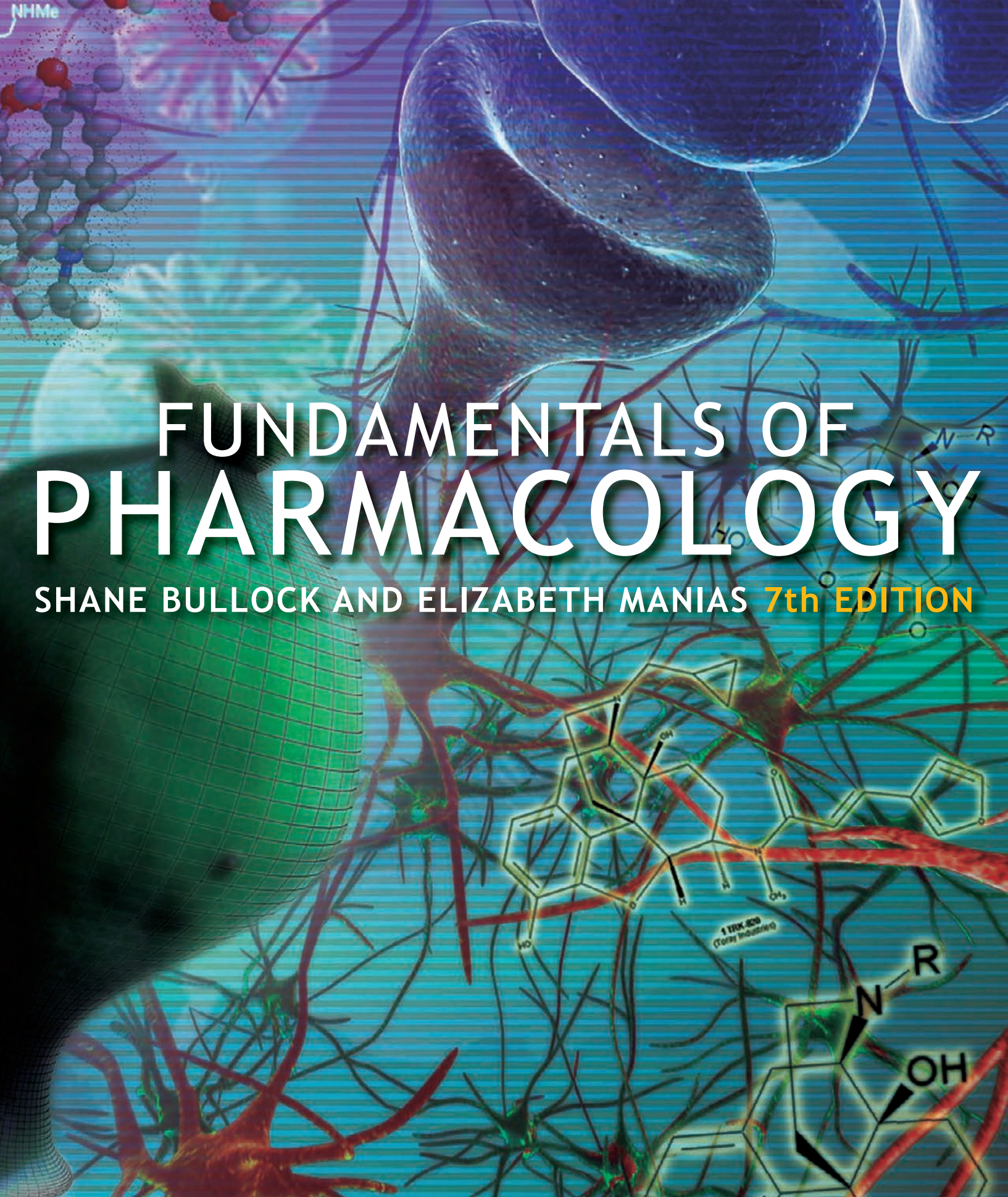

FUNDAMENTALS OF PHARMACOLOGY

SHANE BULLOCK AND ELIZABETH MANIAS 7th EDITION

ALWAYS LEARNING

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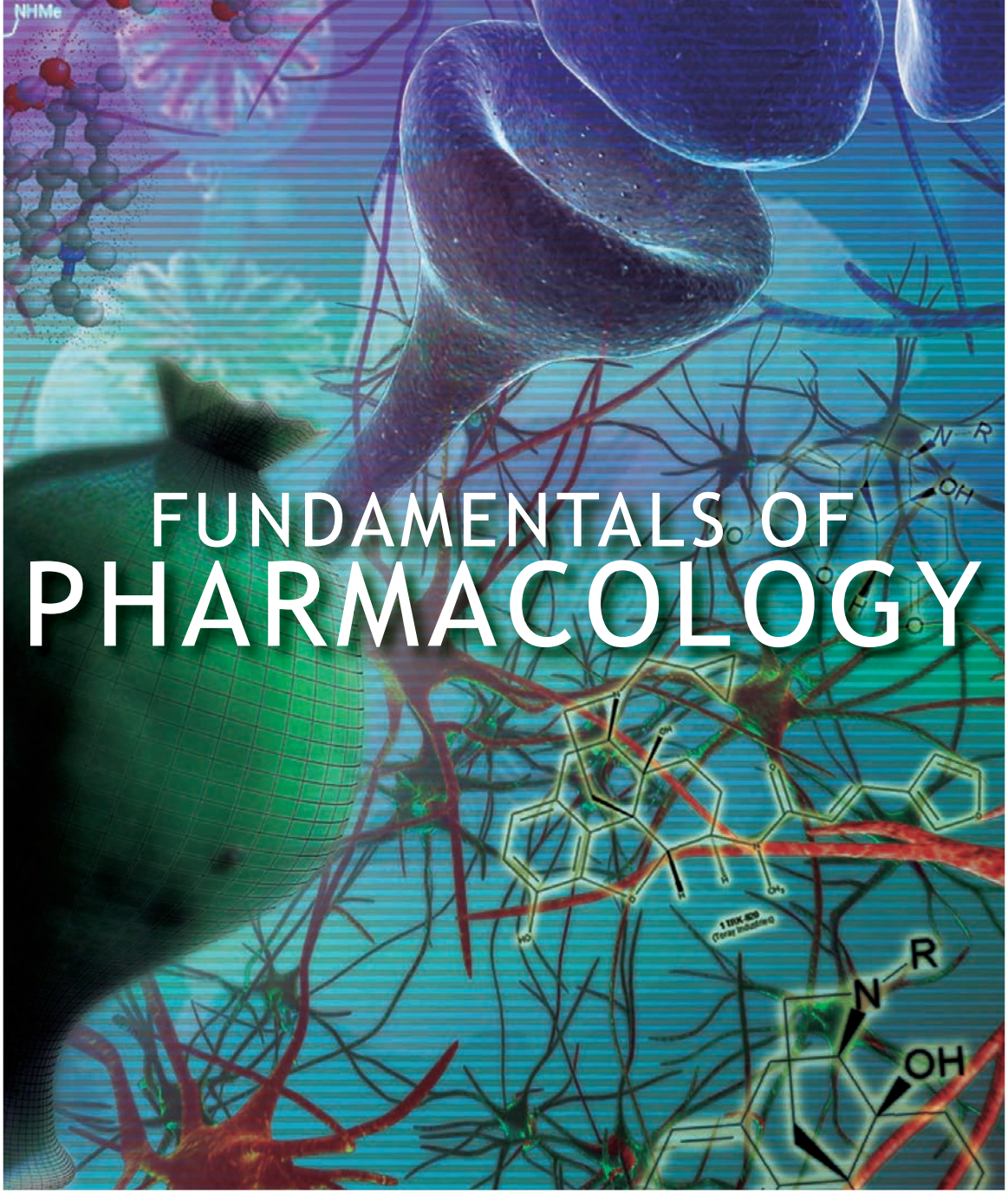

FUNDAMENTALS OF PHARMACOLOGY

SHANE BULLOCK AND ELIZABETH MANIAS 7th EDITION

Pearson Australia
Unit 4, Level 3
14 Aquatic Drive
Frenchs Forest NSW 2086

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Cover illustration © MEDI-MATION/Science Photo Library
Typeset by Midland Typesetters, Australia

Printed in China

1 2 3 4 5 18 17 16 15 14

National Library of Australia
Cataloguing-in-Publication Data

Author:	Bullock, Shane, author.
Title:	Fundamentals of pharmacology / Shane Bullock, Elizabeth Manias.
Edition:	7th edition.
ISBN:	9781442563100 (paperback).
ISBN:	9781442564411 (Vital Source)
Notes:	Includes index.
Subjects:	Pharmacology—Study and teaching (Higher). Drugs—Study and teaching (Higher)
Other Authors/Contributors:	Manias, Elizabeth, author.
Dewey Number:	615.1900711

CONTENTS

PREFACE

Fundamentals of Pharmacology is primarily a text for undergraduate and postgraduate students in the health science disciplines, particularly those in nursing. Students of other health disciplines whose roles involve pharmacological therapy (such as pharmacy, podiatry, optometry, paramedic and physiotherapy), as well as those studying basic science, should find much of the material relevant to their studies. Qualified health professionals and pharmaceutical company sales representatives will also find the information useful in their daily roles. Unashamedly, we have written a pharmacology textbook for students of the health professions that does not compromise the scientific basis of the discipline. Many pharmacology texts previously published have been strong on clinical considerations, yet relatively weak in the science of pharmacology.

Our approach

Philosophically, our goal is to empower health professionals through an understanding of the fundamental scientific principles of pharmacology. We believe that, to promote understanding, the effects of drugs on physiological and pathophysiological processes have to be clearly explained. 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 what adverse effects to expect, as well as the precautions and contraindications to consider.

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

This book is primarily designed to establish the foundations in pharmacology. We encourage students to refer to the electronic and hard copy references commonly found in the clinical setting and in hospital wards, such as the *Australian Medicines Handbook*, *MIMS* or *Therapeutic Guidelines*, for more detailed information regarding individual therapeutic agents (e.g. dosage, special precautions and toxicological information).

We hope that you will find this textbook a valuable companion in your pursuit of a fundamental understanding in a most fascinating area of clinical knowledge—pharmacology.

Changes in the seventh edition

This edition reflects the availability of medicines in Australia and New Zealand at the time of publication. Consistent with information currently available to us, we have updated new medicines that have entered the marketplace, as well as those that have been removed since the last edition.

We use the word "medicine" rather than "drug" or "medication" where appropriate. This change was implemented in recognition of the increasing use of the word "medicine" as evidenced by a number of industry websites such as:

- the National Prescribing Service (www.nps.org.au);
- Australian Prescriber (www.australianprescriber.com); and
- the Therapeutic Goods Administration (www.tga.gov.au/industry/pm.htm).

Where appropriate, the therapeutic approaches associated with the management of important clinical conditions, such as cardiovascular disease, diabetes mellitus and psychiatric illness have been brought up to date with current clinical guidelines.

FULL COLOUR FIGURES AND TABLES

This edition is printed in full colour for the first time. Chapter figures are more dynamic, providing the representations of structures and processes with greater depth and vibrancy. Receptors are rendered more often in figures as G-protein-coupled or ion channels rather than basic geometric shapes.

A number of new figures and tables have been included to assist students in visualising difficult pharmacological concepts, the sites of actions of drugs and the range of drug effects expected in a person when particular drug groups are administered.

END-OF-CHAPTER AND END-OF-SECTION FEATURES

The book contains over 800 end-of-chapter questions to assist in the consolidation of learning—all of these have been reviewed.

New and revised integrated case studies appear at the end of sections to assist with making links between theory and practice.

ACKNOWLEDGMENTS

We would like to thank a number of people who have contributed to the development of this textbook, and this edition in particular. Elizabeth wishes to thank her family for their patience and support, and for giving her an appreciation of things beyond the world of medicines. She would also like to thank her colleagues and students, who have provided her with helpful comments about the textbook and made suggestions for improvement.

For Shane the writing of this edition was fuelled by the primary producers situated around his homebase in the Gippsland region of Victoria—yummy cheese, chutney, jam and wine. With respect to the latter indulgence, students are advised to do as I say (see Chapter 24) rather than as I do. He is grateful to the backyard chooks who proved to be a more receptive and attentive audience than other family members when workshopping new ideas for the book.

We would like to thank the team at Pearson Australia for the preparation of this edition. Our thanks to Mandy Sheppard for her support, encouragement and good humour. We are also grateful for access to the expertise of Katie Pittard, Emma Gaulton and Rebecca Pomponio. It is always a pleasure working with you. We thank our copy editor, Anneliese Gillard, and proofreader, Jane Tyrrell, for their valuable advice on contemporary word usage and for picking up on our writing idiosyncrasies.

Thanks also to the proposal reviewers:

- Peter Athanasos, Flinders University
- Dr Hemant Mehta, Australian Catholic University
- Rebekkah Middleton, University of Wollongong
- Dr Srinivas Nammi, University of Western Sydney
- Dr Nicole Reinke, James Cook University
- Dr Ross Richards, Charles Sturt University
- Dr Scott Smid, The University of Adelaide
- Dr Jenny Wilkinson, Charles Sturt University

Shane Bullock and Elizabeth Manias
July 2013

FEATURES


CHAPTER 1

A HISTORICAL PERSPECTIVE

LEARNING OBJECTIVES

After completing this chapter, you should be able to:

1 Define the term pharmacology.
2 Identify the roles of medicines in human society.
3 Identify the three ages of pharmacology.
4 Briefly describe the major characteristics of each of the three ages and their implications for society.

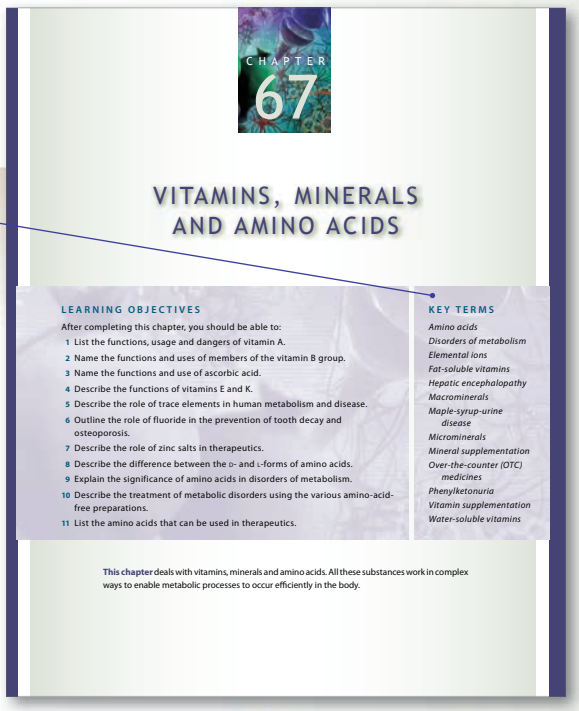
KEY TERMS

Biotechnology
Genetic engineering
Natural products
Pharmacology
Recombinant DNA technology

Pharmacology is a branch of medical science that deals with the properties and characteristics of chemical agents used for medicinal or other purposes. The actions and effects of these chemical agents on physiological systems are of particular interest. The physiological systems in which these effects are observed may be organs or tissues isolated from the body and artificially maintained—*in vitro* situations—or within living whole organisms—*in vivo* situations. In an etymological sense, the word 'pharmacology' is derived from two Greek words: *pharmakos*, which means medicine or drug, and *logos*, which means study.

Learning Objectives make clear what students will learn in each chapter.

Key Terms introduce students to new terminology and are helpful when revising for exams.


CHAPTER 67

VITAMINS, MINERALS AND AMINO ACIDS

LEARNING OBJECTIVES

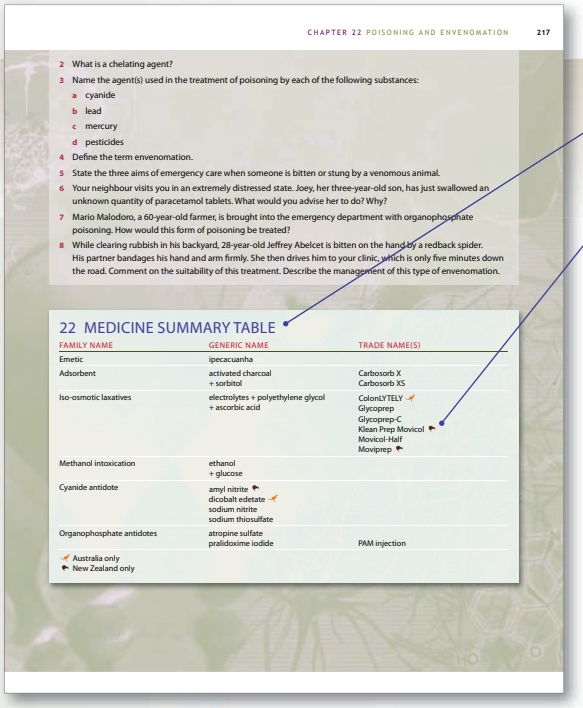
After completing this chapter, you should be able to:

1 List the functions, usage and dangers of vitamin A.
2 Name the functions and uses of members of the vitamin B group.
3 Name the functions and use of ascorbic acid.
4 Describe the functions of vitamins E and K.
5 Describe the role of trace elements in human metabolism and disease.
6 Outline the role of fluoride in the prevention of tooth decay and osteoporosis.
7 Describe the role of zinc salts in therapeutics.
8 Describe the difference between the D- and L-forms of amino acids.
9 Explain the significance of amino acids in disorders of metabolism.
10 Describe the treatment of metabolic disorders using the various amino-acid-free preparations.
11 List the amino acids that can be used in therapeutics.

KEY TERMS

Amino acids
Disorders of metabolism
Elemental ions
Fat-soluble vitamins
Hepatic encephalopathy
Macrominerals
Maple-syrup-urine disease
Microminerals
Mineral supplementation
Over-the-counter (OTC) medicines
Phenylketonuria
Vitamin supplementation
Water-soluble vitamins

This chapter deals with vitamins, minerals and amino acids. All these substances work in complex ways to enable metabolic processes to occur efficiently in the body.



CHAPTER 22 POISONING AND ENVENOMATION 217

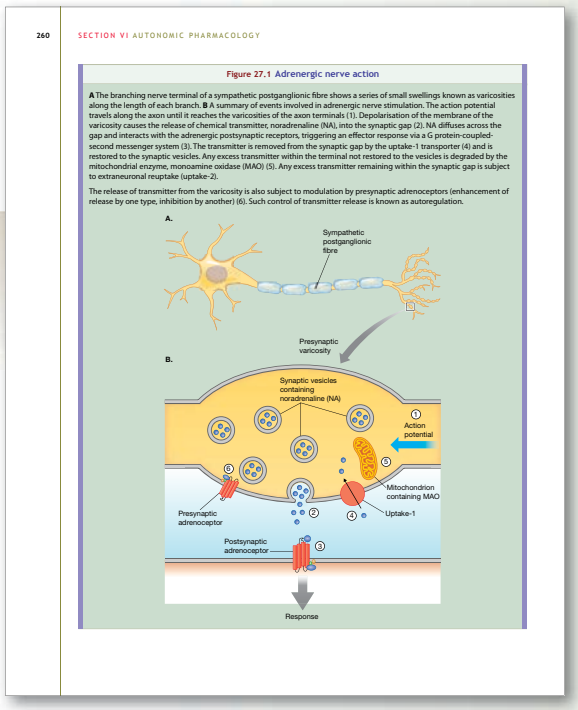
2 What is a chelating agent?
3 Name the agent(s) used in the treatment of poisoning by each of the following substances:
a cyanide
b lead
c mercury
d pesticides
4 Define the term envenomation.
5 State the three aims of emergency care when someone is bitten or stung by a venomous animal.
6 Your neighbour visits you in an extremely distressed state. Joey, her three-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?
8 While clearing rubbish in his backyard, 28-year-old Jeffrey Abelcet is bitten on the hand by a redback spider. His partner bandages his hand and arm firmly. She then drives him to your clinic, which is only five minutes down the road. Comment on the suitability of this treatment. Describe the management of this type of envenomation.

22 MEDICINE SUMMARY TABLE

FAMILY NAME	GENERIC NAME	TRADE NAME(S)
Emetic	ipecacuanha	
Adsorbent	activated charcoal + sorbitol	Carbosorb X Carbosorb XS
Iso-osmotic laxatives	electrolytes + polyethylene glycol + ascorbic acid	ColonLYTELY Glycoprep Glycoprep-C Klean Prep Movicol Movicol-Half Moviprep
Methanol intoxication	ethanol + glucose	
Cyanide antidote	amyl nitrite dicobalt edetate sodium nitrite sodium thiosulfate	
Organophosphate antidotes	atropine sulfate pralidoxime iodide	PAM injection

Australia only
New Zealand only

Medicine Summary Tables provide a handy list of family names, generic names and trade names for specific medicines. **Icons** indicate medicines that are only available in Australia or New Zealand. Special considerations are listed where necessary.



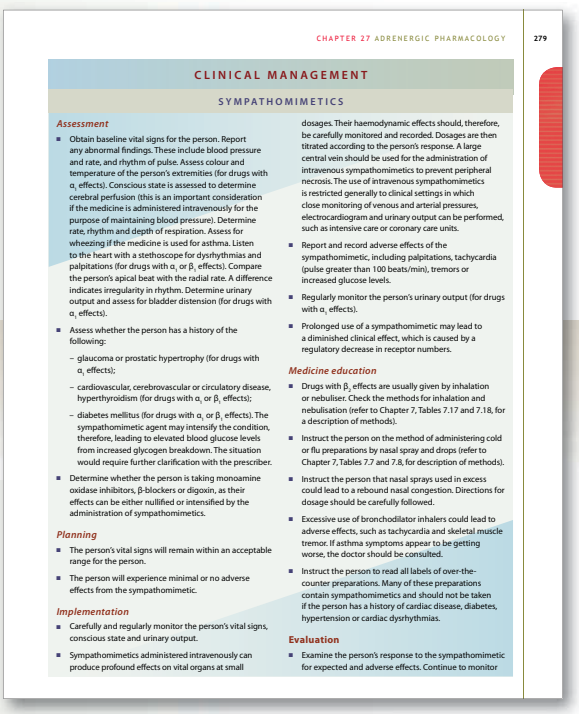
260 SECTION VI AUTONOMIC PHARMACOLOGY

Figure 27.1 Adrenergic nerve action

A The branching nerve terminal of a sympathetic postganglionic fibre shows a series of small swellings known as varicosities along the length of each branch. **B** A summary of events involved in adrenergic nerve stimulation. The action potential travels along the axon until it reaches the varicosities of the axon terminals (1). Depolarisation of the membrane of the varicosity causes the release of chemical transmitter, noradrenaline (NA), into the synaptic gap (2). NA diffuses across the gap and interacts with the adrenergic postsynaptic receptors, triggering an effector response via a G protein-coupled-second messenger system (3). The transmitter is removed from the synaptic gap by the uptake-1 transporter (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 (uptake-2).

The release of transmitter from the varicosity is also subject to modulation by presynaptic adrenoceptors (enhancement of release by one type, inhibition by another) (6). Such control of transmitter release is known as autoregulation.

Figures illustrate and clarify complex processes, aiding student comprehension.



CHAPTER 27 ADRENERGIC PHARMACOLOGY 279

CLINICAL MANAGEMENT

SYMPATHOMIMETICS

Assessment

- Obtain baseline vital signs for the person. Report any abnormal findings. These include blood pressure and rate, and rhythm of pulse. Assess colour and temperature of the person's extremities (for drugs with α_1 effects). Conscious state is assessed to determine cerebral perfusion (this is an important consideration if the medicine is administered intravenously for the purpose of maintaining blood pressure). Determine rate, rhythm and depth of respiration. Assess for wheezing if the medicine 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 person'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 person 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_1 effects). The sympathomimetic agent may intensify the condition, therefore, leading to elevated blood glucose levels from increased glycogen breakdown. The situation would require further clarification with the prescriber.
- Determine whether the person is taking monoamine oxidase inhibitors, β-blockers or digoxin, as their effects can be either nullified or intensified by the administration of sympathomimetics.

Planning

- The person's vital signs will remain within an acceptable range for the person.
- The person will experience minimal or no adverse effects from the sympathomimetic.

Implementation

- Carefully and regularly monitor the person'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 carefully monitored and recorded. Dosages are then titrated according to the person'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 and urinary output can be performed, such as intensive care or coronary care units.
- 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 person'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.

Medicine education

- Drugs with β_2 effects are usually given by inhalation or nebuliser. Check the methods for inhalation and nebulisation (refer to Chapter 7, Tables 7.17 and 7.18, for a description of methods).
- Instruct the person on the method of administering cold or flu preparations by nasal spray and drops (refer to Chapter 7, Tables 7.7 and 7.8, for description of methods).
- Instruct the person that nasal sprays used in excess could lead to a rebound nasal congestion. Directions for dosage should be carefully followed.
- 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 person to read all labels of over-the-counter preparations. Many of these preparations contain sympathomimetics and should not be taken if the person has a history of cardiac disease, diabetes, hypertension or cardiac dysrhythmias.

Evaluation

- Examine the person's response to the sympathomimetic for expected and adverse effects. Continue to monitor

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

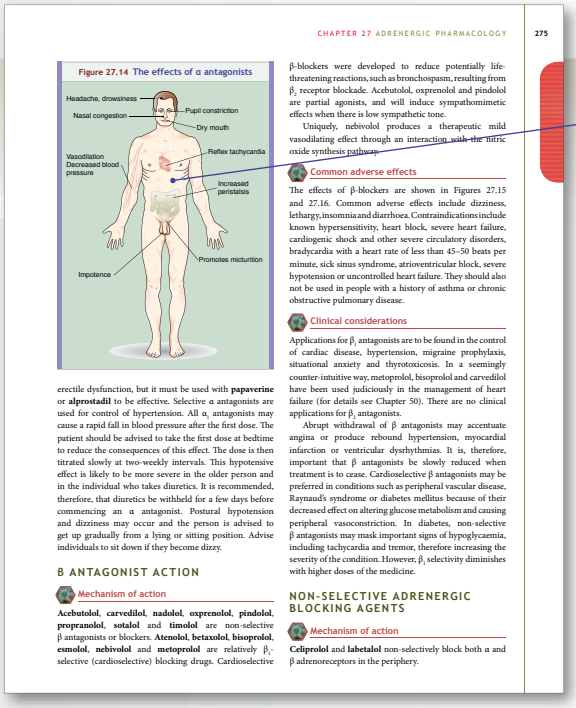


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Figure 27.14 The effects of α antagonists

erectile dysfunction, but it must be used with **papaverine** or **alprostadil** to be effective. Selective α antagonists are used for control of hypertension. All 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 to reduce the consequences of this effect. The dose is then titrated slowly at two-weekly intervals. This hypotensive effect is likely to be more severe in the older person and in the individual who takes diuretics. It is recommended, therefore, that diuretics be withheld for a few days before commencing an α antagonist. Postural hypotension and dizziness may occur and the person is advised to get up gradually from a lying or sitting position. Advise individuals to sit down if they become dizzy.

β ANTAGONIST ACTION

Mechanism of action

Acebutolol, **carvedilol**, **nadolol**, **oxprenolol**, **pindolol**, **propranolol**, **sotalol** and **timolol** are non-selective β antagonists or blockers. **Atenolol**, **betaxolol**, **bisoprolol**, **esmolol**, **nebivolol** and **metoprolol** are relatively β_1-selective (cardioselective) blocking drugs. Cardioselective β-blockers were developed to reduce potentially life-threatening reactions, such as bronchospasm, resulting from β_2 receptor blockade. Acebutolol, oxprenolol and pindolol are partial agonists, and will induce sympathomimetic effects when there is low sympathetic tone.

Uniquely, nebivolol produces a therapeutic mild vasodilating effect through an interaction with the nitric oxide synthesis pathway.

Common adverse effects

The effects of β-blockers are shown in Figures 27.15 and 27.16. 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, bradycardia with a heart rate of less than 45–50 beats per minute, sick sinus syndrome, atrioventricular block, severe hypotension or uncontrolled heart failure. They should also not be used in people with a history of asthma or chronic obstructive pulmonary disease.

Clinical considerations

Applications for β_1 antagonists are to be found in the control of cardiac disease, hypertension, migraine prophylaxis, situational anxiety and thyrotoxicosis. In a seemingly counter-intuitive way, metoprolol, bisoprolol and carvedilol have been used judiciously in the management of heart failure (for details see Chapter 50). 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, therefore, important that β antagonists be slowly reduced when treatment is to cease. Cardioselective β antagonists may be preferred in conditions such as peripheral vascular disease, Raynaud's syndrome or diabetes mellitus because of their decreased effect on altering glucose metabolism and causing peripheral vasoconstriction. In diabetes, non-selective β antagonists may mask important signs of hypoglycaemia, including tachycardia and tremor, therefore increasing the severity of the condition. However, β_1 selectivity diminishes with higher doses of the medicine.

NON-SELECTIVE ADRENERGIC BLOCKING AGENTS

Mechanism of action

Celiprolol and **labetalol** non-selectively block both α and β adrenoreceptors in the periphery.

Human Models visually illustrate the effects, both positive and negative, of pharmacological agents on the human body. Male and female human models are used to illustrate the effects of pharmacological agents.

CHAPTER 28 CHOLINERGIC PHARMACOLOGY 311

CASE STUDY 1

Mrs JH is a 62-year-old woman who has had rheumatoid arthritis in her hands, hips and knees for about eight years. She is receiving weekly assistance from her local district nursing service because of impaired mobility. For the arthritis, she is taking the non-steroidal anti-inflammatory drug ibuprofen daily and receives intermittent hydrocortisone therapy when the condition worsens.

You are caring for Mrs JH. She tells you 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. Mrs JH is prescribed eye drops containing a miotic agent. This medicine 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 groups of drugs are well suited as miotics?*
  b *What receptor types are they acting on 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 19, explain why Mrs JH may be predisposed to glaucoma.*

CASE STUDY 2

Mr FT is a 22-year-old man who has been admitted to your hospital 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 of times in the ambulance as he was transported to hospital. You note the following 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 carefully monitored during this critical period. His recovery is without complications. He is discharged from hospital several days later.

Questions

1 *Underlying Mr FT'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 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 3

Mr JJ, aged 68 years, visits the outpatient clinic for a check-up relating to his asthma condition. He has occasional bouts of acute asthma, which is adequately controlled using a salbutamol inhaler. Mr JJ indicates 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 two 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 27.*
2 *To which drug group does timolol belong, and how does it act to lower intraocular pressure? You may wish to refer to Chapters 27 and 83.*
3 *What is the potential problem for Mr JJ using salbutamol and timolol?*

CASE STUDY 4

Ms RW is a 50-year-old woman who is suffering from sinus bradycardia (a slow heart rate). Recently, she has had some problems maintaining a normal blood pressure. She is given a medicine 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.*

Case Studies with Accompanying Questions immerse students in scenarios involving people taking medicines, family members and health professionals. Students are given the opportunity to apply knowledge, practise drug calculations and dosages, and convey their understanding of pharmacological principles and interactions in a variety of clinical settings.

18 SECTION I PHARMACOLOGY WITHIN THE SOCIAL CONTEXT

CHAPTER REVIEW

- Advertising of medicines can affect the medicine management activities of health professionals.
- Advertising can influence the medicinal activities of consumers.
- Over-the-counter preparations are available to consumers without a prescription, and often without supervision of a health professional.
- The generic name of a medicine is the shortened, simplified version of the chemical name.
- The brand name is the trademark used by a pharmaceutical pharmaceutical company to identify the preparation of a particular drug.
- Generic prescribing means that a pharmacist can supply any formulation of a particular medicine.
- Generic substitution means that a pharmacist can supply any formulation of the medicine without referring back to the prescriber.
- Polypharmacy, which is a major problem for older people, involves the excessive or inappropriate use of medicines.
- The traditional beliefs and values of a particular culture influence an individual's perceptions and expectations about drug therapy.

FURTHER READING

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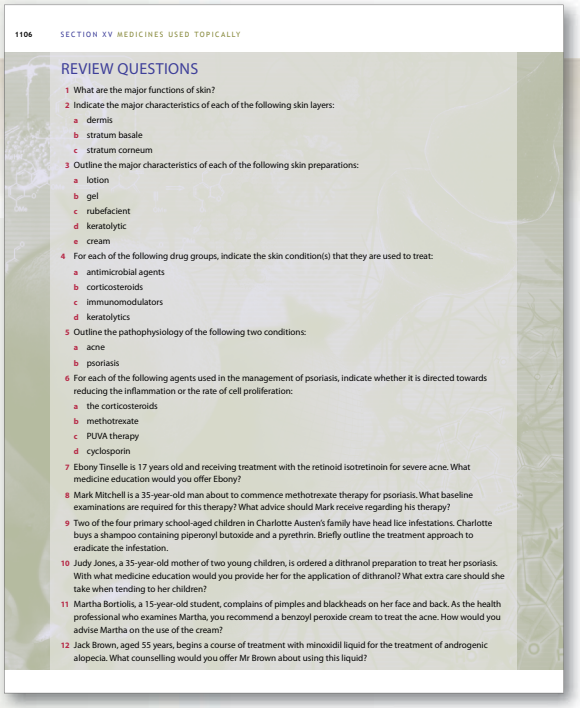
WEB RESOURCES

A Brief History of Pharmacology **pubs.acs.org/subscribe/journals/mdd/v04/i05/html/05timeline.html**
Australian Bureau of Statistics **www.abs.gov.au/AUSSTATS**
What is Pharmacology? **www.pharmacology.med.umn.edu/whatispharm.html**
Everybody (Health Consumer Information) **www.everybody.co.nz**
Māori Health **www.health.govt.nz/our-work/populations/maori-health**
New Zealand Deserves Better. Direct-to-Consumer Advertising (DTCA) of Prescription Medicines in New Zealand: for Health or Profit? **journal.nzma.org.nz/journal/116-1180/556**
Office for Aboriginal and Torres Strait Islander Health **www.health.gov.au/oatsih**

Chapter Review summarises the essential information in each chapter, providing a quick revision tool.



1106 SECTION XV MEDICINES USED TOPICALLY

REVIEW QUESTIONS

1 What are the major functions of skin?
2 Indicate the major characteristics of each of the following skin layers:
   a dermis
   b stratum basale
   c stratum corneum
3 Outline the major characteristics of each of the following skin preparations:
   a lotion
   b gel
   c rubefacient
   d keratolytic
   e cream
4 For each of the following drug groups, indicate the skin condition(s) that they are used to treat:
   a antimicrobial agents
   b corticosteroids
   c immunomodulators
   d keratolytics
5 Outline the pathophysiology of the following two conditions:
   a acne
   b psoriasis
6 For each of the following agents used in the management of psoriasis, indicate whether it is directed towards reducing the inflammation or the rate of cell proliferation:
   a the corticosteroids
   b methotrexate
   c PUVA therapy
   d cyclosporin
7 Ebony Tinselle is 17 years old and receiving treatment with the retinoid isotretinoin for severe acne. What medicine education would you offer Ebony?
8 Mark Mitchell is a 35-year-old man about to commence methotrexate therapy for psoriasis. What baseline examinations are required for this therapy? What advice should Mark receive regarding his therapy?
9 Two of the four primary school-aged children in Charlotte Austen's family have head lice infestations. Charlotte buys a shampoo containing piperonyl butoxide and a pyrethrin. Briefly outline the treatment approach to eradicate the infestation.
10 Judy Jones, a 35-year-old mother of two young children, is ordered a dithranol preparation to treat her psoriasis. With what medicine education would you provide her for the application of dithranol? What extra care should she take when tending to her children?
11 Martha Bortiolis, a 15-year-old student, complains of pimples and blackheads on her face and back. As the health professional who examines Martha, you recommend a benzoyl peroxide cream to treat the acne. How would you advise Martha on the use of the cream?
12 Jack Brown, aged 55 years, begins a course of treatment with minoxidil liquid for the treatment of androgenic alopecia. What counselling would you offer Mr Brown about using this liquid?

Review Questions check that students remember and understand the clinical significance of key chapter content.

CHAPTER 21 PAEDIATRIC AND GERIATRIC PHARMACOLOGY 207

FURTHER READING

Buxton IL, 2006, 'Pharmacokinetics and pharmacodynamics: the dynamics of drug absorption, distribution and elimination', in Brunton LL, Lazo JS & Parker KL (eds), *Goodman and Gilman's Pharmacological Basis of Therapeutics*, 11th edn, McGraw-Hill, New York, pp. 1–39.

Eshkoli T, Sheiner E, Ben-Zvi Z & Holcberg G, 2011, Drug transport across the placenta, *Current Pharmaceutical Biotechnology*, 12(**5**): 707–14.

Hughes CM, Roughead E & Kerse N, 2008, 'Improving use of medicines for older people in long-term care: contrasting the policy approach of four countries', *Healthcare Policy*, **3**(3): e154–e167.

Jacqz-Aigrain E & Choonara I, eds, 2006, *Paediatric Clinical Pharmacology*, Informa HealthCare, London.

Khojasteh SC, Wong H & Hop CECA, 2011, *Drug Metabolism and Pharmacokinetics Quick Guide*, Springer, New York.

Koch S, Gloth MF, Nay R (eds), 2010, *Medication Management In Older Adults: a Concise Guide For Clinicians.* Springer Science and Business Media, New York.

Le Couteur D, McLachlan A & de Cabo R, 2012, Aging, drugs, and drug metabolism. *Journals of Gerontology. Series A: Biological Sciences & Medical Sciences*, **67**(2): 137–39.

McCance K & Huether SE, 2009, *Pathophysiology*, 6th edn, Elsevier Mosby, Sydney (for age-related and disease-related changes in body structure and function).

Sissung TM, Troutman SM, Campbell TJ, Pressler HM, Sung H, Bates SE and Figg WD, 2012, Transporter pharmacogenetics: transporter polymorphisms affect normal physiology, diseases, and pharmacotherapy, *Discovery Medicine*, 13(**68**): 19–34.

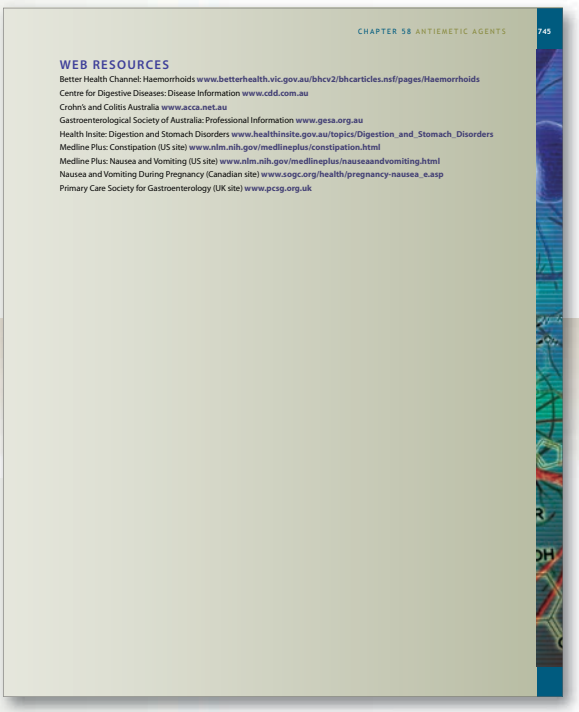
The Royal Australian College of General Practitioners, Australasian Society of Clinical and Experimental Pharmacologists and Toxicologists, Pharmaceutical Society of Australia, 2012, *Australian Medicines Handbook*, AMH Pty Ltd, Adelaide.

Weier N, He SM, Li XT, Wang LL & Zhou SF, 2008, 'Placental drug disposition and its clinical implications', *Current Drug Metabolism*, **9**, 106–21.

WEB RESOURCES

Australian Government Department of Health and Ageing **www.health.gov.au**
Australian Statistics on Medicines **www.tga.gov.au/hp/medicines-statistics-2010.htm**
Clinical Trials (US site) **www.clinicaltrials.gov**
Health Insite **www.healthinsite.gov.au/index.cfm**
Interactive Clinical Pharmacology **www.icp.org.nz**
Medicines Australia (Pharmaceutical Industry Group) **www.medicinesaustralia.com.au**
Medsafe **www.medsafe.govt.nz**
NZ Ministry of Health **www.moh.govt.nz/moh.nsf**
Pharmacokinetics: An Introduction (US site) **www.4um.com/tutorial/science/pharmak.htm**
Therapeutic Goods Administration (TGA) **www.tga.gov.au/index.htm**
Trials Central: online register of US clinical trials **www.trialscentral.org**

Further Reading lists appear at the end of each section and provide information for students wishing to pursue a topic in further detail for assessment or interest.



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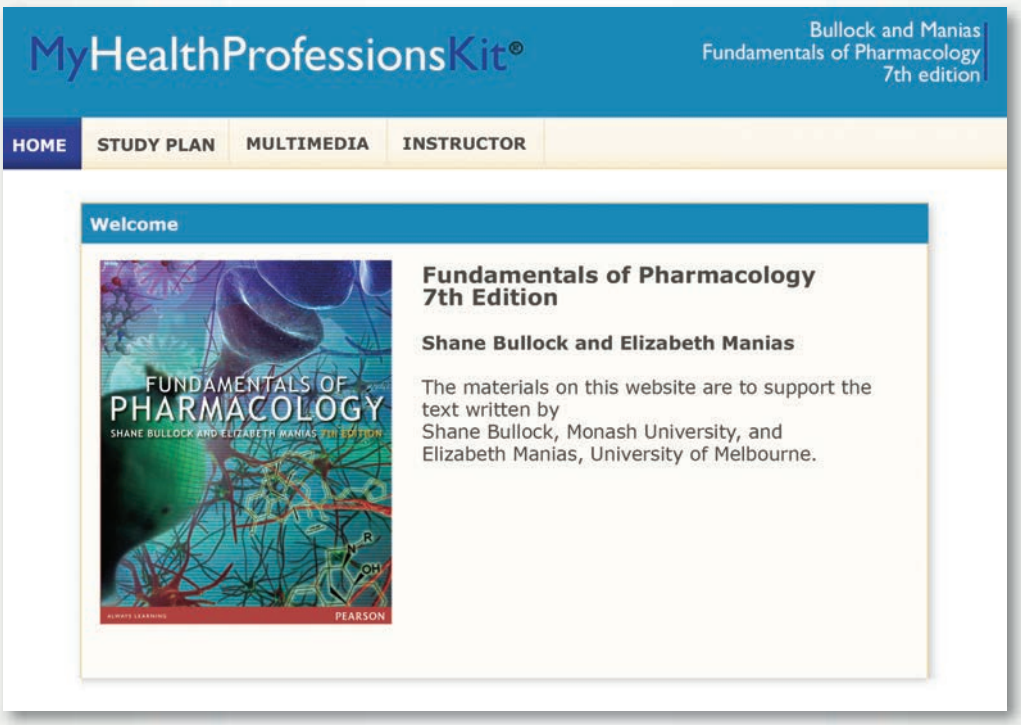
WEB RESOURCES

Better Health Channel: Haemorrhoids **www.betterhealth.vic.gov.au/bhcv2/bhcarticles.nsf/pages/Haemorrhoids**
Centre for Digestive Diseases: Disease Information **www.cdd.com.au**
Crohn's and Colitis Australia **www.acca.net.au**
Gastroenterological Society of Australia: Professional Information **www.gesa.org.au**
Health Insite: Digestion and Stomach Disorders **www.healthinsite.gov.au/topics/Digestion_and_Stomach_Disorders**
Medline Plus: Constipation (US site) **www.nlm.nih.gov/medlineplus/constipation.html**
Medline Plus: Nausea and Vomiting (US site) **www.nlm.nih.gov/medlineplus/nauseaandvomiting.html**
Nausea and Vomiting During Pregnancy (Canadian site) **www.sogc.org/health/pregnancy-nausea_e.asp**
Primary Care Society for Gastroenterology (UK site) **www.pcsg.org.uk**

Web Resources lists appear at the end of each section and provide links to relevant websites for further study and online research.

TEACHING AND LEARNING PACKAGE



FOR STUDENTS

MyHealthProfessionsKit is an online study tool that will help you understand, revise and master the concepts in the textbook.

MyHealthProfessionsKit gives you access to these study resources:

- multiple-choice revision questions;
- interactive 'drag and drop' revision activities;
- animations demonstrating the mechanisms of action for various medicines;
- glossary flashcards to test your knowledge of key pharmacology terms;
- realistic drug calculation scenarios to give you practice;
- searchable eBook (if you have purchased the MyLab with eBook option).

FOR INSTRUCTORS

Computerised TestBank

Create professional-looking customised printed or online exams in just minutes using Pearson's TestGen software. Build tests from the database of over than 600 true–false and multiple-choice questions, edit questions or add questions of your own.

PowerPoint Slides

Lecture slides pair key points with images from each chapter to facilitate effective lectures and classroom discussions.

Solutions Manual

This manual provides the answers to the end-of-chapter exercises in the text. You have the option of making this manual available to your students.

Digital Media Library

All figures and tables from the textbook are provided in jpeg format.

FIGURES AND TABLES

SECTION

I

PHARMACOLOGY WITHIN THE SOCIAL CONTEXT

O, (abundant) is the powerful grace that lies

In herbs, plants, stones ...

WILLIAM SHAKESPEARE—*ROMEO AND JULIET*

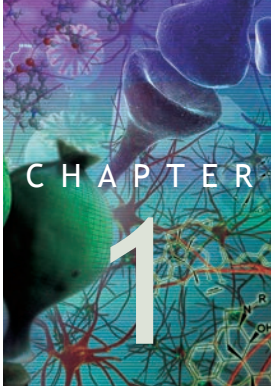
The quote from Shakespeare's *Romeo and Juliet* alludes to two important points explored in this section. The first is that medicines can be obtained from a variety of sources within our environment. The other is that these substances produce a powerful effect on the body. The nature of the effect of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

Historical records show that medicine use has long been a part of human culture. A brief outline of the history of medicine use and the sources from which medicines 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 medicine use, and health professionals must be aware of these issues and implement effective strategies to deal with them. Some of the issues raised in Chapter 2 include the following:

- the use of generic substances versus proprietary medicines;
- medicine advertising;
- perspectives of medicine use in the older person;
- cultural differences;
- the use of over-the-counter (OTC) preparations.

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



A HISTORICAL PERSPECTIVE

LEARNING OBJECTIVES

After completing this chapter, you should be able to:

1. Define the term pharmacology.
2. Identify the roles of medicines in human society.
3. Identify the three ages of pharmacology.
4. Briefly describe the major characteristics of each of the three ages and their implications for society.

KEY TERMS

Biotechnology
Genetic engineering
Natural products
Pharmacology
Recombinant DNA technology

Pharmacology is a branch of medical science that deals with the properties and characteristics of chemical agents used for medicinal or other purposes. The actions and effects of these chemical agents on physiological systems are of particular interest. The physiological systems in which these effects are observed may be organs or tissues isolated from the body and artificially maintained—*in vitro* situations—or within living whole organisms—*in vivo* situations. In an etymological sense, the word 'pharmacology' is derived from two Greek words: *pharmakos*, which means medicine or drug, and *logos*, which means study.

SUBSTANCE USE AND SOCIETY

The use of chemical substances for medicinal and social purposes mirrors the course of human history itself. In fact, it probably even predates human history, as evidence of medicine use seems apparent among other animals (particularly chimpanzees, which have recently been shown to consume foods for their antibacterial, antifungal or antiworming properties). The methods used to identify useful pharmacological agents involve trial and error as well as careful observation. Indeed, many valuable therapeutic agents were 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 civilised, there exists a culture of using chemical agents 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 time line 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 21st century, when biotechnological products are the focus of attention. While there is some overlap between the three eras, each era tended to dominate at certain time periods.

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 BCE. 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 its medicinal uses were documented. Alcohol has been used as a skin antiseptic, 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 24).

The period in which therapeutic agents were derived from plants is by far the longest: the first recorded use dates back to around 2700 BCE. Every culture throughout history has used plant derivatives—the leaves, fruit, bark, roots, flowers and sap—as a means to heal. Agents such as **atropine**, **ergotamine**, **curare**, **morphine**, **reserpine**, **cocaine** and **marijuana** were extracted from these sources. Indeed, the origins and uses of just a few of these substances broaden the view of pharmacology and remind us that there is more to this area of study than simply popping pills into sick people's mouths.

ATROPINE: LEGENDS AND LADIES

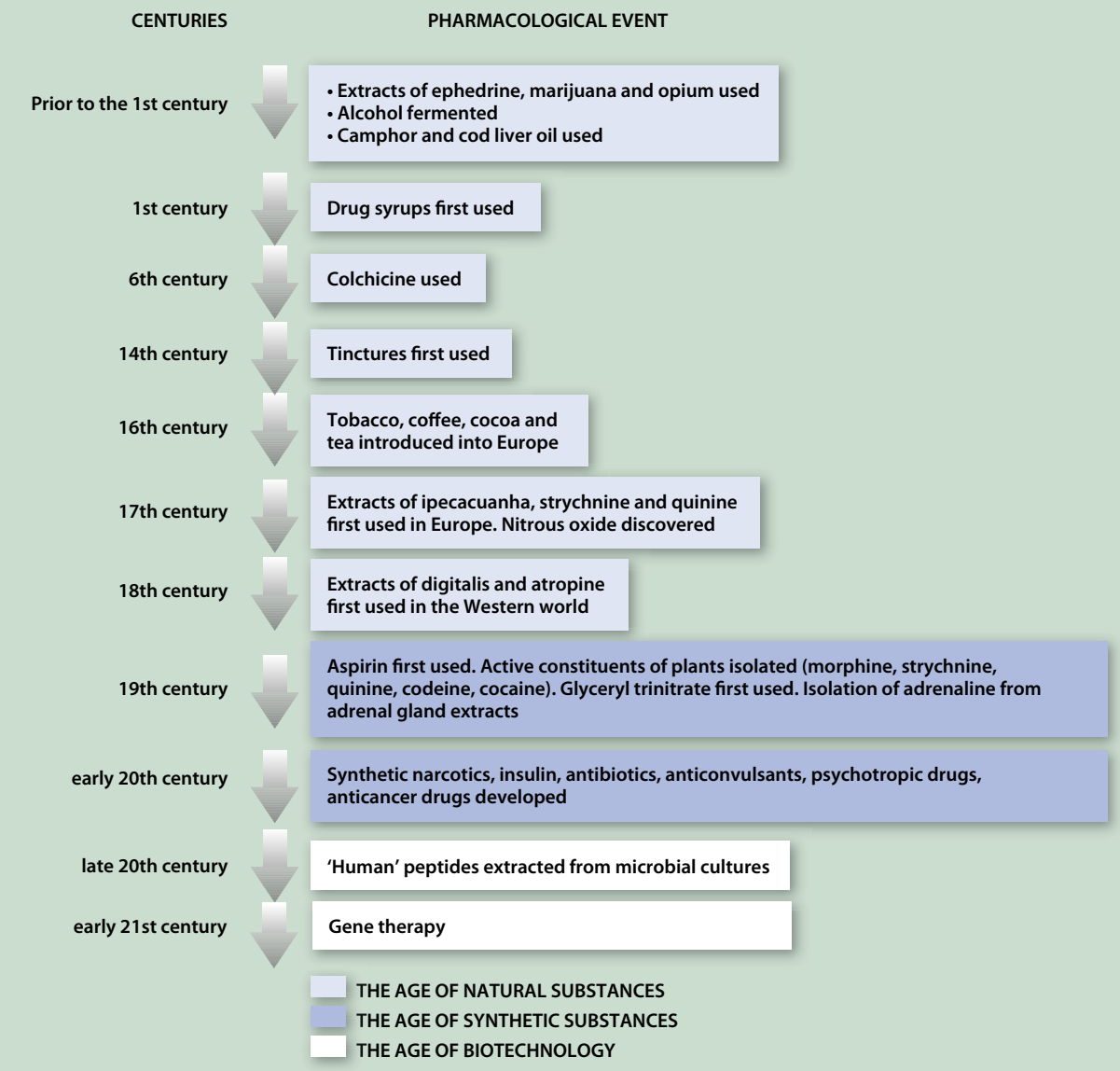
Atropine is derived from the fruits of various plants of the potato family, particularly the deadly nightshade, *Atropa belladonna*. As is obvious from the common name, the fruits of this plant have long been known to be poisonous. Throughout history, deadly nightshade has been used for nefarious purposes 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, although for a non-cosmetic/medical purpose, 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 medicines are used respectively to treat migraine and to induce uterine contractions in obstetrics, but in overdose can cause seizures and hallucinations (not surprisingly, as lysergic acid diethylamide, LSD, is a derivative of ergotamine). It has been suggested that many witches in the Middle Ages, and even up to the Salem witchcraft trials in America in the 17th 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 Cafergot (a brand name for an ergotamine preparation) could have had them burnt at the stake in previous eras?

Figure 1.1 A time line highlighting some major pharmaceutical events

A historical time line showing use of major pharmaceutical substances. The time line is divided into three distinct periods: the age of natural substances; the age of synthetic substances; and the age of biotechnology.



TUBOCURARINE: MACUSIS AND MUSCLES

Tubocurarine has been used in surgery to paralyse skeletal muscle, a procedure that makes the surgeon's task easier. (Nowadays, newer medicines have replaced it.) This medicine is derived from plants belonging to the genus *Strychnos* (some of which also provide strychnine). An impure preparation of the medicine is called curare, and has been used as an arrow poison by the Macusi Indians of Guyana. The interesting fact about this medicine is that the Macusi, unwittingly, were making use of an important pharmacological property—the nature of medicine absorption. The majority of medicines are given by mouth—but some, if given by this route, are not absorbed. Tubocurarine is one of these. The Indians observed that death would soon come to the shot animal as curare was absorbed into the blood from the arrow wound. However, no harm came to the tribe as they consumed the meat of the animal that had been 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 itself 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 6th 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 Peruvian Indians 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. Today, cocaine is used as a local anaesthetic only occasionally, principally in nasal surgery. Like the Macusi Indians who used curare, the Peruvian Indians who used cocaine crudely applied some pharmacology. The leaves of this plant were mixed with lime prior to chewing. This prolonged the effect of the medicine by altering its rate of excretion from the body, and showed that medicine preparation has an important influence on therapeutic effect in the body. (Medicine 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 modern 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 serpentine,* and was used in India to treat the mentally disturbed. 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 (i.e. that an imbalance in the level of brain neurotransmitters may underlie the behaviour).

MARIJUANA: MALINGERER OR MEDICINE?

Marijuana is, in most countries, a substance of abuse; as (until recently) its effects have not been widely considered to be of clinical value. This substance comes from the plant *Cannabis sativa,* and has been used intermittently since about 2700 BC as a sedative or analgesic. After World War II particularly, it became a common recreational drug, and was outlawed by the World Health Organization as a drug of abuse with no therapeutic use. This may be inaccurate as the main active substance 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 agents. Substances containing (or derived from) THC are called cannabinoids. There are clinical applications for the cannabinoids. An example is as appetite stimulants for people living with HIV/AIDS who experience significant weight loss.

ANTIBIOTICS: MEDICINAL MOULDS

In the early part of the 20th 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). During the 1930s and 1940s penicillin was isolated and purified, and it became the precursor of other antibiotics, such as **streptomycin** for the treatment of tuberculosis. 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 are all around us. You probably have some common clinical agents growing in your gardens at home (see Figure 1.2)—a heart medicine from the purple foxglove (see Chapter 50), atropine from the deadly nightshade (see Chapter 28) and anticancer agents from the common periwinkle plant (see Chapter 80). Indeed, that we are surrounded by natural substances with medicinal properties is the reason for the use of herbal and alternative medicines. However, for many of these natural medicines, 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 medicines. The number of potential medicines that remain undiscovered