsing–remitting form of MS (see Chapter 36).

■ MECHANISM OF ACTION

Glatiramer is a synthetic polypetide constructed using the L-isomers of four naturally occurring amino acids: glutamic acid, lysine, alanine and tyrosine. It was designed to mimic a protein in myelin, myelin basic protein, and was expected to induce MS in an animal model. On the contrary, however, it was found to suppress disease in animal models and came to be tested in human disease. The mechanism of action of glatiramer is not understood well, but it is thought that it might interfere with binding on antigen-presenting immune cells or promote suppressor T-cell function. Preclinical studies using the animal model for MS as well as human clinical trials have shown that glatiramer reduces the frequency of relapses in the relapsing–remitting form of this disease.

◆ COMMON ADVERSE EFFECTS

The most common adverse effects are local reactions around the subcutaneous injection site, including redness, pain, induration and itching. Systemic adverse effects include flushing, chest pain, palpitations and dyspnoea.

✚ CLINICAL CONSIDERATIONS

Rotate injection sites to reduce the incidence and discomfort of local reactions. A history of hypersensitivity reactions or asthma may increase the risk of allergic reactions.

CLINICAL MANAGEMENT

Immunostimulating agents

Assessment

- Assess patients ordered immunostimulants (vaccines) for a history of an immunocompromised state during acute or febrile illness, pregnancy and breast feeding. Vaccines, particularly those made from live viruses, are usually contraindicated in these conditions.
- Review the patient's record of immunisation to determine the response to these vaccines.
- Determine whether the patient has an allergy to horses, feathers or hens' eggs. Assess whether there is a family history of allergy to these items. Generally, vaccines prepared using these sources should not be administered to these patients. Children with egg allergies can safely be given the measles, mumps and rubella (MMR) vaccine scheduled from 12 months of age, provided this is done under close medical supervision.

- Perform a baseline assessment of vital signs and compare with subsequent observations.
- Skin tests may be done on some patients, particularly those with some history of allergy, in order to determine the effect of the vaccine.

Planning

- The patient will achieve immunisation of the condition for which the vaccination is intended, without adverse effects.
- The immune responsiveness of the patient will improve after administration of an immunostimulant.

Implementation

Antisera

- Observe for allergic reactions arising from non-human antisera, including fever, chills, rashes and anaphylactic shock. Adverse reactions to human immunoglobulins are rare.
- For immunoglobulins requiring large volumes for administration, the gluteal muscle is preferable to other muscle sites. Large volumes may also be administered intravenously.

Vaccines

- Administer paracetamol to young children and infants half an hour before the vaccine to prevent a febrile reaction.
- Always have emergency equipment and drugs, including adrenaline, readily available when protein-containing vaccines are administered (see Table 11.2 in Chapter 11 for further information on measures to take for an anaphylactic reaction).
- Use the vastus lateralis area for injection in young children and infants. Administer oral vaccines before injectable vaccines if performed during the same session. Use the deltoid muscle in older children and adults.
- Observe and document the presence of fever, tachycardia, dyspnoea, backache, headache and irritability during intravenous infusion of vaccination.
- Following administration of the vaccine, observe the patient for about 20–30 minutes for any adverse reaction, such as anaphylaxis.
- Administer paracetamol to infants and young children every 4 hours after administration of vaccines to reduce the severity of a febrile reaction.

Cytokines

- For patients administered interferons, observe for fever, chills, tachycardia, nausea, diarrhoea and anorexia. Monitor for low white blood cell and platelet counts.
- For patients administered interleukins, monitor for fluid retention, dyspnoea, fatigue and anaemia. Document weight and blood pressure as indications for oedema.
- Minimise flu-like reactions from interferons by administration of paracetamol.
- For a patient on interferon therapy, monitor the cardiac rhythm if a past or present cardiac abnormality is detected.
- During interferon therapy for hepatitis B or C, perform a liver biopsy at commencement of therapy. Perform complete blood count, electrolyte levels, liver function tests and creatinine levels at commencement and once a month thereafter. For patients with renal or hepatic impairment, more intense monitoring may be warranted, especially in the first 3 months of treatment.
- For a patient receiving interferon beta for multiple sclerosis, a yearly magnetic resonance scan and neutralising antibody testing should be undertaken.
- A complete blood examination with differential white cell count and platelet count should be completed before therapy with colony-stimulating factors. Monitor plasma creatinine, uric acid and liver function tests. These blood tests should be repeated twice-weekly during therapy. Monitor cardiac function in patients with pre-existing cardiac conditions.
- Bone pain, a common adverse effect of colony-stimulating factors, can be alleviated by administration of paracetamol or aspirin.

Patient teaching

- Ensure that records for vaccination are kept up to date.
- The application of an icepack at the injection site can lessen the discomfort caused by a vaccine.
- Advise parents on the use of paracetamol before and after vaccination of their child to reduce febrile reactions and discomfort.
- Warn patients taking interferon that driving and operating heavy machinery should be avoided if drowsiness and dizziness occur.
- Advise patients on interferon to avoid medications that may cause drowsiness and dizziness unless these have been approved by the doctor.
- Advise patients on interferon to take doses at night in order to avoid daytime fatigue.
- Impress on patients taking interferon the importance of having regular white blood cell and platelet counts.

Evaluation

- Evaluate the ability of immunisation to stimulate the immune system and to prevent a particular infection without producing adverse effects.
- Evaluate the ability of the immunostimulating agent to relieve a particular condition without producing adverse effects.

Immunosuppressants

- For clinical management of drugs affecting the adrenal cortex, see Chapter 58.

Assessment

- Assess patients ordered immunosuppressants for the presence of infection. Exercise caution in these conditions when administering immunosuppressants. Assess vital signs. Often, temperature and pulse rate are increased in the presence of infection. Auscultate the chest for normal breath sounds. Take note of any audible crackles. Assess the colour, amount and consistency of sputum. Yellow or green sputum is often indicative of infection. Determine the presence of gastrointestinal infections, as indicated by increased intensity of bowel sounds, abdominal pain and diarrhoea. Urinary tract infections often cause frequency of urination and burning sensation during urination. Vaginal infections often cause itchiness and vaginal discharge. Assess the skin for the presence of skin lesions. Compare with subsequent observations.
- If applicable, perform a baseline antibody titre and compare with future titres after therapy.
- Determine a history of allergy for patients ordered antithymocyte or antilymphocyte medications. These are globulin preparations, which could cause adverse allergic reactions.

Planning

- Planning depends on the reason for administration. The patient will not experience organ rejection or the patient will experience an alleviation of the autoimmune condition after treatment with these agents.
- The patient will not experience infection following the use of immunosuppressants.

Implementation

- As these patients have an increased susceptibility to infection, maintain a clean environment and keep the patient away from individuals with infections. Perform all procedures using aseptic techniques.
- Monitor the white blood cell count. This will be elevated in the presence of infection. In some cases, a T-cell count will be performed.
- Monitor the patient's vital signs and observe for manifestations of infection.
- Monitor patients for fever, malaise, diarrhoea, nausea, vomiting and crackles in the lungs.
- Note that manifestations of serum sickness may occur up to 14 days after administration of medication. Manifestations include rash and pain in the extremities and joints.
- The administration of these agents is often accompanied by premedication with antipyretics, antihistamines, analgesics and corticosteroids in order to prevent adverse effects.
- For patients on antithymocyte globulin, monitor for jugular vein distension, fluid intake and output, fluid balance and body weight. Perform full blood examination, platelet count and white blood cell count.
- For patients receiving azathioprine, monitor intake, output, fluid balance and body weight. Observe for manifestations of impaired renal function, as shown by decreased urine output, elevated serum creatinine and urea levels. Observe for impaired liver function, as indicated by elevated liver enzymes.
- Dilute oral doses of ciclosporin with milk or orange juice.
- Monitor patients receiving ciclosporin for fluid input and output and body weight. Inspect teeth and gums regularly for bleeding and gum hyperplasia.
- For patients on ciclosporin, monitor liver function tests, full blood examination, white cell count and platelet count. Observe for bleeding, jaundice, fever and fatigue.
- For patients on muromonab-CD3, monitor for elevated temperature. Febrile reactions often occur with the first two doses of this drug. Monitor vital signs regularly and frequently during this time. Place a cooling blanket over the patient if the temperature rises above 38.5 °C.
- As muromonab-CD3 may cause fluid retention, monitor the patient's fluid input and output, fluid balance and dependent oedema.

Patient teaching

- Ensure the patient maintains follow-up visits with the doctor to assess effectiveness of treatment in preventing graft rejection or manifestations of autoimmune disease. Regular follow-up is also important because these agents have been associated with an increased incidence of various cancers.
- Advise patients on the importance of preventing infection. Measures include avoiding people who have a known infection, washing hands before handling food and after visiting the lavatory, using bed linen

that is separate from the rest of the family's, and avoiding the use of shared eating utensils. Explain the importance of maintaining a well-balanced diet in preventing infection.
- Instruct patients that they should not receive vaccines made from live viruses.
- Warn patients that serum sickness may develop, but this might not occur for 14 days after the dose.
- Advise patients on azathioprine that oral doses should be taken after meals to prevent gastric irritation.
- Inform patients on azathioprine that oral ulcers may develop (see Table 11.14 in Chapter 11 for measures to implement for this condition).
- Warn patients on ciclosporin that tremor may develop.
- For patients on ciclosporin, reinforce the importance of regular dental care, including brushing teeth, flossing and visits to the dentist.
- Advise patients on muromonab-CD3 that trembling and shaking of the hands after the first dose is common.

Evaluation

- Evaluate the effectiveness of the agent in preventing rejection of a transplanted organ or alleviating the manifestations associated with autoimmune disease.

SUMMARY

- Immunomodulating agents are drugs that alter immune responsiveness. Immunostimulants enhance immunity, while immunosuppressants inhibit excessive or inappropriate immune responses.
- Immunity involves humoral and cellular responses. Lymphocytes, basophils, eosinophils, monocytes, macrophages and mast cells play key roles in immune responsiveness.
- T-cells play a significant immunomodulating role. Some T-cell subpopulations can stimulate and others suppress immune cell proliferation. T-cell activation and proliferation is a common target for immunosuppressant therapy.
- Cytokines are produced by immune and other body cells and promote inflammation and immune responsiveness.
- Antisera are used as a form of passive immunity for short-term immune protection, whereas vaccines stimulate active immunity in their recipients.
- Observe for allergic reactions to non-human antisera. Make sure that adrenaline is available when using non-human antisera in case anaphylaxis occurs.
- Individuals need to remain within the medical vicinity for about 15 minutes after vaccination in order to monitor for any adverse reactions.
- A number of cytokines are used clinically, including interferons, colony-stimulating factors and interleukin-2.
- Blood cell counts and renal, hepatic and cardiac function may need to be monitored during treatment with cytokines.
- Important immunosuppressive groups include the corticosteroids, the calcineurin inhibitors, the antiproliferative agents and the monoclonal antibodies.
- An increased risk of infection and malignancy development is a major concern associated with immunosuppressant therapy.

1 Outline the functions of the following immune cells:
   (a) macrophages;
   (b) basophils;
   (c) B-cells;
   (d) T-cells.

2 What type of immunity (active or passive) does each of the following immunomodulating agents confer after administration?
   (a) vaccines;
   (b) antisera;
   (c) cytokines.

3 What is the principle underlying the action of vaccines?

4 In general, what adverse reactions would you expect after the administration of an immunomodulating agent derived from an animal source?

5 State the mechanism of action of each of the following immunosuppressants:
   (a) calcineurin inhibitors;
   (b) muromonab-CD3;
   (c) monoclonal antibodies;
   (d) the antiproliferative agent azathioprine;
   (e) etanercept.

6 If a patient experiences an anaphylactic reaction after vaccination, what emergency drug would be administered? What other measures should be taken?

7 Rachel Quinlan, a 32-year-old electrician, is prescribed ciclosporin after a successful heart transplantation for cardiomyopathy. What adverse effects of ciclosporin would you advise Ms Quinlan about? What patient education would you offer Ms Quinlan to protect herself against infection?

8 Ronaldo Ricoletto, a 28-year-old labourer, comes into the emergency department after stepping on a rusty nail. What assessment would you make of Mr Ricoletto's vaccination status? Explain.

9 Why is a patient observed for approximately 20 minutes after administration of a vaccine?

10 What types of patient should avoid vaccines containing live viruses?

11 Fred Jamieson is a 75-year-old man in hospital for hip-replacement surgery. His doctor has advised him to be vaccinated for influenza before he is discharged from hospital. Fred confides to you that he would rather not because he has heard that you can catch the flu from the vaccine. How do you respond to Fred's concerns?

75 DRUG SUMMARY TABLE: VACCINES AND IMMUNOMODULATING DRUGS

FAMILY NAME	GENERIC NAME	TRADE NAME(S)
Immunostimulants	Aldesleukin	Proleukin
	Bacillus Calmette-Guérin	ImmuCyst
		OncoTICE
	Glatiramer	Copaxone
Interferons	Interferon alfa-2a	Roferon-A
	Interferon alfa-2b	IntronA
	+ Ribavirin	
	Interferon alfa-N	
	Interferon beta-1a	Avonex
		Rebif
	Interferon beta-1b	Betaferon
	Interferon gamma-1b	Immukin
	Peginterferon alfa-2b	Pegasys
		PegIntron
		ViraferonPeg
Growth factors	Filgrastim	Neupogen
	Pegfilgrastim	Neulasta
	Lenograstim	Granocyte
Immunosuppressants	Etanercept	Enbrel
Corticosteroids	Dexamethasone	
Calcineurin inhibitors	Ciclosporin (cyclosporine)	Neoral
		Sandimmun
	Tacrolimus	Prograf
Antiproliferative agents	Azathioprine	Imuran
	Leflunomide	Arava
	Mycophenolate	CellCept
	Sirolimus	Rapamune
Monoclonal antibodies	Basiliximab	Simulect
	Daclizumab	Zenapax
	Infliximab	Remicade
	Palivizumab	Synagis
	Rituximab	

CYTOTOXIC DRUGS

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CHAPTER SEVENTY-SIX

OBJECTIVES

KEY TERMS

Bone-marrow suppression (myelosuppression)
Cancer
Cell cycle
Drug resistance
Drugs and pregnancy
Neoplasia
Selective toxicity

After completing this chapter, the reader should be able to:

- **define the principle of selective toxicity as applied to neoplastic chemotherapy;**
- **identify the properties distinguishing cancerous cells from normal cells;**
- **outline the stages of the cell cycle;**
- **describe the mechanisms of action of the major groups of antineoplastic agents;**
- **state the general adverse effects associated with cytotoxic drugs.**

THE PRINCIPLE OF SELECTIVE TOXICITY AS APPLIED TO infectious diseases (see Chapter 66) is equally applicable in the treatment of neoplastic disease, where the abnormal cancerous cells are destroyed while normal host cells are spared. In order to achieve this, we must first identify the properties of neoplastic cells that differ from normal cells and then exploit those differences.

In general, the most significant physiological difference between cancerous and normal cells is the rate at which the cells reproduce (an accelerated rate for the former). It is this property that cancer drugs, otherwise known as cytotoxic agents, exploit in order to achieve selective toxicity. Therefore, a knowledge of the processes involved in cellular reproduction is needed in order to understand the mechanisms of action of the cytotoxic drugs. The embodiment of the process of cellular reproduction is the cell cycle.

THE CELL CYCLE

Typically, when we think of the processes involved in somatic cell reproduction, we think of the actual division of the cell – mitosis. This is only one stage in the process, however. There are other stages where the cell is preparing for division that are characterised by replication of cellular components. Components such as nucleic acids (DNA and RNA), proteins and other substances that characterise both the structural and functional identity of the cell must be duplicated so that the progeny will be identical to the parent cell in every way.

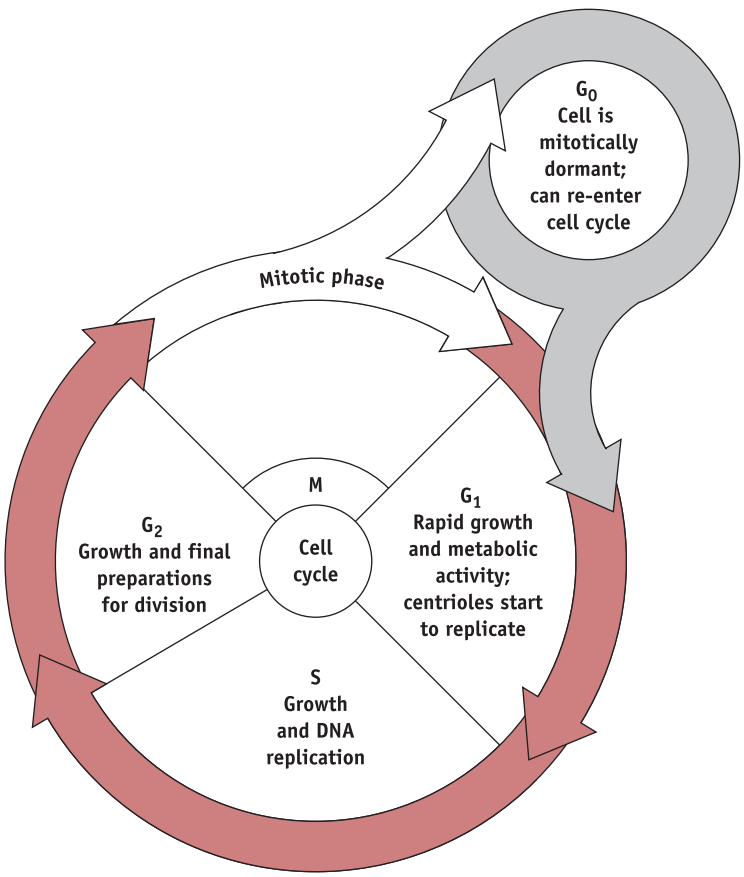
Thus, the cell cycle is partitioned into five phases symbolised by letters: G_1, S, G_2, M and G_0 (see Figure 76.1). G stands for 'gap' (or sometimes 'growth'), S stands for 'synthesis' and M represents 'mitosis'. The G_1, S and G_2 phases represent what is otherwise known as the interphase. In interphase, the cell undergoes normal cellular processes, contributing to bodily function.

The first phase, G_1, is characterised by RNA synthesis. In the S phase, the double-stranded DNA molecule separates and a new complementary strand to each original strand is synthesised; the result is that the original cellular DNA is duplicated. The G_2 phase is where RNA synthesis is completed and proteins are produced. During the M phase, nuclear and cytoplasmic cleavage occurs; this phase is achieved through the cooperation of chromosomes, centrioles and spindle fibres in order to deposit equal amounts of nuclear material in each of the newly formed cells.

In the G_0 phase, a cell is essentially in a resting state, remaining uncommitted to any aspect of cellular division. Within a normal tissue, not all cells divide simultaneously, and many are found in this dormant phase. The

FIGURE 76.1 THE CELL CYCLE

The first phase, G_1, is characterised by RNA synthesis. In the S phase, the double-stranded DNA molecule separates and a new complementary strand to each original strand is synthesised. The result is that the original cellular DNA is duplicated. The G_2 phase is where proteins are produced and RNA synthesis is completed. The M phase is actual nuclear and cytoplasmic cleavage. In the G_0 phase, a cell is essentially in a resting state, remaining uncommitted to any aspect of cellular division.



proportion of dormant cells varies from one tissue type to another and depends on the developmental stage of the individual. For example, the majority of cells within adult tissues are in G_0, but when cells die they are replaced by cells emerging from the G_0 phase. In contrast, during embryonic life, as tissues develop, most cells divide rapidly. The proportion of cells in a tissue involved in cell division is known as the growth fraction; this is small in the adult example and large in the embryonic example. The growth fraction of a tissue bearing a cancerous tumour increases.

The duration of the cell cycle varies from tissue to tissue. Some tissues, such as muscles and nerves, have almost lost the ability to divide. Other tissues, such as hepatic tissue, remain predominantly dormant unless traumatised. Others still divide very rapidly: worn-out cells in areas of significant wear and tear are constantly being replaced by new cells. Examples of this type of cell are hair follicles, skin cells and cells lining the gastrointestinal tract. Also included in this category of rapidly dividing cells are gametes, bone-marrow cells, and cells of the developing human in utero.

The cell cycle can be as short as a few hours and as long as several years. As a general rule, the durations of the M and S phases are constant for all cells. The durations of the G_0, G_1 and G_2 phases, however, vary from one cell type to another and determine the period of the total cell cycle. An important term associated with the duration of the cell cycle is the tissue doubling time – the time taken for the tissue mass to double. When a tumour develops within a tissue, the doubling time is generally shorter than normal.

GENERAL ADVERSE EFFECTS OF CYTOTOXIC DRUGS

As stated above, different body cells have different rates of reproduction. A number of normal cell populations are known to have a rapid turnover time, namely bone-marrow cells, hair cells, skin cells, cells lining the gastrointestinal tract, gametes and the developing human fetus. In cancer therapy, the principle of selective toxicity is theoretically directed against the rapidly proliferating neoplastic cells while sparing normal cells. In practice, however, tissues comprising rapidly dividing normal cells are also severely damaged. Indeed, a clear pattern of general adverse reactions across the different groups of cytotoxic drugs is apparent and will now be described.

Adverse reactions associated with cytotoxic agents can be grouped into two distinct categories: immediate effects and delayed effects. The immediate effects occur soon after drug administration, while delayed effects are observed some time after drug therapy commences.

Immediate effects are those such as nausea and vomiting, mouth ulcers, anorexia, blistering and necrosis of skin. The gastrointestinal disturbances are the result of irritation and damage to the cells lining the tract. A drug that induces skin blisters is known as a vesicating agent. Health-care workers must take precautions when administering these drugs in order to avoid damaging both their own and the patient's skin. Intravenous catheters must be secure in order to avoid extravasation of the drug into surrounding tissues, and protective apparel, such as gloves, must be worn in case of spillage. The consequences of tissue necrosis following extravasation can be very serious and include substantial scarring of the affected limb and, sometimes, limb amputation. Some cytotoxic agents (e.g. the alkylating agent **carmustine** and the cytotoxic antibiotic **doxorubicin**) can produce facial flushing if intravenously infused too quickly.

Delayed effects associated with cytotoxic drug therapy include alopecia (hair loss) and suppression of bone-marrow cells. Both of these effects can have a dramatic impact on the patient's body image and lifestyle, including interactions with other people and activity. As a result of the bone-marrow suppression, conditions such as thrombocytopenia, agranulocytosis, anaemia and leucopenia can occur. Unfortunately, the changes in leucocyte levels often induce a degree of immunosuppression, which, in turn, reduces the patient's natural capacity to fight the cancer. This effect must be weighed against the benefit of such treatment. There are now a number of immunomodulating agents, however, that can provide some relief from the effects of bone-marrow suppression (see later in this chapter). Many cytotoxic agents can induce peripheral neuropathies and may affect heart, liver, kidney and lung function. Therefore, the function of these organs should be monitored during therapy.

Given the seriousness of the conditions under which these drugs are used, contraindications are few. Drug hypersensitivity, extreme myelosuppression and severe impairment of the heart, liver and kidney are the main contraindications. All cytotoxic agents are contraindicated for at least part of the time during pregnancy (usually during the first trimester). Some agents must not be used at any time during gestation.

For the health-care professional, there is a further concern associated with long-term exposure to cytotoxic agents. Given the nature of their actions on DNA, many of these drugs are potential carcinogens. The health-care professional must take every precaution when handling and disposing of these drugs in order to minimise the personal and environmental risk. This is achieved by wearing protective apparel (gloves and masks) when preparing and administering cytotoxic drugs and by following the guidelines provided by the employing institution for correct disposal. Reconstitution should be carried out in designated areas by trained personnel. Pregnant staff members should not handle cytotoxics.

CYTOTOXIC AGENTS

There are three distinct groups of cytotoxic drugs: (i) cell-cycle-non-specific drugs, which are effective regardless of whether the tumour cells are dividing or in the dormant phase and act to sterilise the cell; (ii) cell-cycle-specific drugs, which must be administered at a time when tumour cells are proliferating; and (iii) tissue-specific agents, which deprive tissue tumours of a substance necessary for proliferation.

Cell-cycle-non-specific drugs

This group includes the alkylating agents and a number of powerful and toxic antibiotics. These drugs appear to bind to components of the DNA molecule directly, irreversibly disabling the mechanism for cellular division. This effectively sterilises the cell. These agents are efficacious regardless of whether cells are resting in the dormant phase or participating in the cell cycle, although cells involved in the latter appear more sensitive.

ALKYLATING AGENTS

The alkylating agents comprise a group of chemicals with diverse structures whose common feature is to form a chemical bond with the DNA molecule that disables mitosis.

■ MECHANISM OF ACTION

There are a number of drugs that act by inserting an alkyl group in the structure of DNA. An alkyl group cannot exist in a free form but always as part of a larger compound. Examples of alkyl groups are methyl ($-CH_3$), phosphate ($-PO_4$), amino ($-NH_2$), hydroxyl (–OH) and carboxyl (–COOH) groups. Common targets on the DNA molecule for alkylation are the bases guanine, adenine and cytosine.

The insertion of an alkyl group leads to the formation of cross-links between the two strands. This action prevents the separation necessary for replication and may ultimately lead to shearing of the DNA molecule. Without functioning DNA, the process of nucleic acid and protein synthesis necessary for cellular proliferation ceases. Cells in late G_1 or S phase of the cell cycle appear to be most sensitive to the effects of these drugs.

Important alkylating agents include the nitrogen mustards (**chlorambucil**, **cyclophosphamide**, **ifosfamide**, **melphalan**), the nitrosoureas (**lomustine**, carmustine, **fotemustine**), the platinum complex cytotoxics (**carboplatin**, **cisplatin**, **oxaliplatin**) and **thiotepa**, **busulphan**, **dacarbazine** and **procarbazine**. The sulphonamide derivative **amsacrine** also belongs to this group. A relatively new member of this group is **temozolomide**, which is related to dacarbazine and leads to the production of the same active metabolite.

◆ COMMON ADVERSE EFFECTS

The alkylating agents cause suppression of bone-marrow cells and damage to the gastrointestinal lining, such as mouth ulcers and intestinal denudation. Immune function, both cellular and humoral, is suppressed. In general, the alkylating agents are known to be potent vesicants.

Pulmonary fibrosis, liver damage and renal failure have been observed during treatment with these drugs. Some alkylating agents, such as cyclophosphamide and ifosfamide, produce significant urotoxicity in the form of haemorrhagic cystitis. In order to prevent or reduce this reaction a drug called **mesna** is administered concurrently. This binds to the metabolites of the cytotoxic drugs that damage the urinary tract mucosa, without affecting their alkylating activity.

✚ CLINICAL CONSIDERATIONS

The complete blood count and liver and kidney function must be monitored during therapy with an alkylating agent. Prophylactic use of anticonvulsants is advised during busulphan therapy. Advise patients that urine appears orange-red following amsacrine treatment. Intravenous carmustine degrades rapidly in polyvinyl chloride (PVC) and light. It should, therefore, be stored in and administered from a glass container and protected from light. Fotemustine is light-sensitive and intravenous infusions of it should be protected from light.

With oral cyclophosphamide treatment, instruct the patient to take the dose in the morning with plenty of water and to empty the bladder frequently. Advise patients on ifosfamide to drink plenty of water and to frequently empty the bladder during treatment. During mesna treatment, monitor urine for haematuria in order to determine the clinical effectiveness of treatment. As high doses of ifosfamide may lead to fluid retention, monitor the fluid balance and give **furosemide** if needed.

Observe for allergic reactions to melphalan, which can occur after several courses of intravenous therapy. Inform patients on lomustine, melphalan and temozolomide to take the agent on an empty stomach to facilitate absorption. A serotonin antagonist combined with a corticosteroid reduces the onset of nausea and vomiting in most patients treated with carboplatin, cisplatin and oxaliplatin.

ANTIBIOTIC-TYPE AGENTS

Doxorubicin, **dactinomycin** (actinomycin D), **daunorubicin**, **mitomycin** and **bleomycin** are diverse antibiotic substances derived from a variety of *Streptomyces* species. They are too toxic to be used as antimicrobials, but they have applications in the chemotherapy of cancer. Doxorubicin, **epirubicin** and daunorubicin belong in a subgroup called the anthracyclines. **Idarubicin** and **mitozantrone** are derivatives of the anthracyclines.

■ MECHANISM OF ACTION

All of the cytotoxic antibiotics bind to DNA and prevent the subsequent synthesis of RNA and proteins. These agents also induce breaks in the strands of DNA and may lead to the generation of destructive free radicals.

◆ COMMON ADVERSE EFFECTS

Bone-marrow suppression is a major adverse effect of these drugs. Stomatitis, gastrointestinal upset and alopecia can occur during treatment but cease when the treatment is stopped. Cardiac toxicity is observed with the anthracyclines, but there is less toxicity associated with their derivatives.

Bleomycin is less toxic to bone marrow but tends to cause dermatological alterations, such as hyperpigmentation, redness and, sometimes, ulceration. Pulmonary fibrosis can occur during this therapy. Mitomycin may induce serious renal impairment.

✚ CLINICAL CONSIDERATIONS

Monitor hepatic and renal function and complete blood count at baseline and before each cycle of treatment. Assess cardiac rate and rhythm, perform an electrocardiogram (ECG) and determine the left ventricular ejection fraction at baseline and following three cycles of treatment. To determine the cardiotoxic dose limit, the dose received at each cycle is added up.

These agents should not be given intrathecally, intramuscularly or subcutaneously; parenteral therapy should be administered intravenously. Advise the patient that urine may appear a different colour for up to 2 days following treatment: urine turns a blue-green colour with mitozantrone and red-orange with other antibiotic-type agents.

When using bleomycin, perform a weekly chest X-ray at baseline and during therapy as a means of determining respiratory toxicity. Dactinomycin is potentially irritating to tissues, and therefore extravasation should be avoided with this agent.

Daunorubicin is now available in a formulation where the drug is encapsulated in microscopic synthetic vesicles called liposomes. These liposomes are made of cholesterol and other lipids and are selectively taken up by the tumour cells, where the cytotoxic drug is released. This delivery system has been developed to get more drug to the target tissues, sparing the normal cells from toxicity. The formulation is used in human immunodeficiency virus (HIV)-infected individuals with Kaposi's sarcoma. The rationale for therapy is that this formulation protects the immunosuppressed patient from further immunosuppression caused by cytotoxic drug therapy. Neuropathy and alopecia rates have been shown to be lower using this form of daunorubicin, but neutropenia appears to be more severe.

Cell-cycle-specific drugs

These drugs are effective against tumour cells that are participating in the cell cycle and not those resting in the dormant G_0 phase. Because of this, the drugs are administered in discrete blocks of time separated by distinct intervals in order to catch the majority of cancerous cells as they move around the cell cycle and in and out of the dormant phase. Principally, their actions are directed against either the S or M phase.

ANTIMETABOLITES

■ MECHANISM OF ACTION

Drugs in this group are primarily antimetabolites that substitute themselves into the chemical makeup of the DNA molecule during replication. As a consequence, they can cause misreading of the genetic code or a fracture in the structure of the DNA, which prevents progress into the G_2 phase. This action may or may not also halt RNA synthesis. The antimetabolites can be divided into a number of subgroups that reflect their site of action. The subgroups include analogues of folic acid, the pyrimidines and the purines.

Folic acid is a dietary factor important in the synthesis of the nucleotides of DNA and RNA. Important steps in the folic acid pathway and drug sites of action are shown in Figure 76.2 (see p. 826). Most of the folic acid analogues block the conversion of dihydrofolate (dihydrofolic acid) to tetrahydrofolate (tetrahydrofolic acid) by inhibiting the enzyme dihydrofolate reductase. **Methotrexate** is an important representative of this group. Another member of the group, **raltitrexed**, acts to inhibit the enzyme thymidylate synthetase, which limits the availability of tetrahydrofolate. As an antidote to methotrexate overdose or high-dose therapy, **calcium folinate** may be administered. This leads to an increased availability of tetrahydrofolate for nucleotide synthesis.

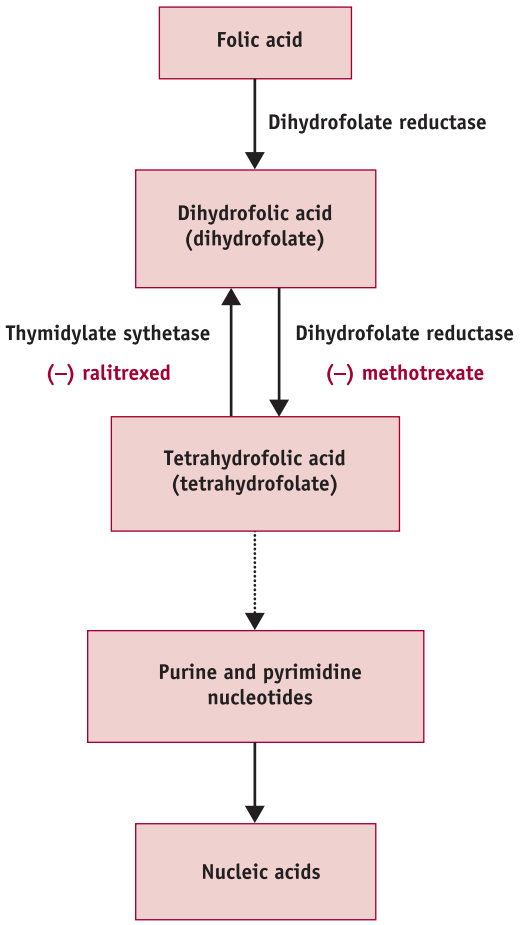
Pyrimidine analogues block the synthesis of the pyrimidine nucleotides thymine, cytosine and uracil, or substitute for these chemicals in nucleic acids. As a result, the synthesis and/or function of DNA and RNA is disrupted. Established agents from the group include **5-fluorouracil** (5-FU), **cytarabine** and **gemcitabine**. Another member of this group, **capecitabine**, is a prodrug of 5-FU, which is converted into the active principal once it is taken up into a tumour.

As an adjunct to 5-FU therapy for a form of colon cancer, the immunostimulant **levamisole** can be administered. This enhances cell-mediated immunity by stimulating the proliferation of T-cells and the phagocytotic activity of macrophages.

In a similar way to the pyrimidine analogues, the purine analogues block the synthesis of the purine nucleotides

FIGURE 76.2 FOLIC-ACID PATHWAY AND SITES OF ACTION OF FOLIC ACID ANALOGUES

Folic acid and its metabolites are key cofactors in the production of purine and pyrimidine nucleotides. Tetrahydrofolic acid is the active metabolite in the pathway. It is also the rate-limiting step. The sites of action of the folic acid analogues are represented in the figure. They inhibit key enzymic steps.



adenine and guanine, or substitute for them in the structure of nucleic acids. Representative drugs of this group include **mercaptopurine**, **thioguanine**, **fludarabine** and **cladribine**.

Another antimetabolite, which does not fit neatly into the subgroups above, is **crisantaspase** (L-asparaginase). This is an enzyme derived from a bacterial source (usually *Escherichia coli*), which exploits a difference in metabolism between cancer cells and normal cells. Some cancer cells cannot synthesise the amino acid asparagine, which is required for cell division, and therefore must obtain it from the blood, whereas most normal cells can manufacture asparagine themselves. Crisantaspase depletes the blood levels of asparagine by converting it into aspartic acid, effectively blocking cancer cell proliferation.

◆ COMMON ADVERSE EFFECTS

General toxic effects associated with the antimetabolites include bone-marrow suppression and damage to the gastrointestinal lining (stomatitis and ulceration). Methotrexate can induce pneumonitis and liver damage. Gastrointestinal disturbances are common.

Levamisole tends to induce flu-like symptoms, such as fever and musculoskeletal pain.

The adverse effects of crisantaspase are relatively mild compared with those of other antimetabolites and occur because of the immune response to a foreign organic substance. They include rashes, fever, joint pain and gastrointestinal disturbances.

✚ CLINICAL CONSIDERATIONS

Monitor complete blood count and renal and hepatic function during and following therapy with these agents. Capecitabine may cause numbness and tingling of the hands and feet, which can be alleviated with **pyridoxine**. Diarrhoea caused by capecitabine can be alleviated by lowering the dose and giving **loperamide**. Fever commonly occurs during the first month of cladribine therapy, which may necessitate anti-infective treatment.

Resuscitation equipment must be available during crisantaspase therapy in case an allergic reaction occurs. Crisantaspase is a contact irritant and care should be taken to avoid contact with skin and mucous membranes. Monitor serum amylase and blood glucose levels during crisantaspase therapy.

During high-dose cytarabine therapy, observe closely for signs of neurological toxicity. For patients receiving fludarabine, observe for visual changes, as these are an indication of neurotoxicity. Suspend 5-FU treatment if painful red hands develop, and treat the condition with pyridoxine. If diarrhoea occurs during 5-FU therapy, reducing the dose and administering loperamide can often help. If thrombocytopenia occurs, levamisole treatment should be delayed until this condition is corrected.

Mercaptopurine therapy should cease if the patient develops jaundice. Methotrexate tablets are taken once a week on a set day. Patients are requested to report a cough or any difficulty in breathing, as these manifestations may indicate the onset of pulmonary toxicity of methotrexate therapy. With calcium folinate, the time from acute methotrexate poisoning to administration of calcium folinate is critical to the outcome. Commence treatment as soon as possible to achieve a beneficial effect on myelosuppression. If severe diarrhoea or stomatitis occurs with raltitrexed, stop treatment until the symptoms have resolved and recommence at a lower dose.

OTHER S-PHASE INHIBITORS

Topotecan and **irinotecan** are semisynthetic derivatives of the plant extract camptothecin. **Hydroxyurea** is also a well-established cytotoxic agent. These drugs exert their action during the S phase of the cell cycle.

■ MECHANISM OF ACTION

The camptothecin derivatives inhibit an enzyme involved in the replication and repair of DNA. The inhibition of this particular enzyme, topoisomerase I, results in fractured DNA strands.

Hydroxyurea acts to inhibit the conversion of ribonucleotides into deoxyribonucleotides, a vital step in the synthesis of DNA. Of particular therapeutic usefulness is that hydroxyurea produces a potentiation of the effects of radiotherapy and of the cytotoxicity of the alkylating agents and antimetabolites.

◆ COMMON ADVERSE EFFECTS

Severe neutropenia and diarrhoea are the most serious adverse effects associated with the camptothecin derivatives. In addition to the typical cytotoxic adverse effects, irinotecan produces cholinergic stimulation.

Hydroxyurea can also cause blood-cell depression, gastrointestinal disturbances and alopecia.

✚ CLINICAL CONSIDERATIONS

Irinotecan should be used cautiously in patients with asthma, cardiac disease, urinary obstruction and gastrointestinal obstruction. Intravenous **atropine** is recommended for patients who develop diarrhoea within 24 hours of therapy. With irinotecan, note that prolonged diarrhoea is potentially life-threatening. Consider withholding the dose and treating with loperamide before recommencing with a lower dose of irinotecan.

Treat stomatitis occurring with hydroxyurea using topical non-steroidal anti-inflammatory drugs and oral analgesics. For patients unable to swallow hydroxyurea capsules, the capsules may be opened and the contents mixed with a glass of water.

MITOTIC POISONS

Mitotic poisons are derived from natural sources and include the vinca alkaloids, the epipodophyllotoxins and the taxanes. The vinca alkaloids, derived from the periwinkle plant (*Vinca rosea*), consist of **vinblastine**, **vindesine**, **vincristine** and **vinorelbine**. The epipodophyllotoxins comprise **podophyllotoxin**, **etoposide** and **teniposide**. Podophyllotoxin is a natural product derived from the mandrake plant (*Podophyllum petatum*), while the other two are derivatives.

The taxanes **paclitaxel** and **docetaxel** were originally derived from the Pacific yew tree (*Taxus brevifolia*). This plant is an endangered species, however, and these substances are now semisynthetic derivatives from *Taxus baccata*, a relative of the Pacific yew.

■ MECHANISM OF ACTION

Chromosomes are connected to the centrioles by spindle fibres, which are necessary for the completion of nuclear division. Centrioles and spindle fibres are made from the cellular organelles called microtubules. The vinca alkaloids and podophyllotoxin act to prevent the formation of mitotic spindle fibres. Without these, the mitotic process is incapacitated.

The taxanes act to stabilise microtubules, inhibiting the normal reorganisation of the network essential for mitosis to occur. Paclitaxel, first approved for the treatment of metastatic ovarian cancer unresponsive to other therapy, is now also used for advanced breast cancers. There is evidence that this drug may potentiate the cytotoxic effects of radiotherapy. Docetaxel is more effective than paclitaxel against tumour cells, but it is also more toxic to human cells. Docetaxel is used in the treatment of advanced breast cancer when paclitaxel is found to be ineffective, and in small-cell lung cancers.

The action of the other epipodophyllins resembles that of the camptothecin derivatives (see above). It involves forming a complex with topoisomerase (an enzyme involved in DNA repair) and DNA. This results in DNA strand breaks and cell death.

◆ COMMON ADVERSE EFFECTS

Serious toxicity is associated with bone-marrow depression and gastrointestinal damage. Hair loss, nausea, vomiting and diarrhoea may occur.

As microtubules have other roles in the body (e.g. phagocytosis, axonal transport), impairment of these functions may result in neurological toxicity. The vinca alkaloids may induce paraesthesias, such as numbness and tingling, and muscle weakness. Peripheral neuropathy has been observed during paclitaxel therapy.

✚ CLINICAL CONSIDERATIONS

With the vinca alkaloids, perform a complete blood count at baseline and before subsequent doses. To avoid crystallisation of the vinca alkaloid in the tissues, apply warm compressors to extravasation sites. These drugs should not be injected into extremities with impaired circulation, because thrombosis may occur. Laxatives that soften the bowel motions are often given to prevent constipation with vinca alkaloids.

Etoposide and teniposide are infused slowly over 60 minutes in order to avoid hypotension and bronchospasm. Continuous observation of the vital signs are required during the first 30 minutes of the infusion. Capsules of etoposide should be taken on an empty stomach.

Before taxane therapy, ensure emergency treatment is available for potential anaphylaxis. Mild symptoms such as rash or erythema do not warrant stopping taxane treatment. Measure complete blood count and liver function at baseline and before each cycle. Monitor cardiac rate and rhythm if the patient has experienced cardiac problems during previous cycles.

Tissue-specific agents

A number of endocrine tissues require specific hormones to be available for normal proliferation and development. Oestrogens and progesterone are essential for the growth of both endometrial and breast tissue, and the prostate is dependent on androgens for its development. A tumour developing within these tissues still requires the hormone for growth of cancerous cells. When the hormonally dependent tumour is deprived of the specific hormone, its growth is greatly retarded.

Chemotherapeutic agents that are tissue-specific can be of three types: (i) antagonists and/or inhibitors of the hormone on which the tissue is dependent; (ii) agents that act to disrupt pituitary function and thus decrease secretion of pituitary hormones; and (iii) miscellaneous agents.

HORMONAL ANTAGONISTS AND INHIBITORS

■ MECHANISM OF ACTION

Antiandrogenic drugs such as **flutamide** and **cyproterone** are used in the treatment of prostate cancer. These drugs compete with androgens for cellular uptake into the prostate. As a result, the prostatic tumour is deprived of the androgens necessary for growth and diminishes in size.

Medroxyprogesterone acetate is a potent progestin (see Chapter 58) indicated in the treatment of endometrial and breast cancers. As a progestin, it counteracts the proliferative effect of oestrogens on these tissue cells, especially the cancerous cells. It also has applications in renal tumours of endocrine origin. **Megestrol** is another progestin used in the treatment of endometrial and breast cancers.

Tamoxifen and **toremifene** are selective oestrogen receptor modulators (SERMs; see Chapter 58). They have oestrogenic effects on some tissues (bone and endometrium) and on blood coagulation, but they have antioestrogenic effects on breast tissue. Tamoxifen also decreases the local production of insulin-like growth factor (IGF-1) and a tumour growth factor called transforming growth factor (TGF). As a result, mediators necessary for breast tumour development are unavailable to the malignant cells. Tamoxifen is used in the treatment of breast cancer and as prevention of this cancer in high-risk women. Toremifene is used in the treatment of postmenopausal women with breast cancer. It has a similar efficacy to tamoxifen.

Another approach in the treatment of advanced breast cancer is to inhibit the biosynthesis of oestrogen, depriving the oestrogen-dependent tissues of the breast of a key growth factor. These drugs are known as aromatase inhibitors and include **anastrozole** and **letrozole**. They are so effective at blocking oestrogen synthesis that they are recommended for use only in postmenopausal women. The aromatase inhibitors are used when a breast cancer continues to progress after treatment with tamoxifen.

A similar approach is associated with **aminoglutethimide**. This is used in some countries for the treatment of metastasising prostate and breast cancers. This drug interferes with the synthesis of all steroid hormones, depriving the metastatic cancer of the sex hormones required for growth. Aminoglutethimide also inhibits adrenal cortex hormone production, which makes it useful in the treatment of hypersecretion of adrenal hormones associated with adrenocortical tumours and Cushing's disease.

◆ COMMON ADVERSE EFFECTS

Gastrointestinal disturbances are common adverse effects of these drugs. Impaired fertility may result from treatment with sex hormone antagonists. In women, menstrual irregularities may develop depending on their stage of life (i.e. premenopausal or menopausal). Common adverse effects of the sex hormones and their antagonists are given in Chapter 58.

Common adverse effects of aminoglutethimide include lethargy, rashes, nausea, ataxia and dizziness. It is no longer available in the UK.

✚ CLINICAL CONSIDERATIONS

During antiandrogen therapy, liver function is monitored at baseline and then every 3 months. In the case of the antiandrogen cyproterone, the risk of hepatotoxicity means that its use in prostate cancer is restricted to short courses. The patient should contact their doctor immediately if they experience any symptoms of jaundice, including yellowing of the eyes and skin, dark urine and itchiness.

The SERMs are given at the completion of chemotherapy as a means of increasing the disease-free survival rate. Tamoxifen and toremifene may cause bone pain during therapy, but patients should be reassured that this manifestation means that the drug is producing a good response. Monitor the serum calcium levels during therapy, as tamoxifen and toremifene may potentiate hypercalcaemia relating to bone metastasis at the start of therapy. The risk of thromboembolic episodes should also be assessed. If that risk is significant, then this aspect requires careful monitoring during treatment.

Aromatase inhibitors are taken with food in order to avoid problems with nausea and vomiting. They do not affect adrenal corticosteroid synthesis, aldosterone or thyroid

hormone production. As a result, replacement corticosteroid therapy is not required with these agents.

DISRUPTION OF PITUITARY FUNCTION

Leuprorelin, **goserelin**, **buserelin** and **triptorelin** are analogues of luteinising hormone-releasing hormone (LH-RH) (see Chapter 56). These drugs are also known as gonadotrophin-releasing hormone (GnRH) analogues. They can be used in the management of prostate cancer. **Octreotide**, a somatostatin analogue, is useful in the treatment of tumours associated with the hypersecretion of peptide hormones such as insulin, gastrin and growth hormone.

■ MECHANISM OF ACTION

When administered for a prolonged period, GnRH analogues act on the pituitary gland to reduce the secretion of gonadotrophic hormones. As a consequence, the levels of androgens in male patients are reduced greatly. In combination with an antiandrogen, such therapy can result in a significant blockade of androgen secretion. Another agent in this category that is indicated for prostatic cancer therapy is the synthetic progestin **norethisterone**, which is a potent inhibitor of gonadotrophic hormone release.

Octreotide mimics the action of somatostatin and results in inhibition of the secretion of growth hormone. It is used in conditions such as giantism and acromegaly. Somatostatin is also secreted by the pancreas and inhibits the production of the gastropancreatic peptide hormones (see Chapters 56 and 57). Such treatment is useful in some tumours of the gastrointestinal tract.

◆ COMMON ADVERSE EFFECTS

Common adverse effects of the GnRH analogues include hot flushes, impotence, changes in blood pressure, sweating and chills. Octreotide may cause local reactions at the injection site and gastrointestinal disturbances.

MISCELLANEOUS TISSUE-SPECIFIC AGENTS

CYTOKINES

The immunomodulating agents **interferon alfa-2a**, **interferon alfa-2b** and **aldesleukin** (see Chapter 75) also have an antineoplastic action. The interferons are indicated in the treatment of a number of cancers, including hairy-cell leukaemias. Aldesleukin (interleukin-2) is recommended in the therapy of metastatic renal cell cancer.

■ MECHANISM OF ACTION

The mechanism of action of these drugs is believed to involve the enhancement of cytotoxic immune-cell responsiveness (cell-mediated immunity) in relation to specific tumour cells. Aldesleukin also stimulates the secretion of a number of cytokines, including tissue necrosis factor, gamma-interferon and interleukin-1.

◆ COMMON ADVERSE EFFECTS

Interferons may induce flu-like symptoms such as fever, malaise and musculoskeletal pain.

Common adverse reactions of aldesleukin include fever, chills, anaemia, diarrhoea, nausea, vomiting and reactions at the local injection site. This treatment can induce capillary leak syndrome when administered intravenously (see Chapter 75). This condition can be severe and result in death.

TRETINOIN

Tretinoin is a retinoid, a group of substances related closely to vitamin A (see Chapter 61). It is used in the treatment of acne (see Chapter 78).

■ MECHANISM OF ACTION

Tretinoin has been found to inhibit the proliferation of leukaemic cells in vitro. It is quite effective in inducing short-term remission in patients with promyelocytic leukaemia. A course of conventional chemotherapy should follow this in order to ensure long-term remission.

◆ COMMON ADVERSE EFFECTS

A serious adverse effect associated with tretinoin therapy is hyperleucocytosis, characterised by fever and dyspnoea, which requires a course of high-dose corticosteroid treatment. Other adverse effects include skin reactions, oedema, nausea, vomiting and bone pain. This drug is highly teratogenic.

✚ CLINICAL CONSIDERATIONS

Tretinoin is highly teratogenic, and contraceptive measures should be adhered to strictly during therapy.

MONOCLONAL ANTIBODIES

Rituximab and **trastuzumab** are monoclonal antibodies (see Chapters 46 and 75) that are useful as cytotoxic drugs.

■ MECHANISM OF ACTION

Rituximab is raised against a specific surface antigen on B-lymphocytes. It is used in non-Hodgkin's lymphoma characterised by malignant proliferation of B-cells. When the monoclonal antibody binds to the surface antigen, humoral immune processes initiate B-cell lysis. This leads to a dramatic decrease in malignant B-cell numbers. Studies suggest that its efficacy may be similar to that of cladribine and fludarabine in the management of blood malignancies.

Trastuzumab is directed against a breast cell receptor called human epithelial growth factor receptor-2 (HER2). This receptor is overexpressed in particularly aggressive and malignant forms of breast cancer. Studies have shown that treatment with trastuzumab inhibits the proliferation of human breast cancer cells that overexpress HER2. In clinical trials, when trastuzumab was used in combination with other cytotoxic agents, an improved response rate and increased survival was observed.

◆ COMMON ADVERSE EFFECTS

Common adverse effects include hypersensitivity reactions and falls in leucocyte levels. Trastuzumab treatment has resulted in cardiotoxicity.

✚ CLINICAL CONSIDERATIONS

Before rituximab therapy, premedicate with paracetamol, an antihistamine and a corticosteroid about 30–60 minutes before the dose. Emergency treatment, such as adrenaline, antihistamine and corticosteroid, should be available in case of anaphylaxis during rituximab or trastuzumab therapy.

RADIOACTIVE SAMARIUM

A chelating agent (see Chapter 21 for further information) comprising radioactive **samarium** is indicated as palliation for painful bone metastases.

■ MECHANISM OF ACTION

The samarium chelating agent binds preferentially to bone and is used in the chemotherapy of bony metastases. It delivers a highly specific and localised dose of radiation to the bony metastases.

◆ COMMON ADVERSE EFFECTS

Common adverse reactions include increased pain initially and myelosuppression. As the samarium isotope is excreted in urine, the bladder wall is vulnerable to radiation exposure. Regular voiding of contaminated urine should be encouraged in order to reduce exposure time.

IMATINIB

A novel agent for the management of chronic myeloid leukaemia (CML) is **imatinib**, a tyrosine kinase inhibitor.

■ MECHANISM OF ACTION

Tyrosine kinases are intracellular enzymes required for cellular proliferation. They are involved in a cascade of reactions that lead to gene transcription. Tyrosine kinases are important in the proliferation of cancerous cells. When inhibited, cancer-cell growth is disrupted.

Imatinib targets an abnormal tyrosine kinase associated with the proliferation of myeloid cells associated with CML. It induces a dramatic inhibition of proliferation of leukaemic cells and malignant cell death.

◆ COMMON ADVERSE EFFECTS

Imatinib can induce suppression of bone-marrow cells. Other common adverse effects include gastrointestinal disturbances and severe fluid retention. Liver toxicity has been observed during treatment.

✚ CLINICAL CONSIDERATIONS

Imatinib therapy requires liver transaminases, alkaline phosphatase and bilirubin levels to be monitored before and during treatment.

BACILLE CALMET-GUÉRIN

The **Bacille Calmet-Guérin** (BCG) vaccine was discussed in Chapter 75. An instillation of BCG can also be used in the therapy of carcinoma of the urinary bladder.

■ MECHANISM OF ACTION

BCG is a live attenuated preparation of *Mycobacterium bovis* bacteria. When instilled into the urinary bladder of a patient with bladder carcinoma in situ, it induces a local inflammatory reaction. This reaction appears to promote the elimination of superficial tumours.

◆ COMMON ADVERSE EFFECTS

Localised urinary irritation is a common adverse effect of this treatment. This can result in dysuria, urgency, cramping and urinary frequency. Systemic flu-like symptoms and anaemia may also occur. There is an increased risk of tuberculosis associated with this therapy.

✚ CLINICAL CONSIDERATIONS

BCG therapy involves the patient not drinking for 4 hours before and 2 hours after bladder instillation in order to prevent urine production during the retention period using BCG. The patient is advised to urinate after 2 hours and to disinfect the toilet bowl before flushing.

ANAGRELIDE

Anagrelide is used for a neoplastic condition that is characterised by a proliferation of cells but is not a cancer per se. An example is essential thrombocythaemia, where platelet numbers are elevated.

■ MECHANISM OF ACTION

Anagrelide is an inhibitor of phosphodiesterase III. The drug reduces platelet production and at higher doses platelet aggregation. Thus, it is used to treat primary (essential) thrombocythaemia.

◆ COMMON ADVERSE EFFECTS

Common adverse effects include headache, asthenia, oedema, abdominal pain, palpitations, diarrhoea, nausea and anaemia.

✚ CLINICAL CONSIDERATIONS

Platelet count and complete blood count must be measured before and during treatment. If the platelet count has fallen, the anagrelide dose should not be increased until the count has flattened.

THERAPIES USED TO MITIGATE DRUG-INDUCED MYELOSUPPRESSION

A common adverse reaction occurring during cytotoxic drug therapy is myelosuppression. As a consequence, blood-cell production is inhibited, affecting the formation of mature erythrocytes, platelets and leucocytes. One important white blood cell type affected is the neutrophils; deficiency is called neutropenia. The clinical effects resulting from neutropenia include fever and increased susceptibility to infection.

COLONY-STIMULATING FACTORS

Cytokine therapy in the form of the granulocyte colony-stimulating factors (G-CSFs) **filgrastim**, **lenograstim**, **pegfilgrastim** and **molgramostim** can be used to mitigate these effects. G-CSFs are described in Chapter 75. The G-CSFs are administered during cytotoxic therapy for non-myeloid malignancies as daily subcutaneous injections. Treatment continues for as long as the drug-induced neutropenia would be expected to persist.

◆ COMMON ADVERSE EFFECTS

Treatment is usually tolerated well, but bone pain is a common adverse effect. This pain is usually controlled using a non-narcotic analgesic such as **paracetamol**. Other common adverse reactions associated with filgrastim include alopecia, nausea, vomiting, fever and headache.

AMIFOSTINE

The organic thiophosphate **amifostine** has an entirely different mechanism of action from that of the G-CSFs. It is used to treat the neutropenia induced by radiotherapy and cytotoxic drugs that bind to DNA (e.g. alkylating agents).

■ MECHANISM OF ACTION

In animal studies, amifostine has been shown to protect normal cells but not tumour cells against the effects of radiotherapy and chemotherapy on DNA. The active metabolite of amifostine readily enters non-malignant cells, where it deactivates cytotoxics such as alkylating agents and protects against the effects of ionising radiation. The selectivity of the cytoprotective effects of amifostine may be due to the lower alkaline phosphatase content and pH of malignant cells compared with normal cells. These differences lead to a lower amount of active metabolite in malignant cells. Amifostine is administered by slow intravenous infusion, usually over 15 minutes.

◆ COMMON ADVERSE EFFECTS

Common adverse reactions during infusion include hypotension, flushing and a warm (or, sometimes, cold) sensation. Other adverse effects include nausea, vomiting, hiccup, sneezing and allergic reactions.

✚ CLINICAL CONSIDERATIONS

When giving an amifostine infusion, blood pressure is monitored every 5 minutes. Stop the infusion if blood pressure drops signficantly from normal levels. If low blood pressure persists, an infusion of **normal saline** can be given and the head of the bed tilted back. Giving the amifostine infusion over more than 15 minutes can increase the incidence of adverse effects. Give prophylactic antiemetics and **dexamethasone** beforehand to reduce nausea and possible anaphylaxis.

ERYTHROPOIETIN

A possible consequence of myelosuppression is anaemia. **Erythropoietin** can be used to counteract the anaemia induced by cytotoxic therapy of non-myeloid malignancies. The action and effects of erythropoietin are described in Chapter 50.

CHEMICAL PROPERTIES OF CYTOTOXIC DRUGS

Many of the cytotoxic drugs are degraded by exposure to light or heat and thus rendered ineffective for clinical use. Protection from light is facilitated by covering the intravenous bag with black plastic wrapping.

COMBINATION CYTOTOXIC DRUG THERAPY

Another problem associated with antineoplastic therapy is that, like microbes, cancerous cells can develop resistance to drug therapy. This might be achieved through bypassing a metabolic step that has been interrupted by a cytotoxic drug in order to manufacture a substance necessary for proliferation. Therapeutically, this problem can be overcome by administering a combination of cytotoxic drugs with different actions that are all effective against a particular cancer.

There are other good reasons to use combination drug therapy. As antineoplastic drug groups act on different aspects of the cell cycle or cell growth, a combination of antineoplastic drugs that act on different parts of the cell cycle will kill more cancer cells than one drug alone. Importantly, by using this approach, a potentiation of drug effects is achieved without necessarily increasing drug toxicity. There are standard drug combinations for certain types of cancer, although regimens vary slightly between institutions and may be modified as part of the ongoing evolution of cancer chemotherapy. Such therapy should preferably take place only in expert centres. Although it is accepted practice to refer to these drug cocktails by their acronyms (using the first letter of the generic or trade name of the constituent drugs), the same acronym is sometimes used for regimens containing different drugs or different doses of the same drugs. This can lead to confusion and the reader should consult the literature for further details of specific combinations.

CLINICAL MANAGEMENT

Antineoplastic agents

Assessment

- Undertake a detailed examination of the patient, including condition of the hair, nails, skin and mouth, height, weight and vital signs. Compare with subsequent observations.
- Determine previous responses to antineoplastic therapy.
- Make an assessment of the cancer under treatment and its response to therapy.
- Assess laboratory blood studies, including haematocrit, haemoglobin, full blood examination, liver function tests, renal function tests and serum electrolyte levels.
- Perform diagnostic tests as required, such as bone scans, liver scans and bone biopsies.

Planning

- The agents will be effective in treating the patient's neoplastic disease.
- The patient will be free of adverse reactions to the antineoplastic agents.

Implementation

- Handle antineoplastic agents in strict accordance with institutional policies and precautions.
- Monitor the patient's vital signs, body weight and fluid balance.
- Monitor the patient for manifestations of bone-marrow depression, including fever, sore throat, rash, dysuria, decreased level of consciousness and severe reduction in white blood cell levels. Use meticulous handwashing techniques when caring for these patients. If the patient's white blood cell count is very low and there is bone-marrow depression, isolate the patient in a single room to reduce the incidence of infection. Aim to maintain a white blood cell count of greater than 3×10^9/l. Do not permit visits from people with infections. Monitor the full blood examination, haematocrit, haemoglobin and platelet count regularly. Monitor patients on steroids, as these agents may mask the manifestations of infection. Avoid the display of cut flowers and plants in the patient's room, as these could carry potentially dangerous microorganisms.
- Monitor the patient for bleeding tendencies, which are associated with a low platelet count. Manifestations include bruising, petechiae (haemorrhagic spots on the skin), bleeding gums, nose bleeds, and blood in the faeces and urine. Watch the platelet count closely. Mouthwashes are preferred to toothbrushes and dental floss, which can aggravate bleeding gums. Check faeces regularly for occult blood and monitor urinalysis. Observe venipuncture sites for haematoma. Apply pressure to venipuncture sites for at least 10 minutes after the procedure to prevent bruising. Handle the patient gently. Keep cot sides padded, if used. Avoid the use of restraints. Inspect skin regularly for bruising. Do not use intramuscular injections on these patients.
- Monitor the patient for manifestations of stomatitis, as shown by inflamed oral membranes and pain on chewing and swallowing. Observe the condition of the mouth at least once per shift. Inspect for the development of oral candidiasis. Monitor fluid input and output. If chewing or swallowing is difficult, order a liquid diet for the patient. Maintain a fluid intake of about 2000 ml/day to prevent dehydration. Use mouthwashes to clean the mouth if toothbrushing is painful. Apply lip balm regularly and avoid mouthwashes that contain alcohol.

- Monitor the patient's urinary output, and serum creatinine, urea and potassium levels. Nephrotoxicity may occur with these drugs, especially from cisplatin and high doses of methotrexate.
- Monitor the patient for manifestations of hepatotoxicity, such as jaundice, orange-coloured urine and elevated liver enzyme levels. Antineoplastic agents may cause liver damage when taken over a prolonged period.
- Monitor for manifestations of anorexia arising from drug therapy and the cancer itself. Observe dietary intake and monitor body weight. To prevent nausea and vomiting, encourage the patient to eat small, frequent meals and to avoid foods with a strong odour.
- Monitor for diarrhoea caused by antineoplastic agents, which could adversely affect fluid and electrolyte balance. If diarrhoea occurs, place the patient on a clear-liquid or low-fibre diet while at the same time maintaining a fluid intake of at least 2000 ml daily. Monitor electrolyte levels regularly. (See Table 11.15 in Chapter 11 for further information.)
- Monitor the incidence of nausea and vomiting during antineoplastic therapy. Monitor fluid and electrolyte balance. Administer antiemetics before therapy to reduce the incidence of nausea and vomiting. Keep the environment as odour-free as possible. Limit the oral intake to clear fluids on the evening before or the day of antineoplastic therapy (see Tables 11.10 and 11.17 in Chapter 11 for further information).
- Monitor for alopecia and provide emotional support to the patient during this time. Reassure the patient that the hair will grow back after the course of antineoplastic therapy.
- Monitor for the incidence of extravasation during intravenous antineoplastic therapy. Extravasation may lead to tissue necrosis. Observe for redness, swelling and pain at the injection site and decreased infusion rate. If extravasation has occurred, stop the infusion and remove the intravenous cannula. Apply a cold or warm compress to the affected area and keep the area elevated for a few hours to prevent oedema.
- Take great care in handling antineoplastic agents, as toxicity can occur with repeated exposure. Use Luer lock fittings on intravenous infusions to prevent accidental detachment of connections. Follow the institutional policies and guidelines established for the preparation of antineoplastic drug administration. Wear disposable gloves during preparation and administration of medications. Depending on institutional policy, a gown may need to be worn during preparation and administration.
- Monitor the patient for elevation in uric acid levels, which may occur through the release of breakdown products from rapidly dividing cancers during antineoplastic therapy. For this reason, allopurinol may be ordered. Keep the patient well hydrated to prevent the development of urate crystals in the kidneys. Maintain fluid intake to at least 2000 ml daily to promote adequate flushing of the kidneys. Check, however, that hydration to this level is not a contraindication, as in cases of kidney or heart disease, elderly patients and very young patients.
- Avoid the need to cut tablets in half, as in the case of chlorambucil tablets, by using different doses on alternate days.
- Consider the collection and storage of sperm or eggs before treatment if future fertility is important for the patient.

Patient teaching

- Teach the patient about the manifestations of bone-marrow depression, as already noted.
- Advise the patient to avoid contact with people who are suffering from colds and other infections during susceptible times, e.g. following a course of therapy. The patient should avoid crowds of people, where transmission of infection occurs easily, and avoid children, who are likely to carry communicable diseases.
- Discourage the patient from eating raw vegetables and fruit, as these could be a source of microorganisms.
- Advise the patient to wash their hands carefully after using the bathroom and after contact with other people. Ask family members to wash their hands carefully before making contact with the patient.
- Teach the patient about the manifestations of bleeding tendencies.
- Advise the patient to avoid using razor blades and to use an electric razor instead.
- If gums bleed, stop flossing. Always use a soft-bristle toothbrush. If brushing causes bleeding, use a mouthwash instead. Baking soda and water makes a good cleansing solution for teeth and gums.
- Advise the patient not to walk around barefoot, as foot injuries may cause excessive bruising and bleeding.
- Instruct the patient to avoid using aspirin and other over-the-counter preparations unless these have been approved by the doctor or pharmacist. These preparations may increase the tendency for bleeding. The patient should also avoid alcohol, as this can have an adverse effect on platelet function.
- Teach the patient about the manifestations of stomatitis as noted above.

- Advise the patient on measures to relieve the pain associated with stomatitis (see Table 11.14 in Chapter 11 for further information).
- Instruct the patient to be aware of the possible loss of appetite. Small, frequent meals are preferable to heavy, infrequent servings. Encourage the patient to eat foods high in vitamin C and protein in order to allow for cellular growth and repair.
- Advise patients with diarrhoea to avoid foods that are likely to cause gastrointestinal irritation, including coffee, spicy foods, fruits, fruit juices and raw vegetables. If there is anal irritation, advise the patient to wash the area with mild soap and water and to gently pat the area dry after each bowel motion (see Table 11.15 in Chapter 11 for further information).
- Encourage the patient to avoid eating spicy, fatty and dairy foods when nauseated. Dry biscuits, ginger ale and cola may lessen the feeling of nausea (see Table 11.10 in Chapter 11 for further information).
- If nausea and vomiting continue to be a problem, an antiemetic may be prescribed before meals or antineoplastic therapy and then continued for up to 24 hours after therapy.
- Advise the patient that hair loss can be camouflaged by the use of a scarf or wig. Hair loss may occur from the head, eyelashes, nose and pubic area. Reassure the patient that hair will grow back once the course of therapy is complete.
- Advise the patient to use a mild shampoo on the remaining hair. If the scalp is dry, a thin layer of moisturiser will help. Brush and comb the hair very gently.
- Warn the patient that these drugs are contraindicated during pregnancy and that menstrual irregularities are common. If appropriate, advise the female patient on contraception. Pregnancy should be avoided for 3–4 months after completing the course. Some sources advise that both men and women should avoid being involved in the conception of a child for about 2 years after treatment. It is important to advise the patient that infertility, which may occur with antineoplastic agents, may not be reversible.

Evaluation

- Evaluate the patient's response to antineoplastic therapy.
- Determine whether any adverse reactions have occurred and monitor the patient's response to these reactions.

SUMMARY

- The principle of selective toxicity is applicable to the treatment of neoplastic disease; that is, identifying differences between normal cells and cancerous cells and using drugs that exploit these differences.
- The cell cycle has five phases. The G_1 phase is characterised by RNA synthesis. The S phase is where DNA is duplicated. In the G_2 phase, protein and RNA synthesis occur. The M phase is where the cytoplasm and nucleus divide. The G_0 phase is a resting phase, where a cell is uncommitted to cell division.
- Cytotoxic drugs can be divided into cell-cycle-non-specific agents (alkylating agents, antibiotics), cell-cycle-specific agents (antimetabolites, other S-phase inhibitors) and tissue-specific agents (hormonal agents, miscellaneous agents).
- Adverse effects of cytotoxic drug therapy comprise immediate effects (e.g. gastrointestinal disturbances, tissue ulceration, skin blistering) and delayed effects (e.g. hair loss, bone-marrow suppression, organ toxicity).
- Generally, it is important to monitor the complete blood count and gastrointestinal, heart, liver and kidney function during cytotoxic drug therapy.
- A number of drugs can be used to mitigate the toxic effects of cytotoxic agents. These include the colony-stimulating factors, mesna, amifostine, erythropoietin and calcium folinate.

1 Define the cell cycle and describe each of the major phases.

2 Briefly describe the principle of selective toxicity in relation to neoplastic therapy.

3 (a) Indicate the effectiveness of neoplastic therapy on cancerous cells in the G_0 phase.
(b) What therapeutic strategies could be employed to ensure that cancer cells entering and leaving the G_0 phase intermittently are targeted?

4 Compare and contrast cell-cycle-specific and cell-cycle-non-specific cytotoxic agents.

5 Explain how tissue-specific drugs are useful in the treatment of cancer.

6 State the immediate and delayed adverse effects generally associated with antineoplastic therapy.

7 Stomatitis is a common problem following the administration of antineoplastic therapy. What comfort measures can you offer for this condition? (See Table 11.14 in Chapter 11 for assistance.)

8 Which body organs are particularly vulnerable to damage during cytotoxic drug therapy?

9 Why is evaluation of fluid and electrolyte balance following cytotoxic therapy important?

10 Marcus Maas, 45 years old, is receiving cytotoxic drug therapy for lung cancer. What blood tests would be required during this treatment? Why?

11 With Marcus's therapy, changes in blood cell levels would be expected. Which specific blood-cell types would be affected? As a result, what complications would have to be monitored for closely?

12 Martine de Tol is 42 years old. She has been diagnosed with breast cancer and is receiving therapy with the selective oestrogen receptor modulator (SERM) tamoxifen. Shortly after the commencement of treatment, she experiences bone pain. What advice would you offer Martine?

13 Jennifer Pfiffer is 52 years old and is about to commence treatment with the alkylating agent cisplatin for bladder cancer. It is anticipated that she will develop severe neutropenia during therapy and so she will be treated with the granulocyte colony-stimulating factor (G-CSF) filgrastim. What patient education will you offer Jennifer regarding the effects of neutropenia? A common adverse effect associated with filgrastim therapy is bone pain. How should this be controlled?

76 DRUG SUMMARY TABLE: CYTOTOXIC DRUGS

FAMILY NAME	GENERIC NAME	TRADE NAME(S)
Alkylating agents	Amsacrine	Amsidine
	Busulfan	Myleran
	Carboplatin	Paraplatin
		Carbosin
	Carmustine	BiCNU
		Gliadel
	Chlorambucil	Leukeran
	Cisplatin	
	Cyclophosphamide	Endoxana
	Dacarbazine	DTIC-Domo
	Estramustine phosphate	Estracyt
	Ifosfamide	Mitoxana
	Lomustine	
	Melphalan	Alkeran
	Procarbazine	Natulan
	Oxaliplatin	Eloxatin
	Temozolomide	Temodal
	Thiotepa	
	Treosulfan	
Antibiotic cytotoxic agents	Bleomycin	
	Dactinomycin (actinomycin D)	Cosmegen Lyovac
	Daunorubicin	DaunoXome
	Doxorubicin	Caelyx
		Myocet
	Epirubicin	Pharmorubicin
	Idarubicin	Zavedos
	Mitomycin	Mitomycin C Kyowa
	Mitoxantrone	Novantrone
		Onkotrone
Antimetabolites	Cytarabine	
	Capecitabine	Xeloda
	Cladribine	Leustat
	Cytarabine	DepoCyte
	Fludarabine	Fludara
	Fluorouracil	Efudix
	Gemcitabine	Gemzar
	Mercaptopurine	Puri-Nethol
	Methotrexate	
	Pemetrexed	Alimta
	Raltitrexed	Tomudex
	Tegafur + uracil	Uftoral
	Tioguanine (thioguanine)	Lanvis
S-phase inhibitors	Hydroxycarbamide (hydroxyurea)	Hydrea
	Irinotecan	Campto
	Topotecan	Hycamtin

FAMILY NAME	GENERIC NAME	TRADE NAME(S)
Mitotic poisons	Docetaxel	Taxotere
	Etoposide	Etopophos
		Vepesid
	Paclitaxel	Taxol
	Podophyllotoxin	Condyline
	Vinblastine	Velbe
	Vincristine	Oncovin
	Vindesine	Eldisine
	Vinorelbine	Navelbine
Cytokines	Aldesleukin	Proleukin
	Filgrastim	Neupogen
	Lenograstim	Granocyte
	Pegfilgrastim	Neulasta
	Interferon alfa-2a	Roferon-A
	Interferon alfa-2b	IntronA
Hormonal antagonists and inhibitors	Anastrozole	Arimidex
	Bicalutamide	Casodex
	Buserelin	Suprefact
	Cyproterone	Cyprostat
	Diethylstilbestrol	
	Ethinylestradiol	
	Exemestane	Aromasin
	Fulvestrant	Faslodex
	Flutamide	Drogenil
	Letrozole	Femara
	Medroxyprogesterone	Farlutal
		Provera
	Megestrol	Megace
	Norethisterone	
	Tamoxifen	Nolvadex-D
	Toremifene	Fareston
Pituitary hormone disruption	Buserelin	Suprefact
	Goserelin	Zoladex Implant
	Leuprorelin	
	Octreotide	Sandostatin
	Triptorelin	Gonapeptyl Depot
Other agents	Trastuzumab	Herceptin
	Anagrelide	Xagrid
	Bacillus Calmet-Guérin (BCG) vaccine	
	Calcium folinate (leucovorin)	
	Calcium levofolinate (levoleucovorin)	Isovorin
	Disodium folinate	Sodiofolin
	Imatinib	Glivec
	Mesna	Uromitexan
	Tretinoin	Vesanoid

GENE THERAPIES

77

CHAPTER SEVENTY-SEVEN

OBJECTIVES

KEY TERMS

Ethics
Ex-vivo procedures
Gene therapy
Germ-line therapy
In-vivo procedures
Somatic gene therapy
Vectors

After completing this chapter, the reader should be able to:

- **define gene therapy and identify some applications where the technique could be used;**
- **outline the types of gene therapy;**
- **describe the two main techniques that could be used in gene therapy;**
- **state problems associated with gene therapy that limit its wider use in clinical practice.**

GENE THERAPY INVOLVES THE INSERTION OF GENES INTO human cells in order to produce a clinical benefit. The potential of this therapy is tremendous. It has been suggested that the effects of the faulty genes that cause a range of debilitating and potentially fatal single-gene diseases, such as muscular dystrophy, cystic fibrosis and an inheritable severe combined immunodeficiency (SCID), could be neutralised by insertion of the normal gene into the body cells of the affected person. Possible applications for gene therapy also exist in other chronic diseases where there is a significant genetic component to the pathophysiology, such as in cancer, cardiovascular disease, diabetes mellitus, asthma and arthritis. Although the results of clinical trials are encouraging, there have been some problems, and these will be outlined in this chapter. There have been instances of moderately successful clinical applications of gene therapy, but it is clear that this technology is some years from being used widely in clinical practice.

TYPES OF GENE THERAPY

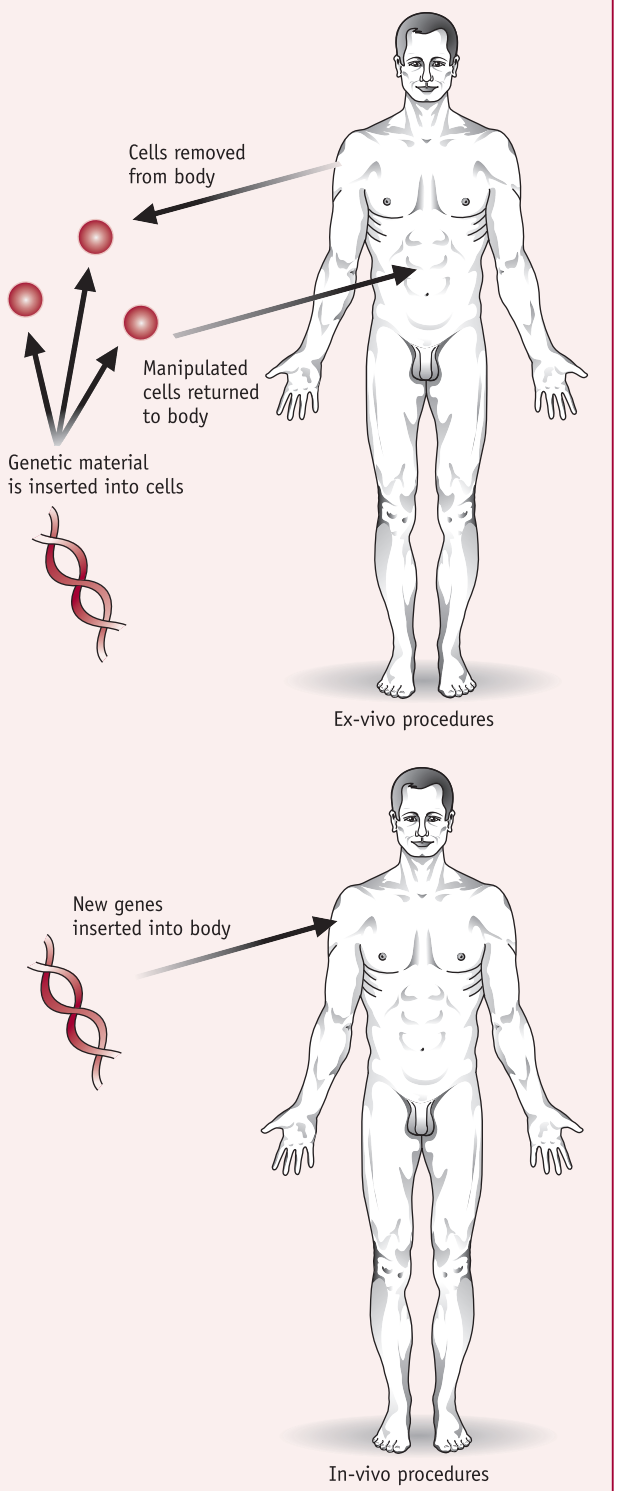
There are two forms of gene therapy: (i) somatic gene therapy, where genes are inserted into somatic (body) cells but cannot be inherited because the treatment does not affect the sex (germ) cells (sperm, ova) and (ii) germ-line therapy, where manipulation of germ cells means that the inserted gene can be inherited. Although the prospect of offering an intergenerational cure for a number of severe and debilitating genetic diseases is attractive, there are serious ethical concerns about germ-line therapy being used for selective breeding to 'manufacture' the perfect human baby through the enhancement of culturally or physically 'desirable' traits and elimination of 'undesirable' traits. Broadly speaking, much of society regards the use of gene therapy to alleviate the clinical symptoms of a person's illness as ethically acceptable but considers it unacceptable to use this procedure to manipulate human traits such as eye, hair and skin colouring. As germ-line therapy is ethically unacceptable in most countries, the focus of research and development is on somatic therapy, and it is this approach that will be discussed in this chapter.

GENE THERAPY TECHNIQUES

In some ways, gene therapies can be considered to be a sophisticated form of drug delivery, inducing changes in cellular activity that correct abnormal function. Gene therapy relies upon two main approaches (see Figure 77.1): ex-vivo procedures, whereby cells are taken from the individual, genetically altered outside the body and then reinserted in the individual, and in-vivo procedures, in which genes are delivered directly to particular cells in the body.

Genes can be introduced into cells either by using a virus as a carrier (a vector) or by linking to some sort of synthetic delivery system. When using viral vectors, it is essential that the virus has been inactivated, rendering it incapable of replication and dissemination, in order to remove the chance that it might itself cause disease. To achieve this, viral replication genes are removed and replaced with the therapeutic genes. In this way, the virus delivers the genes to the first cell it enters but is then incapable of further replication and infection of other cells. An ideal vector should also have low immunogenicity (so that it is unlikely to produce an immune or inflammatory response) and a negligible tendency to induce genetic mutations in cells, which may lead to cancer. Synthetic delivery systems involve attaching or incorporating DNA sequences in plasmids or liposomes (lipid vesicles) or complexing them with gold or phosphate salts. Another approach has been to inject 'naked' (uncomplexed) DNA sequences directly into tissues. The major advantages associated with synthetic vectors are that there is no infectious or mutagenic potential and they are cheaper to produce on a large scale.

FIGURE 77.1 GENE THERAPY TECHNIQUES



For each delivery method, the introduced genes must be taken up accurately into the nuclei of the target cells in a reliable fashion, the inserted genes should be expressed normally and for a prolonged period, and the desired

therapeutic products from the genes should be produced in a controlled way. To date, viral methods have been shown to produce more stable and efficient gene integration.

TECHNICAL PROBLEMS ASSOCIATED WITH GENE THERAPY

Current gene therapies have a number of limitations preventing their wider use in clinical practice. Even in cases of relatively simple genetic disorders, such as cystic fibrosis and haemophilia, both single-gene disorders characterised by the absence of only one normal protein, technical problems have hampered attempts at curative gene therapy. Some problems that have manifested include the following:

- Genes can be delivered to cells but, at this stage, the defective genes cannot be removed or replaced. This is of particular importance in diseases where the defective gene product contributes directly to disease pathophysiology, i.e. where the condition is not solely the result of lack of expression or function of a particular gene product.
- Effective clinical therapy for some diseases requires efficient gene incorporation into most of the target cells, which may be distributed widely throughout the body, and are sometimes located in relatively inaccessible regions, rather than being present in one discrete site. This is a particular concern with ex-vivo techniques, where the proportion of target cells with the introduced gene may be low, the gene expression may be inadequately regulated or vary significantly from cell to cell.
- Expression of genes can decline rapidly with time. For long-term expression and subsequent long-term benefit, the transferred genes need to be incorporated in the chromosomal DNA rather than just taken up into the nucleus. This is a difficult problem, but retrovirus vectors appear to be more successful in achieving this than other viruses.
- The most successful viral vectors tend to be small, but human gene sequences with all their regulatory components are large. Consequently, they are difficult to accommodate in such a small delivery vector.

GENE THERAPY SUCCESSES

Despite the technical problems, there have been some widely publicised achievements. Notably, clinical trials of gene therapy in children with a form of severe combined immunodeficiency (SCID), a condition in which the patient has a deficient immune system and must be isolated from all environmental pathogens, have indicated that patients have responded well to gene therapy. In a form of SCID characterised by the absence of the enzyme adenosine deaminase, gene therapy involving the ex-vivo manipulation of peripheral blood mononuclear cells and bone-marrow stem cells using retroviral vectors provided considerable clinical benefit. The initial success of this therapy has been mitigated, however, by the emergence of leukaemias in a number of treated patients (see below).

Promising clinical advances have also been reported in clinical trials of gene therapies for a number of other single-gene diseases, including muscular dystrophy, haemophilia and chronic granulomatous disease.

A high proportion of gene therapy clinical trials to date have involved treatments for cancers rather than for inheritable diseases. The general aim of these trials has been to boost the patient's immune function in order to rid the body of cancerous cells. In such cases, gene therapy could also allow the insertion of pro-apoptotic (programmed cell death) 'suicide' genes into cancerous cells, thus causing cell death.

FUTURE DEVELOPMENTS

A promising application of gene therapy involves the engineering of cells to act as implants from which therapeutic agents can be released into the body in a controlled fashion. Such implants have been proposed for the endogenous release of nerve growth factors (e.g. in Alzheimer's disease and Parkinson's disease), monoclonal antibodies, interferons, **erythropoietin** and **insulin**. In a more complex therapy, the secretion of these substances by the engineered cells could additionally be switched on or off by the administration of specific drugs.

Another, more technically challenging approach involves combining genetically altered cells with synthetic materials to create biosynthetic tissue frameworks that could act as functional organ transplants and drug-releasing implants. Genetically modified skin fibroblasts layered on to collagen-coated polyethylene fibres to produce lattices that can be implanted have been developed. Although not directly involving gene therapy, similar procedures in which bladder cells from patients with a genetic disorder causing insufficient development of the bladder have been cultured in vitro before transfer on to collagen frameworks and reimplantation have resulted in the successful enlargement and restoration of effective function of the bladder, thus demonstrating the vast potential of this approach.

SAFETY CONSIDERATIONS

As gene therapies involve the genetic manipulation of cells and the use of viruses, monitoring by an appropriate authority and stringent safety procedures are required. All materials and treatments should be tested well before use to ensure that they are safe. There has already been one death as a result of gene therapy: in the USA in 1999, an 18-year-old man died during gene therapy; the conclusion

was that his death was due to a severe immune reaction to the viral vector used, compounded by poor liver function and a probable parvovirus infection. Another incident relating to gene therapy safety occurred in France in 2002, when a child receiving gene therapy for SCID developed leukaemia. Although it is argued that the child may have been more susceptible to leukaemia because of a family history of cancer and an acute chickenpox infection that triggered a proliferation of lymphocytes, the possibility that the use of a viral vector caused the activation of a cellular oncogene (cancer-causing gene) cannot be ruled out. The subsequent emergence of leukaemia in two further patients with SCID led to the suspension of this trial until the safety of the technique has been investigated and improved.

SUMMARY

- Gene therapy involves the transfer of genes into human cells for therapeutic effect.
- There are therapeutic applications in the treatment of inheritable diseases and chronic diseases, such as cancer, cardiovascular disease and arthritis.
- Somatic gene therapy is where genes are inserted into body cells, but not the gametes. Germ-line therapy involves the transfer of genes into gamete cells.
- When cells are removed from the body, genetically altered and then placed back in the body, the procedure is termed ex vivo. When genes are delivered directly into body cells, the procedure is termed in vivo.
- Viral and non-viral vectors can be used to transfer genes, but the technology is still problematic. It will be some time before gene therapy can be used widely in clinical practice.

1 Define the term 'gene therapy'.

2 Describe the two types of gene therapy. Which form is ethically unacceptable, and why?

3 For each of the following examples, indicate whether it is an ex-vivo or in-vivo procedure:
(a) removing white blood cells from a person, introducing a gene into the cells in vitro, and then injecting those cells back into the person's body;
(b) administering, by inhalation, an aerosol containing viral vectors to be incorporated in the epithelial cells of the bronchioles;
(c) genetically engineered cells implanted into a person's peritoneal cavity and then secreting and releasing insulin.

4 State four technical problems associated with gene therapy that limit the widespread use of this technique clinically.

CASE STUDY XIV.1 Mr BT is a 47-year-old man admitted to hospital with prostate hypertrophy requiring a transurethral resection of the prostate (TURP). The procedure is completed without complication and Mr BT returns to the ward with an indwelling catheter in place. It remains in situ for 3 days.

After the catheter is removed, Mr BT experiences urinary frequency and a burning sensation during micturition. A urine sample is taken and sent to the microbiology laboratory for analysis. The microbiology report shows the following.

- *Microscopy*: white blood cells ++; Gram-negative rods.
- *Culture*: *Pseudomonas aeruginosa*.
- *Sensitivity*: amoxicillin – resistant; cephalexin – sensitive; trimethoprim – resistant; gentamicin – sensitive.

His medical history indicates hypsersensitivity to penicillin.

QUESTIONS

1 *Which antibacterial agent(s) would be effective in the therapy of Mr BT's urinary tract infection?*

2 *State the general mechanisms of action of each of these agents.*

3 *Outline the pathophysiology underlying Mr BT's hypersensitivity to penicillin.*

4 *Given the fact that Mr BT is allergic to penicillins, is cephalexin therapy contraindicated here?*

CASE STUDY XIV.2 JS, aged 6 years, visits the community health centre with his mother after experiencing fever, earache and a feeling of 'fullness' in his left ear. A yellow exudate oozes from the ear. During examination, the community doctor notices a bulging yellow eardrum and diagnoses acute bacterial otitis media. The doctor prescribes amoxicillin mixture 40 mg/kg/day in three divided doses, at 8-hour intervals for 5 days. As the community health nurse, it is your role to explain to JS's mother how to administer the antibiotic medication. She tells you that JS is normally very apprehensive about taking medicines.

Amoxicillin mixture contains 125 mg/5 ml. JS weighs 20 kg.

QUESTIONS

1 *Calculate how much amoxicillin mixture (in milligrams) JS should receive each day. To what volume does this correspond? How many millilitres would JS receive at each dose?*

2 *How would you advise JS's mother about the method used to administer this dose to JS?*

3 *What measures could his mother use to encourage her son to take the medication?*

4 *Once opened and reconstituted with water, where should JS's mother store the amoxicillin mixture? Explain.*

5 *What safety precautions could JS's mother take to ensure that her son does not come into contact with the mixture while it remains in storage?*

6 *What specific information would you offer JS's mother about the administration of the amoxicillin mixture?*

CASE STUDY XIV.3 KY is a 12-year-old boy and has recently been diagnosed with acute lymphoblastic leukaemia (ALL). He has been admitted to hospital for treatment. His parents and his four siblings are devastated by the news but are rallying around the boy in support.

KY's initial therapy will comprise the corticosteroid dexamethasone and the cytotoxic agents vincristine, L-asparaginase, daunorubicin, methotrexate and cytarabine. He experiences gastrointestinal upset but responds well to therapy; however, he does require close monitoring of his condition. KY receives adjunct therapy with the colony-stimulating factor filgrastim.

KY's siblings are tissue-typed for bone-marrow transplantation. One of the children is considered a good match. While awaiting the transplantation, KY develops a fever. He receives intravenous therapy with doxycycline to reduce the risk of sepsis. This crisis passes.

Following bone-marrow transplantation, KY makes good progress and moves into remission.

QUESTIONS

1 *Describe the mechanism of action of the corticosteroids and indicate the adverse effects that require monitoring during treatment with these drugs.*

2 *To which cytotoxic drug groups do each of the drugs in the case study belong?*

3 *Describe the mechanisms of action of each of the drug groups identified in question 2.*

4 *What are the common immediate and delayed adverse reactions associated with cytotoxic drugs?*

5 *Describe the clinical management of a patient with increased susceptibility to infection.*

6 *To which antimicrobial drug group does doxycycline belong? Is it considered a bactericidal or bacteriostatic agent?*

7 *Define the term 'antimicrobial drug spectrum of activity'. What is the spectrum of activity of doxycycline? Why choose a drug with this spectrum of activity in KY's case?*

CASE STUDY XIV.4

You are a health-care professional participating in an immunisation programme. Children and some adults from the community are receiving vaccinations in accordance with the government's vaccination schedule. You will be a member of the team administering the vaccines.

QUESTIONS

1. *What is the difference between passive and active immunity?*
2. *Which form of immunity is induced by vaccines?*
3. *Name the different ways in which a vaccine can be prepared.*
4. *What is the major advantage of recombinant vaccines over the older forms of vaccine?*
5. *Why do some types of immunisation require multiple vaccination?*
6. *State the common adverse effects of vaccination. How could the discomfort associated with vaccination be minimised before injection?*
7. *For how long after the vaccination should a patient be observed? What kinds of reaction are you looking for during this time?*

CASE STUDY XIV.5

RS was once a patient in the hospital of a major city. The records office of this hospital then suffered from accidental flooding due to a burst water pipe. Many records were damaged by the water, leaving much information irretrievable, including most of RS's clinical details.

RS has since died, and his death has resulted in a coronial inquiry. The coroner's office has asked for RS's clinical records from the hospital, and the information that could be obtained from the waterlogged records is given below. This refers mainly to the drug therapy used in the treatment of RS over the past 2 years and an occasional decipherable diagnosis. The drugs are listed in the order given from RS's initial admission date until his death.

12/11/01–14/02/02	Commenced zidovudine capsules 100 mg po q 5 h.
15/02/02–17/02/02	Zidovudine dose increased to 200 mg po q 4 h.
18/02/02–25/02/02	Benzocaine and cetylpyridinium chloride mouthwash prn q 12 h.
18/02/02–27/02/02	Zidovudine syrup 200 mg po q 4 h.
18/02/02–27/02/02	Two amphotericin lozenges to be sucked slowly qid.
28/02/02–	Zidovudine capsules 200 mg po q 4 h. Ketoconazole 200 mg d with food.
28/02/02–07/05/02	Ketoconazole shampoo twice weekly for 4 weeks.
15/04/02–01/06/02	Didanosine tablets 150 mg bd to be chewed.
02/06/02–	Zalcitabine tablets 750 g tds.
02/06/02–14/06/02	2 cm capsaicin (0.075%) cream to painful area tds.
31/07/02–	Protein purified derivative (PPD) skin test given, which resulted in an indurated area of 9 mm.
06/08/02–06/06/03	Isoniazid tablets 100 mg tds.
06/08/02–06/06/03	Pyridoxine hydrochloride tablets 25 mg om.
23/07/02–06/08/02	Trimethoprim + sulphamethoxazole double strength (Bactrim DS) bd pc.
23/07/02–06/08/02	Pentamidine aerosolised 300 mg/d. Pentamidine IV 300 mg/d.
07/08/02–09/09/03	Pentamidine aerosolised 300 mg/monthly. Developed severe diarrhoea.
09/09/03–16/09/03	Vancomycin 1 g IV bd by slow infusion.
16/09/03–	Kaposi's sarcoma diagnosed. No cytotoxic therapy recommended.
18/09/03–25/10/03	Sulphadiazine 1.5 g q 4 h by slow IV infusion. Pyrimethamine 50 mg stat, 25 mg d.
18/10/03–20/10/03	Calcium folinate 3 mg IM d.

Note: Refer to Appendix A for information about prescription abbreviations.

QUESTIONS

1. *What condition did RS have? What is its cause?*
2. *Define all the Latin prescription abbreviations used above.*
3. *Is the use of Latin abbreviations recommended today? Give reasons for your answer.*
4. *What is the mechanism of action of zidovudine?*
5. *Zidovudine is a prodrug. What does this term mean? Give three other examples of prodrugs used clinically for the following conditions:*
   (a) insomnia;
   (b) hypertension;
   (c) Parkinson's disease.
6. *Why is zidovudine relatively non-toxic to humans?*
7. *What is the most likely reason for increasing Rodney's dose of zidovudine after approximately 3 months?*
8. *What could be a reason for the use of cepacaine? Which ingredient in cepacaine would be pharmacologically active with regard to the most likely symptom that RS displayed, given that it was not due directly to a virus? Cepacaine can be used to suppress the symptoms of bacterial pharyngitis. How do we know that a bacterial infection of the throat was not a problem with RS at this time?*

9 *Why were the zidovudine tablets replaced with syrup for the short period in February 2002?*

10 *Why were amphotericin lozenges prescribed? Why should they be sucked slowly? What alternative drug could be used here? Why is amphotericin sometimes administered intrathecally?*

11 *Why was ketoconazole introduced into RS's drug regimen at this stage in his illness until the terminal stages of his illness? What is a likely reason for the use of the ketoconazole shampoo? What is the normal dosage protocol used with ketoconazole shampoo?*

12 *What is an undesirable consequence of ketoconazole in male patients?*

13 *Why was the prescription for the zidovudine withdrawn in February? Why was the change to didanosine and zalcitabine instituted at this time? What is the mechanism of action of these drugs?*

14 *Suggest why capsaicin cream was prescribed, and the probable cause of the condition.*

15 *What does PPD stand for? Explain its use and the mechanism whereby the induration was produced. If the indurated area was about 4 mm in diameter, what would this mean?*

16 *Why would isoniazid be prescribed? Why would pyridoxine be given concurrently? What could be prescribed instead of isoniazid? What are two major adverse effects of isoniazid therapy? What enzyme deficiency can cause problems with isoniazid therapy?*

17 *Why, with Bactrim™, was a proprietary name used on the prescription while all other drugs were prescribed generically?*

18 *Bactrim can be used for many infections. What would be the purpose of using Bactrim in this case, and how can you be more or less certain of the cause of the infection?*

19 *How does Bactrim control infections?*

20 *Why must care be taken in the use of Bactrim in elderly patients?*

21 *Why was pentamidine administered both intravenously and via the lungs directly? Why was pentamidine continually used in aerosol form by RS until near his death?*

22 *What was the most likely organism causing diarrhoea in RS in the September before his death? Most cases of diarrhoea are not treated with antibiotics. Why in this case was an antibiotic used immediately on diagnosis? What is the likely source of the organism causing the diarrhoea? What drug could have been used instead of the vancomycin?*

23 *The symptoms and progress of Kaposi's sarcoma can be ameliorated successfully by chemotherapy with such drugs as etoposide, vinblastine and/or bleomycin. They were withheld in RS's case, even though his illness was not in its terminal stages. Why is treatment of Kaposi's sarcoma in many patients with RS's disease not treated aggressively with antineoplastic drugs and/or radiotherapy?*

24 *Why would treatment with sulfadiazine and pyrimethamine be commenced?*

25 *What would be the purpose of the calcium folinate injections?*

26 *What is a more common use of pyrimethamine?*

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WEB RESOURCES

Johns Hopkins Division of Infectious Diseases: Antibiotic Guide www.hopkins-abxguide.org/

Microbial World: Penicillins and Other Antibiotics http://helios.bto.ed.ac.uk/bto/microbes/penicill.htm

National Institute of Health and Clinical Excellence www.nice.org.uk

Real Millenium Bugs: Immune to Antibiotics www.abc.net.au/science/slab/antibiotics/surviving.htm

Travellers' Health Guide www.dh.gov.uk/PolicyAndGuidance/HealthAdviceForTravellers/fs/en

Vaccines www.jr2.ox.ac.uk/bandolier/booth/booths/vaccine.html

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DRUGS USED TOPICALLY

Skin is like wax paper that holds everything in without dripping.

ART LINKLETTER – *A CHILD'S GARDEN OF MISINFORMATION*

Although it is useful to view skin as wax paper in order to explain its water-resistant qualities, this analogy does not account for the general structure and function of living tissue. Unlike wax paper, the tissues of the skin and surface of the eye allow some chemicals to pass through with relative ease.

Drugs administered to the surface of a tissue are absorbed into and incorporated in the deeper tissues of that structure. Once absorbed, they alter the nature of the physiological processes taking place therein; this is desirable in order to correct the imbalance that underlies the condition being treated. Put simply, the drugs become a part of those processes. In this section, we focus on drugs used in the treatment of skin (Chapter 78) and eye (Chapter 79) conditions.

A number of the drugs mentioned in these chapters have been discussed in detail elsewhere in the book, such as the corticosteroids and antimicrobial agents. Wherever appropriate, cross-references to previous chapters are made. We also introduce some new drug groupings that are applicable only in the context of the skin or eyes, such as ophthalmic staining agents, keratolytics and wetting agents.

XV

DRUGS USED IN DISEASES OF THE SKIN

78

CHAPTER SEVENTY-EIGHT

OBJECTIVES

After completing this chapter, the reader should be able to:

- **list some of the different vehicles used in skin preparations;**
- **describe the use of skin cleansers, counter-irritants and rubefacients;**
- **explain the dangers of excessive sun exposure and the use of sunscreens;**
- **identify the drugs used to treat psoriasis;**
- **list the drugs used to treat acne;**
- **outline the treatment of and preventive measures for nappy rash;**
- **describe the treatments for dandruff, scabies and pediculosis (lice infestations);**
- **describe the treatment for warts, hyperhidrosis and baldness.**

KEY TERMS

Ointments
Creams
Lotions
Gels
Counter-irritants
Acne
Psoriasis
Lice
Scabies
Desloughing
Sunscreens
Nappy rash
Baldness

THE SKIN IS THE LARGEST ORGAN OF THE BODY AND IS susceptible to a large number of diseases. Many of these diseases are due to infections; most of the drugs used to treat such infections are dealt with in the chapters on antimicrobials. Other common diseases of the skin are due to inflammatory conditions resulting from allergies. The drugs used in the treatment of these dermatoses are dealt with in the chapter on corticosteroids (Chapter 58).

Embedded in the skin are structures called appendages, such as the nails, hair follicles, sweat and sebaceous glands, all of which are subject to disease. This chapter deals with drugs and compounds used to treat some of the conditions associated with these appendages and also covers the treatment of some other skin problems not dealt with adequately in other chapters.

Numerous preparations are available from pharmacies for applying to the skin. Some have exotic names, such as Tiger Balm and Seahorse Balm. It is doubtful whether many of these preparations are of any real pharmacological value, but many have an important placebo effect. It is not the purpose of this book to discuss such preparations, which often have obscure ingredients. Nevertheless, it is important to be aware of their existence, as many of them can lead to allergic skin problems. It must always be borne in mind that substances applied to the skin may have the potential for systemic absorption, with resultant systemic adverse effects. This is not common, except with some of the corticosteroid preparations, especially in ointment form.

VEHICLES USED IN SKIN PREPARATIONS

Medications applied to the skin, whether for systemic or local treatment, have to penetrate at least the superficial cells. Vehicles that are used to carry drugs into the superficial layers of the skin are therefore types of drug-delivery system. In order for drugs to be carried into the cells, the keratin layer of the epidermis must be penetrated; if this is broken, excessive absorption may occur, with resultant systemic effects. The vehicles are usually inert substances acting as carriers for the drugs they contain. Many vehicles are available; reference to types of skin preparation is made in Chapter 7. What follows is a brief description of the properties of the various common skin preparations.

Lotions

A lotion is a liquid preparation prepared for skin application and is usually intended to have a cooling or antiseptic action on the skin. Many lotions contain alcohol, which evaporates quickly, enhancing the cooling effect usually due to the water in most lotions. A common example is **calamine lotion**, an emulsion of zinc oxide, rosewater and glycerine used for sunburn. This type of lotion, which contains a solid, is a convenient way of applying a powder to the skin with an added cooling action. Many lotions are available. The Latin term *lotio* is still occasionally used to describe the various preparations; for example, calamine lotion may be referred to as *lotio calaminae*. Care should be taken not to be overzealous in the application of lotions to large surface areas, especially in elderly and infirm patients, as hypothermia may result from the excessive cooling action.

Creams

Creams are aptly named because they resemble the dairy product of the same name with respect to consistency. There the resemblance stops, however; milk cream contains a high amount of emulsified fats with water, whereas pharmaceutical creams are aqueous preparations containing little or no fat or lipid substances. Pharmaceutical preparations with a high fat content are called ointments. Creams are generally of low viscosity and following application to the skin tend to disappear fairly quickly due to the evaporation of the water, any fats present being taken up into the superficial cells of the epidermis. This can lead to some hydration of the epidermal cells, leading to a softening of the keratin layer – hence, the cosmetic use of creams, a multimillion-pound industry.

Gels

Gels are generally translucent preparations. They serve the same function as creams but tend to be less messy. Gels have become popular vehicles for the application of anti-inflammatories and rubefacients to sports injuries; they are also used as toothpastes. Being less messy than creams, gels are particularly useful for application to hairy areas of the body.

Ointments

Ointments have a high fat content and/or high viscosity. Being viscous and non-evaporative, they adhere to the skin, acting as an occlusive dressing. This can lead to some skin maceration, and so ointments are useful in dry, scaly conditions. This occluding action makes for good penetration of a drug if the ointment is used as a vehicle. Used alone, ointments may be used to protect some areas of the body, such as to protect the lips from drying out.

Skin cleansers

Skin cleansers are used for several reasons, some not related directly to keeping clean in the usual sense of the word. Skin cleansers can be used to remove the accumulation of cell debris that occurs in ulcers and to remove the excessive keratin accumulation that occurs in hyperkeratoses. In ichthyosis (fish-skin disease), there is severe dryness and scaling of skin; moisturising and removing this scaling helps to relieve the condition.

Substances used to treat these conditions are varied, and only a few are mentioned in this chapter.

For simple skin cleansing, mild soaps with the addition of antiseptic substances are useful. This type of preparation is useful in the prophylaxis of acne and other skin infections. Skin cleansers are used in hospital wards and operating

theatres to reduce the risk of nosocomial infections. A full discussion of the antiseptics used in this situation is given in Chapter 70.

Desloughing agents

To remove cell debris and exudate from infective skin conditions and ulcers, weak desloughing agents are all that is usually needed. These agents include the keratolytics mentioned below; in many cases, antiseptic cleansers suffice.

Scaling disorders can be treated with creams containing urea. Urea is hygroscopic and, by attracting water to dry cells in hyperkeratotic skin conditions, helps to alleviate the condition. The addition of mildly acting keratolytics, such as lactic acid, further enhances the desquamation process. Other weak organic acids, such as **salicylic acid** and benzoic acids, can be substituted for lactic acid. Salicylic acid and lactic acid in high concentrations are very keratolytic and can be used to soften and remove the excessively hard skin that occurs in corns. Both have also been used in the treatment of warts.

Alpha-hydroxy acids (AHAs) have become very much in vogue in recent years as exfoliants of the skin and are promoted vigorously as anti-wrinkling and anti-ageing substances for rejuvenation of the skin. Lactic acid is a hydroxy acid, as are malic acid, citric acid and tartaric acid, but the most widely used is glycolic acid. There is no doubt that these preparations, sometimes termed 'cosmeceuticals', reduce flakiness and moisturise the epidermis and may have some anti-wrinkle properties, but not to the degree purported by some companies. Some dermatologists use these creams with some success; preparations containing more than 10 per cent hydroxy acids should be used only under medical supervision.

According to a 1999 report, the US Food and Drug Administration (FDA) had received more than 100 reports on adverse reaction to these exfoliants, but the realistic figure has been put at over 10 000. These included severe erythema, inflammation (especially around the eyes), burning, blistering, bleeding, rash, pruritis and skin discoloration.

AHAs also increase sensitivity to the sun by removing the upper protective stratum corneum. A study sponsored by the cosmetics industry demonstrated that users of 4 per cent glycolic acid required 13–50 per cent less ultraviolet (UV) radiation to reach a standard minimal redness. If this finding can be extrapolated to encompass the general population, then there are tens of thousands of AHA users who now have an enhanced risk of skin cancer and, ironically, sun-induced skin ageing.

Counter-irritants and rubefacients

These terms are more or less synonymous. A counter-irritant when applied to the skin stimulates the nerve endings by inducing an inflammatory response. This results in reddening of the skin – hence the term 'rubefacient', which means to make red. If pain is being transmitted from the skin or from areas lying beneath the skin and rubefacients are rubbed into the area, the nerve signals being carried to the central nervous system (CNS) by these afferent fibres are increased. Somehow, this increase in afferent messages to the CNS is thought to cause the pain signals to be ignored. This explains the term 'counter-irritant'. The mechanism of action is still a matter of conjecture. There is no doubt, however, that counter-irritants work and provide relief in many cases. Counter-irritants are not always substances; they can also be physical in nature: think of the relief that a hot-water bottle provides to a 'sore tummy' or the relief following application of a hot poultice to stiff or strained muscles.

Many chemicals, when applied to the skin, cause a local vasodilation. Such chemicals include camphor and menthol, which explains the strong smell of many of these preparations. Extracts of chilli peppers are very effective – think of the effect on one's tongue. One of the authors of this book knows of at least one instance where the heat produced by a preparation containing a chilli extract was so intense that a local anaesthetic cream had to be applied to negate the pain caused by the rubefacient. Care may be needed when applying these preparations, and areas of sensitive skin and the eyes must be avoided. Thorough handwashing is imperative after applying such preparations.

Sunscreens

The incidence of melanoma in Britain is increasing, with around 8000 cases diagnosed annually. Australia has the highest incidence of melanoma in the world. This is due mainly to exposure of the skin to the sun: UV rays are harmful to living cells, and hence the use of UV in sterilisation procedures; the intensity of UV rays in Australia is higher than in the rest of the world, owing to a hole in the ozone layer in the upper atmosphere. UV rays stimulate melanocytes to produce more melanin and thus protect the deeper layers from the rays. The melanin produced results in a tan, which many people find desirable. In reality, a tan is often the result of sunburn and can be likened to scar tissue. Tanned skin tends to age rapidly and results in premature wrinkling. More seriously, UV rays damage nucleic acids; it is this that leads to skin cancers, or melanomas, which can be fatal without treatment. The best way to prevent melanoma is to avoid the sun's direct rays. This is not always practicable, and so some form of skin protection is needed. This can be obtained by wearing more clothing and covering up exposed skin (consider the fact that Arab women rarely get skin cancer). Exposed areas of skin should be protected with a sunscreen, substances that block out or scatter the harmful UV rays.

Some substances used as sunscreens are opaque and simply shut out the offending rays. Zinc oxide is often used for this purpose and is available in various colours.

Titanium dioxide, a common ingredient of paint, is another compound with a similar effect. Unfortunately, these substances block the pores and cannot be used over large areas because of the risk of producing hyperthermia. They can also be extremely messy. Of more practical value are the substances that absorb UV rays. Many aromatic organic compounds do this, most with long chemical names, such as dimethylaminobenzoic acid and padimate. The higher the concentration of these compounds, the better the protection. This concentration is shown on sunscreen applications as the sun protection factor (SPF). The higher the SPF number, the more effective the screening power. Some of these compounds thoretically filter out the wavelengths of the UV light that cause severe damage but allow through the wavelengths that cause tanning. This does not prevent photoageing of the skin.

COMMON SKIN CONDITIONS AND THEIR TREATMENT

Psoriasis

Psoriasis is a skin disease of unknown aetiology characterised by the appearance of epidermal thickening and silvery-white scaly patches on the skin. These lesions are more common on extensor surfaces of the limbs and the scalp, but eruptions can be widespread, involving most areas of the skin. There is no cure for psoriasis, but remissions are often produced by the therapies available, which include using UV light either alone or in combination with drugs, as well as topical and systemic treatment. Occasionally, psoriasis is precipitated by use of drugs such as lithium, chloroquine, non-steroidal anti-inflammatory drugs (NSAIDs), beta-blockers and angiotensin-converting enzyme (ACE) inhibitors; in such cases, psoriasis does not usually appear until the drug has been taken for weeks or months.

TOPICAL TREATMENTS

Emollients such as aqueous cream are used to treat dryness, cracking and scaling but may also have an anti-proliferative effect. Topical treatment may include corticosteroids (see Chapter 58), which help to reduce inflammation and itch, but these are unsuitable as the only treatment of extensive plaques, as early improvement is not usually maintained and there is a possibility of deterioration. Mild steroid creams are used on the face and flexures. Stronger creams are reserved for the scalp, hands and feet. Two other groups of substances are often used to treat psoriasis, namely the anthroquinolones and **tar** preparations.

The anthroquinolone commonly used is **dithranol**. This is an antimitotic that slows down the cell divisions in the hyperplastic skin lesions. It is a skin irritant and should not be used in active lesions. Application to normal skin should be avoided. It may be useful to protect normal skin surrounding lesions with a petroleum-jelly-based preparation. Areas of thinner skin, such as the genitals, intertriginous zones and the face, should be avoided. Dithranol can stain clothing and bedding, and so adequate cover should be provided to the treated part.

Tar products have a similar action to dithranol but are less irritant to skin and are especially useful for the treatment of psoriasis of the scalp. For such use, they are available incorporated in shampoos.

Salicylic acid together with an emollient cream may be used on scalp psoriasis. This acid is a keratolytic and useful where the psoriatic scales are thick.

Tazarotene, a retinoid, is effective in psoriasis. It must be applied sparingly to the plaques, avoiding the surrounding skin in order to reduce possible irritation.

✚ CLINICAL CONSIDERATIONS

Hands must be washed after dithranol use, and gloves should be worn to prevent staining. If redness appears, the dose and frequency of application should be decreased. To prevent damage to the surrounding normal skin, soft paraffin may be applied. Only the affected areas should be treated, as these preparations are irritant to normal skin.

SYSTEMIC TREATMENTS

There are several systemic treatments for psoriasis. They are used in severe, resistant, unstable or compacted cases and are started only under specialist supervision.

Methotrexate, an antimetabolite used in cancer chemotherapy (see Chapter 76), can be used to suppress cell division in psoriatic lesions. Due to its adverse-effects profile, it is reserved for recalcitrant cases. The antirejection drug **ciclosporin** (see Chapter 75) has also been used with some success.

✚ CLINICAL CONSIDERATIONS

Complete blood examinations and renal and hepatic function tests are conducted before starting treatment with methotrexate and at regular intervals after treatment commences. The methotrexate dose is reduced or stopped if leucopenia or thrombocytopenia occurs. For ciclosporin therapy, the plasma creatinine concentration is checked regularly during treatment. Blood pressure is monitored before and during ciclosporin treatment; ciclosporin is ceased if hypertension develops and does not respond to antihypertensive therapy or a drop in dosage.

ACITRETIN

Acitretin, a metabolite of etretinate, is used in the treatment of psoriasis. Etretinate is a retinoid derived from vitamin A and has the effect of normalising affected

epithelium. The action is probably via an initial speeding up of cell division in the lesions; this increase in activity leads to an increase in desquamation of lesional cells. Maximum benefit takes 4–6 weeks or longer. As retinoids are teratogenic, pregnancy must be excluded before treatment and for 2 years after treatment. The main side effects are dry skin and cracking lips. Apart from its teratogenicity, this is the least toxic of the systemic treatments for psoriasis. Liver function and blood lipids should be monitored.

◆ COMMON ADVERSE EFFECTS

The major adverse effects associated with the retinoids are as follows:

- *Hepatic toxicity*: in view of this, liver function tests should be undertaken at various frequencies, as indicated by the manufacturer.
- *Reversible increases in blood lipids*, mainly in the triglyceride fraction, are common. Patients with a personal and/or family history of hyperlipidaemias should have a blood lipid profile taken at varied intervals, according to the manufacturer's information or the dermatologist's decision.
- *Pseudotumour cerebri* (*benign cranial hypertension*): patients reporting headaches, nausea and/or vomiting and visual disturbances should be examined ophthalmoscopically for papilloedema; if present, treatment should be stopped and the patient referred to a neurologist.

Many other adverse reactions occur, some of which are given below in the discussion of acne; information about other reactions can be obtained from drug reference books. Patients should be instructed not to take multivitamin preparations unless they are vitamin A-free. Patients wearing contact lenses may experience some discomfort due to a drying of ocular secretions.

✚ CLINICAL CONSIDERATIONS

Patients on retinoid therapy are advised to protect their skin from sunlight by wearing protective clothing and by using a sunscreen. Female patients should ensure they have adequate contraceptive cover before, during and following retinoid treatment. White soft paraffin is used to treat dry lips and lubricating eye drops are administered to treat eye irritation.

ULTRAVIOLET RADIATION

UV radiation can be used either alone or in combination with the drugs mentioned above. A unique combination of UV therapy and drug treatment used in the treatment of psoriasis is PUVA therapy. The drugs used are called psoralens, of which **methoxsalen** is commonly used. These compounds are derived from citrus and other fruits. Bergamot oil, present in Earl Grey tea, contains psoralens. Psoralens act by combining with DNA. In the presence of UV light, DNA synthesis is then inhibited. Thus, when patients treated with psoralens are exposed to UV light of a certain wavelength, cell division is inhibited and the increased cell proliferation of the psoriatic lesions is suppressed. This exposure results in an increase in melanocyte activity, which causes an increase in tanning. This leads to photoageing of the skin in some individuals, and an increase in the incidence of skin cancer may result, although this is controversial.

PUVA therapy is useful in the treatment of abnormal pigmentation patterns, such as occurs in vitiligo.

✚ CLINICAL CONSIDERATIONS

PUVA therapy may be given two or three times a week; however, the treatments must be at least 48 hours apart. Wrap-around sunglasses with UV-ray-absorbing properties must be worn during daylight hours for 24 hours following treatment with oral psoralens. Particular foods are avoided during therapy because of their natural photosensitiser characteristics. These foods include carrots, celery, mustard, figs, limes, parsley and parsnips. A number of examinations should be performed before and after treatment, including eye examinations, measurement of antibody titre and liver function.

VITAMIN D

High doses of **vitamin D** have been known for some time to be of benefit in some patients with psoriasis, but they have not been used because of the high probability of hypervitaminosis D developing (see Chapter 61). The action of vitamin D on the keratinocytes in the skin, which contain vitamin D receptors, is to decrease their proliferation, which is about seven times faster in psoriasis. A vitamin D analogue, **calcipotriol**, is available, which has a 100–200 times lower hypercalcaemic action than natural vitamin D. This avoids the most serious problem of hypervitaminosis D, especially when calcipotriol is used topically in order to avoid high systemic levels. This suppression of keratinocyte differentiation and proliferation is not a cytotoxic effect but is a normal regulatory function of vitamin D. As hypercalcaemia could still be a problem with calcipotriol if absorbed in large amounts, this drug should not be applied to severe extensive psoriatic lesions; the maximum application should be no more than 100 g per week. Even then, blood calcium levels should be checked every 3 months. The other main adverse effects of calcipotriol are skin reactions and, occasionally, photosensitivity at the site of application. The ointment should not be applied to the face, as facial dermatitis has been known to occur.

✚ CLINICAL CONSIDERATIONS

Calcipotriol is not applied to the face, skin folds or scalp because these areas are particularly susceptible to irritation. Plasma calcium and renal function are monitored regularly.

If calcium levels are elevated, treatment is discontinued and calcium monitoring resumed until levels are normal. Treated areas are protected from light with appropriate clothing and sunscreen use. Hands must be washed thoroughly after application in order to avoid inadvertent transfer to unaffected body areas.

Eczema

Eczema, or dermatitis, may be acute or chronic and refers to a specific reaction in the skin with many possible causes. The different types of eczema all exhibit spongiosis of the epidermis, which is the accumulation of oedema in the keratinocytes, giving the appearance of a sponge when viewed under the microscope. The epidermis and the dermis may become thickened (lichenification) with time.

Types of eczema include atopic, allergic contact, irritant and seborrhoeic. Atopic eczema is the most common and is sometimes referred to as endogenous eczema. It is due to excessive immunoglobulin E (IgE) antibody, which leads to a hypersensitivity to some environmental antigens. Onset may be in the first 3 months of life, and the major symptom is itching. Allergic contact eczema is often referred to as contact dermatitis and is a delayed hypersensitivity reaction (see also Chapter 17) that follows contact with allergens such as nickel (used in jewellery), rubber and certain drugs. Irritant eczema may be due to occupational and domestic irritant chemicals. Seborrhoeic dermatitis or eczema usually affects the scalp and is commonly known as dandruff. There is no cure for eczema, but contributory factors should be removed if possible and any irritants should be avoided.

✚ CLINICAL CONSIDERATIONS

Greasy emollients should be used regularly and liberally to counteract skin dryness. Bath and shower emollients may also be used. Treatment with emollients should continue even when the condition improves.

Topical corticosteroids such as hydrocortisone are used in varying potencies, depending on the severity of the condition. If any infection is present, a short course of a topical antibacterial is used, usually for a week. In more severe and persistent cases of infection, systemic antibiotics may be used. Antiseptic shampoos may be used on the scalp.

Bandages containing **ichthammol** may be used over the corticosteroid in order to reduce pruritus. Ichthammol is a sulphurous tarry product that is mildly antiseptic, reduces itching and lessens hardening and thickening of the skin.

Drugs that affect the immune response are sometimes prescribed for atopic eczema by specialist dermatologists when there is a failure to respond to conventional therapies. **Tacrolimus** and **pimecrolimus** by topical application are immunosuppressants licensed for atopic eczema that does not respond to conventional steroid therapy. The long-term safety of these drugs is still being evaluated, and so the National Institute for Health and Clinical Excellence (NICE) does not recommend them as first-line treatment. Occasionally, systemic immunosuppressants such as **ciclosporin** and **azathioprine** may be used in severe eczema (see Chapter 75).

DANDRUFF

Dandruff is one of the most common skin conditions; in a lifetime, very few people escape it. Dandruff is occasionally referred to as seborrhoeic dermatitis as it occurs at sites of greatest sebum production. Pityriasis capitis and vulgaris (the fungus involved may be *Pityrosporum ovale*) are other terms for dandruff. Dandruff may not be confined to the scalp but can occur on the eyebrows, under the beard and on other hairy areas of the body. It commonly presents as flaking of the scalp, producing embarrassing 'snow' on dark clothes. If severe, itching may result. A greasy rash may develop on affected areas, especially at the hair margin. In babies, this is commonly called cradle cap. Some forms may be due to a superficial fungal infection, and recent evidence has shown antifungal drugs to be effective in its treatment.

Many treatments are available for dandruff, including shampoos sold in supermarkets. Many of these may work purely because of their detergent action in cleaning the hair and scalp. Nevertheless, some products are more effective than others, principally those containing **selenium sulphide** or **zinc pyrithione**. Both of these compounds have antifungal properties, which may be related to their effectiveness. Selenium sulphide may decrease sebum production, which may be a factor in its action. Selenium sulphide is highly toxic if taken internally and is an irritant to the eyes; great care must therefore be taken in its use. In some countries, selenium sulphide is a prescription-only product because of its toxicity. Zinc pyrithione is considerably less toxic and should be preferred to selenium sulphide, except in unresponsive cases.

Severe dandruff may require treatment with corticosteroid agents, some of which are available for scalp application. Shampoos containing coal or wood tar are sometimes effective but leave the hair rather smelly. Mild keratolytics such as salicylic acid-containing shampoos are also sometimes of use.

Dandruff may be due partially or totally to a fungal infection and thus may be responsive to treatment with antifungals. **Ketoconazole** has been formulated as a shampoo and **econazole** as a foaming solution (see Chapter 74). When used as such, they provide only temporary relief from seborrhoeic dermatitis and dandruff, and both disorders recur on cessation of treatment. The shampoo should be applied to a wet scalp and left for 3–5 minutes before rinsing thoroughly. This should be done twice weekly for

up to 4 weeks followed by a period of at least 4 weeks without treatment. The shampoo appears to be very safe, with no conclusive adverse effects of any significance being reported. As with most shampoos, eye irritation can occur. As ketoconazole is teratogenic, its use, even topically, should not be considered in pregnancy.

✚ CLINICAL CONSIDERATIONS

Anti-dandruff shampoos are best used for a period of time followed by a period without treatment. It is important to avoid contact with eyes because of the irritant properties of anti-dandruff preparations.

Acne

Acne vulgaris is a disease of the sebaceous glands, commonly occurring during puberty. The incidence of acne tends to decline with age and is unusual in adults, although it can persist for many years. Sebaceous glands secrete sebum, the natural oil of the skin. Testosterone is partially responsible for the secretion of sebum, and it may be that acne is due to an increase in responsiveness of the sebaceous glands to varying levels of this hormone that occur around puberty. When too much sebum is produced, the duct of the gland may become blocked; bacteria become trapped beneath the sebum plug and then proliferate in the duct, leading to a pustule or a small abscess. When sebum blocks the duct, it becomes oxidised into a black substance producing the blackhead or comedo (plural: comedones). If a pustule materialises, a whitehead is produced. The bacterium usually present is *Propionibacterium acnes*. There is no evidence that diet affects the progress of this condition. These lesions are cosmetically unattractive and can be quite painful; severe psychological distress can result. It is wrong to consider acne as a teenage problem to be endured until the person grows out of it, especially now good treatment with a high success rate is available.

Several treatments are available, the major successful types of which are discussed below. These are **benzoyl peroxide**, antimicrobials, retinoids and some miscellaneous compounds. Some older remedies, which include **sulphur** and **resorcinol**, are still used, but with limited success. Antiandrogenic compounds, such as the oestrogens, can be used in the treatment of acne in women.

Apart from the very common acne vulgaris, various other forms of acne exist, of which acne rosacea is the most common. As comedones are not present and the treatment may be different from that for acne vulgaris, this may not be a type of acne at all and is often just called rosacea. The cause is completely unknown, but the treatment suggests it is an infection. Rosacea occurs in adults of all ages and is confined mainly to the nose, although the cheek and brow may be affected. Rosacea is usually chronic, even with treatment. In severe cases, nasal rosacea can lead to rhinophyma, gross disfigurement of the nose that may require plastic surgery. The initial treatment is to use topical **metronidazole**, the only adverse effect being an occasional erythema. Unresponsive cases can be treated with long-term antibiotics similar to that used in acne. In recalcitrant cases, **isotretinoin** may be effective.

BENZOYL PEROXIDE

Benzoyl peroxide is a powerful oxidising agent that at least partially relieves some cases of acne by having bactericidal action. It is effective in mild to moderate acne. Benzoyl peroxide is mildly keratolytic. The preparation is obtainable in several strengths, and it is advisable that patients start with a lower strength and increase to higher strengths gradually. Benzoyl peroxide may cause minor skin reddening in susceptible individuals. There have been some reports that benzoyl peroxide is carcinogenic but, considering its widespread use for many years, this is not seen as a problem.

✚ CLINICAL CONSIDERATIONS

Benzoyl peroxide is applied to the affected area after it is washed with mild soap and water. Contact must be avoided with the eyes, mouth and other mucous membranes. It is important to avoid contact with the hair and coloured fabrics, because discoloration may occur.

ANTIMICROBIALS

To be effective against *P. acnes*, the antimicrobial must be able to penetrate the sebaceous gland, a property that the tetracyclines have. This makes tetracyclines ideal chemotherapeutic agents for the treatment of acne. Once treatment has proven effective with a tetracycline, such as **doxycycline** or **minocycline**, a maintenance dose of one capsule every 2 days may be all that is required to prevent further lesions developing. This results in few, if any, adverse effects with long-term therapy. The main risk involves opportunistic yeast infections, which may be prevented by concurrent administration of **nystatin**. Other chemotherapeutic agents used in the treatment of acne are **erythromycin**, **clindamycin** and **cotrimoxazole**. Clindamycin is available as an alcoholic lotion and erythromycin as a gel specifically for the topical treatment of acne. This avoids the systemic effects and opportunistic infections that occur with oral administration. (Further details about these antimicrobials can be found in Chapter 68.)

An antimicrobial called **azelaic acid** (a relatively simple fatty acid, also known as 1,7-heptanedicarboxylic acid) is effective against *P. acnes* and is available as a cream for topical application. It appears to be successful in the treatment of many cases of acne and, in view of its apparent safety, it offers another remedy for this condition. It is less likely to cause local irritation than benzoyl peroxide. Azelaic acid also increases comedolysis.

◆ COMMON ADVERSE EFFECTS

The adverse reactions appear to be superficial at the site of application and include skin irritations and discolorations. Azelaic acid is relatively new, however, and long-term effects are still not known.

✚ CLINICAL CONSIDERATIONS

Following antibacterial treatment, improvement is apparent after 6 weeks. Topical treatment is often required for around 12 weeks before maximum benefit is obtained, however. Systemic antibiotic treatment is often required for at least 6 months for optimal results to be achieved.

Patients with dark complexions should avoid using azelaic acid, as hypopigmentation may result. The treatment is applied after washing the affected area with mild soap and water. Warn the patient that irritation may occur at the start of treatment, but that this effect subsides over time. Improvement is usually apparent after 4 weeks, but therapy is often required for up to 6 months for maximum benefit.

RETINOIDS

These compounds are derivatives of vitamin A (see Chapter 61). Like vitamin A, they have an effect on epithelial cells. The effect of the oral preparations of these compounds can be quite dramatic. They appear to work by increasing the rate of epithelisation of the cells lining the sebaceous duct. This epithelisation is so rapid that the lining cells desquamate, resulting in an opening up of the pores, leading to easier drainage of the sebum. **Tretinoin** is the compound used topically. This substance may exacerbate the acne during initial therapy and often leads to a reddening of the skin, especially at the angles of the nose. Tretinoin has also been used with some success to reverse wrinkling of the skin caused by excessive sun exposure.

Isotretinoin is an oral retinoid (also available topically) reserved for the treatment of severe acne not responsive to other therapies. Isotretinoin is teratogenic and should not be given under any circumstances to women of childbearing age, unless adequate contraceptive measures are taken. The adverse effects are many, but the chance of producing permanent remission in the disease is high; therefore, if used under adequate supervision, it is a godsend for many patients. Many countries restrict the prescribing of this drug to dermatologists only.

Adapalene is related to the retinoids but may have fewer cellular effects and thus fewer of the adverse effects shown by the retinoids. The only side effects of any consequence involve erythematous reactions, which are worse following exposure to sunlight. There is a suggestion that the susceptibility of the skin to UV rays is increased, and so adapalene may be carcinogenic in such circumstances; patients should be advised of this. Although no teratogenic effects have been shown in humans, adapalene is classified as a group D drug in pregnancy.

✚ CLINICAL CONSIDERATIONS

Clinical aspects relating to retinoid therapy use were addressed under the discussion of psoriasis.

HORMONE TREATMENT FOR ACNE

Co-cyprindiol (cyproteone acetate with ethinylestradiol) contains an anti-androgen. It is as effective as an oral antibiotic, but it gives contraception as well.

■ MECHANISM OF ACTION

This drug is probably beneficial in acne as it reduces sebum secretion, which is under the control of androgens.

✚ CLINICAL CONSIDERATIONS

If hirsutism is present, there are additional benefits to this drug, as hair growth is androgen-dependent.

Venous thromboembolism occurs more frequently in patients taking this drug rather than a combined oral contraceptive. The drug is licensed for severe acne and hirsuitism – it should not be used only as a contraceptive. The drug should not be used in people with a family history of thromboembolism.

Nappy rash

Nappy rash is a common condition in babies and is due mainly to the production of ammonia from the bacterial degradation of urine. This degradation takes time, and so frequent changing of nappies helps to prevent the problem. The use of barrier creams containing **simeticone** or zinc oxide may help in cases where frequent changing is difficult and in babies prone to the condition. In severe cases, antibiotics and corticosteroid creams (not ointments) may be necessary. Another cause of nappy rash is the presence of detergents or harsh soaps in reusable nappies. The solution is to make sure the rinsing process is adequate.

✚ CLINICAL CONSIDERATIONS

Barrier creams are most effective when applied after bathing. They should also be applied at regular intervals throughout the day. When using corticosteroid creams as well, barrier creams should be applied at different times from the corticosteroids in order to facilitate a better response; for example, the barrier cream can be applied in the morning and the corticosteroid cream at night.

Scabies and pediculosis

Parasitic lice of the genus *Pediculus* cause pediculosis. These species can cause head-lice and body-lice infestations. Another species, *Phthirus pubis*, causes pediculosis pubis and is commonly referred to as crabs. Lice feed on human blood and lay their eggs, called nits, on hair shafts. When a louse has its blood meal, irritation may be produced, which can eventually lead to a severe inflammatory reaction.

Treatment of lice infestations is effective, but strict attention to the manufacturer's instructions is important in order to ensure eradication of the parasite.

The mainstay of lice treatment is the use of anticholinesterase insecticides (see Chapter 27). These drugs are all relatively toxic to humans but, as humans metabolise the compounds more rapidly than the lice and the drugs are absorbed poorly through the skin, they have a high safety factor. Head lice are best treated with shampoos containing **carbaryl**, **malathion** or pyrethrins. Carbaryl is a potential human carcinogen and is restricted to prescription-only use.

A pyrethroid, **permethrin**, is usually successful in eradicating both the lice and their eggs with one 10-minute application, as the compound remains on the scalp, producing an effect for up to 2 weeks. This residual activity is not affected by chlorinated water in swimming pools or by normal shampooing.

Body lice can be treated with the application of **benzyl benzoate** emulsion to the body from the neck down, leaving the drug on for 24 hours. The application can be removed by taking a hot bath afterwards. Several other applications may be necessary.

All of these substances are toxic, especially if ingested, and should be treated with respect.

A small mite, *Sarcoptes scabiei*, which burrows about in the human skin emerging only to copulate with another mite, causes scabies. The mite is transmitted by close contact with an infected person and is more common in conditions of overcrowding and poor hygiene. Transmission can take place venereally. The burrowing mite produces an itch, which is often intense; scratching can lead to excoriation and secondary bacterial infections.

The treatment of scabies is similar to that of body lice, the only exception being **crotamiton**. Crotamiton is acaricidal (mite-killing); being antipruritic, it has an added advantage. Daily applications are needed for several days in order to eradicate the parasite. Crotamiton is much less toxic than the anticholinesterases, but it is not as effective.

✚ CLINICAL CONSIDERATIONS

For the treatment of pediculosis, pyrethrins in combination with **piperonyl butoxide** act within about 10 minutes. The latter is useful for the treatment of pubic lice. The application should then be washed off thoroughly. A repeat application may be necessary a day later, but no more than two treatments should be given in a week. A fine comb, preferably soaked in vinegar, should be used after treatment to remove any nits. It may be desirable to treat the whole family and close friends (a diplomatic approach being needed!), as the lice pass rapidly from person to person.

For the treatment of scabies, two treatments about 1 week apart are recommended for patients and their contacts with symptoms of an itch and rash. One treatment is usually appropriate for contacts without symptoms. Pruritus associated with scabies may continue for about 7–10 days following successful treatment and can be alleviated with the use of calamine lotion or an antihistamine.

Warts

Warts, or verrucae, are growths of viral origin usually occurring on skin and the adjacent mucous membrane. Warts are more common in children, but they can occur at any age. When they occur on the soles of the feet, they are termed plantar warts. They have a tendency to disappear spontaneously – hence the abundance of household remedies that appear to work. The most successful treatment for warts is surgical removal or destruction of the lesion by extreme cold (liquid nitrogen) or high-frequency electric current.

Drug treatment of warts involves the use of corrosive chemicals that destroy the lesion and the virus. As warts are surrounded by healthy skin, care must be taken to protect this during treatment. An application of petroleum jelly to the surrounding tissue affords good protection. Mildly corrosive chemicals such as salicylic acid and lactic acid are often successful, but many treatments are required for complete eradication. These substances are sometimes incorporated in plasters for direct application to the wart. The plant resin **podophyllum** is a mitotic poison (see Chapter 76) and has proven very successful in the treatment of genital and perianal warts. The resin is dissolved in tincture of benzoin for application as a lotion, or it can be incorporated in an ointment for the treatment of plantar warts. Only four applications of this drug are usually required for dehiscence of the wart. The podophyllum is very irritant to normal skin, which must be well protected. This drug, if absorbed, can produce severe systemic reactions, including nausea, vomiting, abdominal pain and diarrhoea. In extreme cases, hepatic and renal failure can result. Applying the podophyllum for 1- to 6-hour periods and then washing off the drug can avoid these systemic effects. This process can be repeated every 2–3 days. Large or friable areas should not be treated. Podophyllum is contraindicated in pregnant women.

Glutaraldehyde, which has virucidal properties and is not too harmful to normal skin, has proven to be an effective treatment. As glutaraldehyde causes proteins to denature, the tissue becomes hardened at the application site and penetration of subsequent applications of glutaraldehyde decreases. After initial treatment, filing down of the hardened tissue with a nail file or fine sandpaper improves the efficacy of the glutaraldehyde.

As warts are viral infections, there is no real reason why a specific antiviral drug or immunomodulator cannot be made to treat the condition. **Interferon**, an immunomodulator (see Chapter 75), has been used intralesionally and

systemically, with beneficial results but severe adverse effects. The immunomodulator **imiquimod** has been designed specifically to treat the papilloma virus that causes genital warts. These warts have a peak incidence in 20- to 24-year-olds and have an annual incidence of about 1 per cent in Europe and the USA. In severe cases, these cause large warty overgrowths termed condylomata acumata and condylomata lata. Transmission is usually by sexual contact (orogenital, genitogenital, anogenital, oroanal) but may also be via unknown mechanisms; cigarette smoking somehow appears to be a risk factor. Genital warts, no matter how small, treated with often frequent, ablative therapies can cause both physical and psychological pain, and the recurrence rate can be as high as 72 per cent. Imiquimod acts by stimulating the production of naturally occurring cytokines, mainly subtypes of interferon alfa but also some other important natural antiviral substances. Imiquimod has no direct antiviral properties. Imiquimod is applied directly to the lesions as a cream, usually for at least 16 weeks, when the majority of cases show complete healing with a recurrence rate of only 13 per cent. The main adverse effects are erythema, pruritus, pain and tenderness at the site of application. **Paracetamol** can be used to lessen these symptoms, which are considerably less troublesome than when using other treatments. Absorption is minimal and systemic effects are extremely rare. Women tend to respond better to this drug than men. When the glans is affected in uncircumcised men, attention to personal hygiene is important.

Imiquimod is also licensed in the UK for the treatment of superficial basal cell carcinoma.

✚ CLINICAL CONSIDERATIONS

Podophyllum resin is best applied to only a small number of warts at any time. Application to normal skin must be avoided. There is a risk of systemic toxicity if the preparation is applied to large areas for prolonged periods or to mucous membranes. Before applying the preparation, the hard skin on the wart surface should be abraded and the surrounding normal skin protected with white soft paraffin. The paint or ointment is applied with a cotton wool bud to all lesions, allowed to dry, left for 6–8 hours and then washed with soap and water.

With podophyllotoxin, there is a 7-day treatment cycle involving twice-daily application for 3 days followed by no treatment for 4 days. This pattern of treatment may be repeated for up to four cycles. The doctor usually applies the first treatment and advises the patient about appropriate use for further applications.

Glutaraldehyde with formaldehyde should not be used on facial and anogenital warts because of the preparation's irritating effect on the skin and the ability of glutaraldehyde to cause brown staining of the skin. Before applying, the affected area is abraded with an nail file or pumice stone and the surrounding area protected with white soft paraffin.

Imiquimod is applied to the affected area three times a week for about 8 hours, and then washed off with soap and water. The treatment may be continued for a total of 16 weeks, or until the warts clear. Hands should be washed before and after application; the patient should be advised not to shower or bathe for 8 hours after application.

Hyperhidrosis

Hyperhidrosis is the excessive production of sweat and is often a medical rather than a personal problem. Sweat is acted on by skin bacteria, producing various organic acids, which contribute to body odour. This odour can be suppressed by the use of deodorants, which, apart from containing perfumes, contain antibacterial substances to inhibit the bacterial breakdown. Perspiration is a necessary physiological response to heat and, therefore, total prevention is not advisable. Sweat from certain areas of the body can be embarrassing if produced in excessive amounts, and suppression using antiperspirants may be necessary. The most common antiperspirant is **aluminium chloride**. This has powerful astringent properties and acts by coagulating proteins in the sweat glands and thus suppressing the sweat production. In severe refractory cases, a 20 per cent aluminium chloride solution (Driclor™) can be used. This concentration is much higher than the antiperspirants sold in supermarkets, which contain 1–2 per cent aluminium hydroxide. The strong solution is best used under medical supervision. **Zirconium oxychloride** is a similar but less toxic agent. These substances can produce inflammation with granuloma formation, which necessitates withdrawal of the treatment.

Antimuscarinic drugs, such as **diphemanil methylsulphate**, can act through the skin to suppress sweat production. There is no fear of granuloma formation with these drugs and they are efficient. Systemic effects are unlikely, as skin absorption is poor.

Botulinum toxin has been tried, successfully, to treat severe hyperhidrosis (see Chapter 79).

✚ CLINICAL CONSIDERATIONS

Patients who experience an inflammatory reaction following use of a particular antiperspirant are advised to try an alternative preparation. Underarm shaving, if done, should be performed at a time when the antiperspirant is not being used in order to prevent an irritant skin response.

Baldness

Baldness is a concern for many men, and some go to extraordinary lengths to conceal this condition. For some, the drug **minoxidil** in lotion form may be the answer. This may be applied to the bald areas for periods of up to 1 year before any response is seen. The response may only

be a downy growth, or there may be no response at all. Minoxidil is fairly expensive.

✚ CLINICAL CONSIDERATIONS

Minoxidil topical solution is applied to a dry scalp twice daily. A hair dryer should not be used because this may decrease the effectiveness of minoxidil. About 4 months of application is required before any assessment can be made about the effectiveness of the preparation. Unfortunately, following discontinuation of minoxidil, a relapse to the pretreatment appearance of the hair and scalp may occur.

CLINICAL MANAGEMENT

Drugs used in diseases of the skin

Assessment

- Assess the area of skin over which the preparation is to be applied. Determine the type and extent of lesion treated and determine whether the skin is dry, cracked, weepy, moist, hairy or flaky. Document baseline observations of the skin.
- Determine the nature of the skin preparation that is most suitable for a particular skin condition. A lotion or paste is suitable for a weeping skin surface, while a greasy ointment is suitable for dry, cracked skin. Creams may be used for dry or wet skin and are cosmetically more elegant than ointments.
- Assess whether the female patient is pregnant, as some preparations, such as the topical and systemic retinoids, are contraindicated during pregnancy.
- Assess whether the patient is elderly, immobile or debilitated. These patients tend to experience an increased susceptibility to loss of skin integrity.
- Assess the patient's exposure to factors that may aggravate the skin condition, such as wind, harsh soaps and detergents, air-conditioning, exposure to the sun and contact with affected individuals (as in the case of lice and scabies infestations).

Planning

- The patient's skin condition will be resolved without the incidence of adverse effects.

Implementation and patient teaching

- Ensure that the area over which the preparation is to be applied is dry and clean. Wash and dry the hands before application.
- Protect clothes and bed linen from the preparation before application.
- Monitor for hypersensitivity reactions that the patient may have experienced to these preparations. For example, dithranol and retinoid preparations are often associated with hypersensitivity reactions.
- When applying a preparation to the face, take care to avoid the eyes and mouth. Place the preparation on the forehead first, and then work down to the nose and chin. Work the preparation outwards to the cheeks.
- When applying a preparation to a skin lesion, always place it in the centre of the lesion and then work outwards, to avoid introducing infection into the lesion. Apply the amount of preparation required in the hand. Do not remove an additional amount of the preparation from the container once the hands have been in contact with the lesion, unless the hands have been washed first.
- When using a scabicide, all family members should be treated simultaneously in order to avoid reinfestation. A scabicide is applied thinly to the whole body, except the head, and washed off after 24 hours. Bed linen and clothing should be washed and dried on hot settings the morning after each treatment. Mattresses, pillows, prams, car seats, soft toys and chairs should be sprayed with insect spray. The patient should be examined 2 weeks after the start of treatment to determine the adequacy of therapy.
- A lice preparation is applied to the head and scalp and washed off usually after 24 hours. Body lice are effectively treated in a similar manner. The patient may take a warm bath first to open up the pores and burrows. Egg cases (nits) are removed by combing wet hair with a fine-tooth comb. All clothes and bed linen should be laundered to prevent reinfestation. Combs, brushes, scarves and other headgear should not be shared and should be washed regularly in hot water. All mattresses, carpets and upholstery should be vacuumed regularly.
- The prescriber should apply the first treatment for warts and then instruct the patient on its proper use. Before application, hard skin on the wart surface should be abraded with a pumice stone or nail file. Surrounding skin should be protected with white soft paraffin. The preparation should be applied on all lesions with a cotton bud, allowed to dry, left for 6–8 hours, and then washed off with soap and water. Contact with normal skin should be avoided.

- For greater absorption of a preparation, the patient may take a warm bath or apply a hot pack before using the skin preparation.
- Monitor the area of skin or lesion treated. Note other manifestations associated with the condition, such as itchiness of the area and difficulty in sleeping.
- Note that dithranol preparations may cause the skin and hair to darken. Wash hands after use, and wear gloves to prevent staining. Talc or soft paraffin may be applied to normal skin around the affected areas to prevent excessive staining and irritation. Clothing coming into contact with dithranol will be stained immediately. The preparation must be applied sparingly to the affected areas only and washed off by bathing or showering. Wash the bathtub or shower with hot water and follow up immediately with a household cleaner to remove any remaining deposits.
- Dithranol should be kept in a dark place. If the preparation turns dark purple, it is no longer effective.
- For patients ordered a coal tar preparation, use low concentrations on the face, flexures and genitals in order to reduce the potential for skin irritation.
- Patients receiving retinoid, coal tar, calcipotriol and psoralen therapy must avoid direct exposure to sunlight and use a sunblock when outside.
- After taking oral psoralens, it is important to avoid sun exposure for at least 12–48 hours. Wrap-around sunglasses should be worn during the day for 24 hours following psoralen application. Certain foods contain substances that are natural photosensitisers, such as limes, figs, parsley, parsnips, mustard, carrots and celery. These foods should be avoided while taking psoralens.
- Ophthalmic examination, measurement of antinuclear antibody titre and hepatic function should be performed before and every 12 months after starting psoralen therapy. Skin should be examined for malignancy every 6 months during therapy.
- Advise the patient on retinoid therapy, such as acitretin, to avoid taking vitamin A preparations in excess of the minimum recommended daily allowance.
- Inform the patient on retinoid therapy to use white soft paraffin to treat dry lips and lubricating eye drops to treat eye irritation.
- For patients on preparations for acne treatment, a healthy, well-balanced diet should be consumed. Diet restrictions have no effect on the severity of acne.
- For patients on tetracycline preparations for the treatment of acne, therapy must be administered for at least 6 months for maximal response. (See Chapter 68 for further information about the clinical management of tetracycline preparations.)
- Monitor serum calcium and renal function at 3-month intervals in patients receiving calcipotriol. If calcium levels are elevated, treatment should be discontinued and calcium levels monitored weekly until normal. Concurrent use of calcium and vitamin D should be avoided during calcipotriol therapy.

Evaluation

- Evaluate the skin for improvement of the condition.

SUMMARY

- Many different vehicle types are used in skin preparations.
- Skin cleansers can be used to moisten and desquamate the epidermis.
- The application of counter-irritants and rubefacients can help control underlying pain.
- Sunscreens, used properly, can help to minimise ultraviolet (UV) damage to the skin and reduce the risk of melanoma.
- Acne, a curse of adolescence, can be treated and cured in most cases.
- Dandruff and seborrhoeic dermatitis can be kept under control by the judicious use of shampoos and, in severe cases, oral therapy.
- Scabies and other arthropod infestations are often very contagious but can be kept under control by topical medications.
- Warts are best treated with liquid nitrogen, but some types respond well to topical medications.
- Excessive sweating often needs more than supermarket deodorants and antiperspirants.
- In some cases, baldness can be treated topically.

1. Rubefacients produce local heat on application to the skin. How does this help in the treatment of strains and sprains?
2. In the treatment of acne using tetracyclines, why is nystatin sometimes given concurrently?
3. Explain what is meant by PUVA therapy.
4. How can a lumbar sympathectomy help with severely sweaty feet?
5. Explain the difference between an antiperspirant and a deodorant.
6. Why are oral contraceptives usually prescribed along with isotretinoin to women?
7. Antiandrogenic drugs can be used in the treatment of acne. Why?
8. Why will penicillin not be of much use in the treatment of acne?
9. Acne often undergoes remission during pregnancy. Why?
10. Corticosteroid-containing creams may exacerbate acne. Why?
11. What non-pharmacological measures can be used to treat mild acne vulgaris?
12. Suggest further uses that could be investigated for imiquimod cream.
13. As the emergency nurse, you are required to apply benzyl benzoate emulsion to Massimo Cino, a 75-year-old patient with pediculosis. How would you use this preparation?
14. Explain the precautions you would take for the patient in applying podophyllum for the treatment of genital warts.
15. Judy Jones, a 35-year-old mother of two young children, is ordered a dithranol preparation to treat her psoriasis. With what patient education would you provide her for the application of dithranol? What extra care should she take when tending to her children?
16. Martha Bortiolis, a 15-year-old student, complains of pimples and blackheads on her face and back. As the community nurse who examines Martha, you recommend a benzoyl peroxide cream to treat the acne. How would you advise Martha on the use of the cream?

78 DRUG SUMMARY TABLE: DRUGS USED IN DISEASES OF THE SKIN

FAMILY NAME	GENERIC NAME	TRADE NAME(S)
Acne preparations	Adapalene	Differin
	Azelaic acid	Skinoren
	Benzoyl peroxide	Brevoxyl
		PanOxyl
	+ Erythromycin	Benzamycin
	+ Clindamycin	Duac
	+ Hydroxyqunialone	Quinoderm
	Clindamycin	Dalacin T
		Zindaclin
	Erythromycin	Zineryt
		Stiemycin
	Tetracycline	Topicycline
	Isotretinoin	Isotrex
	+ Erythromycin	Roaccutane
		Isotrexin
Scabicides	Crotamiton	Eurax
Antipsoriatic preparations	Acitretin	Neotigason
	Dithranol	Dithrocream
		Micanol
	Tarazotene	Zorac
Wart preparations	Glutaraldehyde	Glutarol
	Imiquimod	Aldara
	Podophyllum	Condyline
		Warticon
	Salicylic acid	Cuplex
		Duofilm
		Occlusal
		Salactol
		Salatac
		Verrugon
Lice and scabies treatments	Benzyl benzoate	
	Carbaryl	Carylderm
	Malathion	Derbac-M
		Prioderm
		Quellada M
	Permethrin	Lyclear
	Phenothrin	Full Marks
Dandruff preparations	Ketoconazole	Daktarin Gold
		Dandrazol
		Nizoral
	Selenium sulphide	Selsun
Baldness treatment	Minoxidil	Regaine

DRUGS AND THE EYE

79

CHAPTER SEVENTY-NINE

OBJECTIVES

KEY TERMS

Autonomic nervous system
Conjunctivitis
Glaucoma
Miosis
Mydriasis
Ophthalmology
Trachoma

After completing this chapter, the reader should be able to:

- **briefly describe the structure and function of the major parts of the eye;**
- **identify the classes of drugs used in the treatment of conditions affecting the eye;**
- **state the rationale for use, mechanisms of action, characteristics, adverse drug reactions and general contraindications of use of drugs in these conditions.**

A NUMBER OF THE KEY DRUG GROUPS MENTIONED elsewhere in this book are used in ophthalmology. Drug groups such as the antimicrobials, corticosteroids, adrenergic drugs, muscarinic drugs and non-steroidal anti-inflammatory drugs (NSAIDs) have ophthalmic indications. In this chapter, the effects of these drugs on the eye and the implications for care during therapy are emphasised. Other drugs, such as the ophthalmic stains and the wetting agents, are introduced here. Consideration is also given to the ways in which ophthalmic agents are prepared and administered.

STRUCTURE AND FUNCTION OF THE EYE

The eye is a complex organ with a specific and specialised function to perform as a visual receptor system. It is useful briefly to revise the structure and function of the eye in order to set the scene for the pharmacology that follows. Eye structures are represented in Figure 79.1.

External to the eyeball are the accessory structures: the eyebrows, eyelids, lacrimal apparatus, conjunctiva and extrinsic muscles. The main function of the eyebrows, eyelids and conjunctiva is to protect the eye. The extrinsic muscles are skeletal muscles that move the eyeball, anchor it within the orbit and offer some support to maintain the shape of the eyeball. The lacrimal apparatus secretes tears that moisten, cleanse, lubricate and provide immune protection to the surface of the eye. Tears formed in the lacrimal gland spread across the surface of the eye and drain into the nasal cavities via the nasolacrimal ducts.

The eye is a hollow sphere filled with fluids called humours. The eye is divided into two segments, or cavities, by the transparent lens – the anterior and posterior cavities. The anterior cavity is filled with a watery fluid called aqueous humour, while the posterior cavity is filled with a gel-like fluid called vitreous humour. Aqueous humour provides nutrients to the avascular structures of the eye: the cornea and lens. It is produced by the ciliary body in the posterior chamber and circulates through the pupil to the anterior chamber, where it drains back into the circulation via the canal of Schlemm (located in the lateral margin of the chamber at the base of the iris). Vitreous humour helps to maintain the shape of the eye and holds the retina in position at the back of the eye.

There are three layers forming the wall of the eyeball. The outermost is a tough, dense, avascular layer called the fibrous tunic. Most of the fibrous tunic is white and opaque and is known as the sclera or white of the eye. Part of its anterior surface is transparent and bulges forward. This part is called the cornea and allows light to enter the eye.

The middle layer is called the vascular tunic, or uvea. It is pigmented and has three regions: the choroid, ciliary body and iris. The choroid is pigmented brown to absorb light and is highly vascular so that it can supply blood to all layers of the eye. The ciliary body is the anterior margin of the choroid. It consists of two parts: the ciliary muscles (smooth muscles that control lens shape) and the ciliary processes (which contain capillaries that secrete aqueous humour). The lens is attached to the ciliary muscle by suspensory ligaments. The functions of the ciliary body are controlled by the parasympathetic nervous system. The doughnut-shaped iris determines eye colour. It is the

FIGURE 79.1 THE PARTS OF THE EYE

This figure shows the major structures of the human eye.

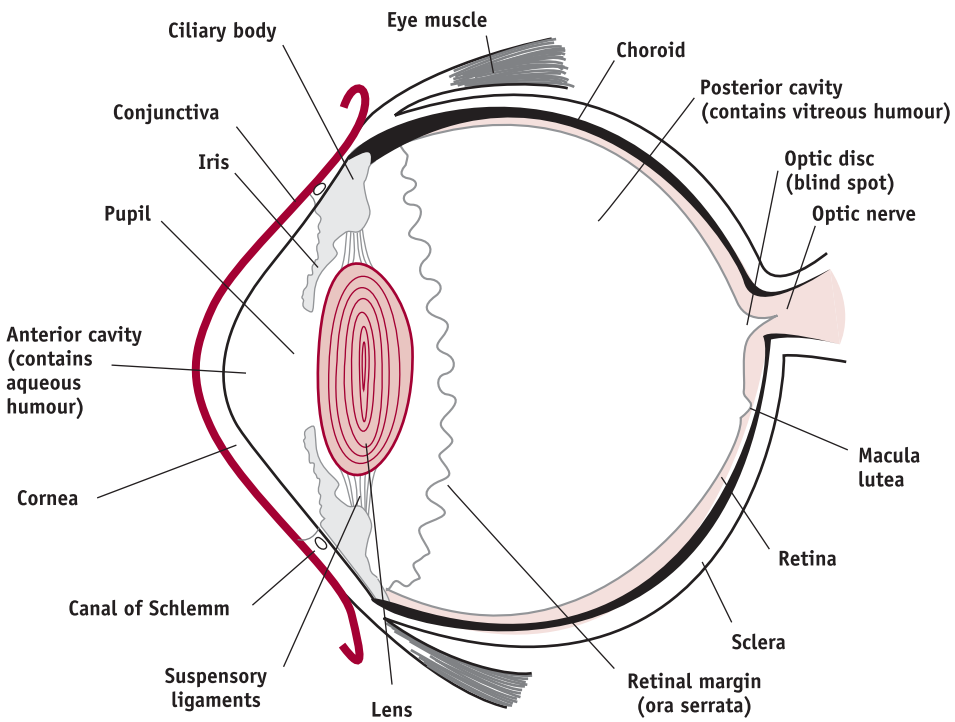


TABLE 79.1 AUTONOMIC NERVOUS INNERVATION OF THE EYE

Structure of the eye	Effects of parasympathetic stimulation	Effects of sympathetic stimulation
Iris	Contraction of circular muscle: pupil constriction (miosis)	Contraction of radial muscle: pupil dilation (mydriasis)
Ciliary muscle	Accommodation	Relaxation (for far vision)
Ciliary processes	Increased outflow of aqueous humour; vasodilation	Vasoconstriction; increased production of aqueous humour
Lacrimal apparatus	Increased secretion; vasodilation	Vasoconstriction
Conjunctival vasculature	Vasodilation	Vasoconstriction

most anterior structure of the uvea. It consists of circular and radially arranged bands of smooth muscle, innervated by the autonomic nervous system, which control the size of the central opening: the pupil. The iris separates the anterior cavity into the anterior and posterior chambers.

The autonomic nervous system plays an important part in the regulation of eye functioning. Structures such as the iris, ciliary body, lens, lacrimal glands and ocular vasculature receive autonomic innervation. The effects of this stimulation are summarised in Table 79.1. A general discussion of autonomic function and drug effects can be found in Section VI.

The innermost layer is the sensory tunic, or retina. This contains the photoreceptors that convert light into the language of the nervous system: nerve impulses. Light that enters the eye is focused by the lens on to a region of the retina called the macula, directed specifically at the central pit known as the central fovea. The optic nerve originates in this layer at a region called the optic disc, or blind spot.

OPHTHALMIC PHARMACOLOGY

Drug absorption

Most of the drugs used in ophthalmology are administered locally. Local routes of administration include the topical, periocular and intraocular routes. In topical administration, drugs are applied to the surface of the eye in the form of drops, lotions, ointments or impregnated filter paper. Periocular routes refer to the placement of drugs alongside and external to the eyeball, allowing diffusion into the eye; subconjunctival and retrobulbar injections are examples of the periocular route. In subconjunctival injection, the drug is introduced underneath the conjunctiva, where it diffuses through the sclera. Retrobulbar injections introduce the drug behind the eyeball, inside the extraocular tissue. With intraocular injection, drugs are instilled into the anterior chamber (intracameral injection) or the posterior cavity (intravitreal injection). Only small amounts of drug can be injected intraocularly, as large amounts may be toxic to internal eye structures. The advantages of administering the drug locally are that this delivers the agent directly to the site of action, its effects are more immediate, smaller doses of the drug are used and any systemic adverse effects are minimised.

Drugs applied topically enter the eye through the cornea. To do this, the drug must pass through three layers. The outermost corneal layer consists of epithelium, the middle layer is connective tissue (stroma), and the innermost layer is also epithelium (endothelium). The epithelial layers have a high lipid content, while the stroma has a high water content. To be absorbed well through the cornea, drugs require both lipophilic and hydrophilic characteristics. Water-soluble drugs are best absorbed through lipid when they are in a non-ionised state. The pH of the environment greatly influences the degree of ionisation and, ultimately, the amount of drug that can be absorbed (see Chapter 13). This is considered during the formulation of ophthalmic preparations.

Other factors that influence the rate of absorption into the eye include corneal damage and drug binding. Some water-soluble agents may be absorbed better when the outermost lipophilic epithelial layer is removed or abraded, resulting in unexpectedly high concentrations within the eye. Some drugs, such as the antiseptic **benzalkonium chloride** (see 'Miscellaneous agents' later in this chapter), may be absorbed into or bind to soft contact lenses, resulting in reduced effectiveness of the drug.

Drugs can be lost from the eye by several means before they cross the cornea. Blinking and lacrimal secretion can rapidly disperse the drug, leaving only a very short time for absorption. The drug may be absorbed systemically via the vasculature of the conjunctiva, or it may drain away into the nasal cavities through the nasolacrimal duct, crossing into the circulation via the nasal mucosa. The latter can be minimised by applying pressure over the duct openings located in the medial corner of the eye.

Pharmaceutics

Drug formulations and administration are dealt with in general in Chapter 7. A few aspects specific to ophthalmology deserve special mention here.

Most eye preparations are solutions, where the unit of concentration is usually expressed as '% solution'. This unit translates to g/100 ml. As an example, a 2% **pilocarpine** solution is equivalent to 2 g pilocarpine in 100 ml solution.

Ophthalmic solutions are formulated so that the active principal has an acceptable shelf life. The shelf life of the preparation can be affected by oxidation, pH, light, heat and hydrolysis. If necessary, the active principal can be protected from these effects by the addition of an antioxidant and a buffer and by storing the drug in a cool, dark place. The eye must be protected from damage by the preparation. Damage can result from microbial contamination and the extremes of pH and tonicity. The solution must be sterilised, and a preservative can be added to the solution to inhibit microbial growth (see 'Miscellaneous agents' later). Although they are often more expensive, single-use solutions such as Minims™ avoid the need for the addition of a preservative, but these must still be sterilised. The literature suggests that the eye can tolerate solutions with a pH range varying from 3.5 to 10.5 and a tonicity ranging from 0.7 to 2 per cent.

Eye drops are common and convenient preparations (see Chapter 9 for a description of how to correctly administer eye drops). Aqueous solutions disperse rapidly after topical administration. Therefore, they must be in a state that can be absorbed quickly. Substances such as **methylcellulose** and **polyvinyl alcohol** can be added to the drops to increase the viscosity of the solution and, as a result, increase the contact time of the drug with the eye. Another way to enhance absorption of some drugs is to use eye drops prepared in an oily solution. Some aqueous preparations cause ocular reactions, such as stinging, burning, oedema and irritation. Lowered tolerance to contact lenses during eye therapy is a common adverse effect.

Eye ointments have a greasy base and, in general, tend to be more stable than solutions. They are usually applied to the conjunctival sac or margin of the lid.

ANTIMICROBIAL AGENTS

By whatever means they occur, ocular infections have the potential to cause significant damage to the tissues of the eye, resulting in permanent visual impairment. Early recognition of the causative agent and prompt treatment can reduce the degree of damage. Common pathogens affecting the eye include Gram-positive bacteria (e.g. *Staphylococcus*, *Streptococcus* and *Pneumococcus* species), Gram-negative bacteria (e.g. *Escherichia coli* and *Pseudomonas* and *Proteus* species), viruses (e.g. herpes virus) and other microbes (e.g. *Chlamydia* species).

Antibacterial agents

A number of antibacterial agents (see Chapter 68) are used in the treatment of topical eye infections, such as conjunctivitis, blepharitis and keratitis. The antibacterial agents used tend to be broad-spectrum antibiotics. A number of these are known for their toxicity when administered systemically. When these drugs are applied locally, however, their toxicity is greatly reduced and the risk of triggering the development of multi-resistant strains of bacteria is minimised. Adverse reactions common to all antibacterial agents are that prolonged therapy may induce overgrowth of non-susceptible microbes and that the ophthalmic preparations may impede local healing processes.

CHLORAMPHENICOL

Chloramphenicol is an antibiotic that penetrates the conjunctiva and cornea well to reach susceptible microbes. Common adverse effects involve local irritation, such as itching and burning sensations. Hypersensitivity reactions can occur. Unfortunately, systemic absorption and its consequent side effect, aplastic anaemia, have been reported following chronic use. The drops are usually tolerated well however, and the *British National Formulary* (BNF) states 'the recommendation that chloramphenicol eye drops should be avoided because of an increased risk of aplastic anaemia is not well founded'.

AMINOGLYCOSIDES

The aminoglycosides **gentamicin**, **tobramycin**, **framycetin** and **neomycin** are used for eye infections. Neomycin can be used alone or in combination with other agents, such as **bacitracin**, **gramicidin** and **polymixin B**, to broaden its spectrum of activity. The aminoglycosides used topically are tolerated well, with minor eye irritation being the most common adverse reaction. Hypersensitivity reactions may also occur.

TETRACYCLINE

Tetracycline is available for ophthalmic use. A photosensitivity reaction in the skin called photodermatosis may occur in susceptible individuals; therefore, excessive exposure to ultraviolet (UV) radiation should be avoided.

QUINOLONES

Ciprofloxacin and **ofloxacin** are quinolones (see Chapter 68) that are available as ophthalmic preparations. Common adverse reactions include ocular burning and discomfort. Photosensitivity reactions have been reported in association with oral administration of these drugs. Avoiding exposure to excessive sunlight is recommended when

these drugs are applied topically. Ciprofloxacin is used for the treatment of corneal ulcers, where intensive application through the day and night is needed.

OTHER ANTIMICROBIAL AGENTS

Propamidine, available as **dibromopropamidine** in an eye ointment, is a broad-spectrum antimicrobial agent with activity against *Acanthamoeba keratitis*. Adverse reactions are rare, the most significant being a sensitisation reaction following repeated application. The use of this drug should be discontinued immediately in such circumstances.

Fusidic acid is available as an ophthalmic antibacterial agent. It is effective only against Gram-positive bacteria and is indicated mainly for prophylaxis and treatment of susceptible eye infections, e.g. staphylococcal infections. Its ability to penetrate purulent sites and aqueous humour is good. It is generally tolerated well but may cause a stinging sensation on application.

✚ CLINICAL CONSIDERATIONS

When using an antibacterial agent, it is important never to pad a discharging eye, as this leads to continual reinfection of the area. Antibacterials are used only if there is a bacterial infection causing mucopurulent discharge. The debris and mucous surrounding the eye are cleared with normal saline solution before applying the antibacterial preparation. If no improvement is obtained after 2 days, the diagnosis is reviewed and swabs may be taken for confirmation of the type of infection present.

Trachoma

Trachoma is a form of chronic chlamydial keratoconjunctivitis. It has been estimated that around four million people worldwide have this condition. It is the second most common cause of blindness in the world. It is characterised by inflammatory follicles in the conjunctiva. Trachoma can progress to cause vascularisation and ulceration of the cornea, scarring of the conjunctival membrane and deformity of the eyelids. The consequences are visual impairment and blindness. It is transmitted by direct contact with eye and nasal discharges and soiled materials (e.g. clothes, linen, towels). Flies may contribute to the spread of the condition. A newborn infants may come into contact with the infectious agent during birth if the mother has a genital chlamydial infection.

The drugs of choice for the treatment of trachoma in adults are a 2- to 3-week course of oral sulphonamides (see Chapter 67) or oral tetracycline (see Chapter 68). Tetracyclines are contraindicated in young children, and so oral forms of the macrolides **erythromycin** and **azithromycin** (see Chapter 68) are used instead. Concomitant treatment with topical sulphonamide eye drops may also be indicated.

Antiviral agents

Aciclovir is available for ophthalmic use to treat eye infections caused by herpes simplex. **Ganciclovir** and **foscarnet** can be used to treat cytomegalovirus (CMV), which induces retinitis; the drug comes in the form of slow-release ocular implants, which may be inserted surgically to treat immediate sight-threatening CMV retinitis.

Cidofovir is used to treat CMV in patients with acquired immunodeficiency syndrome (AIDS) for whom other drugs are inappropriate.

◆ MECHANISM OF ACTION

Antivirals interfere with viral DNA synthesis. Their mechanisms of action are described in detail in Chapter 73. People with human immunodeficiency syndrome (HIV)/AIDS are very susceptible to severe CMV infection because of their immunocompromised status. CMV retinitis can lead to blindness.

◆ COMMON ADVERSE EFFECTS

Common adverse reactions include irritation, stinging, itching, inflammation, pain, photophobia, clouding of vision and lacrimation.

Ganciclovir treatment may lead to a loss of visual acuity, haemorrhage and retinal detachment. Foscarnet can cause renal impairment. Cidofovir is a toxic drug and is likely to induce proteinuria and neutropaenia. Other common adverse effects are asthenia, nausea, alopecia, rashes and fever.

✚ CLINICAL CONSIDERATIONS

For herpes simplex epithelial keratitis that recurs continually, advise patients to keep a spare supply of the antiviral preparation and to start treatment at the first sign of recurrence. Symptomatic relief may be achieved by using cool compresses and topical lubricant.

Advantages of cidofovir over the other drugs is that it is administered less often and that the onset of resistance may be slower than for ganciclovir. Cidofovir is infused once a week for 2 weeks and thereafter given every 2 weeks. **Probenecid** is also administered to delay its clearance.

CORTICOSTEROIDS

Corticosteroids (see Chapter 58) are used in the treatment of inflammation of allergic, traumatic and microbial origins. They are used in the treatment of bacterial infections to suppress inflammation and inhibit the fibroblast proliferation that might lead to scarring. Many of the corticosteroids used in ophthalmic preparations are quite potent and include **betamethasone**, **dexamethasone**, **fluorometholone**, **hydrocortisone**, **prednisolone** and **rimexolone**.

◆ COMMON ADVERSE EFFECTS

The potential to cause harm during treatment with these drugs is high. During prolonged use, candidal infections can arise. As corticosteroids tend to depress immune responsiveness, they are always combined with ophthalmic antibacterial agents when used in the treatment of bacterial infections, because of their potential to worsen the infection. Corticosteroids are contraindicated in viral infections of the cornea and conjunctiva because they actually enhance the development of the infection. In any eye condition characterised by thinning of the cornea, corticosteroid treatment can cause perforation. Moreover, impaired healing can occur during corticosteroid therapy. Other adverse reactions to watch out for during this therapy are the development of glaucoma in susceptible individuals (see Chapter 18) and cataract formation associated with long-term use.

Intraocular pressure and lens structure need to be monitored regularly during treatment.

✚ CLINICAL CONSIDERATIONS

In view of their potentially vision-threatening effects, topical ocular corticosteroids, used alone or in combination with antibacterials, should be prescribed only under close supervision by a qualified ophthalmologist. Treatment is not extended beyond 2 weeks. The ophthalmologist may need to monitor ocular pressure and integrity of the corneal epithelium.

MYDRIATIC AGENTS

These are drugs that produce pupil dilation (mydriasis) either by relaxing the parasympathetically innervated circular muscle of the iris (the constrictor pupillae) or by stimulating the sympathetically innervated radial muscle of the iris (the dilator pupillae) to contract (see Table 79.1). Antimuscarinic drugs related to **atropine** act by the former mechanism and sympathomimetic agents related to **noradrenaline** induce the latter. Mydriatic agents are used for the purposes of ophthalmic examination and surgery, in inflammatory conditions involving the iris or ciliary body, and in testing the optical properties of the eye.

✚ CLINICAL CONSIDERATIONS

To reduce initial stinging caused by mydriatrics, advise the patient to close their eyes and to avoid rubbing immediately after instillation. The patient should be instructed not to drive while their vision is disturbed and to wear dark glasses to help reduce the glare from bright lights.

Antimuscarinics

■ MECHANISM OF ACTION

The antimuscarinic agents induce relaxation of the parasympathetically innervated ciliary muscle responsible for accommodation. As a result, the suspensory ligaments attached to the lens become taut, and the lens stretches and becomes flatter, focused for far vision. This inability to adjust the lens for near vision is called cycloplegia. As the ciliary muscle is deep within the eyeball, the ability of the antimuscarinic mydriatics to cause cycloplegia depends on their rate of absorption, duration of action and potency.

◆ COMMON ADVERSE EFFECTS

The most common adverse reaction is blurred vision. Systemic absorption can occur with this therapy and causes antimuscarinic effects such as tachycardia, dizziness, dry mouth and constipation. These drugs can cause an elevation in intraocular pressure and are contraindicated in glaucoma, especially narrow-angle glaucoma.

✚ CLINICAL CONSIDERATIONS

Atropine is potent and long-acting; its effects may last for days after administration. The effects of **homatropine** and **cyclopentolate** last for up to 24 hours, while **tropicamide** is short-acting (up to 4 hours) and produces very little cycloplegia.

Sympathomimetics

■ MECHANISM OF ACTION

Sympathomimetic agents with α-agonist activity are used as mydriatic agents. Their advantage is that they do not produce cycloplegia; however, blurred vision may still occur as a result of mydriasis. Applied topically, they constrict ocular blood vessels, counteracting conjunctival hyperaemia and congestion. In other words, they act as ocular decongestants.

Specific drugs in this group include **phenylephrine**.

◆ COMMON ADVERSE EFFECTS

The main concern about these agents is the degree of systemic absorption through the conjunctival vasculature directly and through the nasal mucosa after nasolacrimal drainage. Systemic adverse reactions include hypertension, tachycardia and anxiety; hence, topical sympathomimetics should be used with caution in people with hypertension, heart disease and thyrotoxicosis. The sympathomimetics are contraindicated in glaucoma, particularly the narrow-angle form.

LOCAL ANAESTHETICS

Local anaesthetics (see Chapter 42) induce anaesthesia and analgesia and are used in ophthalmic surgery, contact-lens fitting and procedures such as tonometry (a non-invasive, indirect measure of intraocular pressure). They also relieve the pain and irritation associated with the presence of foreign bodies, infection, inflammation and trauma. The local anaesthetics used for ophthalmic purposes are **tetracaine**

(amethocaine), **lidocaine** (lignocaine), **oxybuprocaine** and **proxymetacaine**. They produce their desired effects within minutes and last between 30 minutes (proxymetacaine) and 4 hours (lidocaine).

■ MECHANISM OF ACTION

Local anaesthetics block nerve transmission by inhibiting the movement of sodium ions across the nerve membrane.

◆ COMMON ADVERSE EFFECTS

Common adverse reactions include eye irritation, stinging, burning, photophobia, conjunctival injection (dilation of conjunctival blood vessels) and allergic reactions. These drugs may also inhibit the blink reflex, and so it is important to protect the eye from irritants and foreign bodies while the drug is active.

✚ CLINICAL CONSIDERATIONS

It is important to warn patients beforehand that local anaesthetics can cause initial stinging. To reduce the stinging, patients are instructed to close their eyes after instillation and to dab away the tears without rubbing the eyes.

GLAUCOMA

Glaucoma is a condition characterised by an increase in intraocular pressure within the anterior cavity. The increased intraocular pressure, if severe enough, can impair vision. This impairment can range from a loss of peripheral vision and a loss of visual acuity to blindness. There are two types of glaucoma – a chronic open-angle form and an acute closed-angle (narrow-angle) type. The pathophysiology of glaucoma is represented diagrammatically in Figure 79.2. Open-angle glaucoma is by far the most common form, accounting for around 90 per cent of cases; it is responsive to drug therapy. It is characterised by impaired diffusion of aqueous humour through the trabecular network to the canal of Schlemm, where absorption occurs. Closed-angle glaucoma arises when the anterior chamber is narrow and the canal of Schlemm is obstructed completely as the iris thickens during pupil dilation. Closed-angle glaucoma requires surgery to correct the condition. Most of the drugs used in the treatment of open-angle glaucoma are used also in the acute management of narrow-angle glaucoma before surgery.

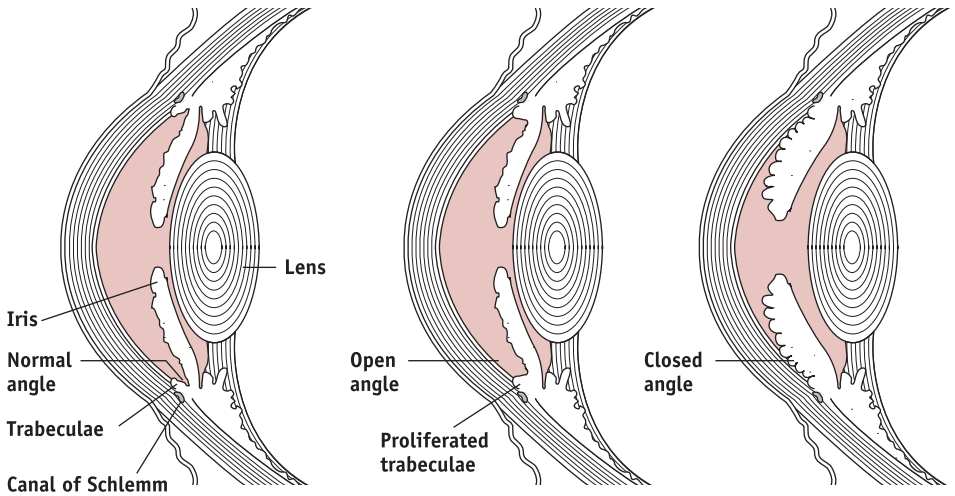
Drug therapy is directed towards reducing the raised intraocular pressure. Broadly speaking, the drugs used either reduce the formation of aqueous humour or enhance the drainage of aqueous humour from the eye. Some drugs, such as **adrenaline**, possess both of these actions. In clinical practice, drugs with each action may be combined in therapy and work synergistically (see Chapter 15) to control the condition.

Beta-blockers

The beta-blockers are considered the drugs of first choice in the treatment of glaucoma. They are relatively safe,

FIGURE 79.2 PATHOPHYSIOLOGY OF GLAUCOMA

(a) Normally, aqueous humour drains through the trabeculae and exits the anterior cavity via the canal of Schlemm.
(b) In open-angle glaucoma, the trabeculae proliferate, making the drainage of equeous humour more difficult.
(c) In closed-angle glaucoma, when the iris bulges during pupil dilation, the drainage pathway is completely closed.



highly efficacious, act longer than the cholinergic agonists and have no effects on pupil size or accommodation.

■ MECHANISM OF ACTION

Beta-blockers (**timolol**, **levobunolol**, **carteolol**, **metipronol**, **betaxolol**) lower the cyclic adenosine monophosphate (cAMP) levels within the ciliary body necessary for aqueous humour production (see Table 79.1). Betaxolol is relatively selective for β_1 receptors. The effects of timolol and levobunolol last longer than those of betaxolol.

◆ COMMON ADVERSE EFFECTS

Common adverse effects include paraesthesias, dry eyes, blurred vision and eye irritation. Systemic absorption is observed; the generalised adverse effects associated with this treatment can include bronchospasm in patients with asthma (less of a risk when betaxolol is used), bradycardia, and masking of the manifestations of hypoglycaemia. Contraindications for use include severe cardiac disease, asthma and chronic obstructive pulmonary disease (COPD) when beta-blockers should not be given unless there is no alternative treatment.

✚ CLINICAL CONSIDERATIONS

Some patients may need a few weeks of treatment to stabilise the pressure-lowering response. The intraocular pressure is determined after 4 weeks of treatment. Advise the patient to monitor the pulse rate and to report a slow rate to the prescriber.

Miotics

Miotics are muscarinic agonists. The muscarinic agonists used in glaucoma include **pilocarpine**.

■ MECHANISM OF ACTION

Miotics act primarily to increase the drainage of aqueous humour out of the anterior cavity through the canal of Schlemm. They achieve this through miosis (pupil constriction) and contraction of the ciliary muscles responsible for accommodation. These effects, mediated by the parasympathetic nervous system (see Table 79.1), open the trabecular meshwork and dilate collecting channels to the canal of Schlemm.

◆ COMMON ADVERSE EFFECTS

Systemic adverse effects are few; headache is the most common of these. The most common adverse effects are ocular and include pupil constriction – accommodative spasm involving the ciliary muscles that results in myopia and loss of visual acuity. Dilation of conjunctival and uveal blood vessels may lead to hyperaemia. Uveal hyperaemia can lead to retinal detachment. These agents are contraindicated in acute iritis, where miosis is undesirable.

✚ CLINICAL CONSIDERATIONS

Advise patients on muscarinic agonists to exercise caution during night-time driving and when performing hazardous activities in poor light. Miosis is potentially permanent with long-term use of muscarinic agonists, and these drugs may constrict the visual field and affect vision in dim light. Patients need to remain under medical supervision for periodic tonometric readings.

Carbachol is a muscarinic antagonist that is more potent than pilocarpine but is absorbed poorly. It is usually reserved for patients who do not respond to pilocarpine treatment. Miotics are short-acting and require repeated administration two to three times a day.

Pilocarpine is also available as a sustained-release insert called an ocusert. This delivery system eliminates the need for repeated daily administration and produces effective therapy at significantly lower dosages. The insert is an elliptically shaped unit, which is placed in the upper conjunctival cul-de-sac by the patient. The insert releases a constant amount of drug through a polymer membrane on to the surface of the eye for a period of 7 days. Two units with different release rates are currently available: 20 μg/h and 40 μg/h. The release rate is determined by the thickness of the membrane (see Chapter 9 for further information about the ocusert).

An ocular preparation combining the beta-blocker timolol and the muscarinic agonist pilocarpine is also available. As discussed previously, the former drug decreases the production of aqueous humour while the latter increases aqueous humour outflow. Such a combination makes good sense: the patient receives the benefit of a synergistic effect on intraocular pressure without increasing the magnitude of the adverse reactions, and has the convenience of having to administer only one preparation.

Acetylcholine cannot be applied topically to the surface of an intact eye because it is degraded by cholinesterase before it can produce its clinical effect. It is reserved for intraocular injection into the anterior chamber during eye surgery, particularly in cataract operations. Solutions of acetylcholine are very unstable; therefore, they need to be prepared immediately before use and the excess discarded afterwards. Adverse effects are observed rarely but include corneal oedema, clouding and decompensation. Systemic adverse effects are rare but when observed include bradycardia, breathing difficulties and sweating.

Sympathomimetic agents

The sympathomimetic agents **dipivefrine**, **brimonidine** and **phenylephrine** can be used in the management of glaucoma.

■ MECHANISM OF ACTION

The sympathomimetics can decrease the formation of aqueous humour and increase its outflow. As a consequence,

there is a fall in intraocular pressure. The mechanism involves an activation of adrenoreceptor subtypes associated with the ciliary body.

Dipivefrine, an adrenaline prodrug, is absorbed into the eye better than adrenaline itself because the former is more lipid-soluble. Following absorption, dipivefrine is converted rapidly into adrenaline. Adrenaline can decrease the production of aqueous humour and enhance its drainage from the eye through a combination of α and β receptor effects on the ciliary body. The activation of α receptors, triggered by phenylephrine and dipivefrine, induces constriction of the ciliary vasculature, decreasing aqueous humour production (see Table 79.1). It is interesting that pharmacological antagonists such as adrenaline and the beta-blockers both produce falls in intraocular pressure.

Apraclonidine is related to the antihypertensive agent **clonidine** (see Chapters 26 and 44). It is a relatively selective α_2 agonist that, through prejunctional α receptor activation (see Chapter 26), produces the desired ophthalmic effects. **Brimonidine** is another selective α_2 agonist. A major advantage of this receptor selectivity is the absence of the mydriasis associated with other ophthalmic sympathomimetic agents. Compared with the beta-blockers, however, the reduction in intraocular pressure produced by brimonidine is small, and it appears to have more adverse effects.

◆ COMMON ADVERSE EFFECTS

Due to its better absorption, dipivefrine can be administered at lower doses than adrenaline would be, resulting in fewer adverse effects, both locally and systemically. Common adverse effects of dipivefrine and phenylephrine include headache, stinging sensation during instillation, mydriasis and blurred vision. Topical administration greatly reduces systemic absorption, but the patient should be monitored for changes in heart rate, rhythm and blood pressure, anxiety and tremor. An important contraindication to use is in the treatment of closed-angle glaucoma, where mydriasis would aggravate the condition.

Common adverse effects of the α_2-selective agonists include ocular hyperaemia, pruritus and discomfort. Systemic absorption of apraclonidine can occur, resulting in headache, dry mouth and chest pain. Its use is restricted to monotherapy in patients with open-angle glaucoma who cannot take beta-blockers. Lowered blood pressure has been reported with brimonidine treatment.

For all the sympathomimetics used in glaucoma, caution should be exercised in patients with hypertension, heart disease and diabetes mellitus, in patients on antidepressants and in patients receiving systemic sympathomimetic therapy.

✚ CLINICAL CONSIDERATIONS

Apraclonidine should be used only in the short term for lowering the intraocular pressure, as it is associated with allergic blepharoconjunctivitis with chronic use. It also loses its effectiveness after 3 months of treatment. It is used perioperatively. In using brimonidine, drowsiness may affect performance and driving ability. Dipivefrine has an additive effect when used in combination with miotics, carbonic anhydrase inhibitors and betaxolol. If it is used in combination with betaxolol, the effectiveness of therapy is improved when dipivefrine is instilled before the beta-blocker.

Diuretics

Carbonic anhydrase inhibitors (**acetazolamide**, **brinzolamide**, **dorzolamide**) and **mannitol** are diuretic agents that reduce intraocular pressure. Mannitol is not a first-line drug in the treatment of glaucoma. It is usually reserved for patients who have not responded well to other drugs.

■ MECHANISM OF ACTION

Carbonic anhydrase inhibitors act on the enzyme responsible for the conversion of carbon dioxide to bicarbonate and hydrogen ions (and back again). The mechanism of action of this group in glaucoma is different from that described for the kidneys in Chapter 47. In the eye, carbonic anhydrase plays a significant role in aqueous humour formation by the ciliary body cells. In the ciliary bodies, carbonic anhydrase facilitates the secretion of bicarbonate ions into the aqueous humour. Carbonic anhydrase inhibitors therefore decrease the formation of aqueous humour. Glaucoma has become the main clinical indication for the carbonic anhydrase inhibitors. Most of these drugs must be administered systemically. Dorzolamide and brinzolamide are available as topical preparations, and so the incidence of systemic adverse effects is minimised. A combined preparation of the beta-blocker timolol and dorzolamide is available.

Mannitol is an inert sugar alcohol administered intravenously; it remains trapped within the bloodstream, increasing plasma osmolarity. This change in plasma osmolarity induces a fluid shift from the anterior cavity back into the plasma, reducing intraocular pressure by enhancing aqueous humour outflow.

◆ COMMON ADVERSE EFFECTS

The carbonic anhydrase inhibitors are related closely to the sulphonamide antibacterial agents. As such, they produce a similar profile of adverse effects, including rashes, kidney stones and aplastic anaemia. Other adverse effects associated with this group are depression, paraesthesias, anorexia, electrolyte disturbances (especially potassium) and metabolic acidosis. Contraindications for use include deficient sodium and potassium levels.

Adverse effects of mannitol are mainly systemic and include fluid and electrolyte imbalances, acidosis, headache, nausea and vomiting.

✚ CLINICAL CONSIDERATIONS

Topical carbonic anhydrase inhibitors may cause temporary discomfort after instillation. If the patient experiences blurred vision, driving and operating machinery shoud be avoided until sight improves. Acetazolamide tablets should be taken with meals to prevent nausea and vomiting. Systemic therapy with acetazolamide is usually avoided because of the high incidence of adverse effects.

As mannitol causes marked diuresis, anaesthetised and other unconscious patients require urinary catheterisation. Fluid and electrolyte levels are monitored for possible acidosis, electrolyte loss and dehydration. Mannitol crystals can be redissolved by warming the container in warm water and shaking vigorously.

Prostaglandins

■ MECHANISM OF ACTION

Research has shown that prostaglandins also have a role in the movement of aqueous humour through the eye. Prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) promotes uveoscleral outflow of aqueous humour and reduces outflow resistance. In other words, $PGF_{2\alpha}$ enhances the drainage of aqueous humour and reduces intraocular pressure. It appears to have no effect on aqueous humour production.

Synthetic analogues of $PGF_{2\alpha}$, **latanoprost** and **travoprost**, are available for use in clinical practice. These are prodrugs that are converted to $PGF_{2\alpha}$ after absorption into the eye. Clinical studies indicate that the efficacy of these drugs in reducing intraocular pressure is comparable to that of the beta-blocker timolol.

◆ COMMON ADVERSE EFFECTS

Common adverse reactions include stinging, burning, itching, hyperaemia, redness of the eye, lengthening and increased number of eyelashes and blurred vision. The mechanism underlying the changes to eyelashes is probably related to the mitogenic effects of this group of drugs. Interestingly, a significant proportion of individuals receiving this drug for a prolonged period report a change in eye colour due to altered iris pigmentation. Melanin secretion is stimulated, leading to an increase in brown pigmentation.

✚ CLINICAL CONSIDERATIONS

Travoprost can be used as first-line monotherapy or in combination with timolol. Currently, latanoprost is indicated only for people with open-angle glaucoma and ocular hypertension who are intolerant or unresponsive to established drugs. These drugs are long-acting agents that need to be administered only once daily. Their systemic absorption from the eye is significant and requires metabolism by the liver.

It is important to warn patients, especially those with green eyes, of a possible irreversible change in iris pigmentation.

Prostamides

Bimatoprost and **latanoprost** are prostamide analogues, a group of drugs that increase uveoscleral outflow and are used to reduce intraocular pressure in ocular hypertension and open-angle glaucoma.

■ MECHANISM OF ACTION

Prostamides are naturally occurring substances that have been identified only recently. They are related to the eicosanoids (see Chapter 30), and cyclo-oxygenase (COX) enzymes (see Chapter 40) are involved in their production. Prostamides differ from the prostaglandins in that they are derived from a different precursor substance called anandamide. Anandamide is converted into prostamides by COX-2. The research thus far suggests that the resulting prostamides do not interact with prostaglandin receptors.

Bimatoprost selectively mimics the effects of prostamide and has been shown to be a potent agent in reducing intraocular pressure by increasing drainage of the aqueous humour.

◆ COMMON ADVERSE EFFECTS

Common adverse effects include ocular hyperaemia, itching and thickening and lengthening of the eyelashes. Prostamides also induce increased iris and eyelid pigmentation. Systemic effects include headache and asthenia. At this stage, the adverse effects on renal and respiratory function are unknown. Prostamides appear to be tolerated well and have no apparent drug interactions.

✚ CLINICAL CONSIDERATIONS

Systemic absorption of the eye drops can be minimised by applying pressure to the tear duct after administration.

DRUGS USED IN EYE SURGERY

GELATIN FILM AND HYALURONATE

Gelatin film and **sodium hyaluronate** are degradable non-antigenic substances used to prevent adhesion after ocular surgery. Neither compound impedes the progress of normal healing.

Hyaluronate is the salt of hyaluronic acid, a normal component of connective tissue matrix. Hyaluronic acid is considered a type of intracellular cement holding the matrix together. Hyaluronate is used in ophthalmology as a vitreous humour substitute. It also keeps the anterior cavity open during surgery.

◆ COMMON ADVERSE EFFECTS

A common adverse effect of sodium hyaluronate is a transient rise in intraocular pressure postoperatively.

✚ CLINICAL CONSIDERATIONS

These preparations must be stored in the refrigerator and protected from freezing. They should be allowed to attain room temperature for about 20 minutes before use during surgery.

HYALURONIDASE

Hyaluronidase, an enzyme that breaks down hyaluronic acid, is used in ophthalmology. It is mixed with a solution of local anaesthetic. When injected into connective tissue, hyaluronidase makes the tissue more permeable and enhances the dispersion and absorption of the anaesthetic. It is contraindicated in infection and malignancy as it could enhance the spread of infectious agents and malignant cells.

Anti-inflammatory drugs

During cataract surgery the iris becomes irritated and releases prostaglandins. The prostaglandins stimulate contraction of the circular muscle of the iris, triggering an intraoperative miosis. This is problematic during surgery, as it affects access to the lens. Three NSAIDs have been approved for ophthalmic use to inhibit this response: **diclofenac**, **flurbiprofen** and **ketorolac**. (NSAIDs are discussed in detail in Chapter 40.) Flurbiprofen is related closely to **ibuprofen**.

◆ COMMON ADVERSE EFFECTS

A common adverse reaction is a transient burning sensation when the drug is instilled. An increased bleeding tendency during ocular surgery has been reported for flurbiprofen. These agents are contraindicated in people who have experienced an NSAID-induced acute asthma attack, urticaria or rhinitis.

ALLERGIC CONJUNCTIVITIS

Earlier in this chapter, the role of ocular decongestants (α agonists) in relieving the red and sore eyes characteristic of conjunctivitis was described. Relief is also available in the form of preparations containing either H_1 antihistamines, such as **antazoline**, **pheniramine** and **levocabastine**, or NSAIDs. (The general actions of the H_1 antihistamines and NSAIDs are described in Chapters 29 and 40, respectively. The ophthalmic use of the NSAIDs has already been discussed in this chapter.)

Antihistamines

■ MECHANISM OF ACTION

Histamine and prostaglandin release are associated with inflammatory responses such as vasodilation, increased capillary permeability, oedema formation, swelling, itching and tearing. If the magnitude of these responses is reduced, the patient becomes more comfortable. Levocabastine and **olopatadine** are available as ophthalmic preparations. When antazoline and pheniramine are used, they are normally combined with an ocular decongestant for greater therapeutic benefit. As ocular decongestants induce vasoconstriction, they might also significantly reduce the absorption of any other drugs contained in the preparation, thus prolonging their action. This action is put to good effect when an ocular decongestant is combined with an antibiotic or corticosteroid.

◆ COMMON ADVERSE EFFECTS

Eye irritation is a common adverse effect of topical H_1 antihistamines in the form of a stinging or burning sensation. Headache, sleepiness and blurred vision may also occur.

✚ CLINICAL CONSIDERATIONS

Levocabastine, which is available as an eye preparation combined with a decongestant, should be shaken vigorously before use because it is a microsuspension. The use of an antihistamine and decongestant is often discouraged because of the possibility of rebound congestion.

Allergy prophylaxis

Sodium cromoglycate and **lodoxamide**, available as eye drops, are also used in the treatment of allergic conjunctivitis (e.g. seasonal allergic conjunctivitis, vernal conjuctivitis) and seasonal keratoconjunctivitis.

■ MECHANISM OF ACTION

These drugs act to stabilise mast cells involved in allergic-type antigen–antibody interactions and prevent mast-cell degranulation and mediator release. These drugs are useful as prophylactic agents but are of no use in an acute episode. Clinical studies suggest that they have similar efficacy in the management of seasonal allergic conjunctivitis, but that lodoxamide is more effective for vernal conjunctivitis.

◆ COMMON ADVERSE EFFECTS

Common adverse reactions are a stinging or burning sensation during instillation.

✚ CLINICAL CONSIDERATIONS

Advise the patient that cromoglycate may take about 4–6 weeks to reach its full effect. For best results, mast-cell stabilisers are taken for about 1 month before the start of the hay fever season. They are also effective when given with a low-dose topical steroid during the first month of administration.

MISCELLANEOUS AGENTS

Blepharospasmolytic agents

Botulinum toxin, produced by the bacterium *Clostridium botulinum*, is approved for the treatment of spasm of the eyelids (blepharospasm) and strabismus (ocular misalignment

or deviation). This drug has gained some notoriety associated with its use to reduce wrinkles in ageing skin.

■ MECHANISM OF ACTION

Botulinum toxin blocks the release of acetylcholine from cholinergic nerves. Injections of the toxin have been used in the therapy of skeletal muscle spasm. This substance is extremely toxic to nerves and must be administered into the extraocular muscles by a highly skilled clinician. By causing a localised denervation of the muscle, it induces muscle paralysis. It appears that this paralysis is reversible, as the nerve can grow and reinnervate the affected muscle.

◆ COMMON ADVERSE EFFECTS

Common adverse reactions include drooping eyelids (ptosis), irritation and tearing. This drug can induce reduced blinking, exposing the cornea to injury and irritation. The eye may require protection during therapy in the form of protective drops, contact lenses or patching.

✚ CLINICAL CONSIDERATIONS

Botulinum toxin can be stored as a reconstituted solution for 4 hours in a refrigerator and then must be discarded. Pressure is applied to the injection site immediately after administration to prevent bruising. Preparations currently available are not therapeutically equivalent, and they should not be used interchangeably.

Photosensitisers

The photosensitiser **verteporfin** has been approved in the UK for the treatment of age-related macular degeneration. Only specialists experienced in the management of the conditions should use this drug.

Age-related macular degeneration is characterised by neovascularisation (new blood vessel development) and fibrosis of the choroid capillaries. This causes thickening of the basement membrane of the pigment epithelium. The new vessels induce fluid leakage and haemorrhagic detachment of the pigment epithelium and loss of central vision. There is atrophy of the pigment epithelium and bleeding.

■ MECHANISM OF ACTION

Verteporfin is infused intravenously and taken up preferentially by the neovasculature of the choroid and, to some extent, by the retina. Once activated by red light, it produces oxygen radicals, which results in damage to the neovascular endothelium and vessel obstruction. This prevents bleeding and fluid leakage.

◆ COMMON ADVERSE EFFECTS

Common adverse effects include local inflammation and pain at the injection site, abnormal vision, photosenstivity and asthenia.

Cleansers and lubricants

Dry and irritated eyes can be lubricated using agents such as cellulose derivatives (**carmellose**, **hydroxyethyl cellulose**, **carbomer 940**, **hydroxypropyl cellulose**, **hypromellose**), **paraffin**, **povidone** and polyvinyl alcohol. Polyvinyl alcohol is also used as a wetting agent for hard contact lenses to make the wearing of the lens more comfortable. The surface of an irritated eye can be cleansed of mucus using an astringent such as **zinc sulphate**. **Witch hazel** (*Hamamelis* extract) also has astringent properties that can be used to bring relief to irritated eyes.

◆ COMMON ADVERSE EFFECTS

These agents are tolerated well when applied topically. Adverse reactions are few but include transient blurring of vision, discomfort, sticky eyelashes and hypersensitivity.

✚ CLINICAL CONSIDERATIONS

Preservative-containing drops for dry eyes are packaged in bottles that must be used within 30 days. As they contain a preservative to prevent microbial contamination, they may cause eye irritation. Preservative-free preparations tend to be non-irritant, but they are bulky and more expensive. These preparations are packaged in single-use vials that can be used safely more than once as long are they are discarded 24 hours after opening. Eye ointment and gel preparations are most effective when used before bedtime if symptoms affect sleep or if the patient tends to wake up with dry eyes.

Stains

Staining agents, such as **fluorescein sodium** and **rose bengal**, are used as diagnostic aids to help demonstrate the integrity of ocular tissues, to indicate the presence of foreign bodies on the surface of the cornea, and to determine the fit of new contact lenses. Fluorescein is normally a yellow water-soluble dye that cannot penetrate intact membranes. Tissue damage allows the dye to gain access to the underlying cells, and in this alkaline environment it turns green. Fluorescein is used to identify corneal, conjunctival and retinal lesions. It can also demonstrate the patency of the nasolacrimal ducts. Rose bengal is a brownish-red dye that stains degenerate tissue. It is used to indicate whether there is ocular tissue involvement in facial skin conditions such as dermatitis. The goodness of fit of hard contact lenses over the cornea can be demonstrated using these stains. Spaces between the contact lens and the cornea stain strongly. Both dyes are non-toxic, but rose bengal is more of a tissue irritant. Hypersensitivity reactions such as anaphylaxis may occur in susceptible individuals; thus, emergency equipment should be readily available. Staining agents tend to be available in single-use, disposable sterile units in order to avoid any bacterial contamination that may result from multiple use.

Staining agents tend to permanently stain soft contact lenses and clothes. Staining of skin, urine, nasal secretions and tears is only a temporary effect, however.

Preservatives

Preservatives are common additives in ocular preparations. In this context a preservative is an antiseptic agent that inhibits microbial contamination. This is especially important in multiple-use preparations. Preservatives are also found in contact lens cleaning solutions. Recommended preservatives include **benzalkonium chloride**, **chlorhexidine acetate**, **thiomersal** and **cetrimide**. (Antiseptic agents are discussed in Chapter 70.) Benzalkonium, chlorhexidine and cetrimide alter the permeability of cell membranes. This action can be put to good use to facilitate the absorption of drugs across the cornea. An example of this is the addition of benzalkonium to the poorly soluble but potent miotic carbachol. Benzalkonium and chlorhexidine solutions should be protected from light and are incompatible with fluorescein. In combination with any of these preservative antiseptics, the chelating agent **EDTA** (ethylene diamine tetra-acetic acid) potentiates their antibacterial action. By complexing metal ions normally found within bacterial cell walls, EDTA reduces their structural integrity.

◆ COMMON ADVERSE EFFECTS

Preservatives may cause allergic reactions ranging from mild irritation to severe conjunctivitis and, sometimes, corneal scarring.

✚ CLINICAL CONSIDERATIONS

The shelf life of preserved eye preparations is 28 days after opening, unless indicated otherwise.

ADVERSE EFFECTS OF DRUGS ON THE EYE

There are a number of drugs used for ophthalmic purposes that can permanently damage structures of the eye, such as the cornea, lens and retina. As stated previously, patients receiving treatment with the corticosteroids should be monitored for cataracts. There are also a number of drugs administered systemically for non-ophthalmic purposes, for which effects on the eye need to be monitored closely.

People receiving therapy with the antipsychotic drug group phenothiazines are at risk of cataract development. The phenothiazines can also cause a retinopathy associated with drug-induced changes in the retinal vasculature. This is a relatively rare reaction usually associated with prolonged, high-dose therapy. Methanol poisoning can cause permanent retinal damage (see Chapter 21), as can oxygen therapy under certain circumstances (see Chapter 51). Other drugs, such as **chloroquine** (an antimalarial agent sometimes used as an anti-inflammatory drug, see Chapter 72), bind to the melanin in the pigmented cells of the retina. Prolonged high-dose chloroquine therapy can disrupt retinal metabolism and may cause retinopathy.

Most of the antitubercular agents (see Chapter 69) have the potential to cause optic nerve damage. As the condition is usually treated using a combination of drugs, the risk of optic nerve damage is increased. Careful assessment and monitoring of these patients is important.

Disturbances of colour vision are associated with a number of drugs, such as the antibacterial agent **nalidixic acid**. Health-care staff, however, tend to be more aware of and associate this reaction with the toxic effects of the cardiac glycoside **digoxin**. It has been suggested that digoxin triggers this effect through a direct interaction with cone photoreceptors. Patients taking digoxin who show this effect require an adjustment to their dosage.

CLINICAL MANAGEMENT

Drugs used in diseases of the eye

Assessment

- Assess the patient's eye condition, including peripheral vision and visual acuity, using a Snellen chart. Ask the patient about difficulties with driving, reading and walking around the home. Assess the eyes for any signs of infection, tearing, dryness and exudate.
- Obtain a medical and drug history. Miotics are contraindicated in patients with narrow-angle glaucoma, acute inflammation of the eye, heart block, coronary artery disease, asthma, gastrointestinal obstruction and urinary tract obstruction. Sympathomimetic and antimuscarinic mydriatics are contraindicated in narrow-angle glaucoma. Exercise caution when using mydriatics in patients with hypertension, hyperthyroidism, heart disease and diabetes mellitus.
- Avoid using prostaglandin analogues in children and during pregnancy and lactation due to their unknown effects in these conditions.
- Assess the patient's age. Use of atropine and other belladonna alkaloids may precipitate glaucoma, and great care should be exercised in elderly people.

- Obtain baseline vital signs and compare with subsequent observations.

Planning

- The goal depends on the condition for which the preparation is used. The drug will assist in diagnosing the patient's eye problem; or, the patient's intraocular pressure will be lowered to a safe level; or, the patient's eye infection will be treated successfully.

Implementation

- Make sure that the correct eye preparation is used for the correct eye. Patients with eye conditions often require more than one eye preparation.
- Administer eye preparations using the correct methods (see Table 7.3 in Chapter 7 for information on the correct technique for administering eye ointment and drops).
- Always administer glucocorticoids before other preparations.
- Always administer eye drops before eye ointment.
- Monitor vital signs. Pulse and blood pressure may fall with large doses of cholinergic or beta-blocking agents.
- For patients on beta-blocker eye preparations, monitor for postural hypotension. Advise the patient to arise slowly from a lying or sitting position (see Table 11.20 in Chapter 11 for further information about measures to take for postural hypotension).
- For patients on muscarinic agonists or beta-blocker eye preparations, check breath sounds for crackles and wheezes. These preparations can cause bronchospasm and increase bronchial secretions.
- For patients on carbonic anhydrase inhibitor oral and intravenous preparations, monitor for side effects such as lethargy, loss of appetite, drowsiness, polyuria, nausea and vomiting.
- For patients on carbonic anhydrase inhibitors (oral or intravenous) or osmotic (intravenous) agents, monitor fluid balance by documenting fluid intake and output. Increase fluid intake unless contraindicated (e.g. cardiac or renal disease). Record body weight regularly. Observe for manifestations of dehydration.
- For patients on carbonic anhydrase inhibitors (oral or intravenous) or osmotic (intravenous) agents, monitor serum electrolyte levels.
- For patients on antimuscarinic, cycloplegic or mydriatic eye preparations, monitor for tachycardia, photophobia, dry mouth, constipation and confusion.
- For patients on sympathomimetic eye preparations, monitor for headache, brow pain and dysrhythmias.
- Maintain the patient's safety after administering eye preparations. Assist with ambulation and daily activities until the vision clears.
- Observe for gradual increase in iris pigmentation over several months after the use of prostaglandin analogues. This pigmentation is usually irreversible and occurs in up to 8 per cent of treated eyes. Darkening and thickening of the eyelashes may also occur.
- Topical ocular steroids, used alone or in combination with antibacterials, should not be prescribed without close supervision by a qualified ophthalmologist. Topical steroids may have a serious effect on the patient's vision.

Patient teaching

- Teach patients how to instil eye medications correctly (see Table 7.3 in Chapter 7 for further information).
- If photophobia occurs, advise the patient to avoid bright lights and to wear sunglasses (see Table 11.13 in Chapter 11 for other measures that can be implemented if photophobia occurs).
- Impress on patients that glaucoma cannot be cured, only controlled. Medications should continue to be used as prescribed and not discontinued.
- Advise patients that during the early stages of glaucoma treatment, drugs used for this condition often cause pain and blurred vision. These effects may diminish with time. The use of cold compresses may assist with eye pain.
- In infants, the use of atropine eye drops may cause abdominal distension and constipation. Advise the infant's parents to observe for bowel motions over 24 hours after administration.
- Advise patients that mast cell stabilisers, such as cromoglycate and lodoxamide, may take 3–6 weeks to take effect. Lodoxamide may take less time to show a beneficial effect.
- Advise patients on α_2 agonists, such as apraclonidine and brimonidine, that they may cause dry mouth and nose, altered taste sensation and ocular irritation. Brimonidine may also cause drowsiness and fatigue, and patients should be advised to avoid driving and operating machinery.
- Warn patients about the hazards of driving and operating heavy machinery when vision is blurred. Advise patients that they are unable to drive after eye examinations when mydriatics or cycloplegics have been used. A friend, relative or taxi should take them home. Vision remains blurred for a few hours.
- Soft contact lenses may absorb certain eye medications and preservatives, causing discoloration of the lenses. The wearing of contact lenses (soft or hard)

often delays the clearing of eye infections. For these reasons, advise patients not to wear contact lenses when eye medications are being used.
- After multi-use eye preparations have been opened, the containers should be stored in the refrigerator when not in use. Discard the preparations after 30 days.
- Advise the patient to report changes in vision and blurring or loss of vision.

Evaluation

- Evaluate the drug's effectiveness in performing the role for which it is intended. For example, the drug will assist in diagnosing the patient's eye problem; or, the patient's intraocular pressure will be lowered to a safe level; or, the patient's eye infection will be treated successfully.

SUMMARY

- A number of drugs have been formulated especially for use in ophthalmology. Drug groups prepared for this purpose include anti-inflammatory, antimicrobial, adrenergic and cholinergic agents, local anaesthetics and diuretics.
- Most drugs used in ophthalmology are administered locally. This approach delivers the drug directly to the site of action, produces more immediate effects, allows for smaller effective doses and minimises systemic adverse effects.
- Factors that influence the rate of absorption from local administration include drug solubility, tissue damage to the eye and the degree of drug binding.
- Eye drops are common and convenient ophthalmic preparations. The chemical properties of the preparations are adjusted carefully to prolong shelf life, minimise microbial contamination and protect the eye from drug-induced damage.
- Glaucoma is characterised by an increased intraocular pressure in the anterior cavity of the eye. Drugs are used in the management of the more common form called open-angle glaucoma, where there is impaired diffusion of aqueous humour.
- Some antiglaucomal drugs decrease aqueous humour production (beta-blockers, carbonic anhydrase inhibitors), increase its drainage (muscarinic agonists, prostaglandins, prostamides) or induce both effects (sympathomimetic agents).
- Patients should be taught how to administer ophthalmic medications correctly. The onset of systemic adverse effects should be monitored closely. If the medication is likely to cause blurred vision or drowsiness, the patient should be advised not to drive or operate heavy machinery.
- Common adverse effects of locally administered drugs include burning, stinging, hyperaemia and local irritation. A range of drugs can cause significant damage to the eye, including phenothiazine antipsychotics, methanol, and the antimalarial agent chloroquine.

1 Indicate the uses of the following drug groups in ophthalmology:
(a) corticosteroids;
(b) staining agents;
(c) antimuscarinic agents;
(d) α-adrenergic agonists;
(e) local anaesthetics;
(f) muscarinic agonists.

2 Compare and contrast the following ophthalmic drug groups: miotics, cycloplegics and mydriatics.

3 Outline the complications resulting from the prolonged use of the following drug groups:
(a) corticosteroids;
(b) antimicrobials;
(c) local anaesthetics.

4 Briefly describe the pathophysiology of glaucoma.

5 Which form of glaucoma is the most common, and which form is responsive to drug therapy?

6 Briefly describe the mechanisms of action of the following drug groups used in glaucoma therapy:
(a) diuretics;
(b) anticholinergic mydriatics;
(c) prostamide analogues;
(d) beta-blockers;
(e) α_2 agonists;
(f) prostaglandins.

7 Outline the procedures for administering eye drops and eye ointments. (See Table 7.3 in Chapter 7 for assistance.)

8 For a patient leaving the medical clinic for home, the administration of a cycloplegic agent would result in a very anxious time. Why is this so?

9 While in hospital, Roy Reuters, a 70-year-old patient, is ordered acetazolamide therapy for the treatment of glaucoma. With reference to acetazolamide's mechanism of action, why would you monitor fluid balance and electrolyte levels?

10 Geoffrey Leichhardt is 28 years of age and has acquired immunodeficiency virus (AIDS). He has developed cytomegalovirus-induced retinitis and is being treated with the antiviral agent ganciclovir. Regular blood tests are ordered during therapy. Why? With what patient education do you provide Geoffrey regarding this adverse effect?

11 In what kinds of patient are timolol eye drops contraindicated? Why?

12 What are the storage requirements for eye drops once opened? (See Table 7.19 in Chapter 7 for assistance.)

79 DRUG SUMMARY TABLE: DRUGS AND THE EYE

FAMILY NAME	GENERIC NAME	TRADE NAME(S)
Antibacterial agents	Azithromycin	
	Chloramphenicol	Minims Chloramphenicol
	Ciprofloxacin	
	Erythromycin	
	Framycetin	Soframycin
	Fusidic acid	Fucithalmic
	Gentamicin	Minims Gentamicin
	Neomycin	
	+ Polymixin B, gramicidin	Neosporin
	Ofloxacin	Exocin
	Propamidine	Brolene
	Sulfacetamide	
	Tetracycline	
	Tobramycin	
Antiviral agents	Aciclovir	Zovirax
	Ganciclovir	Virgan
Local anaesthetics	Tetracaine (amethocaine)	Minims Amethocaine
	Lidocaine + fluorescein	Minims Lignocaine and Fluorescein
	Oxybuprocaine	Minims Oxybuprocaine
	Proxymetacaine	

FAMILY NAME	GENERIC NAME	TRADE NAME(S)
Topical corticosteroids	Betamethasone	
	Dexamethasone	Maxidex
	Fluorometholone	FML
	Hydrocortisone + Neomycin	Neo-Cortef
	Prednisolone	Minims Prednisolone
Beta-blockers	Betaxolol	
	Carteolol	Teoptic
	Timolol	Timoptol
Diuretics (carbonic anhydrase inhibitors)	Acetazolamide	Diamox
	Brinzolamide	Azopt
	Dorzolamide	Trusopt
Combination ophthalmic preparations	Antazoline + Witch hazel	Optrex
Antihistamine	Levocabastine	Livostin
	Olopatadine	Opatanol
Sympathomimetic agents	Brimonidine	Alphagan Combigan
	Dipivefrine	Propine
	Ephedrine	Minims Ephedrine
Cholinergic mydriatics	Atropine	Isopto Atropine Minims Atropine
	Cyclopentolate	Minims Cyclopentolate
	Homatropine	
	Tropicamide	Minims Tropicamide Mydriacyl
Anti-inflammatory agents	Sodium cromoglycate	Opticrom Optrex Allergy
Miotics	Pilocarpine	Pilogel
Miscellaneous ophthalmic agents	Fluorescein	Minims Fluorescein
	Hyaluronidase	Hyalase
	Rose bengal	Minims Rose Bengal
	Sodium hyaluronate	Ophthalin
	Verteporfin	Visudyne
	Witch hazel	Optrex
	Botox	Botulinum toxin type A
Prostaglandin analogues	Latanoprost	Xalatan
	+ Timolol	Xalacom
	Travoprost	Travatan
Prostamide analogues	Bimatoprost	Lumigan
Ocular lubricants	Carbomer	Viscotears GelTears Liposic Liquivisc
Cleansers	Carmellose	Celluvisc
	Hydroxyethyl cellulose	Minims Artificial Tears
	Hydroxypropyl cellulose	
	Hypromellose	Tears Naturale

CASE STUDY XV.1

PD is a 72-year-old man with a history of chronic hayfever. His wife persuaded him to go to the doctor about coin-shaped skin lesions that had developed on his body, particularly on his arms and legs. He had tolerated the lesions for a while, thinking they were an allergy of some kind that would go away quickly. The condition recently flared up badly after a seafood meal at a restaurant. The doctor diagnosed the condition as nummular eczema and prescribed him betamethasone ointment to be applied once a day.

After a week of therapy, PD returned to the doctor and complained that the lesions had become very itchy and that he felt a stinging sensation. As much as he tried, he could not refrain from rubbing and scratching the affected areas. An examination revealed that some of the lesions had become infected. PD was prescribed an ointment containing neomycin and bacitracin to be applied twice daily over the affected areas. The doctor asked PD to continue treatment for 5 days and to come back if the infection had not cleared up after this time.

PD returned after therapy, stating that although the eczema had subsided, some of the areas infected had developed a well-defined, moist red rash. The doctor found some scaling in these areas, with some satellite rash development beyond the well-defined border. The doctor diagnosed candidal infection and prescribed nystatin topical cream to be applied four times a day until the rash cleared.

QUESTIONS

1 *Explain the advantages of topical rather than systemic administration of the agents used.*

2 *State two factors that would have contributed to the development of the secondary infection of the inflammatory lesions.*

3 *Explain why the candidal infection developed.*

CASE STUDY XV.2

TH is a 70-year-old widow living independently at home and whom you, as a community nurse, visit regularly. Her ongoing health problems are chronic asthma, hypertension and angina pectoris, but she is managing them well using a combination of drugs and sensible lifestyle. The drugs she is taking for her conditions are:

- for asthma – the inhaled corticosteroid beclomethasone (daily); the inhaled asthma prophylactic sodium cromoglycate (daily); the inhaled β_2 agonist salbutamol (as required);
- for hypertension – the thiazide diuretic hydrochlorothiazide (daily); the α antagonist prazosin (daily);
- for angina pectoris – the peripheral vasodilator glyceryl trinitrate (as required).

Over the past few years her intraocular pressure has been rising and she has recently been diagnosed with open-angle glaucoma. She is prescribed the beta-blocker betaxolol, the prostaglandin analogue latanoprost, and the muscarinic agonist pilocarpine. She has just had these delivered by her local pharmacy. You watch her instil the drops and offer her encouragement and advice about the correct use of these drugs. Within a couple of months of starting therapy, her intraocular pressure is rechecked and found to be reduced.

QUESTIONS

1 *By which routes would the beta-blocker, the prostaglandin analogue and the muscarinic agonist be administered in the treatment of TH's glaucoma?*

2 *Explain how each of the drug groups used to treat her glaucoma relieves the high intraocular pressure.*

3 *Explain how the anatomy of the eye facilitates systemic absorption of topical ocular preparations.*

4 *How can systemic absorption of these drugs be minimised?*

5 *What are the common local adverse reactions associated with topical administration of eye drops?*

6 *Given TH's pre-existing health problems, are there likely to be any precautions associated with her prescribed glaucoma therapy?*

7 *Are there any potential drug interactions between her pre-existing therapy and her glaucoma therapy worth noting?*

8 *What changes to eye structures are associated with prostaglandin analogue therapy? Are these changes harmful to the eye?*

9 *What advice would you give her regarding the adverse effects she might expect when using the beta-blocker and the muscarinic agonist?*

10 *Indicate whether the following drug groups are miotics or mydriatics or have no effect on pupil size when administered topically to the eye:*
(a) sympathomimetics;
(b) corticosteroids;
(c) muscarinic agonists;
(d) carbonic anhydrase inhibitors;
(e) antimuscarinics.

CASE STUDY XV.3

Ms VB, 23 years old, is suffering from seasonal allergic conjunctivitis. This has been precipitated by a lot of smoke in the air caused by a recent factory fire. Her eyes are itching and red, with a watery discharge. She has not had this condition before, and she is finding it uncomfortable to wear her contact lenses. VB drops by her local pharmacy to pick up some drops containing the decongestant naphazoline and the antihistamine pheniramine.

This is not particularly successful, so VB goes to see her doctor. Her doctor prescribes the non-steroidal anti-inflammatory drug (NSAID) ketorolac in eye drops. This treatment reduces the symptoms significantly.

QUESTIONS

1 *What is conjunctivitis?*

2 *Outline the patient education you would offer Ms VB about using the decongestant–antihistamine combination.*

3 *Describe the mechanisms of action of the decongestant, the antihistamine and the NSAID.*

4 *List any other eye preparations that can be used in the treatment of allergic conjunctivitis.*

FURTHER READING

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WEB RESOURCES

British Association of Dermatologists www.bad.org.uk

Eczema help www.undermyskin.co.uk/general/self_help.htm

Eye Care Information www.eyecareinfo.com

Glaucoma Australia www.glaucoma.org.au

National Association for Health and Clinical Excellence www.nice.org.uk

UK Psoriasis Association www.psoriasis-association.org.uk

US National Eczema Association www.nationaleczema.org

APPENDIX A: COMMON PRESCRIPTION TERMINOLOGY

Abbreviation	Latin	Translation
ac	ante cibum	Before meals
bd (or bid)	bis in die	Twice daily
d	dies	Daily
gtt	guttae	Drops
m	mane	In the morning
mist	mistura	Mixture
n	nocte	At night
om	omni mane	Every morning
paa	parti affectae applicandus	To be applied to the affected part
pc	post cibum	After meals
po	per os	By mouth
pr	per rectum	By rectal route
prn	pro re nata	Whenever necessary
pv	per vaginam	By the vagina
q4h	quaque 4 hora	Every 4 hours
qh	quaque hora	Every hour
qid	quater in die	4 times daily
stat	statim	Immediately
tds	ter die sumendum	3 times daily
tid	ter in die	3 times daily
ung	unguentum	Ointment

APPENDIX B: COMMON US GENERIC DRUG NAMES

US	UK
Acetaminophen	Paracetamol
Albuterol	Salbutamol
Epinephrine	Adrenaline
Ergonovine	Ergometrine
Isoproterenol	Isoprenaline
Meperidine	Pethidine
Norepinephrine	Noradrenaline
Rifampin	Rifampicin

APPENDIX C: SI UNITS

The metric system introduced in France in 1790 is now the preferred system of measurement used in medicine, technology and science. In this field, we use SI units, a name derived from the French *Système International d'Unités*.

Several fundamental and derived measurements are used in the SI system, although the measurements of relevance to nursing practice are length, area, volume, mass and amount of substance. Table C.1 indicates these measurements with their accompanying units and symbols.

TABLE C.1 SI UNITS

Measurement	Unit	Symbol
Length	Metre	m
Area	Square metre	m^2
Volume	Cubic metre	m^3
Mass	Kilogram	kg
Amount of substance	Mole	mol

A major advantage of the SI system is that units are related to each other by factors of ten. Commonly used prefixes and their corresponding powers of ten are noted in Table C.2.

TABLE C.2 SI PREFIXES

Power of 10	Prefix	Symbol
10^{-18} (0.000 000 000 000 000 001)	Atto	a
10^{-15} (0.000 000 000 000 001)	Femto	f
10^{-12} (0.000 000 000 001)	Pico	p
10^{-9} (0.000 000 001)	Nano	n
10^{-6} (0.000 001)	Micro	μ, mc
10^{-3} (0.001)	Milli	m
10^{-2} (0.01)	Centi	c
10^{-1} (0.1)	Deci	d
10^{1} (10)	Deca	da
10^{2} (100)	Hecto	h
10^{3} (1000)	Kilo	k
10^{6} (1 000 000)	Mega	M
10^{9} (1 000 000 000)	Giga	G
10^{12} (1 000 000 000 000)	Tera	T

MEASUREMENT OF LENGTH

The fundamental SI unit of length is the metre. The units of length in common use are indicated in Table C.3.

TABLE C.3 SI UNITS OF LENGTH

Unit	Symbol	Metric equivalent
One metre	1 m	Standard
One kilometre	1 km	1000 m
One decimetre	1 dm	0.1 m, 10 cm
One centimetre	1 cm	0.01 m, 10 mm
One millimetre	1 mm	0.001 m, 1000 μm
One micrometre	1 μm	0.000 001 m, 0.001 mm
One nanometre	1 nm	0.000 000 001 m, 0.001 μm

MEASUREMENT OF AREA

The derived SI unit of area is one square metre. Area is derived from length. It is obtained by multiplying the length of one side by the length of another side. Table C.4 lists various units of area and their metric equivalents.

TABLE C.4 SI UNITS OF AREA

Unit	Symbol	Metric equivalent
One square metre	1 m^2	Standard
One square decimetre	1 dm^2	0.01 m^2, 100 cm^2
One square centimetre	1 cm^2	0.000 1 m^2, 100 mm^2

MEASUREMENT OF VOLUME

Units of volume or capacity are derived units based on length. Volume is obtained by multiplying the length of one side by the length of another side and by the depth of the item. The basic derived unit of volume is the cubic metre. A more commonly used unit is one cubic decimetre, which is the same as one litre. A litre is defined as the volume occupied by 100 g pure water at 4 °C. As 1 cm^3 water at this temperature weighs 1 g, then 1000 g occupies a volume of 1000 cm^3. This means that 1000 cm^3 is equal to 1 l and 1 m is equal to 1 cm^3. Table C.5 shows the relationships between the SI units for volume.

TABLE C.5 SI UNITS OF VOLUME

Unit	Symbol	Metric equivalent
One cubic metre	1 m^3	Standard
One cubic decimetre	1 dm^3	0.001 m^3, 1 l, 1000 cm^3
One cubic centimetre	1 cm^3	0.000 001 m^3, 0.001 dm^3, 0.001 l
One litre	1 l	0.001 m^3, 1 dm^3, 1000 ml
One millilitre	1 ml	0.000 001 m^3, 1 cm^3, 0.001 l

MEASUREMENT OF MASS

The fundamental unit of mass is the kilogram. A kilogram is equivalent to the mass of 1 l pure water, while 1 g is the mass of 1 ml or 1 cm^3 of pure water. Table C.6 indicates the relationships between the SI units for volume. In nursing practice, the term 'weight' is often used instead of mass.

TABLE C.6 SI UNITS OF MASS

Unit	Symbol	Metric equivalent
One kilogram	1 kg	1000 g, 1 000 000 mg
One gram	1 g	0.001 kg, 1000 mg
One milligram	1 mg	0.001 g, 1000 μg
One microgram	1 μg, 1 mcg	0.001 mg, 0.000 001 g
One nanogram	1 ng	0.001 μg, 0.000 001 mg

MEASUREMENT OF AMOUNT OF A SUBSTANCE

The fundamental SI unit for an amount of substance is the mole. One mole contains 6×10^{23} identical portions of the substance. For instance, one mole of oxygen molecules contains 6×10^{23} molecules. Table C.7 shows the common units involving the number of mole of a substance.

TABLE C.7 SI UNITS OF AMOUNT OF A SUBSTANCE

Unit	Symbol	Metric equivalent
One mole	1 mol	Standard, 1000 mmol
One millimole	1 mmol	0.001 mol

APPENDIX D: DRUG CALCULATIONS

EXERCISES

1. Your patient is ordered 25 mg atenolol. You have available Tenormin™ tablets that contain 50 mg atenolol. How many tablets would you give?
2. A patient is ordered 100 mg furosemide as a morning dose. You have at your disposal 20-mg and 40-mg strength of Lasix™. What would you administer?
3. Your patient is on an Actrapid™ infusion 50 units in 100 ml 5% glucose running at 4 ml/h. How many units of Actrapid is the patient receiving per hour?
4. Your patient is receiving a morphine infusion consisting of 50 mg morphine in 500 ml 5% glucose via a volumetric pump. The dose ordered is 3 mg/h. How many millilitres per hour will be dialled up on the volumetric pump?
5. Your patient is receiving 25 000 units of heparin in 5% glucose 500 ml at 20 ml/h via a volumetric pump. How many units per hour is the patient receiving? The patient's activated partial thromboplastin time (APTT) result comes back at 32 seconds and the heparin infusion is increased to 35 000 units/500 ml running at 20 ml/h. How many units per hour is the patient now receiving? How many drops per minute (dpm) does this correspond to if a macro-drip is used?
6. Your patient is receiving a potassium chloride infusion of 75 mmol in 500 ml 5% glucose, with the ordered volume being 40 ml/h. How many millimoles per hour is the patient receiving? Your patient's serum potassium level is 4.1 mmol/l and she is ordered 10 mmol potassium chloride IV stat. Potassium chloride ampoules are available as a 25 mmol/10 ml formulation. How many millilitres of the ampoule would you give?
7. Your patient is ordered gentamicin 120 mg. Gentamicin is available as an 80 mg/2 ml formulation. How many millilitres would you give? Gentamicin needs to be diluted in 60 ml and given over 1 hour. How many drops per minute (dpm) would be delivered if a macro-drip was used?
8. Your patient has an infusion of 5% glucose 1000 ml running at a 24-hourly rate. Calculate the dpm if a macro-drip is used. Your patient is ordered vancomycin 500 mg to be given in 50 ml over 1 hour. What would be the dpm during this time?
9. Your patient is ordered 100 ml Haemaccel™ to run over 1 hour. What dpm is required if a macro-drip is used? As the patient's blood pressure remains low (85/50 mmHg), a further 250 ml is ordered to run over 45 minutes. What dpm is required now?
10. Your patient is ordered 20 ml phosphate ions IV. This is diluted to 100 ml via the IV burette and given over 1 hour. What dpm is required if a macro-drip is used?
11. Your patient is on an Actrapid™ infusion of 60 units in 30 ml Haemaccel™. The dose ordered is 5 units per hour. How many millilitres per hour would you dial up on the pump?
12. Your patient is receiving a morphine infusion of 50 mg in 50 ml normal (isotonic) saline. The dose ordered is 3.5 mg/h. How many millilitres per hour are being delivered?
13. Your patient is ordered 2 million units of penicillin to be made up to 80 ml and delivered in 30 minutes. To how many dpm does this correspond if a macro-drip is used?
14. Your patient is ordered gentamicin 100 mg. Gentamicin is available as an 80 mg/2 ml formulation. How many millilitres will you need? The gentamicin is diluted to 50 ml and given over 60 minutes. What dpm will be delivered if a micro-drip is used?

15 Your patient is ordered 500 ml 'stable plasma protein solution' (SPPS) to be run over 2 hours. How many dpm are delivered if a micro-drip is used?

16 Your patient is ordered 400 ml whole blood to be run over 3 hours. How many dpm does this correspond to if a macro-drip is used?

17 Your immunocompromised patient is ordered aciclovir 150 mg in 140 ml 5% glucose to run over 4 hours. How many dpm are delivered if a macro-drip is used?

18 Your patient is receiving 500 mg pethidine in 500 ml 5% glucose. The dose ordered is 15 ml/h. How many milligrams per hour correspond to this dose?

19 A morphine infusion needs to be made up, consisting of morphine 50 mg in 500 ml 5% glucose. If 30 mg/ml ampoules of morphine are available, how many millilitres will be required?

20 Your 78-kg female patient with cardiac failure has a dobutamine infusion consisting of 400 mg dobutamine in 100 ml 5% glucose, running at 12 ml/h. How many micrograms per kilogram per minute is she receiving?

21 Your patient is receiving an adrenaline infusion consisting of 2 mg adrenaline in 100 ml 5% glucose, running at 10 ml/h. How many milligrams per minute are delivered? Following a drop in blood pressure to 80/50 mmHg, the dose is increased to 15 ml/h. How many micrograms per minute are now delivered?

22 Your asthmatic patient weighing 60 kg is receiving an aminophylline infusion consisting of 1 g aminophylline in 1000 ml 5% glucose. If the ordered dose is 4 ml/h, to how many milligrams per hour does this correspond? To how many milligrams per kilogram per hour does this correspond?

23 Total parenteral nutrition (TPN) is ordered for your patient, who has been nil orally for 5 days. The 1-l bag needs to be infused over 24 hours. How many millilitres per hour are set on the volumetric pump? To how many dpm does this correspond if a macro-drip is used?

24 Your patient is ordered 400 ml whole blood to be run over 3 hours. To how many dpm does this correspond if a macro-drip is used?

25 A 3-year-old child weighing 14 kg is ordered ampicillin IV 6 hourly for a mild respiratory infection. What is the maximum amount that can be given safely? The dose range of ampicillin for a mild infection is 15–25 mg/kg/dose 6 hourly.

26 A 6-month-old baby weighing 7 kg is ordered digoxin IV as a stat dose. What amount can be given safely as an initial dose? The initial recommended dose of digoxin is 15 μg/kg stat. Digoxin is available as a 50 μg/2 ml ampoule. How many millilitres would need to be given?

27 A 12-year-old child weighing 39 kg is ordered metronidazole at a maintenance IV 8-hourly dose for the treatment of gastroenteritis. The recommended maintenance dose of metronidazole is 7.5 mg/kg/dose 8 hourly. What dose can be given safely? Metronidazole comes prepared as an infusion consisting of 500 mg in 100 ml. How many millilitres of this preparation need to be administered?

28 How much morphine (in milligrams) would need to be added to 50 ml 5% glucose for the purpose of an infusion used on a 14-year-old child weighing 50 kg? The recommended dose for a morphine infusion is 0.5 mg/kg in 50 ml 5% glucose. How much morphine (in millilitres) is required if 10 mg/ml ampoules are used?

29 An adult has been ordered intravenous gentamicin 140 mg to be infused over 30 minutes. The antibiotic is administered in 50 ml 5% glucose. To how many dpm does this correspond if a macro-drip is used?

30 A female patient with a lung abscess has been ordered intravenous metronidazole 500 mg to be given over 30 minutes. Metronidazole 500 mg comes in a 100-ml infusion bag. To how many dpm does this correspond if a macro-drip is used?

31 A male patient with severe sepsis has been ordered ciprofloxacin 300 mg to be administered 12-hourly, intravenously. The ciprofloxacin is to be administered in 80 ml 5% glucose and given over 30 minutes. To how many dpm does this correspond if a micro-drip is used?

32 A 6-year-old child is ordered oral cetirizine 5 mg to be administered for severe allergic rhinitis. Cetirizine is available as a 1 mg/1 ml solution. What volume of the solution is required?

33 A 35-year-old female patient who suffers from severe migraines is ordered sumatriptan succinate 15 mg to be given intranasally via one nostril. Sumatriptan is available as a 10 mg/0.1 ml nasal spray. What volume of the nasal spray is required?

34 A 42-year-old patient with a lung infection is ordered ceftriaxone sodium 1 g to be administered over 4 minutes. The dose is diluted with 10 ml sterile water for injection. What volume is administered each minute?

35 A 55-year-old male patient with a serious respiratory infection is ordered 2 g intravenous ceftazidime pentahydrate. It is dissolved in 50 ml diluent and infused over 30 minutes. To how many dpm does this correspond if a macro-drip is used?

36 A 22-year-old woman with a severe urinary tract infection is ordered 2 g intravenous cefotetan disodium. It is administered in a solution of 20 ml sterile water for injection over 5 minutes. What volume is administered each minute?

37 A 49-year-old female patient with severe pyelonephritis is ordered 1 g intravenous cefepime hydrochloride. After reconstitution and dilution to 50 ml, this is administered over 40 minutes. To how many dpm does this correspond if a macro-drip is used?

38 A 20-year-old male patient with a serious bacterial infection is ordered intravenous Tazocin™ (piperacillin sodium 2 g and tazobactam sodium 0.25 g) to be administered. The vial is reconstituted with sterile water for injection and diluted further to a final volume of 60 ml before the medication is infused over 30 minutes. To how many dpm does this correspond if a macro-drip is used?

39 A 64-year-old male patient is ordered piperacillin sodium 2 g to be administered prophylactically before surgery. After reconstitution with sterile water for injection, and further dilution to a final volume of 50 ml 5% glucose, it is administered over 50 minutes. To how many dpm does this correspond if a macro-drip is used?

40 A 12-year-old boy is ordered 375 mg phenoxymethylpenicillin benzathine to be administered 6-hourly. You have an oral suspension available, which contains 125 mg/5 ml phenoxymethylpenicillin benzathine. What volume is required in order to deliver the dose?

41 A 56-year-old woman with a systemic staphylococcal infection is ordered dicloxacillin sodium 500 mg. Following reconstitution with sterile water for injection and further dilution to a final volume of 100 ml 5% glucose, it is administered over 1 hour. To how many dpm does this correspond if a macro-drip is used?

42 A 55-year-old female patient with oesophageal candidiasis is ordered 100 mg itraconazole to be swished around the mouth and swallowed twice daily. You have available an oral solution comprising 10 mg/ml itraconazole. What volume is administered?

43 A 77-year-old male patient with Paget's disease of the bone is ordered salcatonin 90 IU daily by subcutaneous injection. You have available 100 IU/1 ml ampoules. What volume is administered?

44 A 56-year-old female patient with hypertension is ordered 12.5 mg oral chlorthalidone. You have available 25-mg tablets. How many tablets are administered?

45 A 67-year-old man with severe oedema is ordered 200 mg oral ethacrynic acid. You have available 50-mg tablets. How many tablets are administered?

46 A 10-year-old boy with asthma is ordered budesonide 200 μg in each nostril by a metered-dose nasal spray. You have available a nasal spray containing 50 μg per metered-dose spray. How many times is the nozzle pressed in order to deliver the required dose to each nostril?

47 A 57-year-old male patient with hypoprothrombinaemia is ordered phytomenadione 6 mg to be administered subcutaneously. You have available ampoules containing 10 mg/1 ml phytomenadione. What volume is administered?

48 A 60-year-old male patient receiving total parenteral nutrition is ordered intravenous zinc 4 mg to prevent zinc deficiency. You have available 5 mg/4 ml ampoules. What volume is required in order to deliver the ordered dose?

Note: More exercises in drug calculations can be found on the *Fundamentals of Pharmacology* website at www.pearsoned.co.uk/galbraith.

ANSWERS

1 0.5 tablet
2 2 × 40-mg tablets, 1 × 20-mg tablet
3 2 units/h
4 30 ml/h
5 (a) 1000 units/h
(b) 1400 units/h
(c) 7 dpm
6 (a) 6 mmol/h
(b) 4 ml
7 (a) 3 ml
(b) 20 dpm
8 (a) 14 dpm
(b) 17 dpm
9 (a) 33 dpm
(b) 111 dpm
10 33 dpm
11 2.5 ml/h
12 3.5 ml/h
13 53 dpm
14 (a) 2.5 ml
(b) 50 dpm
15 250 dpm
16 44 dpm
17 12 dpm
18 15 mg/h
19 1.7 ml
20 10.3 mg/kg/min
21 (a) 3.3 μg/min
(b) 5 μg/min
22 (a) 4 mg/h
(b) 0.07 mg/kg/h
23 (a) 42 ml/h
(b) 14 dpm
24 44 dpm
25 350 mg
26 (a) 105 μg
(b) 4.2 ml
27 (a) 292.5 mg
(b) 58.5 ml
28 (a) 25 mg
(b) 2.5 ml
29 33 dpm
30 67 dpm
31 160 dpm
32 5 ml
33 0.15 ml
34 2.5 ml
35 33 dpm
36 4 ml
37 25 dpm
38 40 dpm
39 20 dpm
40 15 ml
41 33 dpm
42 10 ml
43 0.9 ml
44 0.5 tablet
45 4 tablets
46 4 times
47 0.6 ml
48 3.2 ml

APPENDIX E: COMMON SYMBOLS USED IN MEDICATION CHARTS

Symbol	Meaning
1/24	Administer hourly.
2/24	Administer every 2 hours.
3/24, etc.	Administer every 3 hours, etc.
	Administer one item of medication (e.g. administer one tablet of the medication).
	Administer two items of medication.
	Administer three items of medication.
	Administer four items of medication.
U, u or units	This refers to the measure of mass of certain biological products measured by units rather than the kilogram base (e.g. 10 U Actrapid means that 10 units of Actrapid have been ordered and are to be administered).

APPENDIX F: COMMON WORD MIX-UPS

Drug name 1	Drug name 2
Aldactone (potassium-sparing diuretic)	Aldomet (centrally acting antihypertensive)
amiloride (potassium-sparing diuretic)	amlodipine (calcium channel antagonist)
Becotide (corticosteroid)	Betaloc (cardioselective β_1-blocker)
carbamazepine (anticonvulsant)	Carbimazole (antithyroid)
chlorpropamide (antidiabetic)	chlorpromazine (antipsychotic)
clomipramine (tricyclic antidepressant)	clomiphene (ovulatory stimulant)
Daonil (oral hypoglycaemic)	Deseril (ergot alkaloid derivative, antimigraine)
Estraderm (oestrogen)	Estrapak (mixed hormones)
Feldene (non-steroidal anti-inflammatory drug (NSAID))	Teldane (antihistamine)
Gopten (angiotensin-converting enzyme (ACE) inhibitor)	Capoten (angiotensin-converting enzyme (ACE) inhibitor)
Imdur (nitrate vasodilator)	Imuran (immunosuppressant)
Lamictal (anticonvulsant)	Lamisil (antifungal)
Lasix (loop diuretic)	Losec (proton pump inhibitor)
Losec (proton pump inhibitor)	Zocor (HMG-CoA reductase inhibitor, antihyperlipidaemic)
Maxolon (antiemetic)	Mogadon (benzodiazepine hypnotic)
prednisone (corticosteroid)	prednisolone (corticosteroid)
prochlorperazine (antiemetic)	procyclidine (antiparkinson antimuscarinic)
quinine (antimalarial, muscle relaxant)	quinidine (antidysrhythmic)
thiamine (vitamin supplement)	thyroxine (thyroid hormone)
thioridazine (phenothiazine antipsychotic)	thyroxine (thyroid hormone)
Tofranil (tricyclic antidepressant)	Tryptanol (tricyclic antidepressant)
vitamin K (vitamin supplement)	potassium preparations (the chemical symbol for potassium is K) (electrolyte supplement)
Zocor (HMG-CoA reductase inhibitor, antihyperlipidaemic)	Zestril (angiotensin-converting enzyme (ACE inhibitor))

Note: In this table, generic drug names are indicated by a lower-case initial, while proprietary names are indicated by an upper-case initial. The drug group is indicated in parentheses.

APPENDIX G: DRUG–HERB INTERACTIONS

Herbal medicine	Drug interaction
Agrimony	Insulin ↓
Alfalfa	Warfarin ↑
Betel nut	Phenothiazines ↓
Bilberry	Insulin ↓
Black pepper	Phenytoin, propranolol, theophylline ↑
Buckthorn	Cardiac glycosides ↑
Burdock	Insulin ↑
Calendula	Sedatives ↑
Cayenne pepper	Theophylline ↑
	Angiotensin-converting enzyme (ACE) inhibitor cough ↑
Chamomile	Hypnotics ↑
Chaste tree	Oral contraceptives ↓
Eucalyptus	Amphetamines ↓
Fenugreek	Insulin ↓
Flax	Intestinal absorption ↓
Garlic	Insulin, warfarin ↑
Ginger	Intestinal absorption ↑
Ginkgo	Monoamine oxidase inhibitors (MAOIs), aspirin ↑
Ginseng	Monoamine oxidase inhibitors (MAOIs) manic effect
	Insulin ↑
	Warfarin ↓
Guar gum	Insulin ↓
	Intestinal absorption ↓
Guarana (contains caffeine)	Stimulant activity ↑
	Sedative activity ↓
Hawthorn	Digoxin ↑
Hops	Sedative drugs ↑
Horse chestnut	Warfarin ↓

Herbal medicine	Drug interaction
Horsetail	Digoxin ↑, thiamine ↓
Kava	Sedatives ↑, levodopa ↓
Liquorice	Digoxin, diuretics, corticosteroids ↑
Lupin	Insulin ↓
Milk thistle	Potentiates the action of cisplatin
Nutmeg	Monoamine oxidase inhibitors (MAOIs) ↑
Papain	Warfarin ↑
Passion flower	Sedatives ↑
Rhubarb	Digoxin ↑
St John's wort	Numerous, as it is a potent inhibitor of the cytochrome P450 system (see Chapter 65)
Sassafras	Sedatives ↑
Scotch broom	Monoamine oxidase inhibitors (MAOIs) ↑
Skullcap	Sedatives ↑
Solomon's seal	Insulin ↓
Stinging nettle	Diclofenac ↑ (and perhaps other non-steroidal anti-inflammatory drugs (NSAIDs)
Sweet clover	Salicylates ↑
Valerian	Sedatives ↑

↑, activity increased; ↓, activity decreased.

The following herbal preparations can reduce thyroid function:

- black mustard;
- horseradish.

GLOSSARY

Absorption Process by which a drug enters the blood circulation.

Achlorhydria Lack of hydrochloric acid in the stomach.

Acid-fast Describes the staining characteristics of certain bacteria (e.g. those that cause tuberculosis). When the organism is stained under defined conditions with a red dye, the stain is stable to acid washing.

Acid-labile Describes a drug that is destroyed by acid.

Acid-stable Describes a drug that is unaffected by acid.

Acromegaly Disease caused by excessive production of growth hormone in adults, manifested particularly by large hands and jaws.

Action potential Voltage change that occurs inside a cell (usually a nerve or muscle cell) when it is depolarised due to an interchange of ions between the cell cytoplasm and the extracellular fluid.

Addiction Dependency on a drug, which can be either physical or psychological.

Addison's disease Condition characterised by a lack of hormones being secreted from the adrenal cortex.

Adjunct Drug used in a combination of remedies and that may help in the total therapeutic effect.

Adrenergic Describes a receptor with an affinity for noradrenaline or adrenaline, or a nerve that releases noradrenaline.

Adrenoreceptor See Adrenergic.

Adsorbent Describes a substance that can attach molecules to its surface.

Adverse drug reaction Usually describes an undesirable drug action that can occur in the body and that is often harmful.

Aerosol Colloidal suspension of small particles in a gas.

Affinity Attraction of a receptor for an agonist or antagonist. Also describes the attraction of an enzyme for a substrate.

Agonist Describes a drug or naturally occurring substance that stimulates a receptor.

Agranulocytosis Lack or absence of granular leucocytes (eosinophils, neutrophils, basophils) in the bone marrow and/or the blood. Potentially fatal condition.

Akathisia Pathological restlessness (the subject cannot sit still and continually moves the limbs).

Akinesia Loss of voluntary movement, as can occur in paralysis and in Parkinson's disease, where there is movement but the patient has little control over it.

Alkaliniser Drug that raises the pH of body fluids, usually the urine.

Alkaloid Drug derived from a plant source.

Alkylating agent Anticancer drug that chemically combines with DNA or RNA molecules, thus altering their structure and rendering them biochemically abnormal and inactive.

Allergy Hypersensitivity reaction in which the body's immune system overreacts to innocuous antigens known as allergens.

Alopecia Pathological loss of hair.

Alpha receptor Adrenergic receptor with which only certain adrenergic drugs interact. There are at least two types: α_1, which are postsynaptic, and α_2, which are mainly presynaptic. See also Beta receptor.

Amenorrhoea Cessation of menstruation, which can be primary or secondary. In primary amenorrhoea, menstruation never commences. Secondary amenorrhoea is the cessation of menstruation after the menarche; it could be due to pregnancy, but the term is usually used in abnormal situations.

Amines Organic compounds having an $-NH_2$ group. They can be considered to be derivatives of ammonia.

Amphipathic Having both polar and non-polar groups, thus having both lipophilic and hydrophilic properties.

Anabolic agent Drug that promotes anabolism, used in debilitating states but often abused by sportspeople wanting to increase muscle mass.

Anabolism Synthetic reactions in which simple molecules are converted into complex molecules (e.g. amino acids transformed into proteins).

Anaemia Lack or deficiency of blood cells, usually erythrocytes.

Anaesthetic Drug that promotes unconsciousness and/or insensitivity to pain. General anaesthetics can promote both, but always induce unconsciousness. Local anaesthetics promote insensitivity to pain at the site of administration; if given at sites near major nerves, areas distal to the site of application will be anaesthetised.

Analgesic Drug that promotes a decrease in or cessation of pain.

Analogue Drug that has a similar chemical structure, and usually a similar action, to another.

Anaphylaxis Hypersensitive allergic reaction accompanied by the release of autacoids, such as histamine. If anaphylaxis is local, itching or swelling of the affected part and a sensation of warmth usually result. If it is systemic, there is severe hypotension and bronchoconstriction, which can result in death very quickly; this is a medical emergency.

Angina pectoris Pain in the chest due to lack of blood being supplied to the heart muscle (myocardial ischaemia). This is due to a constriction or blockage of the coronary vessels.

Angioplasty Reconstruction of diseased blood vessels.

Anhidrosis Inability to sweat.

Ankylosing spondylitis Inflammatory condition in which the spinal ligaments ossify, causing abnormal mobility and back pain.

Anoxia Lack of oxygen.

Antacid Drug that neutralises acids, particularly gastric acid.

Antagonist Drug that is attracted to but does not activate a receptor. Sometimes, the word 'blocker' is used to describe such a drug.

Anterograde amnesia Inability to remember events after a drug has been given.

Antianaemic agent Drug used to treat or prevent anaemia.

Antiangina agent Drug used to prevent the onset or treat the pain of angina pectoris.

Antiarrhythmic See Antidysrhythmic.

Antibiotic Drug historically produced from a microorganism that either inhibits the growth of or kills other microorganisms. Today, perhaps wrongly, the term is used to describe most antimicrobial drugs.

Antibiotic-associated colitis Inflammatory infection of the colon due to an opportunistic infection, usually following broad-spectrum antibiotic treatment.

Anticholinergic Any drug that antagonises the action of acetylcholine, usually at an acetylcholine receptor. The term is usually applied to drugs that are specific for muscarinic rather than nicotinic receptors; therefore, the term 'antimuscarinic' is more correct.

Anticholinesterases Drugs that inhibit the enzyme acetylcholinesterase. They are either competitive or non-competitive. Many insecticides are non-competitive anticholinesterases.

Anticoagulant Any substance that prevents blood from clotting.

Anticonvulsant Drug used to stop convulsions or seizures. As not all seizures involve convulsions, the term 'antiseizure drug' is preferred.

Antidepressant Drug used to treat endogenous depression.

Antidote An agent given specifically to counteract a poison or drug.

Antidysrhythmic Drug used to treat dysrhythmia.

Antiemetic Drug that suppresses or stops vomiting.

Antigen Substance that promotes an immune response by causing B-lymphocytes to produce antibodies.

Antihistamine Drug that antagonises the action of histamine, usually at the H_1 receptors.

Antihypertensive agent Drug used to prevent or treat hypertension.

Antimicrobial Drug that either inhibits the growth of, or kills, microorganisms. See also Antibiotic.

Antipsychotic Drug used to treat psychoses. Sometimes termed neuroleptics and major tranquillisers.

Antipyretic Drug used to treat fever or high body temperature.

Antiseptic Antibacterial substance applied topically. Antiseptics are never applied systemically, although some antiseptics taken internally are excreted from the kidneys so quickly that they are called urinary antiseptics. Due to rapid excretion, the internal environment is not harmed.

Antispasmodic Drug that stops or prevents smooth-muscle spasm, especially in the intestine but also in the bladder and uterus. Usually antimuscarinic drugs.

Antitussive Drug used to suppress cough.

Antiulcerant Drug used to treat ulcers, normally of the stomach and duodenum.

Antivenom Antibody to a venom used to treat snake, spider and other animal bites. Sometimes called antivenene.

Anuria Cessation of urine production.

Anxiolytic Drug used to treat anxiety. Sometimes referred to as a sedative or minor tranquilliser.

Aperient Laxative.

Aplastic anaemia Lack of all blood cells, usually due to bone-marrow suppression. Usually fatal.

Arrhythmia Common synonym for dysrhythmia. The term is used wrongly, however, as it literally means absence of beat (i.e. the heart has stopped). See also Dysrhythmia.

Arthralgia Joint pain.

Ascites Abnormal accumulation of fluid in the abdomen.

Asepsis Condition of being free from microorganisms.

Asthenia Loss of muscular strength.

Asystole No contraction of the heart muscle. When the heart is stopped, it is in asystole.

Ataxia Staggering gait due to a cerebellar or spinal cord lesion.

Atheroma Accumulation of fatty substances, usually cholesterol, in the arteries. Also called plaque.

Atherosclerosis Condition of having pathological amounts of atheroma.

Atopic Having a tendency towards allergies.

Autacoid Substance rather like a hormone that is produced by the body. Although autacoids can be transported by the blood, they usually act locally. The action of an autacoid is like that of a drug.

Autonomic tone Normal functioning of the autonomic nervous system (i.e. the neural conduction in the autonomic nervous system when the body is at rest).

Bactericidal Having the ability to kill bacteria.

Bacteriostatic Having the ability to suppress growth of bacteria.

Ballism Jerking and/or twisting type movements.

Beta-blocker Drug that is antagonistic at β receptors.

Beta-lactamases Enzymes produced by some microorganisms that can destroy some penicillins.

Beta receptor Subtype of adrenergic receptor. There are at least two types of β receptor: β_1 and β_2. Some drugs are non-selective, as they can act on more than one β receptor, while some are specific for one type of β receptor.

Bimodal distribution Distribution represented graphically as two peaks.

Bioavailability Amount of an administered drug that is actually available to produce a therapeutic effect (e.g. not all of a tablet may be absorbed).

Bioequivalence A drug is bioequivalent to another drug when they are absorbed and act in the same way following administration. This issue becomes important when considering different brands of a generic drug.

Biotechnology Science of the use of living organisms to produce drugs. The term is not restricted to drugs.

Biphasic As applied to oral contraceptives, having two different doses of hormones in order to try to mimic the normal hormonal fluctuations that occur during the menstrual cycle.

Blockers Drugs that prevent the stimulation of receptors. They can either be antagonists or act by suppressing transmission along a nerve.

Blood–brain barrier Part of the meningeal membranes and capillaries that prevents the entry of many poisons and drugs into the brain.

Blood dyscrasia Any abnormality in blood cells.

Borborygmi Bowel sounds.

Bradycardia Slow pulse or heart beat.

Bradykinesia Slowness of gait.

Brand name Trade or proprietary name given to a drug by its manufacturer.

Broad-spectrum antibiotic Antibiotic that can affect many different families of microorganisms.

Buccal Pertaining to the inner surface of the cheeks.

Bulla Blister.

Candidiasis Fungal (yeast) infection caused by *Candida albicans*.

Carcinogen Cancer-producing substance.

Cardioselective Describes a beta-blocker that acts mainly on the β_1 receptors of the heart.

Cardioversion Use of electrical energy to revert cardiac dysrhythmias other than ventricular fibrillation. It is usually employed in patients with tachyarrhythmias resistant to drug therapy. The electric energy or shock is delivered synchronised to the R wave of the electrocardiogram (ECG). This minimises the likelihood of precipitating ventricular fibrillation during the vulnerable period of the ventricle.

Caseous Literally, cheesy. In pathology, the term refers to necrotic lipids and proteins.

Catalyst Chemical (in pharmacology, usually an enzyme) that speeds up the rate of a reaction without itself being changed.

Catecholamines Group of structurally related substances that have sympathomimetic action. Dopamine, noradrenaline and adrenaline are naturally occurring catecholamines.

Catechol-O-methyltransferase (COMT) Enzyme involved in the catabolism of catecholamines.

Cathartic Powerful laxative.

Cerebrospinal fluid Fluid present inside the ventricles of the brain and in the spinal canal. Similar to plasma but less complex in its constituents.

Cheilosis Inflammation of the lips.

Chelating agent Chemical that binds to metallic ions, rendering them inactive.

Chemical name Name given to a drug that accurately describes its chemical structure.

Chemoreceptor trigger zone (CTZ) Part of the brain that responds to certain chemicals, including some drugs in the blood, and induces vomiting.

Chemotactic factor Chemical released by a cell that attracts a motile cell, such as a neutrophil or macrophage.

Chemotherapy Drug treatment of tumours and infections.

Cholecystitis Inflammation of the gall bladder.

Cholelithiasis Condition of having gall stones.

Cholestasis Blockage of the bile duct.

Cholinergic Describes a receptor that has an affinity for acetylcholine, or a nerve that releases acetylcholine.

Cholinesterase Enzyme that breaks down acetylcholine, especially at synapses.

Cholinolytic Drug that antagonises acetylcholine.

Cholinomimetic Drug that mimics acetylcholine.

Choreas Group of diseases that have as one of their characteristics irregular and involuntary movements of the limbs and face.

Chronotropic Having the property of altering the heart rate.

Cinchonism Symptoms of quinine overdose, including tinnitus, rash, nausea, mental and cardiac disturbances, and circulatory or respiratory failure.

Circadian rhythm Daily body rhythm (e.g. cholesterol is metabolised mainly at night, growth hormone is secreted mainly at night).

Cirrhosis Fatty degeneration of the liver, often caused by excessive alcohol consumption.

Coenzyme Chemical that is necessary in order for an enzyme to carry out its function. Unlike enzymes, coenzymes are chemically changed during an enzymatic reaction but are usually regenerated for further use.

Colic Spasmodic pain caused by abnormal smooth-muscle contraction (e.g. renal colic caused by the smooth muscle of the ureter trying to expel a kidney stone).

Colitis Inflammation of the colon.

Colloid Colloid fluids contain high-molecular-weight particles, which create an increased capillary osmotic pressure, pulling water from the interstitial compartment to the intravascular compartment. These fluids are also called plasma expanders because of their ability to create a large pulling force in moving water from the interstitial compartment to the intravascular compartment. Examples include Haemaccel™, albumin, dextran 40, dextran 70 and stable plasma protein solution. Their advantage over crystalloid solutions is that less volume is needed for administration, as colloids tend to remain in the intravascular compartment.

Complementary therapy Any therapy, pharmacological or non-pharmacological, that is not considered to be a part of conventional Western medical practices.

Compliance Taking a drug or following a treatment regime as instructed.

Computed tomography (CT) Radiographic procedure used to obtain X-ray pictures of sections or layers of the body.

Congener Natural substance that develops during fermentation and that gives distinctive character to beers, wines and spirits.

Conjugation Literally, joining together. Used to describe the combination of a drug with an acid in drug metabolism.

Conjunctivitis Inflammation of the conjunctiva of the eye, usually caused by a bacterial infection, especially *Staphylococcus aureus*, or 'golden staph'. Sometimes called pink eye.

Contraceptive Drug used to prevent conception.

Contraindication Reason for not administering a drug.

Corticosteroids A general name applied to most of the steroid hormones produced by the adrenal cortex. Adrenal sex hormones, although steroids, are not described by this term.

Crohn's disease Chronic inflammatory condition of the colon and/or ileum.

Cross-reactivity Term used in immunology to describe the action of an antibody with a substance that is not its specific antigen.

Crystalloid Intravenous fluid containing low-molecular-weight particles, such as ions. Examples include 0.9% normal saline, Hartmann's solution and 5% glucose. Glucose is not an electrolyte but is still classified as a crystalloid. The advantage of crystalloids over colloid fluids is that the former distribute rapidly throughout the extracellular compartment and can improve capillary perfusion by decreasing blood viscosity.

Culture and sensitivity A swab or sample is taken of a particular body part. This specimen is then placed in an area that is conducive to the growth of microorganisms. Various antimicrobial agents are placed on this specimen; if microorganisms grow, an analysis can be made of the effectiveness of particular agents to inhibit microbial growth.

Cycloplegic Drug that paralyses (relaxes) the ciliary bodies of the eye and allows the lens to thicken. Used in cataract surgery to make the removal of the lens easier.

Cysticercosis Infiltration of tapeworm larvae into tissues.

Cystic fibrosis Inherited disorder in which a thick mucus is produced, especially in the gut and respiratory tract.

Cystitis Inflammation of the urinary bladder.

Cytochrome P450 Group of enzymes, found mainly in the liver, which are involved in phase I of drug metabolism.

Cytokines Chemicals produced from immunocompetent cells that can affect other cells in the immune system.

Cytoplasm Fluid inside a cell.

Cytotoxic Drug used in the chemotherapy of cancer that kills cells.

Decongestant Drug used to relieve nasal congestion (stuffy nose).

Decubitus ulcer Ulcer caused by pressure.

Defibrillation Application of sufficient electrical energy (or shock) to the heart in ventricular fibrillation in order to depolarise enough myocardial cells simultaneously to allow a stable rhythm to be re-established. Direct current (DC) rather than alternating current (AC) energy is used as the former is more efficient and causes less myocardial damage. In contrast with cardioversion, this energy is not synchronised with the R wave of the electrocardiogram (ECG).

Dehiscence Gaping of the edges of a wound.

Dementia Mental disorder affecting mainly intellectual and cognitive functions.

Demulcent Soothing substance that coats and protects mucous membranes.

Dependence See Addiction.

Depot injection Injection, usually into the muscle, that releases the drug slowly into the circulation.

Depression State of mind in which there is a feeling of hopelessness and, in severe cases, thoughts of suicide. Reactive depression is triggered by external events and is usually short-lived, whereas endogenous depression often has no apparent cause and generally needs drug therapy.

Dermatitis Inflammation of the skin; eczema.

Desensitisation Use of allergens in small amounts over a period of time in order to try to suppress the allergic response.

Detoxification Lessening of the toxic effects of a drug or poison.

Dextrose Out-of-date name given to naturally occurring glucose, named for its three-dimensional structure; *dexter* is Latin for 'right'. A form of fructose found in some microorganisms is termed laevulose; Latin *laevus* means 'left'.

Diabetic neuropathy Degeneration of nerves, especially in the lower limbs of people with diabetes, which can cause pain and abnormal reflexes.

Diffusion Random movement of molecules from areas of high concentration to areas of low concentration.

Digitisation Initialisation of treatment with the drug digitalis until a clinical response is obtained.

Dilation Widening. Also written 'dilatation'.

Diplopia Double vision.

Disinfectant Substance used to kill or suppress the growth of microorganisms on non-living surfaces, such as hospital trolleys (cf. Antiseptic).

Distribution Process by which a drug passes from the circulation of blood and lymphatic systems across the cell membranes to a specified tissue.

Disulfiram(-like) reaction Adverse reaction that results when alcohol is taken with the drug disulfiram and also some other unrelated drugs, such as metronidazole.

Diuresis Formation of urine.

Diuretic Drug that increases urine formation.

Diverticulosis Formation of pouches in the wall of the colon.

Dopaminergic Acting like dopamine; describes a nerve that releases dopamine.

Dragee Sugar-coated tablet.

Dulcet Sweet-tasting tablet for chewing.

Durule Type of sustained-release tablet.

Dyskinesia Impairment of voluntary movement.

Dysmenorrhoea Painful or uncomfortable episodes of menstruation.

Dyspepsia Indigestion.

Dysphagia Difficulty in eating and/or swallowing.

Dyspnoea Difficulty in breathing.

Dysrhythmia Abnormal heart rhythm. See also Arrhythmia.

Dystocia Difficulty in childbirth.

Dystonia Abnormal tonicity or tension of skeletal muscles.

Dysuria Painful or burning sensation during micturition.

Effector Body structure, such as a gland or muscle, activated by the nervous or endocrine system.

Efficacy Effectiveness of a drug in causing a response.

Efflux Outward flow of a substance.

Eicosanoid Compound derived from the polyunsaturated fatty acid eicosapentanoic acid (which can be made from the essential fatty acid linoleic acid), such as the prostaglandins.

Elimination Process of ridding the body of a particular compound.

Elixir Pleasant-tasting liquid medicine containing alcohol and/or glycerol and/or a sweet syrup to mask the taste of the active ingredient.

Embolus Something that travels from one point of the body and can eventually block a blood vessel (e.g. a blood clot, fat or air).

Emesis Vomiting.

Emetic Drug that induces vomiting.

Emphysema Loss of elasticity in the lungs causing dilation of the alveoli, with the concomitant difficulty in getting enough oxygen to the body.

Endemic Describes a disease localised to a specific area, country or continent.

Endocrinology Study of the endocrine glands.

Endogenous Arising from within the body.

Endogenous opioid Naturally occurring substance within the central nervous system that has morphine-like activity (e.g. endorphins).

Endomorph Person with a soft round build of body and a high proportion of fat tissue.

Enema Solution of a medication administered rectally.

Enteral route By mouth or orally.

Enteric coat Coating on a tablet that is insoluble in stomach acid. Tablets with such coatings should not be crushed.

Enterohepatic cycle Excretion of compounds from the bile duct and their subsequent reabsorption in the intestine. The compounds can then be recycled back to the intestine (e.g. bile salts).

Envenomation Process whereby the venom of a poisonous creature such as a snake or spider is delivered into the body by a bite from that creature.

Enzyme Protein catalyst responsible for most metabolic processes.

Epidural Above the dura mater.

Epistaxis Bleeding from the nose.

Erythema Reddening of the skin.

Erythema nodusum leprosum Hypersensitivity reaction occurring in leprosy with the appearance of reddened, tender, subcutaneous nodules, often on the shins.

Eukaryote Cell with a well-defined nucleus. All animal cells are eukaryotic.

Euthanasia Mercy killing; administration of drugs to cause death in cases of terminal illness.

Excipient Inert binding material added to drug formulations.

Excoriation Breaking away of surface tissues, as can happen with continual scratching of the skin.

Expectorant Drug that promotes the expulsion of mucus and other secretions from the respiratory tract.

Extrapyramidal symptoms Involuntary muscle movements caused by some drugs that block neural signals along the extrapyramidal tract.

Extravasation Process of materials exuding from blood vessels.

Extrinsic Describes a stimulus arising from outside the body.

Facies Facial appearance.

Fasciculation Slight twitching of skeletal muscle.

Febrile Feverish.

Fermentation Process of converting organic compounds into simpler substances; used in producing alcohol, food and industrial compounds.

Festination Involuntary acceleration of movement, usually walking.

Fibrillation Rapid, uncoordinated beating of the heart muscle. Usually named after where it occurs (e.g. atrial fibrillation).

Fibrosis Abnormal development of fibrous tissue.

First-pass metabolism Metabolism of a drug during its first pass through the liver. This happens when the drug is absorbed into the hepatic portal system.

Galactorrhoea Abnormal lactation (i.e. lactation not as a result of suckling). Can occur in males.

Ganglionic blocker Drug that antagonises nicotinic receptors on postganglionic neurons.

Gangrene Necrosis of tissues, usually caused by ischaemia.

Gastroenteritis Infection of the gastrointestinal tract causing vomiting and diarrhoea.

Gastroparesis Delayed emptying or hypomotility of the stomach.

Generic name Simplified chemical name or artificial name given to a drug by its original manufacturer.

Gene therapy Changing of somatic genes to effect cures from genetic diseases. The process involves inserting genes into somatic cells by a variety of techniques.

Genetic polymorphism Existence of multiple types of gene in a species (e.g. blue and brown eyes are determined by genetic polymorphism). As a result, the expression of the genetic trait has multiple forms.

Giardiasis Intestinal infection caused by the protozoan *Giardia* spp.

Gingivitis Inflammation of the gums.

Glossitis Inflammation of the tongue.

Gluconeogenesis Formation of glucose from non-carbohydrate sources.

Glycogenolysis Breakdown or catabolism of glycogen into glucose.

Glycolysis Breakdown of one glucose molecule into two molecules of pyruvic acid.

Glycoprotein Protein containing carbohydrate residues.

Goitre Enlargement of the thyroid gland.

Gout Very painful inflammatory condition of joints due to deposits of uric acid.

Granulocytopenia See Agranulocytosis.

Granuloma Tumour of granulation tissue.

Gynaecomastia Excessive mammary gland development in males.

Halitosis Bad breath.

Haematemesis Vomiting of blood.

Haematoma Accumulation of blood within a tissue resulting from internal haemorrhage.

Haematuria Presence of blood in urine.

Haemodialysis Treatment involving the removal of certain elements from the blood by passing it through a dialysis medium. A means to restore the correct balance of fluid and electrolytes within plasma.

Haemolysis Rupturing of erythrocytes, resulting in the release of haemoglobin into plasma.

Haemoperfusion Passing of a poisoned person's blood through a medium containing adsorbent beads. This process extracts the toxic agents and/or its metabolites from the blood.

Half-life The time taken for half of the initial drug dose to be inactivated and eliminated from the body.

Hapten Substance that, when combined with a protein carrier, elicits an immune response.

Herpes zoster Shingles.

Hirsutism Abnormal hairiness.

Histamine Endogenous chemical involved in inflammation, allergic reactions, equilibrium and gastric acid secretion.

Homeopathic substances Drugs administered in low doses that may relieve a particular condition but that produce symptoms of the condition when given to healthy people in high doses.

Hydrolysis Breakdown of a compound by the addition of water.

Hydrophilic Able to readily interact with water; soluble in water.

Hydrophobic Averse to interacting with water; insoluble in water.

Hygroscopic Able to take up and retain moisture.

Hyperalgesia Exaggerated pain sensitivity.

Hypertension Abnormally high blood pressure.

Hypertensive crisis Medical emergency characterised by rapid development of a hypertensive state and severe headache. Can occur in patients receiving monoamine oxidase inhibitors after systemic absorption of tyramine-rich foods.

Hypertonic Solution with a relatively high total concentration with solutes compared with another solution.

Hypnotic Drug that induces sleep.

Hypoglycaemic agent Drug that reduces blood glucose levels.

Hypokinesia Partial paralysis.

Hypotension Abnormally low blood pressure.

Hypotonic Solution with a relatively low total concentration of solutes compared with another solution.

Iatrogenic Causation of illness by medical or surgical procedures.

Idiopathic Describing a disease of unknown aetiology.

Idiosyncratic effects Adverse reactions that are peculiar to an individual.

Immunocompromised Describes a person with a weakened immune system, often as a result of drug therapy. Cytotoxic drugs and corticosteroids in large or prolonged doses are common culprits. Immunocompromised patients are more susceptible to infections and may die from what is usually a benign infection.

Immunoglobulins Blood-borne secretions from lymphocytes and plasma cells that provide specific immunity; antibodies.

Immunomodulating agent Drug that alters immunity. Immunomodulating agents can be either stimulants or suppressants.

Immunosuppressant Drug that diminishes immune responsiveness.

Inotropic effect Change in the force of contraction of the heart.

Interleukins Group of secretions from leucocytes that enhance immune responsiveness.

Intertriginous Pertaining to areas of skin that can rub together (e.g. between the folds of the breasts, buttocks or between the ear and scalp).

Intestinal hurry Rapid movement of intestinal contents, usually leading to diarrhoea.

Intradermal Route of administration where a drug is injected into the dermis of the skin.

Intrathecal Route of administration where a drug is injected into the cerebrospinal fluid.

Intrinsic Describes a stimulus arising within a part of the body.

In utero Term meaning in the uterus.

In vitro Literally, 'in glass'. Term applied to experiments carried out in the laboratory and that do not involve the use of living organisms but could involve the use of living cells in culture.

In vivo Term applied to experiments carried out on a living organism.

Irrigant Solution that flushes out debris or other material from a tissue.

Ischaemia Abnormal reduction in blood flow to a tissue.

Isoenzymes Multiple forms of an enzyme that catalyse the same reaction.

Isotonic Describes a solution with an equal total concentration of solutes compared with another solution.

Juxtaglomerular apparatus Complex of cells at the point of contact between the afferent arteriole and the ascending loop of Henle. The cells secrete the enzyme renin.

Keratinocyte Cell found in numerous amounts in the epidermis and that produces keratin, a protein that gives skin its waterproof properties.

Keratolytic agent Drug that causes softening or dissolution of the epidermis.

Leukotrienes Group of chemicals secreted by leucocytes that enhance immune responsiveness.

Ligand Substance that binds to a receptor.

Linctus Cough syrup.

Lipophilic Able to readily interact with lipids; lipid-soluble. See also Hydrophobic.

Lipophobic Averse to interacting with lipids; water-soluble. See also Hydrophilic.

Livedo reticularis Reddish-blue mottling of the skin.

Loading dose Priming dose of a drug that will produce therapeutic levels more quickly.

Magnetic resonance imaging (MRI) Non-invasive means of evaluating information about the chemical makeup of tissues, making diagnosis possible. The process uses a large electromagnet to detect radio-frequency pulses from the alignment of hydrogen protons in the magnetic field. A computer picks up the electromagnetic echo and produces tomographic images with high contrast of soft tissue. The process does not visualise bone, and so soft tissues surrounding bone areas are seen easily.

Mania State characterised by increased motor activity, elation, irritability and talkativeness.

Margin of safety Range of blood drug concentrations lower than those that produce toxic effects.

mec Minimum effective concentration of a drug in the blood considered to be therapeutic.

Melaena Passing of dark stools stained with blood or blood pigments.

Menière's disease Disease of unknown aetiology of the labyrinthine apparatus, which can lead to severe dizziness and nausea.

Mesomorph Person with a compact, muscular build of body.

Metabolism Process of transformation of a drug within the body in order to make it more hydrophilic.

Microaerophilic When applied to microorganisms, indicates that they will grow better at very low oxygen tensions.

Microtubules Components of the cytoskeleton involved in cellular division and movement; also provide part of the supporting network that affords a cell its characteristic shape.

Miotic Drug that induces pupil constriction.

Miscible Able to be mixed.

Monoamine oxidase Important enzyme in adrenergic pharmacology involved in the metabolism of the catecholamines and related substances.

Monophasic As applied to oral contraceptives, where the dose of hormones is fixed from days 1 to 21.

Mood stabilisers Group of drugs used in the treatment of affective disorders characterised by changing emotions.

msc Maximum safe concentration of a drug in the blood.

Mucolytic drug Drug that breaks up mucus.

Muscarinic receptors A subpopulation of cholinergic receptors that can be stimulated by the experimental agent muscarine but not by nicotine; located on the surface of all parasympathetic effectors and some sympathetic effectors.

Muscle relaxant Drug that acts to inhibit contraction in skeletal muscles.

Mutagenic Able to induce a mutation.

Myalgia Muscle pain.

Mydriatic Drug that induces pupil dilation.

Myelosuppression Inhibition of blood-cell production, leading to a deficiency of circulating erythrocytes, leucocytes and platelets.

Narcotic Agent that produces insensibility and stupor.

Narrow-spectrum antibiotic Antibiotic effective against a limited number of microbes.

Natural flora Referring to the bacteria that live in symbiosis with humans in the gut and on the skin.

Nebuliser Apparatus used to disperse a drug in water vapour for administration to the respiratory tract. Sometimes called an atomiser.

Nephrotic syndrome Condition of the kidney tubules leading to marked hyperproteinaemia, with concomitant oedema and, often, high blood pressure.

Neuropharmacology Branch of pharmacology dealing with drugs that affect the nervous system.

Neuropeptides Peptides found within the body that act as neurotransmitters.

Neutropenia Abnormally low levels of neutrophils.

Nicotinic receptors Subpopulation of cholinergic receptors that can be stimulated by the experimental agent nicotine but not muscarine; located in the autonomic ganglion on the cell body of postganglionic fibres and in the neuromuscular junction on the surface of skeletal muscles.

Nocturia Frequent urges to urinate during sleeping periods.

Nomenclature Classified system of names.

Non-depolarising Describes a drug that suppresses excitable cells without depolarising them first.

Non-steroidal Describes a substance whose structure is not that of a steroid hormone.

Nosocomial Originating in a hospital.

Oncogenic Related to the induction of cancer.

Opisthotonus Extreme anterior arching of the back that is common in strychnine poisoning and tetanus. The muscle contractions sometimes lead to a spinal fracture. Treatment is to use a neuromuscular blocking agent.

Osmosis Movement of water molecules along a concentration gradient.

Osmotic laxative Drug that increases the osmotic pressure of the intestinal contents, drawing water from in and around intestinal cells back into the faeces.

Osmotic pressure Pressure created by osmosis. If water moves by osmosis into a cell, the pressure will build up within the cell due to the increase in volume. The resultant osmotic pressure can lead to lysis of the cell.

Ototoxicity Toxicity of the eighth cranial nerve or of the organs of hearing and balance.

Over-the-counter (OTC) preparations Therapeutic substances that can be bought without a written prescription.

Oxidation Increase in the positive charge on an atom or molecule.

Palliative care Care of a person with a disease that is unresponsive to treatment. This involves the mitigation or lessening of the symptoms, often of pain, caused by a disease.

Paracrine Describes secretion of a hormone from a source other than an endocrine gland that acts locally.

Paradoxical excitement State in which excitement occurs when decreased activity would be expected.

Paraesthesias Abnormal sensations such as burning, creeping flesh and tingling.

Parasomnias Unusual disorders of sleep, such as teeth-grinding and restless leg syndrome.

Parasympathetic Pertaining to the division of the autonomic nervous system that changes the activity of autonomic effectors towards a resting state; it enhances the processes of digestion and elimination.

Parenteral Describes entry of a substance into the body via a route other than oral.

Partial agonist Drug that has a less-than-perfect fit with a receptor, but enough to activate a small response.

Pathogenic Disease-causing.

Penicillinase Enzyme, also called beta-lactamase, produced by some microbes that can inactivate penicillin beta-lactam antibiotics.

Peptide Short chain of amino acids. Proteins are long chains of amino acids.

Perineurium Connective tissue wrapping around a nerve.

Peritoneal dialysis Form of dialysis used in patients with renal failure. The dialysis takes place within the patient's peritoneal cavity. A catheter is inserted into the abdominal cavity, and dialysing fluid is infused. The fluid dwells in the cavity and is allowed to flow out by gravity into a drainage bag. The dialysis works by the transfer of fluid and solutes from the blood circulation through the peritoneum. Fluid and solutes move from an area of higher concentration in the body to an area of lower concentration.

Pessary Vaginal suppository.

Pharmaceutics Branch of pharmacy that deals with the formulation of pharmacological agents.

Pharmacodynamics Mechanism by which drugs exert their effects on the body.

Pharmacogenetics Study of how genetic factors influence drug action.

Pharmacokinetics Physiological processes that influence drug levels within the body; that is, absorption, distribution, metabolism and elimination.

pKa Ionisation constant of an acid; indicates the pH at which the highest proportion of a water-soluble drug will be in a non-ionised state.

Placebo Pharmacologically inactive substance given to a patient.

Polymerase Enzyme that causes a polymerisation reaction; that is, the linking together of like molecules to form long chains (e.g. nucleotides are polymerised to form nucleic acids).

Polypharmacy Therapy with a number of drugs concurrently.

Porphyria Condition characterised by impaired porphyrin formation and excretion.

Porphyrins Substances that form the basis of the respiratory pigments of animals (e.g. haem) and plants (e.g. chlorophyll).

Post-herpetic Occasional aftermath of shingles or herpes zoster infection, usually classified as post-herpetic pain, which is severe neural pain and can be difficult to treat.

Post-ictal State immediately following a seizure.

Postprandial Occurring after a meal.

Potency Relates to the relative strength of a drug; the ability of a drug to produce the desired therapeutic effect.

Potentiation Drug interaction whereby the effects of two drugs are enhanced.

Prokaryote Cell without a well-defined nucleus, where the chromosomes are distributed diffusely throughout the cytoplasm. Bacteria are prokaryotic.

Prodrug Drug that is converted rapidly into the active therapeutic agent after absorption.

Prophylactic Drug that prevents an illness.

Prototype Original drug of its type after which other agents were developed.

Pseudocholinesterase Form of cholinesterase not specific to acetylcholine found in the plasma. Its function is unclear, but it is important in the metabolism of a group of nicotinic antagonists called depolarising neuromuscular blocking agents.

Pseudotumour cerebri Swelling of the cerebrum that is not due to neoplasia. Literally, means 'false cerebral tumour'. This enlargement has many causes, one being corticosteroid overuse due to fluid retention, and can be detected by the presence of papilloedema.

Psychopharmacology Branch of pharmacology focusing on drugs that affect brain function.

Psychotropic agents Drugs that modify altered brain states.

Purines Collective term for adenine, uracil and guanine, which form part of the structure of DNA and RNA molecules and the energy-storage molecules adenosine triphasphate (ATP) and guanosine triphosphate (GTP).

Receptors Cellular entities found within cells and on cell surfaces that, when stimulated by an endogenous or exogenous chemical, trigger changes in cell activity.

Recombinant DNA Piece of DNA representing a gene removed from one organism and inserted into another so that the gene characteristic will be expressed in the latter.

Regimen Schedule of dosage and frequency of administration.

Restless leg syndrome Condition of unknown aetiology that gives the patient an almost uncontrollable urge to move their legs.

Retrograde amnesia Loss of memory of events immediately preceding a cause. Causes include head injury and some drugs.

Reye's syndrome Rare form of encephalopathy and liver damage that is associated with aspirin therapy.

Rhinyle Flexible tube used to administer a drug intranasally. One end of the rhinyle is inserted into the nostril and the other end in the mouth. The drug solution within the tube is blown into the nasopharyngeal area.

Rostrocaudal Moving in a direction from front to back.

Rubefacient Topical agent that, when rubbed into the skin, stimulates increased blood flow to the area and creates a soothing feeling of warmth.

Second-messenger system Series of intracellular reactions that alter cellular activity triggered by the activation of receptors on the surface of the cell.

Secretagogue Substance that stimulates secretion.

Sedative Drug with calming effects.

Selective toxicity Therapeutic approach that targets known structural and functional differences between normal human cells and other cells that can cause damage (e.g. microbes, cancer cells).

Sequelae Conditions following or caused by an illness.

Singultus Hiccups.

Solute Particles dissolved in solution.

Solvent Dissolving medium.

Spansule Capsule prepared to alter the release of a drug in the gastrointestinal tract.

Spasmolytic agent Drug used to relieve acute or chronic muscular spasms.

Specificity Describes the situation in which a substance has greater affinity for one receptor or enzyme than for another.

Steady state Describes drug levels within the blood reaching a plateau after repeated dosing at fixed intervals.

Stereoisomerism Situation in which two compounds share identical structures but their spatial conformation is different.

Steroid Lipid substance with a chemical structure that contains four carbon rings.

Stevens–Johnson syndrome Severe immunological reaction to some drugs that leads to bullae formation on the skin and mucous membranes. Many other systemic reactions, such as fever, malaise and cough, occur. This condition can be fatal.

Sublingual Route of administration whereby a drug is absorbed into the bloodstream after being placed under the tongue.

Superinfection Infection occurring when the natural flora of the body are displaced by drug treatment, and an opportunistic infection by yeast or bacteria results.

Suppository Drug in solid form for rectal administration; usually torpedo-shaped.

Suspension Preparation in which a relatively insoluble drug is mixed with a liquid or gas; the solid drug particles are suspended in the liquid.

Sustained-release tablet Pharmaceutical preparation in which the drug is released into the gastrointestinal tract over varying lengths of time.

Sympathetic Pertaining to the sympathetic division of the autonomic nervous system. This division changes the activity of autonomic effectors to prepare the body for a stressful situation; 'flight or fight' responses.

Sympatholytics Group of drugs that suppress sympathetic nervous system responses.

Tachydysrhythmia Faster-than-normal cardiac rhythm.

Teratogen Substance that causes birth defects.

Therapeutic agent Substance that produces beneficial clinical responses.

Therapeutic index Objective measure of the safety of a drug obtained experimentally. Calculated as a ratio of the lethal dose required to kill 50 per cent of the animals in the group, LD_{50}, to the dose that produces an effective therapeutic response in 50 per cent of a group of animals, ED_{50}. The therapeutic index (TI) can be expressed more simply as:

$$TI = \frac{LD_{50}}{ED_{50}}$$

Thrombus Intravascular blood clot that can occlude a blood vessel, causing a thrombosis.

Tincture Solution of a drug in alcohol.

Tinnitus Ringing sound in the ear in the absence of auditory stimulation. Can be an indication of cochlear nerve damage.

Titration of dose Administering incremental doses of a drug in order to attain the desired response.

Tocolytic agent Drug that inhibits uterine contractions.

Tolerance State in which a previously effective drug dose no longer produces a therapeutic effect.

Tophi Uric acid crystals that lodge in body tissues (singular: tophus).

Torsade des pointes Life-threatening ventricular tachydysrhythmia.

Total parenteral nutrition (TPN) Form of nutrition that is administered through a large central vein. Used in patients with high energy and nutritional needs. Components incorporated in TPN include 25–50 per cent glucose, amino acids, electrolytes, vitamins and trace elements.

Toxic epidermal necrolysis Severe skin reaction, usually to drugs, in which the skin necrotises. Can be fatal.

Transdermal Route of administration whereby the drug enters the bloodstream through the skin. For this to occur, the drug must be lipophilic.

Triphasic As applied to oral contraceptives, where the treatment period is divided into three phases. The dose of progestin is altered at least once, and sometimes twice. The dose of oestrogen may change once, but it usually remains constant.

Trophic agent Substance that provides nourishment to a body structure.

Tropic agent Substance that stimulates change in the activity of a body structure.

Tuberculin Purified protein derivative derived from *Mycobacterium tuberculosis*. Injected subcutaneously to determine immunity from tuberculosis (TB).

Ultrasound Diagnostic procedure, not unlike an X-ray, that uses sound waves to create a picture of the internal tissues. The principle is based on the fact that tissues of different density absorb sound differently.

Uraemia Condition caused by the build-up of waste products in the blood due to renal failure.

Uveitis Inflammation of all or part of the uveal tract (the middle layer of the eye), i.e. the iris, ciliary body and choroid.

Vaccine Suspension of inactivated or killed microbes used to confer immunity against a specific infectious agent.

Valency Measure of an agent's ability to combine.

Vasodilator Substance that triggers dilation of blood vessels, used in chemistry and immunology.

Vesicating agent Substance that induces skin blisters. Also known as a vesicant.

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