



PHARMACOLOGY FOR HEALTH PROFESSIONALS

— 5th Edition —

**Bronwen Bryant, Kathleen Knights
Shaunagh Darroch, Andrew Rowland**



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**Bronwen Bryant, Kathleen Knights
Shaunagh Darroch, Andrew Rowland**

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Elsevier Australia. ACN 001 002 357

(a division of Reed International Books Australia Pty Ltd) Tower 1, 475 Victoria Avenue, Chatswood, NSW 2067

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International Standard Book Number: 978-0-7295-4275-3

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A catalogue record for this book is available from the National Library of Australia

Cataloging-in-Publication Data

Senior Content Strategist: Melinda McEvoy

Senior Content Development Specialist: Elizabeth Coady

Senior Project Manager: Anitha Rajarathnam

Tech-checked by Lynne MacKinnon and Jerry Perkins

Edited by Robyn Flemming

Proofread by Annabel Adair

Cover and Internals Design by Georgette Hall

Illustrations by Michael Towey

Index by Innodata Indexing

Typeset by Toppan Best-set Premedia Limited

Printed in China by 1010 Printing International Pvt. Ltd.

Cover image: <https://stock.adobe.com/au/images/deadly-nightshade-atropa-belladonna-from-meyers-lexikon-1895-7-568-569/138935147>

DEDICATIONS

To my daughters Rosemary, Philippa and Alison, who continually inspire, encourage and amaze me; and to their children, as representatives of future generations to benefit from medical research and scholarship.

Bronwen J Bryant

To the Discipline of Pharmacology that has provided the foundation of my academic career and to those who enrich my life, my husband John and my family and friends.

Kathleen M Knights

To my family and friends for their continuous encouragement and humour, to my colleagues for their support and guidance, and to my students for challenging and inspiring me.

Shaunagh Darroch

To my wife Angela and son Aidan with love (even though they'll never read it).

Andrew Rowland



ABOUT THE AUTHORS

Bronwen Bryant

Bronwen became fascinated with pharmacology while studying pharmacy at the University of Sydney. She completed an Honours year, then a Master of Science degree under the supervision of Associate Professor Diana Temple, with research in the areas of biochemical and cardiovascular pharmacology. After two years' research at Riker Laboratories in Sydney, and work in both community and hospital pharmacies to gain registration and experience as a pharmacist, she moved to London and worked as a medical translator and editor.

On returning to Australia, Bronwen carried out research in the laboratory of Professor Michael Rand and Dr David Story at the University of Melbourne, where she completed a PhD on negative feedback control of central autonomic transmission. Academic positions teaching pharmacology followed at the Victorian College of Pharmacy (now Monash University), La Trobe University and the Fiji School of Medicine in Suva. Along the way, she has coordinated pharmacology courses, taught students of virtually every health profession, and carried out research in clinical pharmacology on adverse drug reactions and interactions, non-steroidal antiinflammatory drugs and psychotherapeutics.

Bronwen currently holds the position of Honorary Fellow in the Department of Pharmacology and Therapeutics, Faculty of Medicine, Dentistry and Health Sciences at the University of Melbourne.

Kathleen Knights

Kathie completed a Bachelor of Science (Honours) degree at North East London Polytechnic (NELP), majoring in pharmacology, while working as a research assistant at Guy's Hospital, London. On returning home to Adelaide, she accepted a research position in the Department of Anaesthesia and Intensive Care in the School of Medicine at Flinders University, where she also completed a PhD investigating the hepatotoxicity of the inhalational anaesthetic agent halothane.

Kathie's academic career continued to develop throughout her time at Flinders, progressing from her initial appointment as Lecturer to Professor in Clinical Pharmacology. Her teaching crossed discipline boundaries, covering medicine, nursing, nutrition and dietetics, and paramedic sciences. She was a recipient of the ASCEPT Teaching Excellence Award in 2010, which recognised her outstanding contribution to student learning. She retired in 2014 and is now an Emeritus Professor in the Department of Clinical Pharmacology in the College of Medicine and Public Health, Flinders University. She remains passionate about the discipline of pharmacology.

Kathie's research interests centred on drug metabolism, specifically the metabolism of non-steroidal antiinflammatory drugs and their mechanisms of renal toxicity. An invited speaker at national and international conferences, she has published over 75 research articles and reviews in peer-reviewed international journals and six book chapters.

Shaunagh Darroch

Shaunagh completed a Bachelor of Science degree at Monash University, majoring in pharmacology and physiology. She subsequently moved to the Victorian College of Pharmacy (now Monash University). There she completed a Master of Pharmacy degree under the supervision of Dr Frederick Mitchelson, in the field of cholinergic pharmacology.

Shaunagh's academic career has involved lecturing and tutoring positions, including at Monash University, La Trobe University and Victoria University within the disciplines of pharmacy, paramedicine, nursing and midwifery, podiatry, physiotherapy, and health and biomedical sciences. She has been involved in course and curriculum development, as well as face-to-face and online teaching of basic, advanced and clinical pharmacology, physiology and pathophysiology. She has been a visiting lecturer at the University of Hong Kong, School of Professional and Continuing Education and the Fiji School of Medicine.

Alongside her many research publications and communications, Shaunagh has been a contributor to a number of Australian and international textbooks, including the previous editions of *Pharmacology for Health Professionals*. Her research interests have ranged from G protein-coupled receptors through to paramedic clinical practice.

Shaunagh continues to be an enthusiastic educator and communicator. She is currently involved in curriculum design and development across several universities, in addition to writing and editing consultancies in various disciplines.

Andrew Rowland

Andrew completed a PhD investigating better ways to use *in vitro* models to predict drug metabolism in humans in 2009. He then spent two years as a post-doctoral researcher before taking up an academic position in the School of Medicine at Flinders University. Now Senior Lecturer, Andrew contributes to the teaching of pharmacology and therapeutics within a range of medical and health degrees, including the Doctor of Medicine, Bachelor of Paramedic Science and Masters of Advanced Clinical Practice degrees.

Andrew is an analytical chemist and triallist with a research interest in translating the science of pharmacokinetics into



clinical practice through the optimisation of drug dosing, with a specific focus on precision dosing of anticancer drugs. He has published more than 50 research articles and reviews in peer-reviewed international journals. In 2017, he received the prestigious Certara New Investigator

Award from the Australasian Society of Clinical and Experimental Pharmacologists and Toxicologists and a Vice Chancellors Award for Early Career Researchers in recognition of his 'outstanding contributions to excellence in research' in 2013.

BOOK AT A GLANCE

Get the most out of your textbook by familiarising yourself with the key features of this new edition of *Pharmacology for Health Professionals*.

Colours

DRUG MONOGRAPH 3.1 • Paracetamol

Paracetamol, having little antiinflammatory action, is rather

DRUG INTERACTIONS 22.1 Atorvastatin

DRUG	POSSIBLE EFFECTS
Atorvastatin	...

TABLE 3.1 Examples of drugs available OTC

SYSTEM OR INDICATION	CONDITION TREATED
Gastrointestinal tract	Peptic ulcers

DRUGS AT A GLANCE 22 Lipid-lowering drugs

THERAPEUTIC GROUP	PHARMACOLOGICAL GROUP
Lipid-lowering drugs	...

CLINICAL INTEREST BOX 3.4 Indigenous Australian plants and preparations

The origins of Indigenous Australian ethnobotany and medicinal plant usage predate Western medicine by many millennia, and are still preserved and implemented today. Active constituents of plants, such as tannins, oils, mucilages, latex and gums, vary in strength seasonally and geographically. Traditionally, plants were used as fresh preparations in a range of ways: for inhalation of aromatic oil vapour or of crushed leaves, drinking an infusion of leaves or bark, as 'kinos' (resins and gums), and crushed plants for topical administration as poultices or ointments.

DRUG MONOGRAPHS describe important aspects of either the prototype of a drug group or the most commonly prescribed drug of a group.

DRUG INTERACTIONS TABLES highlight drug interactions of clinical relevance.

TABLES AND BOXES provide additional information and summaries on a range of topics.

DRUGS AT A GLANCE TABLES summarise the main therapeutic groups and give examples of key drugs. This feature will help you to revise chapters.

CLINICAL INTEREST BOXES contain items of general interest, including specialist New Zealand content.

Icons

Specific icons highlight information of relevance to some health professional groups within the Australasian region. Additionally, in some instances, the icons point to Evolve online resources where further information may be found.

- C** Complementary Medicine
- M** Midwifery
- N** Nursing
- P** Paramedic
- NZ** New Zealand

Visit <http://evolve.elsevier.com/AU/Bryant/pharmacology/>.

Text

Chapters have been carefully structured to aid learning. Chapter openings are designed to help you focus and mentally organise content.

CHAPTER FOCUS highlights what you will learn in the chapter.

KEY DRUG GROUPS lists the drug groups addressed in that chapter.

KEY ABBREVIATIONS introduces the abbreviations and acronyms that will be used, and provides a quick reference point.

KEY TERMS lists the essential terminology that is bold-faced in the text.

CHAPTER 3
OVER-THE-COUNTER DRUGS AND COMPLEMENTARY THERAPIES

Key Drug Groups

- COMPLEMENTARY AND ALTERNATIVE MEDICINE PRODUCTS:
 - + Herbal remedies (CIB 3.3); cranberry (DM 3.2)
 - + Indigenous remedies (CIB 3.4)
 - + Traditional Chinese medicines: scutellaria/huang qin (DM 3.3)
- OVER-THE-COUNTER DRUGS:
 - + Listed products
 - + Nutritional supplements: minerals and vitamins (CIB 3.1); fish oils (CIB 3.2)
 - + Pharmacist-Only (S3)
 - + Pharmacy-Only (S2)
 - + Registered products
 - + Unscheduled products: paracetamol (DM 3.1)

Chapter Focus

Many drugs are considered safe for the treatment of minor illnesses without requiring a prescription or regular supervision of a licensed healthcare professional; such drugs are available 'over-the-counter' (OTC). Typical OTC products are analgesics, antacids, laxatives, cough/cold preparations, antihistamines and antidiarrhoeal agents. Nutritional supplements such as vitamins and minerals are also readily available. Problems can occur from people self-medicating in treating minor illnesses – for example, adverse effects, drug interactions, drug toxicity, inadequate treatment, and drug overuse or misuse.

Complementary and alternative medicines (CAM) such as herbal remedies are also available OTC and commonly employed; most of these products are not assessed for safety and effectiveness. This chapter reviews the regulatory differences between Prescription-Only and OTC drugs, herbal remedies, nutritional supplements and CAM products, and discusses general considerations of OTC drugs, herbal remedies and various CAM modalities, issues and problems likely to arise, and marketing and consumer education for their safe administration.

Key Abbreviations

ADR	adverse drug reaction	OTC	over-the-counter
CAM	complementary and alternative medicine	S2	Pharmacy-Only
EBM	evidence-based medicine	S3	Pharmacist-Only
NSAIDS	non-steroidal antiinflammatory drugs	S4	Prescription-Only
		TCM	traditional Chinese medicine
		TGA	Therapeutic Goods Administration

Key Terms

complementary and alternative medicine
contamination
efficacy
evidence-based medicine
herbal remedies
Listed medicines
over-the-counter (OTC) medicines
Registered medicines
safety
self-medication
traditional Chinese medicine

822 UNIT 13 | DRUGS AFFECTING MICROORGANISMS

or vancomycin, for more than 2 days should have plasma drug concentrations monitored at the appropriate times.

- Whenever possible, samples for culture should be taken before initiating antibiotic therapy. Usual sites cultured include sputum, urine, blood, wound or non-healing topical sites.
- Antibiotic therapy should be continued until infection is no longer present; however, the duration should not exceed the usual treatment time established for the suspected infection. Prophylactic antibiotic therapy given after uncomplicated surgery is usually discontinued within 48 hours, with a few exceptions such as cardiac surgery.

KEY POINTS: Combating antimicrobial resistance

- Strategies to combat antimicrobial drug resistance include encouraging optimal use of antimicrobials; selective control, restriction or removal of antimicrobial agents or classes; use of antimicrobial drugs in rotation or cyclic patterns; and use of combinations of antimicrobial drugs to prevent emergence of resistance.
- Superinfection is an infection that occurs during antimicrobial therapy delivered for therapeutic or prophylactic reasons.
- Guidelines have been developed for the prudent use of antibiotics. They include: using an antibacterial drug only when indicated; identifying the infecting microorganism; determining the susceptibility of the microorganism; using a drug with the narrowest spectrum of activity for the known or likely organism; using a single drug unless combination therapy is specifically indicated to ensure efficacy or reduce the emergence of resistance; using a dose of drug that is high enough to ensure efficacy with minimal toxicity and reduces the likelihood of resistance; and using a short duration of treatment (e.g. 1 week) unless evidence indicates that a longer duration is required.

Review exercises

- 1 Providing specific examples, compare and contrast the characteristics and clinical imperatives of intrinsic and acquired mechanisms of resistance to antibiotics.
- 2 Providing examples, describe what is meant by the term 'superinfection'.
- 3 Mr OM, a 50-year-old male, is unresponsive to the narrow-spectrum penicillins and it is concluded that he has a resistant strain of *Staphylococcus aureus*.
- 4 Mrs ST has presented to hospital with a high fever and rash and is diagnosed with a systemic bacterial infection. In determining a treatment plan for Mrs ST, outline the general guidelines for the prudent use of antibiotics.

REFERENCES/ACKNOWLEDGEMENTS & FURTHER READING

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ONLINE RESOURCES

ESMO Guidelines: www.esmo.org/Guidelines

EVQ evidence-based treatment protocols: <https://www.evq.org.au/>

National Cancer Institute: <https://www.cancer.gov/research/ncis/treatment/>

NCCN: Evidence-Based Cancer Guidelines: https://www.nccn.org/Therapeutic_Goods_Administration: www.tga.gov.au/index.htm

More web links at: <http://evolve.elsevier.com/ALU/Bryant/pharmacology/>

KEY POINTS BOXES reinforce your learning and help you to review material.

REVIEW EXERCISES are given for every chapter to help you master the material in manageable parts.

REFERENCES/ACKNOWLEDGEMENTS & FURTHER READING is an up-to-date bibliography at the end of each chapter, with references relevant to Australia and New Zealand as well as overseas.

ONLINE RESOURCES lists key websites where you can find additional information. Further web links are also supplied on the Evolve site for this text.

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PREFACE

Pharmacology is a universal discipline, but the availability of drugs and the patterns of their use differ between countries. Most pharmacology texts are written for health professionals and students in the northern hemisphere; this fifth edition continues to be ideally suited to the needs of all health professionals practising in Australia and New Zealand. The discussion of drugs reflects the names used, and their availability and clinical use, within the Australasian region, and the material on drug legislation and ethical principles focuses on regional aspects. To complement and enhance this regional flavour, information on traditional medicinal plants and patterns of use of medicines by Indigenous Australian, New Zealand Māori and Pacific Islander peoples is interspersed in relevant chapters. We acknowledge that paramedics and practitioners of some other professions, such as nursing, midwifery, podiatry, physiotherapy, optometry and orthoptics, are increasingly being granted limited prescribing rights, and additional information relevant to these emerging roles has been incorporated throughout the fifth edition.

As much of pharmacology is predicated on an understanding of physiology and biochemistry, the fifth edition showcases fully updated, revised and condensed chapters that reduce the overlap of material. The content is more concise and reflects recent epidemiological data, research findings, the introduction of new drugs, withdrawals of old drugs, and changes in recommendations and guidelines from learned bodies on the pharmacological management of disease conditions. Many of the figures have been redrawn and new figures included to enhance understanding and interest. This edition also features:

- ◆ new Key Points boxes that provide a snapshot of important and relevant information
- ◆ new and updated Drug Monographs using either the prototype of a drug group or the most commonly prescribed drug of a group, or drugs that have gained ‘drug of first choice’ status
- ◆ tables containing more details of drug interactions occurring with major drug groups
- ◆ information on recent changes in the pharmacological management of major conditions, including asthma,

cardiac failure, cancers, stroke, dementia, diabetes mellitus, epilepsy, HIV, hypertension, osteoporosis, rheumatoid arthritis, macular degeneration, otitis media, endometriosis, common complications of pregnancy and childbirth, and on anaesthesia in surgery and analgesia and sedation for children

- ◆ new and updated Clinical Interest Boxes, including descriptions of items of special interest specific to New Zealand and of typical pharmacological treatment of common diseases and conditions
- ◆ annotated references as a guide to the quality, readability or informative nature of new reviews on drugs and the management of major diseases, and guidelines for clinical choice and use of drugs
- ◆ enhanced information on the use of complementary and alternative medicine (CAM) modalities, and on interactions between drugs and CAM therapies
- ◆ a full-colour treatment to distinguish the text elements and make navigating the text easy.

With advances in drug development, drugs in clinical use continue to have a high rate of obsolescence; the facts learned for a particular drug may therefore become irrelevant when each year brings new drugs with differing modes of action. With an emphasis on personalised or precision medicine, the challenge for health professionals is to stay up to date with advances in the field of pharmacology and their impact on the quality use of medicines. We have retained both a scientific and a clinical approach, founded on evidence-based medicine and emphasising always the clinical use and therapeutic/adverse effects of drugs. Information on the clinical use of drugs is based especially on data in the *Australian Medicines Handbook*, the *Therapeutic Guidelines* series and reviews in *Drugs*, the *Medical Journal of Australia*, *Australian Family Physician* and *Australian Prescriber*. We are confident that this fifth edition will continue to fulfil the needs of students and academics in all health professions and will make the study of pharmacology logical, enjoyable, easy and, above all, interesting.

2018



ACKNOWLEDGEMENTS

The authors thank all readers (students, academics and colleagues) who have provided helpful and constructive comments, which we have addressed in this edition.

The authors thank and acknowledge the invaluable assistance of the following people, whose time and expertise contributed to the accuracy and clarity of the information:

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The authors and Elsevier Australia are grateful to the following reviewers for their insightful observations and recommendations, which greatly assisted us in developing the fifth edition:

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Colleagues and Editors

We would like to acknowledge the support of our colleagues at Flinders University (KMK, AR), the University of Melbourne (BJB), Victoria University (SD) and the authors who previously kindly gave permission to use or adapt their work for our purposes, in particular Professors John Murtagh, George Sweeney and the late Bill Bowman.

Our role as authors has again been challenging, and we record our thanks to staff and associates of Elsevier Australia, especially Melinda McEvoy, Natalie Hunt, Elizabeth Coady and Anitha Rajarathnam, for their stimulus, guidance and patience; editor Robyn Flemming for her editorial rigour; and pharmacists Jerry Perkins and Lynne Mackinnon for their careful technical checking. It is inevitable that recommendations for drug indications, availability, scheduling and dosage will change and current drug information sources should always be consulted prior to drug administration. We apologise for any errors and welcome comments and feedback on the fifth edition of *Pharmacology for Health Professionals*.

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NOTES TO THE USER

Book Structure

As with previous editions, this book is divided into units: Units 1 and 2 introduce general aspects of the clinical use of drugs and the principles of pharmacology; Units 3–11 consider drugs acting on the major systems of the body, from the autonomic nervous system through to the reproductive system; Units 12–14 cover drugs affecting general pathological conditions, including neoplasia, infections and inflammations; and Unit 15 includes discussions of drugs used in sport and in the treatment of obesity, and a chapter on envenomation and antivenoms.

To enhance learning, chapters begin with a brief introduction of the key physiological, biochemical and pathological processes that underpin the subsequent discussions of pharmacology. We consider that this approach facilitates an understanding of the cellular and molecular aspects of drug action, the rationales for the clinical use of drugs in particular disease processes, and their therapeutic and adverse effects and drug interactions. Throughout each chapter, snapshots of key information are provided in the new Key Points boxes.

In some chapters, information is based on drug groups, with relevant details of the diseases for which they may be indicated, whereas in others the flow of information starts with the diseases or conditions and leads on to a discussion of the drug groups relevant to treatment. Drug Monographs give detailed information on key drugs as prototypes of those commonly used. It should be noted that specific pharmacokinetic data, individual adverse effects and drug interactions vary between drugs in the same group; reference texts and current databases should be consulted for such information.

Terms and spelling

It is inevitable that with harmonisation many spellings and terminologies about which people feel strongly will change. We have agreed on the following usages, and apologise to those we offend:

- ◆ Although the terms ‘adverse effect’, ‘adverse reaction’ and ‘adverse event’ are often used (mistakenly) interchangeably, we have standardised the use of these terms throughout the book. Simply stated, a drug causes an *adverse effect*, a patient suffers an *adverse reaction* to a drug, and an *adverse event* occurs while a person is taking a drug but it is not necessarily due to the drug (see [Ch 8](#) for full explanations).
- ◆ Drugs affecting (a system): we have used this term purposely at times – for example, in ‘Drugs Affecting the Skin’ – to include not only drugs used in the treatment of conditions of the organ or system, but also drugs that may have adverse effects particularly in

that system, or may be administered to that tissue to have an action elsewhere in the body.

- ◆ Drug names: throughout the text, Australian-approved (generic) drug names are used. However, in line with recommendations from the TGA (2016), drug names have been updated consistent with International Non-Proprietary Names (INNs). When these are markedly different from American and/or Canadian names, this may be noted for clarity; thus ‘... paracetamol, known as acetaminophen in the United States ...’. As drugs may be marketed under multiple trade names that are subject to frequent changes or deletions, we have not included trade names except in instances where readers may be so familiar with a trade name as to identify most readily with it – for example, diazepam, marketed as Valium; paracetamol, marketed as Panadol; or sildenafil, marketed as Viagra.
- ◆ Dysrhythmia: although the terms ‘arrhythmia’ and ‘antiarrhythmic drugs’ occur frequently in the literature, we have chosen to use the terms ‘dysrhythmia’ and ‘antidysrhythmic drugs’. The prefix ‘a’ means ‘without’ and, in that regard, the only arrhythmia is asystole.
- ◆ We have now adopted the generally accepted spelling ‘fetus’ rather than ‘foetus’.
- ◆ Gonadotrophin (for example): the suffix ‘trophic’ means bringing nourishment, whereas ‘tropic’ means turning or moving in response to a stimulus; they appear to have become interchangeable in words such as gonadotrophin. There is an understanding that the English term is ‘-trophin’, whereas ‘-tropin’ is American usage. We have standardised on the form -trophin except where the approved name for a hormone or drug is otherwise, as in somatotropin and follitropin.
- ◆ Receptor: because many drugs interact with molecular targets (e.g. enzymes, ion channels and receptors), we have chosen to standardise the use of the term ‘receptor’ in accordance with the IUPHAR Committee on Receptor Nomenclature and Drug Classification 1998 (see [Ch 4](#)).
- ◆ 5-hydroxytryptamine: in line with accepted terminology, the term ‘5-hydroxytryptamine’, abbreviated as 5-HT, is used throughout this book. Use of the term ‘serotonin’ is restricted to the first mention of 5-HT in a chapter (as a reminder that this is synonymous with 5-HT) and in reference to specific drug groups – for example, selective serotonin reuptake inhibitors.

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- 17.2 Geriatric implications of anticholinergic drugs
- 17.3 Bulgarian snowdrops for Alzheimer's disease
- 18.1 Corticosteroid-containing contacts
- 18.2 Angel's trumpet has devilish effects
- 18.3 The first commandment of eye care
- 18.4 Complementary and alternative therapies in ocular medicine
- 18.5 Statins: to stop or not to stop?
- 18.6 Waxing not-so-lyrical
- 18.7 Otitis media in a child
- 18.8 Sudden hearing loss after metronidazole
- 19.1 Substance abuse among Australasian anaesthetists
- 19.2 Complementary and alternative therapies in drug dependence
- 19.3 Poppy seed tea: not a refreshing cuppa!

- 19.4 An overdose in an opioid-dependent newborn baby
- 19.5 Alcohol-based hand sanitiser: NOT TO BE TAKEN!
- 19.6 Amphetamines as neuro-enhancers? Not!
- 19.7 Cocaine and Coca-Cola
- 19.8 Coffee, tea, cocoa, cola or energy drink?
- 19.9 Hallucinogens
- 20.1 Heart failure: The New York Heart Association functional classification
- 20.2 Management of heart failure
- 21.1 Management of acute coronary syndrome
- 21.2 Hypertension
- 21.3 Drugs, complementary/alternative medicines and hypertension
- 21.4 ACE inhibitor cough
- 22.1 Pfizer ceases development of bococizumab
- 22.2 Are fish oils and omega-3 fatty acids beneficial in CV disease?
- 23.1 Drug-mediated acute kidney injury in nursing home residents
- 23.2 Bladder dysfunction: New drug targets in the CNS
- 24.1 Coagulation tests
- 24.2 New oral anticoagulant reversal drug
- 25.1 The Haematological module and the Athlete Biological Passport (ABP)
- 26.1 Puffers and spacers
- 26.2 Oxygen administration in the premature infant
- 26.3 Asthma in the Australian community
- 26.4 Asthma in New Zealand and Pacific Island countries
- 26.5 Not in the script – a case of drug-induced asthma
- 26.6 Sodium cromoglycate: a most unusual drug
- 26.7 Acute asthma in a child
- 26.8 Chicken soup, camphor and CAM
- 27.1 Fluoridated water
- 27.2 Gastro-oesophageal reflux disease
- 27.3 *Helicobacter pylori*
- 27.4 Nausea and vomiting in pregnancy
- 27.5 Alternatives to laxative therapy
- 27.6 Australian medicinal plants
- 27.7 Peppermint oil
- 28.1 Melatonin, hormonal messenger of darkness?
- 28.2 Cows prevent Creutzfeldt–Jakob disease
- 28.3 Dopamine and lactation
- 28.4 Oxytocin in childbirth
- 29.1 Addison's, Cushing's and Conn's
- 29.2 Glucocorticoids, the HPA and alcohol use disorders
- 30.1 History of diabetes and insulin
- 30.2 Diabetes: worldwide, and in Australia and New Zealand
- 30.3 Snail-based, not snail-paced insulin
- 30.4 Units of insulin activity
- 30.5 Insulin in gestational diabetes
- 30.6 Complementary and alternative therapies in diabetes mellitus
- 31.1 Thyroid function tests
- 31.2 Lugol's solution
- 31.3 Rickets, vitamin D and sunshine
- 31.4 Prevalence of osteoporosis in Australia and New Zealand
- 32.1 The 'puberty clock'
- 32.2 Should menstruation be optional?
- 32.3 Management of endometriosis
- 32.4 History of the oral contraceptive pill
- 32.5 Emergency contraception in Australia
- 32.6 'Rhythm methods' for natural family planning
- 32.7 Australian categorisation system for prescribing medicines in pregnancy
- 32.8 Ergot, St Anthony, witches and Dale
- 32.9 Dinoprostone gel for induction of labour
- 32.10 Complementary and alternative therapies in women's conditions
- 33.1 A famous survivor of male breast cancer
- 33.2 Male infertility and androgen deficiency
- 33.3 The 'male pill'
- 33.4 Sex, serendipity, sildenafil and share prices
- 33.5 Beware the blistering beetle!
- 33.6 Complementary and alternative therapies in men's conditions
- 34.1 What patients want to know
- 34.2 Safe handling of cytotoxic agents
- 35.1 Febrile neutropenia caused by cytotoxic chemotherapy
- 35.2 Milestones in the history of antineoplastic chemotherapy
- 35.3 First tissue agnostic anticancer drug approval
- 36.1 The antimicrobial creed
- 37.1 Prehospital treatment of meningococcal infection
- 37.2 Penicillin rash and anaphylaxis
- 37.3 Midwife PBS prescribing of antibiotics
- 38.1 Reactivation of HBV in patients treated with direct acting antivirals
- 38.2 The high cost of curing HCV
- 38.3 The rollercoaster journey to find an HIV vaccine
- 39.1 G and T: the tonic for malaria
- 39.2 Leprosy incidence
- 40.1 NSAIDs and acute myocardial infarction
- 40.2 TNF- α antagonists and infections
- 41.1 Poisoning through the skin
- 41.2 Ancient plants with modern uses
- 41.3 Sunburn, skin cancer and sun protection factors
- 41.4 Nanopharmacology
- 41.5 Vitamin A, Antarctica and acne
- 41.6 Spray-on skin and scaffolding matrices
- 41.7 'Isn't it funny, how a bear likes honey?'



41.8 When tattoos are too much of a good thing
42.1 Some doping-in-sport cases
42.2 Complementary and alternative therapies in sport
42.3 Some attitudes to doping in sport
43.1 New Zealand obesity statistics

43.2 We are what we eat!
44.1 Management of snake bite
44.2 Snake bites and maternal/fetal/neonatal deaths
44.3 Presumptive *Latrodectus katipo* bite and myocarditis
44.4 Irukandji syndrome



DRUG MONOGRAPHS

- | | | |
|--|----------------------------------|---|
| 2.1 Ketamine | 19.2 Alcohol (ethanol) | 30.4 Glipizide |
| 2.2 Vitamin K for newborn babies | 19.3 Thiamine | 31.1 Thyroxine sodium |
| 3.1 Paracetamol | 19.4 Nicotine gum | 31.2 Carbimazole |
| 3.2 Cranberry | 19.5 Cannabis extract for | 31.3 Radioactive iodine |
| 3.3 Scutellaria / <i>huang qin</i> / baical skullcap | oromucosal spray | 31.4 Calcitriol |
| 9.1 Bethanechol | 20.1 Disopyramide | 31.5 Calcitonin salmon (salcatonin) |
| 9.2 Atropine | 20.2 Flecainide | 31.6 Cinacalcet |
| 9.3 Neostigmine | 20.3 Amiodarone | 32.1 Human chorionic gonadotrophin (hCG) |
| 9.4 Pancuronium | 20.4 Adenosine | 32.2 Estradiol valerate |
| 9.5 Suxamethonium | 21.1 Glyceryl trinitrate | 32.3 Levonorgestrel |
| 10.1 Adrenaline | 21.2 Perindopril | 32.4 Clomifene citrate |
| 10.2 Prazosin | 21.3 Valsartan | 32.5 Intrauterine device with copper |
| 10.3 Carvedilol | 21.4 Eplerenone | 32.6 Ergometrine |
| 11.1 Nitrous oxide | 22.1 Atorvastatin | 33.1 Testosterone undecanoate depot injection |
| 11.2 Sevoflurane | 22.2 Evolocumab | 33.2 Dutasteride |
| 11.3 Propofol | 23.1 Furosemide (frusemide) | 33.3 Sildenafil |
| 11.4 Lidocaine (lignocaine) | 23.2 Oxybutynin | 35.1 Cyclophosphamide |
| 12.1 Morphine | 24.1 Enoxaparin | 35.2 Methotrexate |
| 12.2 Fentanyl | 24.2 Warfarin | 35.3 Fluorouracil |
| 13.1 Diazepam | 26.1 Xylometazoline nasal spray | 35.4 Tamoxifen |
| 13.2 Midazolam | 26.2 Salbutamol and terbutaline | 35.5 Erlotinib |
| 14.1 Topiramate | 26.3 Theophylline | 35.6 Pembrolizumab |
| 14.2 Phenytoin | 26.4 Beclometasone inhaled | 37.1 Piperacillin with tazobactam |
| 15.1 Chlorpromazine | 26.5 Codeine and pholcodine | 37.2 Gentamicin |
| 15.2 Aripiprazole | 26.6 Influenza vaccine | 38.1 Aciclovir |
| 15.3 Fluoxetine | 27.1 Nystatin | 38.2 Sofosbuvir |
| 15.4 Lithium | 27.2 Omeprazole | 38.3 Efavirenz |
| 16.1 Dexamfetamine | 27.3 Metoclopramide | 39.1 Metronidazole |
| 16.2 Caffeine | 27.4 Ondansetron | 39.2 Isoniazid |
| 17.1 Baclofen | 27.5 Lactulose | 39.3 Rifampicin |
| 17.2 Levodopa–carbidopa | 27.6 Mesalazine | 40.1 Ciclosporin (cyclosporin) |
| 17.3 Selegiline | 28.1 Octreotide | 40.2 Allopurinol |
| 17.4 Sumatriptan | 28.2 Somatropin, recombinant hGH | 41.1 Amorolfine nail lacquer |
| 18.1 Latanoprost | 28.3 Desmopressin nasal spray | 41.2 Tretinoin creams |
| 18.2 Ketotifen | 29.1 Prednisolone and prednisone | 41.3 Silver sulfadiazine |
| 18.3 Botulinum toxin | 29.2 Fludrocortisone | 42.1 Epoetin alfa |
| 18.4 Betahistine | 30.1 Glucagon | 43.1 Orlistat |
| 19.1 Methadone oral syrup | 30.2 Human insulin | |
| | 30.3 Metformin | |



DRUG MONOGRAPHS A–Z

- 38.1 Aciclovir
- 20.4 Adenosine
- 10.1 Adrenaline
- 19.2 Alcohol (ethanol)
- 40.2 Allopurinol
- 20.3 Amiodarone
- 41.1 Amorolfine nail lacquer
- 15.2 Aripiprazole
- 22.1 Atorvastatin
- 9.2 Atropine
- 17.1 Baclofen
- 26.4 Beclometasone inhaled
- 18.4 Betahistine
- 9.1 Bethanechol
- 18.3 Botulinum toxin
- 16.2 Caffeine
- 31.5 Calcitonin salmon (salcatonin)
- 31.4 Calcitriol
- 19.5 Cannabis extract for oromucosal spray
- 31.2 Carbimazole
- 10.3 Carvedilol
- 15.1 Chlorpromazine
- 40.1 Ciclosporin (cyclosporin)
- 31.6 Cinacalcet
- 32.4 Clomifene citrate
- 26.5 Codeine and pholcodine
- 3.2 Cranberry
- 35.1 Cyclophosphamide
- 28.3 Desmopressin nasal spray
- 16.1 Dexamfetamine
- 13.1 Diazepam
- 20.1 Disopyramide
- 33.2 Dutasteride
- 38.3 Efavirenz
- 24.1 Enoxaparin
- 21.4 Eplerenone
- 42.1 Epoetin alfa
- 32.6 Ergometrine
- 35.5 Erlotinib
- 32.2 Estradiol valerate
- 22.2 Evolocumab
- 12.2 Fentanyl
- 20.2 Flecainide
- 29.2 Fludrocortisone
- 35.3 Fluorouracil
- 15.3 Fluoxetine
- 23.1 Furosemide (frusemide)
- 37.2 Gentamicin
- 30.4 Glipizide
- 30.1 Glucagon
- 21.1 Glyceryl trinitrate
- 32.1 Human chorionic gonadotrophin (hCG)
- 30.2 Human insulin
- 26.6 Influenza vaccine
- 32.5 Intrauterine device with copper
- 39.2 Isoniazid
- 2.1 Ketamine
- 18.2 Ketotifen
- 27.5 Lactulose
- 18.1 Latanoprost
- 17.2 Levodopa–carbidopa
- 32.3 Levonorgestrel
- 11.4 Lidocaine (lignocaine)
- 15.4 Lithium
- 27.6 Mesalazine
- 30.3 Metformin
- 19.1 Methadone oral syrup
- 35.2 Methotrexate
- 27.3 Metoclopramide
- 39.1 Metronidazole
- 13.2 Midazolam
- 12.1 Morphine
- 9.3 Neostigmine
- 19.4 Nicotine gum
- 11.1 Nitrous oxide
- 27.1 Nystatin
- 28.1 Octreotide
- 27.2 Omeprazole
- 27.4 Ondansetron
- 43.1 Orlistat
- 23.2 Oxybutynin
- 9.4 Pancuronium
- 3.1 Paracetamol
- 35.6 Pembrolizumab
- 21.2 Perindopril
- 14.2 Phenytoin
- 37.1 Piperacillin with tazobactam
- 10.2 Prazosin
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- 11.3 Propofol
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- 3.3 Scutellaria / *huang qin* / baical skullcap
- 17.3 Selegiline
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- 33.3 Sildenafil
- 41.3 Silver sulfadiazine
- 38.2 Sofosbuvir
- 28.2 Somatropin, recombinant hGH
- 17.4 Sumatriptan
- 9.5 Suxamethonium
- 35.4 Tamoxifen
- 33.1 Testosterone undecanoate depot injection
- 26.3 Theophylline
- 19.3 Thiamine
- 31.1 Thyroxine sodium
- 14.1 Topiramate
- 41.2 Tretinoin creams
- 21.3 Valsartan
- 2.2 Vitamin K for newborn babies
- 24.2 Warfarin
- 26.1 Xylometazoline nasal spray

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UNIT 1 Introduction to Pharmacology

— CHAPTER 1 — DRUGS AND MEDICINES

Key Drug Groups

- ♦ Australian drugs: **venetoclax**
- ♦ Drugs from plants
- ♦ Essential drugs
- ♦ Families of drugs
- ♦ Historical drugs
- ♦ Prototypes
- ♦ The ideal drug
- ♦ Top 10 drugs in Australia and New Zealand
- ♦ Useful drugs(?): **teriparatide**, **glucosamine**

Key Terms

approved name
(bio)assay
chemical name
clinical trial
dose
dose form/formulation
drug
drug development
formulary
generic name
indication
key, or prototype, drug
medication
medicine
over-the-counter (OTC) drug
pharmaceutical
pharmaceutics
pharmacist
pharmacodynamics
pharmacokinetics
pharmacology/pharmacologist
pharmacopoeia
pharmacy/pharmacist
potency

Chapter Focus

This chapter focuses on the origin, development and scope of pharmacology. It describes the physical and chemical characteristics of drugs, how drugs are named and classified, and how drug information can be sourced. The routes and stages of drug discovery and development, including the phases and important elements in clinical trials of investigational drugs, are outlined. An understanding of these basic areas of pharmacology is important in the quality use of medicines in healthcare.

Key Abbreviations

AMH	<i>Australian Medicines Handbook</i>	INN	International Non-proprietary Name
APF	<i>Australian Pharmaceutical Formulary and Handbook</i>	IU	International Units
		MSF	<i>Médecins Sans Frontières</i> (Doctors Without Borders)
ASCEPT	Australasian Society of Clinical and Experimental Pharmacologists and Toxicologists	NZF	<i>New Zealand Formulary</i>
		OTC	over-the-counter
		PSA	Pharmaceutical Society of Australia
BP	<i>British Pharmacopoeia</i>	RACGP	Royal Australian College of General Practitioners
CIB	Clinical Interest Box		
CMI	consumer medicine information	RCCT	randomised controlled clinical trial
CTN	Clinical Trial Notification	TGA	Therapeutic Goods Administration
CTX	Clinical Trial Exemption	WHO	World Health Organization
DDD	defined daily dose		
DM	Drug Monograph		
HTS	high-throughput screening		

Key Terms—Continued

Prescription-Only drug
proprietary, or trade, name
randomised controlled clinical trial

receptor
route
selectivity

specificity
standardisation
structure–activity studies

INTRODUCTION

PHARMACOLOGY is the study of drugs, including their sources, nature, actions, effects in living systems, and uses. The word ‘**drug**’ is defined by the World Health Organization (WHO) as ‘any substance or product that is used or intended to be used to modify or explore physiological systems or pathological states for the benefit of the recipient’.¹

The prefix ‘pharmaco-’ is derived from the Greek word *pharmakon*, meaning ‘drug’ or ‘medicine’. Hence, we have related terms such as pharmacy, pharmacodynamics, pharmacokinetics, pharmaceuticals and pharmacopoeia (Table 1.1).

Pharmacologists may study the origins, isolation, purification, chemical structure and synthesis, assay (measurement), actions and mechanisms, economics, genetic aspects and toxicity of drugs, as well as their fate in the body and medical uses. Pharmacologists work in universities, hospitals and clinics, research institutions, drug companies, government departments of health, medical publishing – wherever drugs are developed, studied and used.

Pharmacology deals with all drugs used in society – legal and illegal, prescription and ‘over-the-counter’ (OTC) medications, endogenous substances (those produced within the body), natural and synthetic products – with beneficial or potentially toxic effects. The pharmacological agents available today have controlled, prevented, cured, diagnosed and in some instances eradicated diseases, and have improved the quality of life of billions of people.

Medications also have the potential to cause harm. (The ancient Greek word for ‘drug’ was also the word for ‘poison’.) To administer a drug safely, one must know the usual dose, frequency and route of administration, indications and contraindications, significant adverse reactions, major drug interactions, dietary implications (if applicable), and appropriate monitoring techniques and interventions, and apply this knowledge to the particular patient and situation.

¹If you asked a random selection of people – say, students in your university’s cafeteria or commuters at a bus-stop – what the word ‘drug’ means to them, they might come up with many interesting definitions!

DRUGS AND MEDICINES

Unfortunately, the word ‘drug’ has come to have connotations of illicit street drugs. However, it has a much simpler and wider meaning: a drug is a substance that usefully affects living tissues. The terms ‘**medication**’, ‘**medicine**’ and ‘**pharmaceutical**’ usually refer to drugs mixed in a formulation with other ingredients to improve the stability, taste or physical form, in order to allow appropriate administration of the active drug.

CHARACTERISTICS OF DRUGS

Potency, selectivity and specificity

By our broad definition of a drug as a chemical having useful action on living tissue, many substances could be classed as drugs: even oxygen, sugar, salt and water usefully affect the body but can be toxic in overdose. However, useful drugs usually have other important attributes: potency, selectivity and specificity (see [Clinical Interest Box \[CIB\] 1.1](#)).

Potency relates to the amount of chemical required to produce an effect; it is an *inverse* relationship – the more potent the drug, the lower the dose required for a given effect (see [Fig 4.6](#), in [Ch 4](#)). One of the most potent chemicals known is the natural bacterial product botulinum toxin (commonly known as Botox), for which the estimated human median lethal dose (LD₅₀) is about 1–1.5 x 10⁻⁷ g IV for a 70 kg adult. It is used to treat spasm of eye muscles and spasticity, in neurological disorders and in cosmetic surgery ([Drug Monograph \[DM\] 18.3](#)).

Selectivity refers to the narrowness of a drug’s range of actions on particular receptors, cellular processes or tissues. The antidepressant drugs known as selective serotonin reuptake inhibitors such as fluoxetine (Prozac – see [DM 15.3](#)) have fewer adverse effects than older antidepressants because of their more selective actions.

The term **specificity** may be used loosely like ‘selectivity’ – for example, cardiospecific or cardioselective β -blocking agents. Specificity may also refer to the relationship between the chemical structure of a drug and its pharmacological

TABLE 1.1 Some common pharmacological terms^a

Adverse drug reaction	An unintended and undesirable response to a drug
Clinical pharmacology	Pharmacology applied to the treatment of human patients; the study of drugs 'at the bedside'
Dose	The quantity of a drug to be administered at one time, determined by experience as likely to be safe and effective in most people
Dose form/formulation	The form in which the drug is administered – for example, as a tablet, injection, eye-drop or ointment
Drug	A substance used to modify or explore the physiological system or pathological state for the benefit of the recipient
Indication	An illness or disorder for which a drug has a documented specific usefulness
Medicine	Drug(s) given for therapeutic purposes; possibly a mixture of drug(s) plus other substances to provide stability in the formulation; also, the branch of science devoted to the study, prevention and treatment of disease
Pharmaceutics	The science of the preparation and dispensing of drugs
Pharmacist^b	A person licensed to store, prepare, dispense and provide drugs, and make up prescriptions
Pharmacodynamics	What drugs do to the body and how they do it; refers to the interaction of drug molecules with their target receptors or cells, and their biochemical, physiological and possibly adverse effects
Pharmacokinetics	How the body affects a specific drug after administration; that is, how a drug is altered as it travels through the body (by absorption, distribution, metabolism and excretion)
Pharmacologist^b	A person who studies drugs: their source, nature, actions and mechanisms, uses, fate in the body, medical uses and toxicity
Pharmacology	The study of drugs, including their actions and effects in living systems
Pharmacopoeia	A reference book listing standards for drugs approved in a particular country; may also include details of standard formulations and prescribing guidelines (a formulary)
Pharmacy	The branch of science dealing with preparing and dispensing drugs; also the place where a pharmacist carries out these roles
Receptor	Protein structure on or within a cell or membrane that is capable of binding to a specific substance (such as a transmitter, hormone or drug), initiating chemical signalling and causing altered function in the cell
Route	The pathway by which a drug is administered to the body; for example, in the oral route, the drug is taken by mouth and swallowed
Side effect	A drug's effect that is not necessarily the primary purpose for giving the drug in the particular condition; side effects may be desirable or undesirable. This term has been virtually superseded by the term 'adverse drug reaction', which is used throughout this book
Toxicology	The study of the nature, properties, identification, effects and treatment of poisons, including the study of adverse drug reactions

^aSee the Glossary (Appendix 2) for a more complete listing of pharmacological terms.

^bThe roles of these and many other health professionals are described in greater detail in Chapter 2.

CLINICAL INTEREST BOX 1.1 Is glucosamine a useful drug?

Two substances commonly administered to relieve osteoporosis (softening of the bones), teriparatide and glucosamine, may be compared in terms of their potencies, selectivities and specificities.

Teriparatide is a form of human parathyroid hormone (PTH) (see Ch 31), while **glucosamine** is a naturally occurring amino-monosaccharide.

	TERIPARATIDE	GLUCOSAMINE
Potency: active at plasma concentrations of:	High, at 200–300 pg/mL (50–70 picomolar)	Low, at 1.8 microgram/mL (10 micromolar)
Dose:	20 microgram subcutaneously daily	1.5 g orally daily
Biological selectivity:	High: binds to specific PTH cell surface receptors and activates osteoblasts to assist in bone formation and reduce osteoporotic bone fractures	Low: has potential to increase bone deposition; may reduce systemic inflammation and have antioxidative and other activities
Chemical specificity:	High: a recombinant form of PTH	Low: increases production of hyaluronic acid (a glycosaminoglycan) in connective tissues

1 pg = 10⁻¹² g; 1 microgram = 10⁻⁶ g.

As chemicals have potency, selectivity and specificity in order to be useful as drugs, by our definition glucosamine is unlikely to be a useful drug: it requires high doses (more than 100,000-fold higher than teriparatide) and has only general effects on many

tissues of the body. Glucosamine is a popular OTC drug; however, a meta-analysis of clinical trial results has shown that compared with placebo, glucosamine does not reduce joint pain or improve narrowing of joint space (Wandel et al, 2010).

actions; for example, the effects of salbutamol and similar bronchodilators in asthma are due to their chemical similarity to the neurotransmitter noradrenaline (see Fig 1.4, later), and hence their specificity for the β -adrenoceptor.

The ideal drug

In designing a new drug, a research pharmacologist might aim for it to be: easily administered (preferably orally) and fully absorbed from the gastrointestinal tract, not highly protein-bound in the blood plasma, potent, highly specific, selective, with rapid onset and useful duration of action, of high therapeutic index (no adverse drug reactions, no interference with body functions), unlikely to interact with any other drugs or foodstuffs, spontaneously eliminated, stable chemically and microbiologically, readily formulated into an easily taken form, and inexpensive.

Sadly, not even pharmacologists live in an ideal world, and so we must admit that there is no *ideal drug*, whether natural product or synthetic. It has been well said that any substance powerful enough to be useful is also powerful enough to do some harm. The decision to prescribe, administer or take a drug requires a risk–benefit analysis based on the best information available: do the likely therapeutic benefits (efficacy) outweigh the possible harmful effects (toxicity)? This efficacy/safety balance is indeed the main theme of this textbook.

Physical aspects of drugs

In terms of their physical state, drugs may be solids, liquids or gases. Most are solids at room temperature, but some are liquids in the pure state, such as nicotine, halothane (a general anaesthetic) and ethanol, and some are gases, especially general anaesthetics such as nitrous oxide. The formulation of drugs into suitable dose forms will be covered in the section on pharmaceuticals in Chapter 2.

Chemical aspects of drugs

Inorganic/organic

All drugs, whether found naturally in plants, animals, minerals or microorganisms, or synthesised in a laboratory, are chemicals of one sort or another, as described in Clinical Interest Box 1.2. They may be inorganic molecules such as calcium salts used to prevent and treat osteoporosis, or iodine and iron used to prevent mineral deficiencies. The vast majority of drugs, however, are organic molecules; that is, they contain carbon in their structures. All the major classes of organic compounds, including hydrocarbons, proteins, lipids, carbohydrates, nucleic acids and steroids, are represented in pharmacopoeias (see Fig 1.3, later). Many drug molecules are acids or bases, which is important not only for their taste and irritant effects but also for how the drugs move across membranes and are affected by metabolism and excretion (pharmacokinetics – see Ch 5).

CLINICAL INTEREST BOX 1.2 There's no such thing as a chemical-free lunch!

The term 'chemical' simply refers to any substance made up of elements (i.e. hydrogen, carbon, oxygen, etc.), and thus refers to all matter. Unfortunately, it has come to have derogatory connotations of something artificial or hazardous, largely due to misleading advertising by the 'natural products' industry, which is keen to imply that natural products are 'free' of (nasty) chemicals. The International Union of Pure and Applied Chemistry defines chemophobia as an 'irrational fear of chemicals'.

The Royal Society of Chemistry in Britain has become so irate at the misuse of the term 'chemical' that they decided to reclaim the word in its true sense, and offered a reward of £1 million to the first member of the public who could place in their hands any material shown to be chemical-free. As explained in their press release: 'The truth, as any right-minded person will say, is that everything we eat, drink, drive, play with and live in is made of chemicals – both natural and synthetic chemicals are essential for life as we know it' (Royal Society of Chemistry, 2010). Indeed, water and oxygen – the basic essentials for life – are, of course, chemicals, and anyone suggesting they are not, or that any natural product is chemical-free, is simply showing their scientific ignorance.

Note: No one has yet been able to claim the tantalising £1 million reward offered ...

Source: Royal Society of Chemistry (2010).

Molecular size

The sizes of drug molecules can also vary enormously, ranging from tiny lithium, the third-lightest element with an atomic mass of about 7, used as a specific antimanic agent, through to proteins such as insulin (molecular mass 5808 daltons) and erythropoietin (molecular mass 34 kilodaltons). Most drugs are in a more intermediate size range, with molecular weights (relative molecular masses) of between 100 and 1000. For example, aspirin has a molecular weight of 180, testosterone (a steroid hormone) 288, digoxin (a cardiac glycoside) 781, and ciclosporin (an immunosuppressant with a cyclic polypeptide structure) 1203. The size and nature of the molecule have important implications: proteins taken orally would be digested in the gut, so they must be administered by injection; large molecules generally will not readily pass through cell membranes and may need to be administered directly to their site of action.

A BRIEF HISTORY OF PHARMACOLOGY

MEDICINES IN ANTIQUITY AND PRE-SCIENTIFIC ERAS

For many thousands of years and in all civilisations, people have searched for substances to prevent, treat and cure disease.

Discovery of safe drugs presumably developed by trial and error, with many fatalities and adverse effects. Archaeological diggings show that Stone Age people used opium poppies (Ch 12) and Inca civilisations used cocaine (Ch 11). Artefacts discovered in the ruins of Pompeii indicate that first-century Romans used pills and potions, including plant materials (poppy, henbane, *Artemisia*, cannabis) and minerals. The timeline in Table 1.2 summarises the history of medicine and major drug discoveries, and Figure 1.1 shows portraits of four famous people from medical history.

INTO THE 20TH AND 21ST CENTURIES: 'MAGIC BULLETS'

Early in the 20th century, drugs commonly used in medicine were morphine and codeine as analgesics, sodium bicarbonate and glycerine for gastrointestinal problems, sodium bromide as a sedative, sodium salicylate as an antiinflammatory and antipyretic analgesic, and strychnine as a 'tonic'. During the 20th century, medicine made enormous advances, leading to therapeutic revolutions in all areas of medicine. Of 36 major events identified as the most significant in modern medicine

from 1935 to 1999 (Le Fanu, 1999), at least half are directly due to the development of effective drugs to treat diseases that were previously life-threatening.

As knowledge of chemistry, physiology, medicine and pharmacology developed, it was applied to the problem of finding drugs to treat specific conditions. The German chemist Paul Ehrlich, 'the father of chemotherapy', realised when working with synthetic dyes that the biological effect of a compound depends on its chemical composition. A major development was the production of safe, orally active synthetic antimicrobials (sulfonamides). In the 1930s and 1940s, penicillin was discovered, isolated and purified (by Fleming, Florey and Chain), revolutionising the treatment of microbial infections and leading to other antibiotics, such as streptomycin for tuberculosis (TB).

These successes led to a search for the 'magic bullet' – the mythical goal of finding a specific chemical to target a diseased tissue or cell, while leaving all other tissues intact.

Advances in synthetic organic chemistry led to the establishment of large-scale chemical manufacturing plants to produce drugs. Structure–activity studies identified series of molecules with agonist or antagonist actions on many



FIGURE 1.1

Famous people from medical history: **A** Hippocrates; **B** Galen; **C** Hildegard von Bingen; **D** Avicenna

A: Hippocrates (5th century BC, 'the father of medicine') taught that disease can be understood through careful diagnosis. He believed health was due to a balance of four 'humours' ebbing and flowing in the body (blood, phlegm, black bile and yellow bile); hence the related terms 'sanguine', 'phlegmatic', 'bilious', 'choleric' and 'melancholic'. His doctrine that opposites cure (cold treats fever, bleeding treats excess humours) was the basis of medicine for hundreds of years but eventually held up advances. Hippocrates still influences the practice of medicine, as in versions of the Hippocratic Oath proclaimed at many medical graduation ceremonies (see CIB 2.9). **B:** Galen of Pergamon (2nd century) wrote voluminously on medical, scientific, philosophical, ethical and religious issues; he considered that bleeding (removal of large volumes of blood) was appropriate treatment for virtually all disorders. Galen was famous for his knowledge of drugs, both 'simples' (i.e. simple herbal or mineral remedies) and complex mixtures known as 'galenicals', including exotic herbs, amulets, excrement and antidotes. **C:** Hildegard of Bingen was a remarkable writer, composer, prophet, healer and abbess during the Middle Ages. Her books described the causes of many diseases, and the medical and toxic properties of herbal, animal and mineral preparations. **D:** Avicenna (Abu-Ali Ibn Sina Balkhi), the most famous ancient Persian physician, lived in central Asia and Persia around AD 980–1037. He was a 'man for all seasons' – physician, philosopher, astronomer, chemist, mathematician, poet, teacher. His most famous works, *The Book of Healing* and *The Canon of Medicine*, were standard medical textbooks for centuries, even in French medical schools. Avicenna is considered to be 'the father of clinical pharmacology', as he introduced systematic experimentation, quantification, randomised clinical trials and efficacy tests into the study of physiology and infectious diseases.

B Lithograph by Pierre Roche Vignerot. **C&D:** Wellcome Library no. 4213i. CC BY 4.0.

TABLE 1.2 Timeline of medical history and major drug discoveries

TIME PERIOD	COMMENTS
3000–1500 BC	<p>Sumerian civilisation: prescriptions inscribed on clay tablets; vegetable and mineral drugs prepared in milk, beer and wine; supernatural healing rituals carried out by healers and shamans.</p> <p>Egyptian period: diseases believed caused by evil spirits in the body; Imhotep, the god of medicine, and Isis and Horus, gods of pharmacy, worshipped. The Ebers Papyrus, from about 1500 BC, described formulations of over 700 drugs from plant, mineral and animal sources.</p> <p>Chinese medicine dating back beyond 2000 BC included use of poisons and antidotes, acupuncture, diets and moxibustion (burning of incense herbs for heating skin); medicines included ephedra (ephedrine) for asthma and seaweeds (iodine) for goitre.</p> <p>Ancient Indian (Ayurvedic) medicine described many surgical practices and over 1000 natural drugs, including wine (alcohol) and hemp (marijuana) for pain relief.</p>
1100–146 BC	<p>Ancient Greek civilisation: the god Asclepius considered the principal god of healing, with his wife Epione soothing pain, and daughters Hygieia helping prevent disease and Panacea representing treatment (hence the phrase 'a panacea for all ills'). Hippocrates, Greek physician, 'the father of medicine': emphasis on humours and doctrine of opposites.</p>
100 BC – AD 400	<p>Roman Empire: medicine based on Greek traditions of herbal remedies and healing gods. Excellent public health measures introduced: safe water supplies and sanitation. Folk remedies included wound dressings of wine, vinegar, eggs, honey, worms and pig dung. Ephedra (ephedrine, a sympathomimetic agent) was used for asthma, cough and haemorrhage.</p> <p>Dioscorides' textbook <i>De Materia Medica</i> documented use of >600 medicinal plants and minerals, including analgesics, antiseptics, emetics and laxatives; translated into Latin, Arabic and Persian. Indian surgeon wrote the <i>Sushruta Samhita</i>, the classic text of Ayurvedic medicine. Celsus described four cardinal signs of inflammation and stressed importance of moderation, exercise, knowledge of anatomy, and prevention of infection and haemorrhage.</p>
2nd century	<p>Galen, Greek physician/surgeon/druggist: pharmacy based on 'simples' and complex mixtures now called galenicals (see prescription A in Fig 2.4).</p>
5th–11th centuries	<p>Dark Ages in Europe: herbal medicine, folklore, magic, religion, bleeding, surgery and cosmology interwoven and practised in monasteries. Learning carried out in Latin; libraries held Greek, Roman and Arabic medical texts. In some countries, women allowed to practise medicine and midwifery. Meanwhile in Arabia, China and India, medicine and herbal pharmacy developed.</p>
3rd–15th centuries	<p>Golden Age of Islamic medicine: folk medicines included camphor, henna, syrup, aloes, amber and musk; first set of drug standards formulated. Classic Greek medical works translated into Arabic; an extensive library collected in Baghdad. Persian physician Avicenna now revered as 'the father of clinical pharmacology'. Great contribution of Islamic medicine: establishment of teaching hospitals and medical libraries such as in Baghdad, Cairo and Damascus; medical education has depended ever since on this style of training.</p>
12th–14th centuries	<p>Mediaeval period: in Europe, medical schools developed in Salerno, Bologna and Montpellier; pharmacy declared to be separate from medicine; apothecaries documented uses of herbs and spices; alchemists pursued the 'elixir of life'. The Black Death (plague) killed over 25 million people in Europe. Victims of battle wounds usually succumbed to infection, haemorrhage, and shock or pain. Hypnotic (sleep-inducing) and analgesic (pain-relieving) effects of the herbs poppy, henbane and mandrake known and valued.</p>
14th–17th centuries	<p>Renaissance in Europe: rebirth of interest in arts, sciences, politics, economics and medicine. Vesalius (anatomist), Gerard and Culpepper (herbalists) revolutionised medical knowledge.</p> <p>In the Ming dynasty in China, Li Shi-Zhen documented Chinese medical knowledge in his compendium <i>Bencao Gangmu</i>, still the basis for traditional Chinese medicine.</p> <p>Paracelsus (1493–1541), Swiss alchemist and pharmacologist, denounced 'humoral pathology', substituted theory that diseases could be combated with specific remedies, and reduced prevalent overdosing.</p> <p>Infectious diseases, including measles and smallpox, spread from Europe to the 'New World'.</p> <p>Important pharmacological discoveries included:</p> <ul style="list-style-type: none"> ♦ treating gout with colchicum (colchicine) and restriction of wine intake ♦ treating malaria with 'Jesuit's bark' (cinchona, containing quinine) ♦ preventing scurvy (vitamin C deficiency) with oranges and lemons (see CIB 1.4, later) ♦ using willow bark (salicylates) for treatment of fever, and foxglove (digitalis) for treatment of 'dropsy' (oedema) ♦ using extracts of opium, mandrake and hemlock in wine to relieve pain and to allow surgical procedures; and henbane (hyoscyamus, containing hyoscyine), for inducing forgetfulness. <p>Valerius Cordus (a German physician; 1515–1544) compiled the first pharmacopoeia (reference text with standard formulae and recipes); followed by the London Pharmacopoeia (1618), the French Codex (1818), and the pharmacopoeias of the United States (1820), Britain (1864) and Germany (1872).</p>

TABLE 1.2 Continued

TIME PERIOD	COMMENTS
18th–19th centuries	Rational medicine replacing trial-and-error empiricism. Deliberate clinical testing of drugs for their actions was carried out; studies of dose–response relationships led to safer use of drugs. Active constituents of plants isolated: first morphine (1804), followed by quinine, atropine and codeine; digitalis plant shown to be source of cardiac glycosides (digoxin, digitoxin); coca bark shown to contain a useful local anaesthetic, cocaine, purified and used in eye surgery; safer synthetic analogues soon developed. Anaesthetic gas nitrous oxide and volatile liquids ether and chloroform used in surgery, dentistry and obstetrics, providing first safe, painless surgery. Vaccinations developed for smallpox, diphtheria and rabies. Public health measures and quarantines imposed. Nursing developed as a profession. X-rays discovered. Advances in chemistry, especially coal-tar (organic) chemistry, allowed development of hypnotics and sedatives such as chloral hydrate, analgesics (including aspirin) and antiseptics such as carbolic acid.
20th century	Application of organic and synthetic chemistry, and biostatistics, to drug discovery; the first ‘magic bullet’: salvarsan against syphilis; receptor theories developed.
1920s	Insulin isolated (first protein to have chemical structure identified), the most important discovery for treatment of diabetes mellitus; penicillin discovered.
1930s–1940s	First safe oral antimicrobials: sulfonamides, penicillins and streptomycin developed. Use of muscle relaxants with general anaesthetics, making major surgery safer. Chemical warfare agents such as mustard gas led to ‘nitrogen mustard’ anticancer drugs. Cortisone, hormone from the adrenal cortex, identified and synthetically prepared.
1940s–1950s	Autonomic pharmacology studies, structure–activity relationships on α - and β -receptors. DNA shown to be carrier of genetic information. First (modern) randomised controlled clinical trial (streptomycin against tuberculosis). World Health Organization (WHO) set up.
1950s	Chlorpromazine, first effective antipsychotic drug, specific for treatment of schizophrenia. Structure of DNA determined and understanding of molecular genetics expanded rapidly. Oral contraceptives developed – similar to natural oestrogen and progesterone hormones, revolutionising family planning. Poliovirus vaccines, eliminating deaths and paralysis from polio epidemics. First successful organ transplant.
1960s	Declaration of Helsinki prescribed ethical conduct of human medical research. Levodopa used to treat Parkinson’s disease; immunosuppressants made organ transplantation feasible; treatment of hypertension with thiazide diuretics and β -blockers helped prevent strokes; cytotoxic agents (alkylating agents, antimetabolites and antibiotics) developed to treat cancers. Thalidomide disaster, with thousands of infants born with severe malformations, led to tightening of regulations for testing new drugs.
1970s	Recombinant DNA technologies and monoclonal antibodies developed. Antivirals developed for prophylaxis and treatment of viral diseases. Childhood leukaemia treated successfully with cytotoxics and steroids. Ovulatory stimulants used in in-vitro fertilisation. Drug delivery methods and prodrug strategies improved.
1980s–1990s	HIV identified as cause of AIDS. New drugs for thrombolysis, reduction of cholesterol levels, inhibition of synthesis of angiotensin or prostaglandins, antiretroviral therapy of AIDS, and treatment of impotence; new antineoplastic agents for chemotherapy of cancers, inhaled corticosteroids for asthma, atypical antipsychotics for schizophrenia; refinement of treatment protocols. Smallpox eradicated worldwide. The Human Genome Project successfully determined sequence of nucleotide base pairs in human DNA; all the genes of the human genome identified and mapped (2003).
2000–present	Millennial Development Goals set targets to eliminate extreme poverty, hunger and major global diseases. Stem cell therapy developed. Application of combinatorial chemistry and high-throughput screening allows rapid testing of millions of possible drug molecules. Recent innovations include chiral versions of optically active drugs (e.g. levobupivacaine, escitalopram), genetically engineered molecules (insulin glargine), prostaglandin analogues for glaucoma (latanoprost, travoprost), thiazolidinediones and incretin enhancers for type 2 diabetes; and tyrosine kinase inhibitors (imatinib, sorafenib), monoclonal antibodies (trastuzumab, ipilimumab) and BRAF inhibitors (vemurafenib) in cancer chemotherapy.

types of receptors. The importance of using a control group when testing drugs or other treatments was recognised, and the randomised controlled clinical trial became the expected standard.

It is interesting to note early in the 21st century that most of the ‘top 10 drugs’ prescribed in developed countries are for lifestyle diseases, including statins for high cholesterol levels and

calcium channel blockers and angiotensin-converting enzyme inhibitors for cardiovascular diseases (see [Table 1.8](#), later). The ‘big three’ infectious diseases worldwide still awaiting vaccines and cures are AIDS, TB and malaria.

The scientific revolution brought about by molecular biology techniques has enabled the identification and cloning of genes that code for therapeutically useful proteins, including

monoclonal antibodies and receptors. Biochemical pathways in cell division are being elucidated, leading to new anticancer agents (Chs 34 and 35). Meta-analysis techniques have been developed (notably by the Cochrane Collaboration) to analyse results of clinical trials and medical research, and to evaluate scientific data in order to encourage implementation of evidence-based medicine.

KEY POINTS: Introduction to pharmacology

- ◆ Pharmacology is the study of drugs, which are substances used for their beneficial effects on living systems.
- ◆ People have searched for, been fascinated by, used and abused drugs throughout recorded history.
- ◆ Initially, useful natural compounds were discovered by trial and error; they were then studied for their medical actions and adverse effects.
- ◆ Useful drugs have the characteristics of potency, selectivity and specificity.
- ◆ Drugs may be solids (most commonly), liquids or gases. Most are organic (carbon-containing) chemicals.

DRUG DISCOVERY AND DEVELOPMENT

The ultimate goal of drug discovery and development is to produce therapeutic drugs while reducing drop-outs during the process. There are several ways in which potential therapeutic uses of chemicals – natural or synthetic – are determined, summarised as three steps: (1) understand the science, (2) unravel the story, and (3) apply the technology. Drug discovery has been likened to the processes of evolution: a selection process with a high level of attrition and many influences affecting survival of the fittest.

WHERE DRUGS COME FROM

Drugs and biological products are derived from several main sources:

- ◆ microorganisms – for example, fungi used as sources of antibiotics (Fig 1.2A) and bacteria and yeasts genetically engineered to produce drugs such as human insulin
- ◆ plants – for example, *Atropa belladonna* (source of atropine), *Cannabis sativa* (marijuana), *Coffea arabica* (Fig 1.2B; coffee, caffeine), *Digitalis purpurea* (Fig 1.2C; digitalis), *Duboisia* species (hyoscyne, nornicotine), *Eucalyptus* spp. (eucalyptus



FIGURE 1.2

Natural sources of important drugs

A *Penicillium notatum* mould, source of penicillin; **B** *Coffea arabica*, source of caffeine (and coffee); **C** *Digitalis purpurea*, source of digoxin; **D** *Papaver somniferum*, source of morphine and codeine.

A–D: iStockphoto/habari; iStockphoto/kannika2013; iStockphoto/Petegar; iStockphoto/AtWaG

TABLE 1.3 Some drugs from plants

DRUG	SOURCE	MAIN PHARMACOLOGICAL ACTIONS
Aromatic oils	E.g. from eucalyptus, pine, mint	Decongestant, Rx common cold, mild antiseptics
Artemisinins	<i>Artemisia annua</i> (sagewort)	Antimalarial
Atropine	<i>Atropa belladonna</i> (deadly nightshade)	Antimuscarinic, premedication, Rx asthma
Bran	Indigestible vegetable fibre	Laxative, Rx constipation
Caffeine	<i>Coffea arabica</i> (coffee)	CNS stimulant, diuretic
Cocaine	<i>Erythroxylum coca</i>	CNS stimulant, local anaesthetic, addictive
Colchicine	<i>Colchicum autumnale</i> (crocus)	Antiinflammatory, Rx gout
Coumarins	Sweet clover	Anticoagulants, prevent thrombosis
Digoxin	<i>Digitalis lanata</i> (foxglove)	Cardiac glycoside, Rx heart failure
Ephedrine	<i>Ephedra sinica</i>	Sympathomimetic, Rx asthma
Ergot alkaloids, e.g. ergometrine	Mould on <i>Claviceps</i> spp.	Oxytocic, Rx postpartum bleeding
Galantamine	<i>Galanthus nivalis</i> (snowdrop)	Anticholinesterase, used in neurological disorders and Alzheimer's disease
Hypericin	<i>Hypericum perforatum</i> (St John's wort)	Monoamine reuptake inhibitor, Rx depression
Ipecacuanha	Cephaelis root	Expectorant, emetic, Rx poisoning
Morphine	<i>Papaver somniferum</i> (opium poppy)	Analgesic, sedative, antidiarrhoeal, cough suppressant, addictive
Nicotine	<i>Nicotiana tabacum</i> (tobacco)	Vasoconstrictor, CNS stimulant, addictive
Paclitaxel	Yew tree bark	Antineoplastic, Rx cancer
Phyto-oestrogens	Clover, soybeans	Oestrogenic, Rx menopausal symptoms
Pilocarpine	<i>Pilocarpus microphyllus</i>	Muscarinic agonist, Rx glaucoma
Quinine, quinidine	Cinchona bark	Antimalarial, Rx cardiac arrhythmias
Salicylates, including aspirin	<i>Salix</i> spp. (willow)	Antiinflammatory, analgesic, antipyretic
Strychnine	<i>Strychnos nux vomica</i>	CNS stimulant, convulsant
Vincristine	<i>Catharanthus roseus</i> (periwinkle plant)	Antineoplastic, Rx cancer

CNS = central nervous system; Rx = treatment of.
Source: Evans (2009).

oil), *Papaver somniferum* (Fig 1.2D; opium, morphine²)

- ♦ humans and other animals, from which drugs such as bovine insulin, human chorionic gonadotrophin and erythropoietin were or are obtained, sometimes by recombinant techniques
- ♦ minerals or mineral products – for example, iron, iodine and Epsom salts
- ♦ laboratories in which substances are synthesised, such as sulfonamides, β -blockers and antidepressants. Drugs may also be classed as semisynthetic when the starting material is a natural product, such as a plant steroid or microbial metabolite, which is then chemically altered to produce the desired drug molecule.

²The isolation of the pure alkaloid morphine as the active pain-relieving constituent of opium poppies (in 1804) has been described as 'the single most important discovery in medicine', as it demonstrated that pharmacological activities of plants are due to the chemicals they contain.

Development from natural or traditional remedies

For thousands of years, people have been trying natural products – animal, vegetable and mineral – to see if they are useful as foods or in treating disease (see Tables 1.3, 3.2 and 3.3, Figs 1.2, 1.3 [later] and 3.1, and CIB 3.4 and 3.5). Natural products may be used as crude extracts, such as raw opium, tobacco leaves or herbal teas, or purified and/or synthesised and then formulated as pharmaceutical preparations, such as tablets, ointments and injections.

This is called the 'reefs and rainforests' route to new drugs, recognising that there are millions of natural chemicals in the environment to be identified and tested. As biodiversity is lost worldwide, we are losing the chance to discover novel drugs such as anticancer or antibiotic agents. (For example, the recent extinction of Australia's gastric-brooding frogs means we will now never know how the frog's eggs avoided digestion in the mother frog's stomach or being moved on into her small intestine – actions potentially useful in treating gastrointestinal

tract disorders. Research into threatened bear species could elucidate their mechanisms for surviving months of hibernation without losing bone mass or dying of uraemia.) The Wellcome Trust in London has established the Millennium Seed Bank project at Kew Gardens to conserve and screen plants for possible future cures.³

Natural products not necessarily safer

There is a widely held belief that ‘natural’ products are safer than synthetic, man-made drugs (refer back to CIB 1.2), a belief encouraged by health-food and alternative therapy practitioners. A quick scan of naturally occurring substances such as arsenic, botulinum toxin, cantharidin, cocaine, cyanide, deadly nightshade, ipecacuanha, mercury, methanol, physostigmine, strychnine, thallium, tobacco and uranium shows that natural is not always good. It would be foolish to expect all natural products to be automatically safer than those synthesised in laboratories – or vice versa. Any drug’s

safety and efficacy must be tested and proved before it is approved for clinical use (see Smith, 2002).

Active constituents of plant drugs

The leaves, roots, seeds and other parts of some plants may be dried, crushed, boiled and extracted or otherwise processed for use as medicine and, as such, are known as crude drugs or herbal remedies (see Ch 3). Their therapeutic effects are produced by the chemical substances they contain. When the pharmacologically active constituents are separated, purified and quantified, the resulting substances usually have similar pharmacological actions to the crude drugs but are more potent (weight-for-weight), produce effects more reliably, and are less likely to be affected by other constituents or contaminants in the crude preparations. Indeed, the herbal antidepressant St John’s wort has been shown to have a similar mechanism of action – and hence similar therapeutic and adverse effects – as the synthetic selective serotonin reuptake inhibitors such as fluoxetine (see DM 15.3).

Some types of pharmacologically active molecules found in plants, grouped according to their chemical properties, are alkaloids, glycosides, steroids, hydrocarbons, alcohols and phenols, proteins, gums and oils (Table 1.4). Note that the groups are not mutually exclusive – there can be phenolic

³There are many wonderful pharmaceutical gardens worth visiting, including the *Jardin des Plantes de Montpellier* in southern France, established in 1593, and the *Chelsea Physic Garden* (Garden of Medicinal Plants) in London, founded in 1673 as the *Apothecaries’ Garden*.

TABLE 1.4 Pharmacologically active constituents of plant drugs

CHEMICAL CLASS AND STRUCTURE	CHARACTERISTICS	EXAMPLES
Alkaloids: <ul style="list-style-type: none"> ♦ organic nitrogen-containing compounds that are alkaline and usually bitter-tasting ♦ the nitrogen atom is usually in a heterocyclic ring of carbon atoms (Fig 1.3A) 	<ul style="list-style-type: none"> ♦ many alkaloid drugs are amines, so their names often end in the suffix ‘-ine’ ♦ combined as salts to make them more soluble (e.g. morphine sulfate) ♦ plants may have evolved the ability to synthesise bitter alkaloids as a defence against herbivorous animals 	<ul style="list-style-type: none"> ♦ analgesics morphine (Fig 1.3A),* cocaine and codeine ♦ antiasthma drugs ephedrine, theophylline and atropine ♦ vinca alkaloids (anticancer) ♦ alkaloids used in gout (colchicine), malaria (quinine), obstetrics (ergot alkaloids) ♦ ‘social’ drugs: nicotine and caffeine
Carbohydrates: <ul style="list-style-type: none"> ♦ organic compounds of carbon, hydrogen and oxygen 	<ul style="list-style-type: none"> ♦ sugars are a source of energy ♦ gums and mucilages are carbohydrate plant exudates; when water is added, some will swell and form a gelatinous mass, a useful laxative effect ♦ gums are also used to soothe irritated skin and mucous membranes, and may be a rich source of starch 	<ul style="list-style-type: none"> ♦ sugars such as glucose ♦ starches and fibres such as cellulose and inulin, a fructose–furanose polysaccharide (Fig 1.3B) used in kidney function tests (not to be confused with insulin, a protein from the pancreas) ♦ gelling agents such as agar and gums such as tragacanth and <i>Aloe vera</i> products (CIB 41.2)
Glycosides: <ul style="list-style-type: none"> ♦ particular type of carbohydrate that, on hydrolysis, yields a sugar plus one or more additional active substances 	<ul style="list-style-type: none"> ♦ the sugar part is believed to increase the solubility, absorption, permeability and cellular distribution of the glycoside 	<ul style="list-style-type: none"> ♦ digoxin (Fig 1.3C), found in <i>Digitalis</i> (foxglove) plants; known as a cardiac glycoside because of its stimulant actions on the heart ♦ glycosides present in oleanders and some other Australian plants are responsible for their poisonous nature ♦ cane toads also contain cardioactive glycosides

TABLE 1.4 Continued

CHEMICAL CLASS AND STRUCTURE	CHARACTERISTICS	EXAMPLES
Hydrocarbons: <ul style="list-style-type: none"> ♦ organic molecules consisting entirely of hydrogen and carbon ♦ may be straight-chain or aromatic (containing benzene rings) 	<ul style="list-style-type: none"> ♦ derivatives such as organic alcohols and esters contribute the fragrances to many plants and perfumes ♦ commonly used by drug companies and pharmacies when preparing topical formulations of drugs, especially creams and ointments 	<ul style="list-style-type: none"> ♦ fats and waxes ♦ oils such as castor, olive and coconut oil ♦ fatty acids, prostaglandins and balsams
Oils: <ul style="list-style-type: none"> ♦ a subgroup of hydrocarbons ♦ may be terpene-type compounds ♦ may contain many types of functional groups including ketones, phenols, alcohols, esters and aldehydes 	<ul style="list-style-type: none"> ♦ viscous liquids high in hydrocarbon content ♦ often flammable and immiscible with water and aqueous solvents ♦ frequently used as flavouring agents, in perfumery, in chemical industries and as antiseptics ♦ a fixed oil dropped onto filter paper will leave a greasy stain, whereas a volatile oil (which evaporates) will not 	<ul style="list-style-type: none"> ♦ eucalyptus, peppermint and clove oils are volatile oils used in medicine ♦ castor oil (mainly composed of ricinoleic acid, Fig 1.3D) and olive oil are fixed oils ♦ Australian Myrtaceae family and <i>Melaleuca</i> genus plants contain many fragrant and useful oils, including eucalyptus and tea-tree oils
Phenols: <ul style="list-style-type: none"> ♦ phenols contain a benzene ring with a hydroxyl substituent 	<ul style="list-style-type: none"> ♦ phenols are a specialised type of alcohol, a compound containing a hydroxyl group, –OH 	<ul style="list-style-type: none"> ♦ salicylates, including aspirin-like compounds and flavouring agents (e.g. vanillin) ♦ isoflavones, including phyto-oestrogens ♦ coumarins, including the anticoagulant dicoumarol (Fig 1.3E) ♦ cannabinoids from marijuana ♦ hypericin, from St John's wort, used in depression (Fig 1.3E)
Tannins: <ul style="list-style-type: none"> ♦ a specialised type of phenol 	<ul style="list-style-type: none"> ♦ astringent plant phenolics have the ability to tan hides (animal skins) by precipitating proteins ♦ common plant constituents, especially in bark, accounting for some of the brown colour in swamps and rivers and in cups of tea 	<ul style="list-style-type: none"> ♦ in Australian native medicine, kino, the gum exuded from eucalyptus trees, was an important source of tannins, which were used to treat diarrhoea, haemorrhages and throat infections
Isoprenes, terpenes and steroids: <ul style="list-style-type: none"> ♦ terpenes are 10-carbon molecules built up from small 5-carbon building blocks called isoprenes ♦ plant steroids are also synthesised naturally from isoprene sub-units 	<ul style="list-style-type: none"> ♦ plant steroids, with their characteristic 4-ring structures, are used as the starting material for the production of many hormone drugs (Fig 28.2) ♦ the plant sterol diosgenin, from <i>Dioscorea</i> species, has been used in the synthesis of oestrogenic hormones 	<ul style="list-style-type: none"> ♦ carotenoids such as β-carotene and vitamin A ♦ salicylate analgesics including aspirin (acetylsalicylic acid) ♦ pyrethrins (insecticides) ♦ menthol (Fig 1.3F), camphor and thymol, aromatic compounds used in respiratory medicine ♦ gossypol, a Chinese male contraceptive agent (Fig 1.3F)

*In Tasmania and Victoria, the opium poppy *Papaver somniferum* is grown and harvested for production of opium alkaloids, including morphine and codeine.

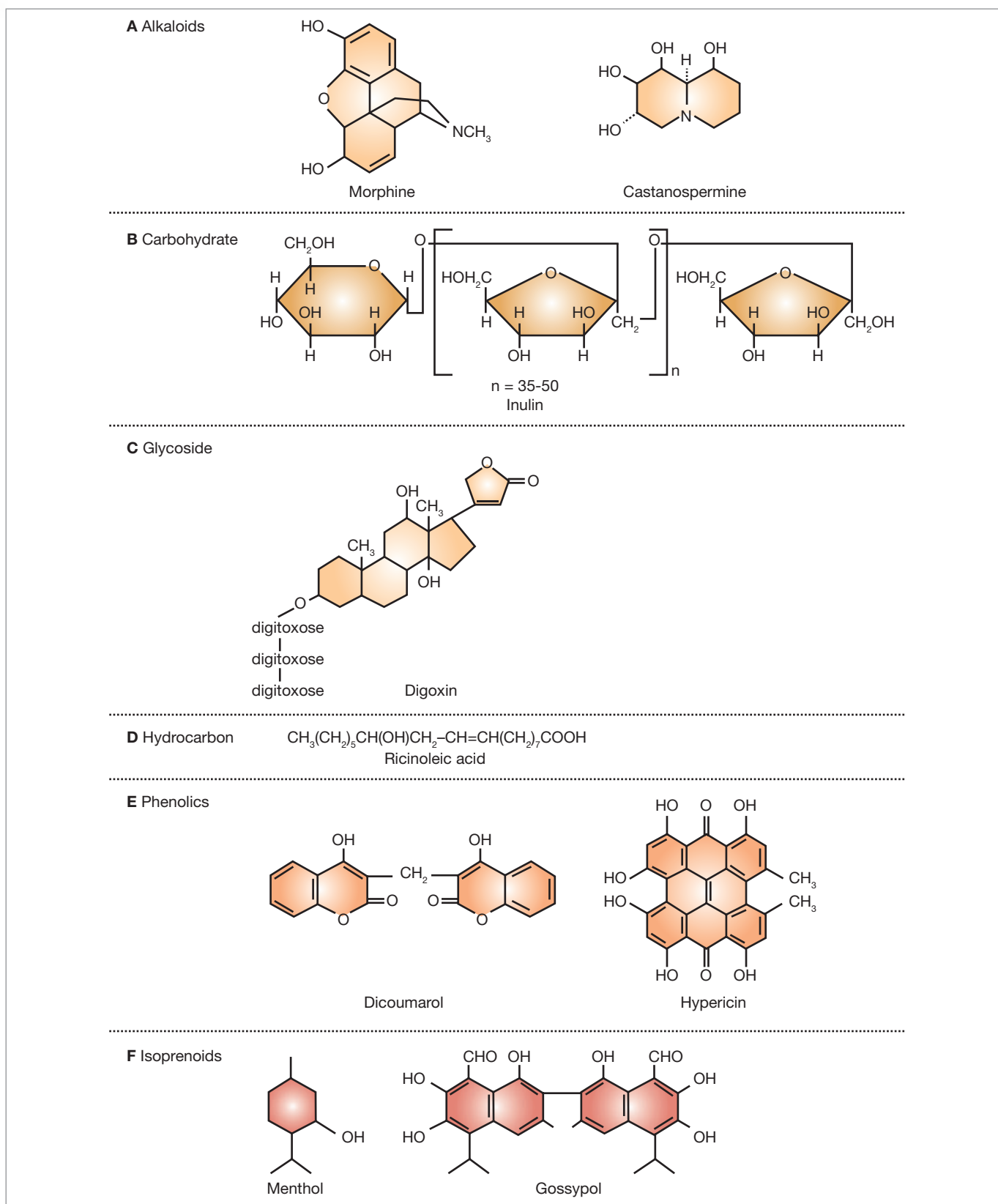
alkaloids, glycoproteins and phenolic glycosides. Figure 1.3 shows the chemical formulae of some drugs that are extracted from plant sources.

Serendipity (sheer good luck)

Although luck plays a part in some drug discoveries, such as Fleming's bacterial culture plate becoming contaminated with a growth of the fungus *Penicillium notatum* which inhibited bacterial growth, it usually takes lateral thinking (e.g. questioning why bacteria were inhibited near the fungus),

intelligence, and years of hard work (extracting the natural antibacterial agent, determining its structure, and developing methods of producing enough penicillin to treat people with bacterial infections) to exploit the lucky find.

Other examples of serendipity in pharmacological discovery are the findings that patients treated with the first safe synthetic oral antibacterial agents, sulfonamides, had a lowering in their blood glucose levels, which led to sulfonylurea oral hypoglycaemic agents; and that hypertensive patients treated with the vasodilator minoxidil tended to grow more hair. The drug is now used mainly as a hair restorer.

**FIGURE 1.3**

Chemical structures of some active drugs derived from plant sources

A Alkaloids: morphine and castanospermine. **B** A carbohydrate: inulin. **C** A glycoside: digoxin. **D** A hydrocarbon: ricinoleic acid. **E** Phenolics: dicoumarol and hypericin*. **F** Isoprenoids: menthol and gossypol.

*A chemistry colleague once described this type of molecule to his students as 'polyhydroxylated-chickenwire'.

Chemical plus pharmacological studies

As chemical techniques developed in the 19th and 20th centuries, the structures of pharmacologically active substances could be determined and similar substances synthesised, then tested for activity. These **structure–activity studies** led to many drug groups:

- The second- and third-generation penicillins were modelled on the first penicillin.
- All the sympathomimetic amines were initially noradrenaline ‘look-alikes’: studies of *Ephedra sinica*, long known in traditional Chinese medicine to be useful in respiratory conditions (asthma), led to the purification of the active ingredient ephedrine, then to synthesis of the related β -receptor-activating antiasthma drugs isoprenaline and salbutamol (with fewer cardiovascular adverse reactions).
- β -blockers, such as propranolol and later atenolol, were designed to act as ligands at the receptor without activating it, and proved useful in cardiovascular diseases. (Chemical structures of β -receptor ligands are shown in Fig 1.4.)

Research carried out by pharmacologists, biochemists and chemists in universities and research institutes may lead to the discovery of new drugs. The pharmaceutical industry monitors such research via the scientific literature, patent applications and scientific conferences.

Active metabolites of existing drugs

Sometimes drugs are found to be more active after metabolism in the body and so the metabolites are tested. Paracetamol (DM 3.1) is one of the metabolites of phenacetin, an early antipyretic analgesic agent, and is much safer than phenacetin. Many of the benzodiazepine antianxiety agents have pharmacologically active metabolites, some of which are drugs in their own right.

Rational molecular design

Structure–activity studies can predict the shape of the active site of a receptor and lead to the design of drugs that may be agonists or antagonists at that receptor. The early antihistamines were modelled on the histamine molecule. Subsequent brilliant pharmacology by Sir James Black⁴ led to the discovery of histamine H_2 -receptors and the development of specific H_2 -antagonists, revolutionising the treatment of peptic ulcer (Fig 27.3).

Computer-aided design

Drug receptors, enzymes, ion channels and transporters are no longer simply ‘black boxes’ referred to by pharmacologists

⁴Black, a Scottish pharmacologist, was awarded the Nobel Prize in Medicine in 1988 for his work on ‘important principles of drug treatment’, discovering beta-blockers and H_2 -antagonists; when surprised to hear of his award, he quipped: ‘I wish I had my beta-blockers handy!’

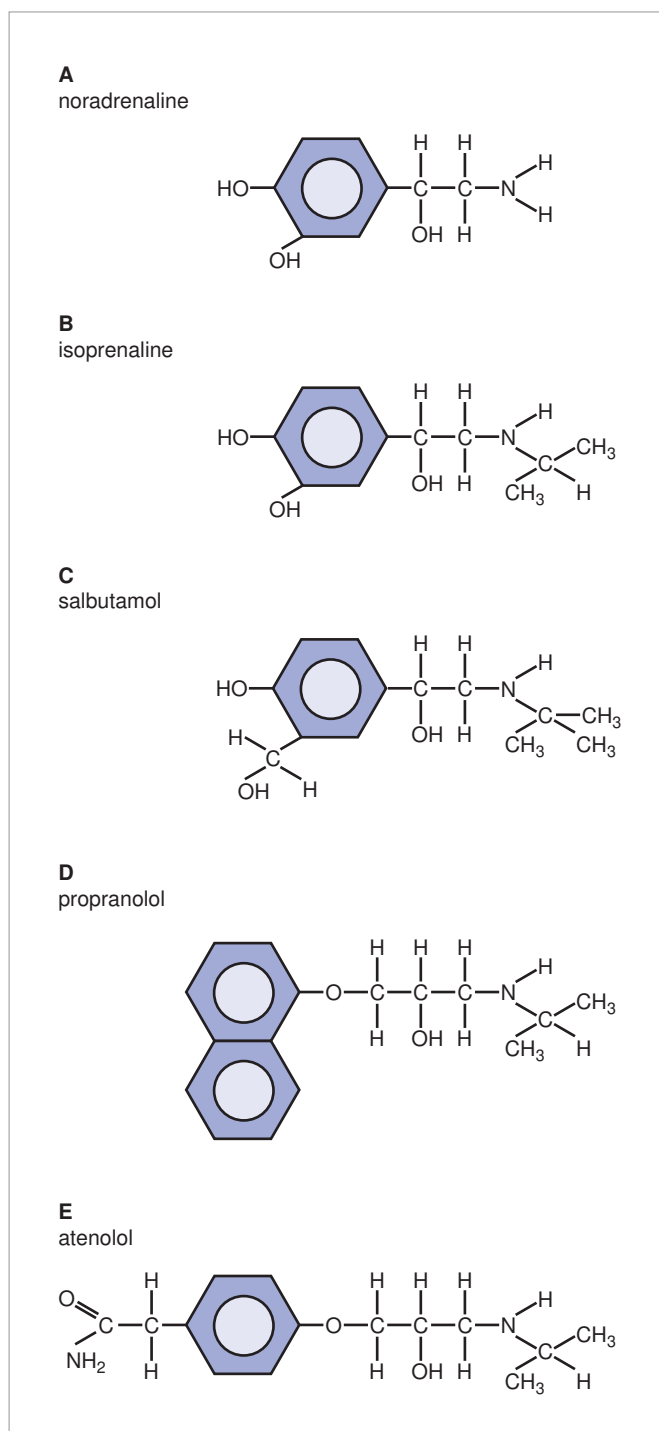


FIGURE 1.4

Structure–activity relationships for some drugs binding to adrenoceptors

A The sympathetic neurotransmitter noradrenaline. **B** Isoprenaline, a non-selective β -adrenoceptor agonist. **C** Salbutamol, a selective β_2 -adrenoceptor agonist. **D** Propranolol, a non-selective β -adrenoceptor antagonist. **E** Atenolol, a selective β_1 -adrenoceptor antagonist with less likelihood of causing asthma. It can be seen that increasing the ‘bulkiness’ of the substituents at the catechol end (two adjacent $-OH$ groups) or the amine end ($-NH_2$) may select for ligand-binding affinity or agonist/antagonist activity at specific receptors.

wishing to explain (or pretend that they understand) drug mechanisms; many are proteins with known amino acid sequences and tertiary structures (three-dimensional shapes), able to be cloned. Computer modelling of their active sites allows testing of chemicals for virtual binding affinity. Using such techniques, angiotensin-converting enzyme (ACE) inhibitors were designed for use in hypertension, dopa-decarboxylase inhibitors for administration with levodopa in Parkinson's disease, the anti-flu drug zanamivir to inactivate the flu virus, and potential anticancer drugs to inhibit steps in the pathways of macromolecular synthesis.

Combinatorial chemistry ('combi-chem') techniques make it possible for millions of new molecules to be synthesised, either actually or virtually. This may involve systematic and repetitive use of commercially available chemical reagents to synthesise 'libraries' of new chemical compounds, preferably small molecules, which are then screened for activities on proteins, receptors, enzymes and transporters.

STANDARDISATION OF DRUGS

Formulations of drugs obtained from natural sources may fluctuate in strength, depending on how extracts are harvested and purified. Because accurate dosage and the reliability of drug effects depend on uniformity of strength and purity, **standardisation** (bringing the preparation to a specified concentration or quality, like the model) and publication of standards are necessary.

Drug standards in Australia and New Zealand

The main standards for drugs in Australia are those published in the *British Pharmacopoeia*⁵ and the *Australian Pharmaceutical Formulary* (APF; see later under 'Drug information sources'). The BP gives detailed, legally accepted standards for hundreds of drugs and herbal products, with chemical information and the approved formulations containing the substance, and lists criteria for purity, chemical methods for identification and assay (measurement), tests, and maximum levels allowed for impurities and storage conditions. Preparations meeting these standards are referred to as the BP preparation. For example, Opium BP is the air-dried latex obtained by incision from the unripe capsules of *Papaver somniferum*, consisting of 'blackish-brown masses of various sizes, ... soft and shiny, after drying become hard and brittle'; it contains not less than 10.0% of morphine and not less than 2% of codeine (*British Pharmacopoeia Commission, 2016*).

The APF is more a reference and 'recipe book' for pharmacists, containing useful medical information and dispensing practice guidelines, plus standard formulae. For

Calamine Lotion APF, for example, it lists the amounts of seven ingredients, gives the method for preparation of the lotion, and describes its uses as 'soothing and protective, antipruritic' (*Sansom, 2015*). The *New Zealand Formulary* (NZF) is more similar to the *Australian Medicines Handbook* (AMH), with detailed information about drugs (see later under 'Drug information: Official sources ...').

Assays

The technique, either chemical or biological, by which the strength and purity of a drug are measured is known as an **assay**; if available, a chemical method is used. For some drugs, either the active ingredients have not been completely identified or there are no available chemical methods. The pharmacological activity of such tissue extracts or pharmaceutical formulations may be standardised by biological methods, or **bioassay**.

Bioassays

Bioassays are typically performed by determining the amount of a preparation required to produce a defined effect on a suitable living tissue (or animal, cell suspension, enzyme, microorganism, etc.), and then comparing the response to that produced by a standard preparation in the same bioassay system. Examples of early bioassays were for the potency of a sample of insulin measured by its ability to lower the blood glucose levels of rabbits, or for the strength of digoxin preparations assayed by their effects on contractions of isolated cardiac muscle tissue.

Bioassays are especially applicable to:

- ◆ substances that are poorly defined chemically
- ◆ mixtures containing chemically very similar substances (e.g. optical isomers, of which only one is active)
- ◆ highly active substances, especially endogenous mediators, present in very small amounts
- ◆ testing drugs in animals to predict effects in humans.

The bioassay method may be *in vitro* (in glass) – for example, using a suspension of an enzyme, cell or tissue culture, a microbiological culture, a standard preparation of an antibody or an isolated organ or tissue; or *in vivo* (in the living organism) – for example, testing the effect of a drug on blood pressure or behaviour.⁶ Some drug actions are virtually impossible to test in animals either *in vitro* or *in vivo*, particularly the effects of CNS-active agents on mood,

⁵The 'BP', as it is fondly known by generations of pharmacy students and pharmacists.

⁶There is currently a worldwide dearth of pharmacologists with the skills necessary to carry out many experimental methods in medical research or to train new generations of students in these techniques. This has come about largely because of the decrease in the number of practical classes held in pharmacology courses and the replacement of animal experiments with computer-modelled 'practicals'. *In-vivo* testing, however, is vital for the analysis of drug actions and development of new drugs – see discussion in Chapter 2 under 'Ethical aspects of pharmacotherapy'.

perception and thought processes. Clinical trials (see ‘[Clinical trials of drugs](#)’, later) are essentially bioassays in humans: the new drug (unknown) is tested against the best currently available therapy (standard drug or placebo) and compared for safety and efficacy.

The design of bioassays usually involves comparison of two preparations and constructing log dose–response curves. If the substances act by similar mechanisms, the curves will be roughly parallel in their mid-sections and so the potency ratio can be determined, allowing the strength of the unknown to be calculated compared to the known standard (see [Fig 4.7](#)). Because of biological variability there may be variations in results quoting the absolute amount of biologically active material. Bioassays are not used as frequently as previously because techniques such as radioimmunoassay (RIA, itself a type of bioassay) and high-performance liquid chromatography (HPLC) have allowed very low levels of chemicals to be measured accurately without using animals.

Bioassays in the BP

The BP 2016 still gives several standard methods for bioassays, including for blood pressure-lowering substances, blood coagulation factors, anticoagulants, interferons, vaccines, antibiotics, endotoxins and pyrogens (substances that cause fever), plus tests for acute toxicity, microbiological sterility or contamination, including examination of herbal products. The BP bioassay method for histamine requires a classical organ bath experiment, testing the ability of histamine samples to contract the isolated guinea-pig ileum muscle in a bath of atropinised physiological saline solution (see [Fig 1.5](#)).

Isolated organ experiments

In these pharmacological experiments, a small piece of animal tissue (such as a length of intestinal smooth muscle) or an entire organ (such as a heart) is ‘isolated’ from the animal’s body and kept alive in warmed, oxygenated physiological saline solution in an organ bath, set up so that responses of the tissue (e.g. contractions of muscle, beats of the heart) can be monitored following administration of a drug solution into the organ bath. The classic experiment is the isolated guinea pig ileum preparation, in which a short strip of gastrointestinal tract (GIT) smooth muscle responds (contracts) to stimulation by various neurotransmitters and other endogenous mediators; a great deal of classical pharmacology can be demonstrated and understood using this simple technique.

The use of isolated tissues for assaying responses reached a sophisticated level in the classic experiments of Sir John Vane at the Royal College of Surgeons in London in the 1960s. A set of five organ baths was set up in vertical series such that the physiological saline solution (or blood from an anaesthetised animal) from the top bath superfused (flowed down over) the next bath, and so on down the cascade ([Fig 1.5](#)). Small samples of GIT smooth muscle from four different species were set up in the baths, and the pattern of contraction or

relaxation responses to seven endogenous mediators, including noradrenaline, bradykinin, prostaglandins and antidiuretic hormone, was studied. Vane discovered the mechanism of action of aspirin and other non-steroidal antiinflammatory drugs, viz inhibition of the synthesis of prostaglandins; for this he was subsequently awarded the 1982 Nobel Prize for Medicine (and knighted by the Queen).

International units of activity

The strength of extracts of natural substances for which the purity is not 100% cannot be expressed in absolute terms such as grams or milligrams, as the whole weight is not due to active ingredient. Such preparations are assayed biologically, and a unit of pharmacological activity is defined. A particular preparation – for example, of a hormone, enzyme, vitamin, vaccine, blood product or plant alkaloid – is designated by the WHO Expert Committee on Biological Standardization as the International Standard preparation, against which other national standard preparations are assayed. In Australia, for example, the Commonwealth Serum Laboratories (CSL) in Melbourne maintained the national standard for insulin, and all CSL insulin preparations were compared to it. The strengths of preparations are expressed in terms of International Units of Activity (IU)⁷ measured in the particular bioassay (see [CIB 30.4](#)), allowing comparison of preparations in terms of their biological efficacies.

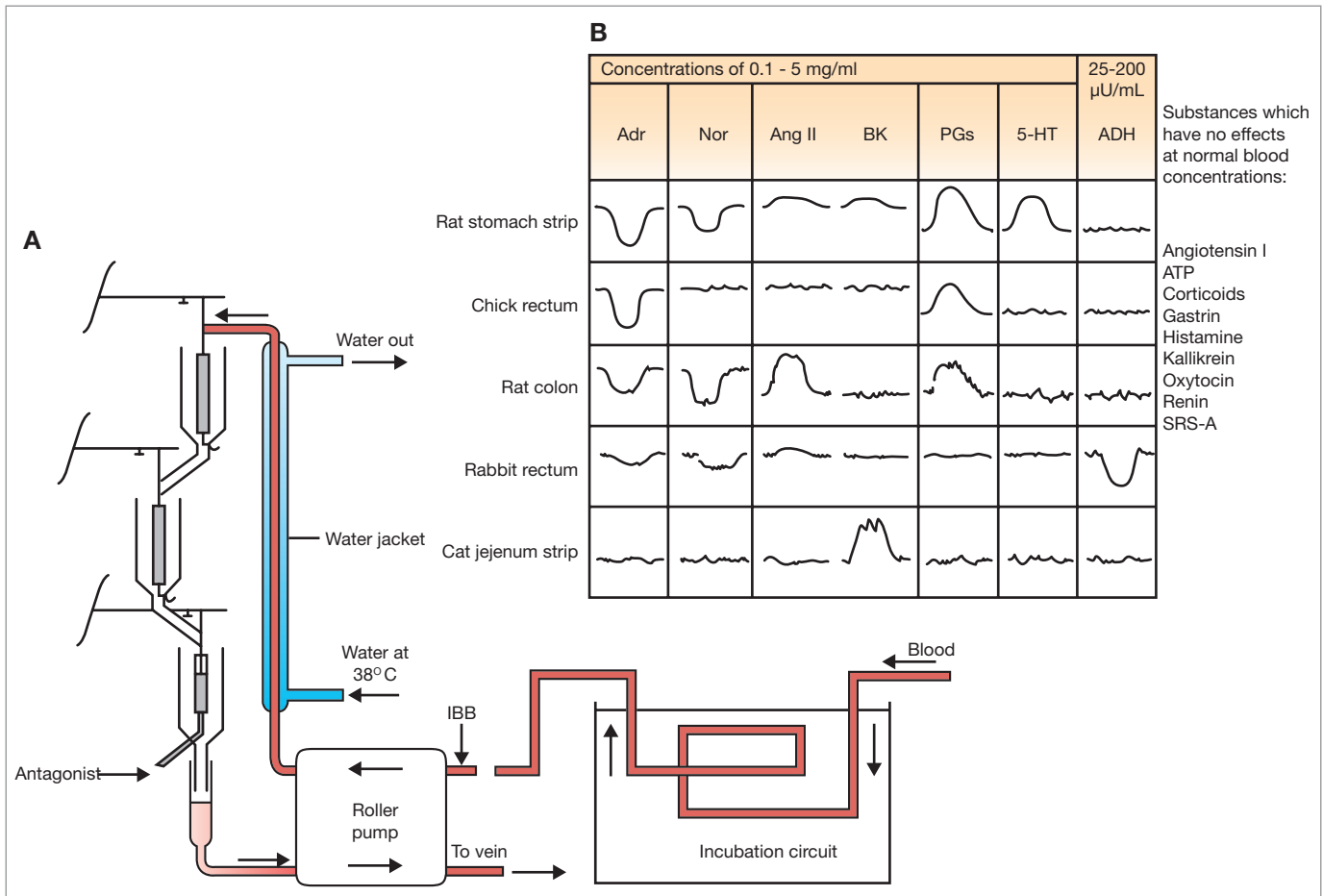
Statistical methods in bioassays

It is well recognised that biological parameters, such as heights of adults, vary within a wide range, and the mean can be calculated as an average value. Consequently, biological experiments need to be repeated many times to get a mean result, and statistical tests can be applied to determine how likely this is to be the ‘true value’. Values may be found to be normally distributed, and when plotted as a frequency distribution will assume a ‘normal’ bell-shaped curve.

Similarly, it can be expected that responses to a dose of a drug will also vary about a mean value. Variations may be due to many causes, especially errors in measurement and inherent biological variability both within and between individuals. In bioassays the same dose (or concentration) repeated several times may therefore give differing responses; likewise, the dose required to give the same response varies. Variability can be partly reduced by refining methods and using a very homogeneous population of animals or very similar subjects; however, this reduces the wide applicability of the results.

Statistical methods must then be applied to deal with random variations and to extrapolate from the sample mean to the population; such techniques are the province of biostatistics, rather than pharmacology. In the pharmacological

⁷The abbreviation IU may become confusing, as the U may be misread as a V (IV: intravenous); some authorities recommend that the term ‘Unit’ be written in full.

**FIGURE 1.5****Parallel assay by the cascade superfusion technique**

A Blood is circulated continuously from the anaesthetised test animal over a succession of test organs, whose responses are measured by a simple transducer system.

B The response of these organs to a variety of test substances (at 0.1–5 ng/mL) is shown. Each active substance produces a distinct pattern of responses, enabling unknown materials present in the blood to be identified and assayed.

ADH = antidiuretic hormone; ADR = adrenaline; ANG II = angiotensin II; ATP = adenosine triphosphate; BK = bradykinin; IBB = into the bathing blood; NOR = noradrenaline; PG = prostaglandin; SRS-A = slow-reacting substance of anaphylaxis; 5-HT = 5-hydroxytryptamine (serotonin). Sources: From Vane (1969 and 1971). Reproduced with permission, thanks to Wiley-Blackwell, Oxford.

context, statistical methods⁸ are typically applied to bioassays studying dose–response relationships, cause–effect correlations, differences between groups of subjects treated differently, and the results of clinical trials. Usually a ‘null hypothesis’ is defined (i.e. that there is no statistically significant difference between the groups being studied), and when results are analysed the null hypothesis is either accepted or rejected. The probability level (*P*) at which the results are accepted as being due to a real difference rather than occurring by chance is usually set at 0.05; that is, there is only a 5% likelihood (1 in 20 chance) that the results could have occurred by chance.

Typical statistical tests employed are either parametric (assuming a normal distribution of results), such as Student’s

t-test, analysis of variance or variance ratio; or non-parametric (when normal distribution cannot be assumed) – for example, the sign test or Wilcoxon rank-sum test.

⁸The first medical statistician credited with applying rigorous mathematical methods in the study of responses to drugs, and developing standard clinical trial methodologies, was Professor Austin Bradford Hill in the Medical Statistics Department of the London School of Hygiene and Tropical Medicine, in the 1950s. Bradford Hill proved that two drugs together, streptomycin and para-aminosalicylic acid, given over a period of several months, markedly improved patients with TB and reduced development of microbial resistance to the antibiotic. And in an epidemiological study of lung cancer, by separating subjects into groups based on their smoking habits, Bradford Hill demonstrated conclusively that the more cigarettes people smoked, the greater their risk of lung cancer.

DRUG DEVELOPMENT

Development of new drugs is regulated by government legislation and administered by government authorities such as the Therapeutic Goods Administration (TGA) in Australia, the Ministry of Health and Medsafe in New Zealand and the Food and Drug Administration in the United States (Ch 2). Regulation protects consumers so that only safe and effective drugs are approved, and protects sponsoring drug companies for their investment in terms of intellectual property and patents.

The pharmaceutical industry

The pharmaceutical industry is constantly searching for potential new drugs; worldwide the industry (sales of pharmaceuticals) was estimated in 2013 to be worth about £600 billion/year (more than A\$1000 billion). Drug companies insist that the high costs of new drugs are to recoup money spent on research; however, drug companies allocate about 20% of their expenditure to marketing and only 2% to discovery of new drugs. The major markets are the United States, Europe, Japan, China and India; Australia accounts for only 1–2% of world sales of pharmaceuticals.

Stages of drug development

Drug development has traditionally been described as occurring in several clearly defined phases, involving multidisciplinary teams:

- ♦ the new idea or hypothesis – routes to drug discovery include selection of a target, ideas for new molecules, discovery of new natural products, optimisation of lead compounds, new hypotheses for disease causation, and research with new molecular biology, genetic engineering and formulation technologies
- ♦ design, purification or synthesis of the new molecule, from various sources (described above under ‘Where drugs come from’)
- ♦ screening new compounds for useful pharmacological activities or possible toxic effects – screening may be broad, to detect all actions, or specific, for affinity for a particular receptor, transporter or enzyme; high-throughput screening (HTS) allows millions of compounds to be run through automated initial screens (CIB 1.3); these three stages may take between two and five years
- ♦ preclinical pharmacology – this includes in-vitro and in-vivo studies: pharmacodynamic actions and pharmacokinetic aspects (the fate of the chemical in the body, including susceptibility to phases of metabolism) are studied in at least three mammalian species
- ♦ toxicology studies (adverse effects) – these include acute toxicity, long-term toxicity (chronic effects and effects on reproduction), and tests for mutagenicity and

carcinogenicity; requirements depend on anticipated exposure and clinical use, whether acute or chronic

- ♦ pharmaceutical formulation and manufacturing scale-up of the synthetic pathway, including stability tests and assay methods; these stages may take one to two years
- ♦ an application to drug-regulating authorities for approval to test on humans – all results, manufacturing information, proposed clinical protocols, names of personnel in the clinical trial team and approval from an ethics committee are submitted
- ♦ if the drug appears to be safe, effective and worth testing, it will go to clinical trial while being closely monitored by authorities; the three phases of a clinical trial may take from five to seven years
- ♦ depending on the results of the clinical trial, the sponsors may apply for registration of the drug and approval to market it for clinical use (one to two years)
- ♦ ongoing post-marketing studies then follow up the drug, monitoring its effects and interactions in the wider community for longer periods.

The costs in time, money and effort

The development of a drug takes a prodigious amount of money, effort and time: it is a high-stakes, long-term, risky business, drug development from idea to market typically taking 10–15 years. Once the idea, chemical or process is patented (to protect the developers from other companies stealing their ideas), the clock starts ticking! In most countries, the duration of a patent is 15–17 years, with a possible short extension. When the patent expires, other companies can manufacture and market the drug under their own trade names and as a ‘generic’ drug. Consequently, companies need to minimise the time taken to get their drug onto the market.⁹

It is estimated that every new drug costs around A\$1 billion for basic and clinical studies and for the costs of application and promotion (a figure of US\$2.6 billion has even been quoted), and that a drug company needs one to two new drugs every three to four years to remain financially viable. (‘Me-too’ drugs are significantly cheaper to develop, as much of the expensive, time-consuming work has already been carried out for the original drug.) High costs are attributed to:

- ♦ the need for evidence of safety and cost-effectiveness
- ♦ increasing emphasis on ‘lifestyle drugs’, which require studies of long-term safety
- ♦ the prevalence of polypharmacy, with its inherent risks of drug interactions

⁹Companies also try to extend their patent protection period when it is running out and maintain monopoly market share for blockbuster drugs, by a process known as ‘evergreening’ – for example, by patenting an optical isomer of the drug, or a modified formulation.

CLINICAL INTEREST BOX 1.3

High-throughput screening

In high-throughput screening (HTS), minute amounts of thousands of small-molecule chemicals from 'chemical libraries' can be screened rapidly through automated biochemical tests for activity. 'Hit' compounds are progressed into a 'lead compound' that may lead to potentially useful drugs. Such screens have been described as 'fishing trips', trawling through millions of compounds in the hope of catching something interesting.

The tests are carried out in an array of hundreds of tiny 'cells' (minute test tubes) or on silicon chips, leading to the term 'in silico' for this type of assay. Most tests measure binding of the new compounds to a particular protein (e.g. receptor, enzyme, ion channel or antibody), gene or RNA fragment in the cell or on the chip. Tests may be based on enzyme-linked immuno-sorbent assays (ELISA) and commonly use high-performance liquid chromatography–mass spectrometry technologies (HPLC–MS) and/or fluorescence methods.

Binding is picked up electrically by a voltage-sensing detector and registers as a 'blip' signal. Positive binding can be followed up in laboratory assays to determine the nature and strength of the binding – for example, whether the compound is an agonist or antagonist at a receptor or whether a particular enzyme activity is enhanced or inhibited.

Proteins, gene fragments and RNA molecules from the huge databases of the Human Genome Project can be checked in different disease states, to test for under- or over-expression of encoded proteins, identify genes implicated in disease, or diagnose inherited diseases or predisposition to cancers. HTS methods can also be applied to pharmacokinetic aspects of new compounds, checking for inhibition or induction of drug-metabolising enzymes. Pharmaceutical characteristics of the compounds can be tested, such as solubility and permeability, and potential for crossing the blood–brain barrier. HTS procedures are also applied to toxicological analysis – for example, detection of compounds in forensic samples in criminal cases or doping control in sport.

The procedures are highly automated, using robot technology, and are computer-controlled. In an HTS facility, millions of compounds can be screened per month, producing 'in silico libraries' of data. Techniques are becoming both higher in capacity and better focused. Using HTS, drug companies hope not only to discover new drugs, but also to reduce the drop-out rate of compounds in the later, more expensive stages of animal and human testing.

An example of a drug discovered and developed in Australia using HTS is detailed in [Clinical Interest Box 1.5](#): 'A new drug from WEHI' (see later).

Source: [Pors \(2011\)](#).

- ◆ increasingly ageing populations, requiring drug testing in many chronic degenerative conditions
- ◆ the high attrition rate: drug development may be abandoned (or drugs withdrawn from use) at any stage because of problems with safety, efficacy, changes in fashion or a better competitor drug (see in [Ch 2](#), 'Why drugs disappear').

To achieve economies of scale, many drug company mergers have taken place, leaving only a few major research drug companies worldwide. Companies are trying to streamline testing procedures and get early information on toxicity or pharmacokinetic problems so as to waste as little time and money as possible.

Clinical trials of drugs

A **clinical trial** is a prospective study carried out in humans to determine whether a treatment that is believed to benefit a patient actually does provide a benefit; thus, it is a type of human experiment. The treatment being tested may be investigational (new) or a new version of an established treatment; it may be a drug, diet, medical device, surgical or physical procedure or other modality.¹⁰ The trial of a new drug provides scientific data on safety (by rate or severity of adverse drug reactions) and efficacy (by statistically significant evidence of effects and difference between treated and control groups). The 'gold standard' of clinical trials is the **randomised controlled clinical trial** (RCCT), in which participants are randomly allocated to treatment groups, and the new treatment is compared to a control (the current best or a placebo treatment). (See [Peace & Chen, 2011](#), for a detailed guide.)

Characteristics

Typically, each subject enrolled in the drug trial is randomly allocated to either a treatment group, to be administered the new drug under test, or to a control group, usually given the current best therapy (or a placebo if there is currently no available treatment). The treatments must be considered equally beneficial before the trial (otherwise, it is unethical to deny one group the better treatment). Results are initially applicable only to this treatment regimen and cannot be widely extrapolated to other related drugs or patient groups. All tests in humans must be approved by a local human research ethics committee.

Clinical trials are generally required for all new drugs and for new uses or formulations of old drugs; however, there are exceptions:

- ◆ Potentially toxic drugs (e.g. anticancer drugs) may go straight to phase II studies (see below) in a small number of patients with the disease, so that volunteers without the disease are not subjected to adverse effects.
- ◆ The rules may be bent for orphan drugs (non-patentable, or for rare diseases; see [Ch 2](#)).

¹⁰Many therapeutic techniques previously used unquestioningly for decades by therapists in professions such as dentistry, physiotherapy, podiatry, optometry and speech pathology are now being subjected to clinical trials (often by honours and postgraduate students), as part of the move to evidence-based medicine.

- ◆ There is public pressure for fast-tracking drugs potentially useful in otherwise fatal diseases such as HIV/AIDS and cancers.

The objectives of RCCTs need to be realistic, valid and specific, yet allow for generalisation. Statisticians are involved to advise on methods to minimise bias, define the trial population, determine sample sizes so that the results can be statistically acceptable, allow for random variability, manage the database and determine the statistical methods to be employed. Clinical trials are a staged process, with few patients in the early phases, and stepwise decision making so that trials can be stopped if clear differences or toxicities become apparent; they are prolonged and expensive to run.

Phase I: the first tests in humans

After extensive testing in vitro and in animals, the drug is administered initially in very low doses to a small number (e.g. 4 to 24) of healthy volunteers, possibly in a research centre or institution, under close medical and scientific supervision. The objectives are to determine in humans the pharmacological activities, pharmacokinetic (PK) parameters including bioavailability, tolerable dosage range and acute toxicity of the drug. (See [CIB 2.11](#) for a first-in-humans trial that went disastrously wrong.)

Phase II: the first administration to patients

The initial efficacy studies test if the drug is indeed effective in a small number (perhaps 50 in each treatment group) of closely supervised patients, usually in major teaching hospitals. The tests are 'single-blind'; that is, patients do not know which treatment they are getting, but the investigators do. The investigators are specialists in the appropriate field, such as oncologists, psychiatrists or rheumatologists. Phase II studies indicate the PK and pharmacodynamic properties, therapeutic range of doses, maximum tolerated dose and common adverse reactions in patients with the disease. They act as 'pilot studies' to optimise the protocol and determine sample sizes in the phase III trial.

After the phase II trial, the drug company may apply for approval to conduct an RCCT. In Australia, data are sent to the TGA's Advisory Committee on Medicines, which assesses formulation, production, efficacy, adverse reactions, protocols and ethical aspects of the proposed trial. If likely benefits outweigh risks, the drug progresses to the next phase.

Phase III: the full-scale randomised controlled clinical trial

This is 'the clinical trial', in which the drug is administered to numerous patients (from several hundred to a few thousand) under the guidance of experienced clinical investigators to ascertain whether, under defined conditions, the drug shows clinical benefit for the disease state, with an acceptably low rate of adverse drug reactions. The trial is usually 'multicentre', carried out simultaneously in different institutions or countries,

to increase the number of subjects and investigators and achieve quicker results; many are partly carried out in Australia. A typical RCCT may cost up to US\$5 million, so it must be designed carefully to ensure statistically significant results are able to be extrapolated to a range of populations. Important elements of the RCCT are as follows:

- ◆ investigators must initially believe that the new treatment is at least as good as the old
- ◆ randomisation of subjects to ensure groups are initially similar in gender, age range, weight range, severity of disease
- ◆ the 'informed consent' form for participants should contain detailed information about the study, potential benefits and adverse reactions, and the option to withdraw at any stage
- ◆ double-blinding is usual, with coded packs of drugs so that neither investigators nor subjects know who received the new drug; after the trial has concluded, results are analysed and the code is revealed
- ◆ ethical aspects: an application must be made to the institution's Ethics Committee for approval to run the trial (discussed in [Ch 2](#)).

Advance planning determines parameters such as the study design (paired, crossover, parallel), criteria for persons to be included or excluded (inclusions are generally wider than those in phase II trials), maximum length, outcome criteria (whether by changes in biomarkers or patient-improvement outcome), justification (who benefits?), information given to patients, protocols, sample sizes required for valid results, monitoring for adverse events, database management and statistical analysis methods, withdrawal procedures and follow-up schedules, regular auditing for safety and quality control (see [Peace & Chen, 2011](#)).

Usually the statistical basis for the trial is the null hypothesis: that there is in fact no difference between the two treatments; in other words, the new drug is just as good as the current therapy. If it becomes apparent that one group is benefiting statistically significantly more than the other, or suffering more adverse reactions, the trial is halted. Results are analysed for statistical equivalence and the null hypothesis is accepted or rejected. It is important that raw data from clinical trials be published (even negative results), so that conclusions can be examined by outsiders not involved with the researchers, drug companies or funding bodies.

Phase IV: post-marketing studies

If the new drug is shown to be safe, efficacious and cost-effective, it may be approved for marketing. However, there are limitations in the testing and trialling processes: the number of people studied and the time allotted to the study have been limited; and certain types of subjects have been excluded, such as children, pregnant women, the elderly, and persons with multiple disease states or taking other drugs.

CLINICAL INTEREST BOX 1.4 The first (recorded) controlled clinical trial

From ancient times it was known that fresh plant food or raw animal meat must be included in people's diet to prevent a horrible disease called scurvy. Sailors on voyages longer than one month, eating dried meat and insect-ridden bread with no fruit or vegetables, developed weak, aching limbs, gum disease and bleeding skin, and were likely to die from wounds that did not heal, infection or blood loss. It is estimated that in 1499, the Portuguese explorer Vasco da Gama lost 116 of his crew of 170 to scurvy. In the 16th century it was known that citrus fruit had an antiscorbutic effect (anti-scurvy); however, its use was not widespread. In that era the concept of vitamins was unknown, and citrus fruit effects were attributed possibly to their acidic nature.

James Lind (1716–94), a Scottish physician, pioneered hygiene in the British Royal Navy, arguing for improved cleanliness of sailors' bodies, clothing and bedding, and fumigation of below-deck areas with sulfur and arsenic. Lind maintained that scurvy caused the death of more British sailors than did French and Spanish firearms.

In 1747, Lind conducted the first systematic clinical trial, when his ship had been at sea for two months and most sailors were already afflicted with scurvy. He divided 12 scorbutic sailors into six groups of two. All received the same diet but, in addition, pairs of sailors were given daily doses of a supplement – either:

- 1 a quart of cider
- 2 25 drops of elixir of vitriol (sulfuric acid)
- 3 six spoonfuls of vinegar
- 4 half a pint of seawater (the control group)
- 5 two oranges and one lemon, or
- 6 a spicy paste plus a drink of barley water.

After six days, group 5 ran out of fruit, but by then one sailor was fit for duty while the other had almost recovered. The two sailors on cider partially recovered.

Lind published the results of his work in 1753 and 1762, recommending citrus fruits and fresh vegetables; but it was generally believed that scurvy had multiple causes, including ill-digested food and bad water. However, in the Royal Navy it was recognised that citrus juices were effective: when James Cook went on his first voyage he carried as antiscorbutic treatments wort (now known to contain 0.1 mg vitamin C per 100 g), sauerkraut (10–15 mg per 100 g), and a syrup of oranges and lemons (the juice contains 40–60 mg of vitamin C per 100 g). By 1795, the Admiralty recommended that lemon juice should be issued routinely to the whole fleet.

The actual antiscorbutic factor, vitamin C or ascorbic acid, was eventually isolated in 1927 by Albert Szent-Gyorgyi, who was awarded the Nobel Prize for Medicine in 1937 for this discovery. (Previously, while puzzling over the identification of the factor, which was known to be chemically related to glucose, he had suggested that it be named 'ignose' or 'godnose'.) It is a small, water-soluble molecule and is on the WHO's List of Essential Medicines. The recommended intake is variably given as 40–90 mg/day; a balanced diet usually provides sufficient without supplementation. There is no sound evidence that high-dose vitamin C supplementation helps prevent cancers, heart disease, cataracts or common cold in people on a varied diet.

Interestingly, the plant with the highest known concentration of vitamin C is the 'Kakadu plum', *Terminalia ferdinandiana*, widespread throughout northwestern Australia, with concentrations of 2300–5300 mg/100 g wet weight (i.e. 2–5% content), compared with 50 mg/100 g for oranges.

Once marketed, the drug is used in many more patients and for longer periods; extended monitoring of safety and efficacy (pharmacovigilance) is then possible. Inevitably, events will surface that were not seen during the trial, such as rare adverse reactions, effects in subgroups of the population and drug interactions. Studies in older people are especially important, as they may have co-morbidities and require many drugs for prolonged periods.

Later, meta-analysis (overview analysis) may be carried out to combine and analyse data from all similar clinical trials. This increases the statistical power, making significant results more likely; however, meta-analysis suffers inevitably from 'publication bias', as negative results are less likely to be published than positive results. (Some regulating authorities and journals require authors to advise in advance when trials are to be carried out, to ensure that results of all trials are published.) Sometimes, different trials will produce conflicting results; the choice to prescribe the drug is then based on clinical judgment.

As part of its post-market vigilance, the TGA encourages drug companies to share their large quantities of information about new drugs, and rates companies' responses with a

T-score for transparency (see 'New drugs' section at the back of *Australian Prescriber* issues). The TGA also carries out laboratory investigations of products on the market and ongoing monitoring to ensure compliance with legislation. The TGA publishes information on a database of Adverse Event Notifications. Consumers are advised to discuss any concerns with a healthcare professional. Medsafe in New Zealand (the New Zealand Medicines and Medical Devices Safety Authority) regulates clinical trials and carries out similar pharmacovigilance.

Pharmacovigilance: the 'blue card'

Through its Advisory Committee on Medicines (ACM; formerly the Adverse Drug Reactions Advisory Committee), the TGA facilitates the reporting by consumers and healthcare professionals of adverse events they suspect are related to medications and medical devices. The paperwork is a one-page form (the 'blue card' – see Fig 1.6) that is readily available online and can be filled in electronically; confidentiality is maintained. Consumers can also report their own adverse reactions via a 1300 telephone number designated the Adverse Medicine Events (AME) Line (1300 134 237).

Reports of adverse reactions are reviewed, entered into a database (Database of Adverse Event Notifications [DAEN]) and analysed for patterns. ACM informs health professionals about adverse events and can recommend actions ranging from no action required, to change of aspects of prescribing or dispensing, through to withdrawal of a drug from the

market. For example, the COX-2 inhibitor lumiracoxib was included in the Pharmaceutical Benefits Scheme (PBS) in 2006 and became widely used; however, by late 2007 the TGA had received eight reports of serious liver damage (including two deaths), so the drug was de-registered. ACM has introduced Medicines Safety Updates (published regularly in the *Australian*

Office use only

Report of suspected adverse reaction to medicines or vaccines
See statement about the collection and use of personal information overleaf, and please attach any additional data to this form

Patient details: or medical record number:		Sex: M <input type="checkbox"/> F <input type="checkbox"/>	DOB:	
		Weight (kg):		

Suspected medicine(s)/vaccine(s)

Medicine/vaccine <small>(please use trade names; include batch number and AUST R or AUST L number if known)</small>	Dosage <small>(Dose number for vaccines eg 1st DTP)</small>	Date begun	Date stopped	Reason for use

Other medicine(s)/vaccine(s) taken at the time of the reaction

Medicine/vaccine	Dosage	Date begun	Date stopped	Reason for use

Reaction(s): Date and time of reaction: / /

Describe with much detail as possible:

Seriousness: Life threatening ☐ Hospitalised ☐ Required a visit to doctor ☐

Treatment of reaction:

Outcome: Recovered ☐ Date: / / Not yet recovered ☐ Fatal ☐ Date: / / Unknown ☐

Sequelae? No ☐ Yes ☐ Describe:

Reporting: Doctor ☐ Pharmacist ☐ Other ☐ Contact details (email or phone)

Name:

Address:

Postcode:

Signature:

Date: / /

FIGURE 1.6

The 'blue card', on which suspected adverse reactions to drugs and vaccines are reported

Source: Adapted from Therapeutic Goods Administration, <https://www.tga.gov.au/sites/default/files/blue-card-adverse-reaction-reporting-form.pdf>

What to report
You do not need to be certain, just suspicious!
 Any information related to the reporter and patient identifiers is kept strictly confidential.
 Adverse drug reaction reports should be submitted for prescription medicines, vaccines, over-the-counter medicines (medicines purchased without a prescription), and complementary medicines (herbal medicines, naturopathic and/or homoeopathic medicines, and nutritional supplements such as vitamins and minerals). Please include timing of reactions relative to medicine administration where relevant.

We particularly request reports of:

- All suspected reactions to new medicines and vaccines
- All suspected drug interactions
- Unexpected reactions, that is not consistent with product information or labelling
- Serious reactions which are suspected of significantly affecting a patient's management, including reactions suspected of causing death, danger to life, admission to hospital, prolongation of hospitalisation, absence from productive activity, increased investigational or treatment costs, and birth defects.

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Delivery Address:

No stamp required if posted in Australia

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FIGURE 1.6 Continued

Prescriber), a Medicines Risk Management Plan based on the European Union guidelines for pharmacovigilance, and a new alert system for recently introduced drugs.

Drug development in Australia

There is little basic research carried out by 'big pharma' drug companies in Australia or New Zealand, where most companies are offshoots of multinationals based overseas. Scientific work in the Australian companies is mainly on formulations suitable for local conditions or preparation of submissions for the marketing of drugs developed overseas. Australia's share of global research and development (R&D) is only about 1.3%, so Australia relies on the rest of the world to develop most advances in knowledge.

Australian medical schools and medical research institutes have an enviable reputation worldwide for medical and healthcare research; new compounds of interest may be discovered, and researchers collaborate with drug companies in developing drugs, after which commercial exploitation and 'value-adding' of the research usually happen overseas. Some drugs that have recently been developed and/or trialled in Australia are summarised in [Table 1.5](#), while [Clinical Interest Box 1.5](#) presents a case study of the discovery and development of venetoclax.

CSL (formerly Commonwealth Serum Laboratories) was set up over 100 years ago to develop 'immune sera' (vaccines). It is now a major producer of antibiotics, diagnostic products, novel biologicals, antivenoms, vaccines and blood products, and markets many pharmaceutical drugs produced by other companies. CSL employs more than 10,000 people in 27 countries, and in February 2018 announced its half-year revenue as US\$4147 million.

Clinical trials in Australia and New Zealand

In Australia, the TGA has overall control of therapeutic goods via pre-market evaluation and approval of products, regulation of clinical trials, roles of Human Research Ethics Committees (HRECs), trials involving gene therapy and related therapies, preventing or stopping a trial, indemnity and compensation, licensing of manufacturers and post-market surveillance. Details of the relevant regulations and guidelines are covered in the TGA booklet *Australian Clinical Trial Handbook 2006* (see details in ['Online resources'](#)). Use of a registered or listed product in a clinical trial beyond the conditions for which registration/ listing has already been granted also requires approval by the TGA. Overseas drug companies favour carrying out trials in Australia, as our regulatory authority (TGA) is respected, and

data generated here is likely to be accepted in the United States and Europe. All clinical trials should be registered in advance at the Australian New Zealand Clinical Trials Registry, based at the National Health and Medical Research Council (NHMRC) Clinical Trials Centre in Sydney; thus, Australian and New Zealand researchers contribute to a worldwide initiative to make public the details of all clinical trials.

There are two main schemes under which drugs (and medical devices) may be trialled. The first is application for approval under the Clinical Trial Exemption (CTX) scheme. An application to conduct a trial is submitted to the TGA, whose delegate reviews the data and may object to the trial or comment on the proposal. When any objections have been satisfactorily met and the local HREC has approved it, the trial may go ahead without further assessment from the TGA. Early phase I and II studies and trials of medical devices most commonly come under the CTX scheme. The scheme is complex, and few trials now come under these rules.

The second approach is notification under the Clinical Trial Notification (CTN) scheme, under which data are submitted to the local HREC, which reviews the data and the trial design and advises the institution if it approves the trial, or can refer the application to the CTX scheme. A CTN form must be submitted to notify the TGA of the trial. Phase III and IV trials and bioequivalence studies are best suited to the CTN scheme.

Principles of good clinical practice must be followed, such as those promulgated by the European Forum for Good Clinical

Practice (www.efgcp.eu/). These principles cover aspects such as: responsibilities of the investigators and the drug company; drug product handling, storage and accounting; reporting of adverse effects; and keeping and archiving of records. There are potential problems relating to lack of transparency about procedures, delaying or withholding of negative results, applying 'spin' to make drugs look better, or participating doctors accepting funding or gifts from sponsoring drug companies.

In New Zealand, approval to trial a new drug not yet approved is submitted to the Standing Committee on Therapeutic Trials (SCOTT), a committee of the Health Research Council of New Zealand. Quite a few clinical trials are carried out in New Zealand, as it is a small, closed, not too mixed population. Medsafe publishes *Guidelines on the Regulation of Therapeutic Products in New Zealand*; Part 11 concerns regulatory approval and good clinical practice requirements. Pharmaceutical companies conducting clinical research must comply with the principles contained in the guidelines; and participating doctors must be familiar with good clinical research practice requirements and assess the proposed research for compliance (see '[Online resources](#)').

FUTURE DRUG DEVELOPMENT

The new genetics

The discovery of the double-helical structure of DNA (published by Francis Crick and James Watson in 1953),

TABLE 1.5 Some drugs developed and/or trialled in Australia

DRUG OR COMPOUND	RESEARCH INSTITUTE OR DRUG COMPANY
PG545, a potential anticancer drug, a heparan sulfate mimetic targeting angiogenesis and metastasis	Progen Pharmaceuticals, Darra, Queensland; now part of TBG Diagnostics Limited
Novel crystalline carbohydrates, including a generic version of the low-molecular-weight heparin fondaparinux	Alchemia P/L, South Melbourne, and the Centre for Drug Discovery and Design, University of Queensland
Blood products: vaccines, sera, factors for bleeding disorders, antibodies for preventing severe infections, antivenoms; interferon beta-1a for treating multiple sclerosis	CSL Ltd, Parkville, Melbourne
Thebaine and oripavine, used to synthesise the opioids oxycodone and buprenorphine, produced in high yields from new strains of opium poppy	Tasmanian Alkaloids P/L, Westbury, Tasmania
Zanamivir (Relenza): treats influenza by binding to neuraminidase protein in flu virus	Victorian College of Pharmacy (now Monash University); CSIRO, Australian National University and Biota Pharmaceuticals, US
High-throughput screening of natural plant compounds and chemicals from the Compounds Australia library has led to a unique chemical from a marine organism that kills malaria parasites	Eskitis Institute and Griffith Institute for Drug Discovery at Griffith University, Brisbane
Lysyl oxidase inhibitors (LOX) targeting fibrotic diseases including pulmonary fibrosis and some cancers; also patents for novel phospho-sugars, pyrans and oligonucleotides	Pharmaxis, Sydney
Three active compounds from elapid snake venoms: Textilinin-1 (a plasmin inhibitor), Haempatch® (a factor Xa-like protein) and CoVase® (a procoagulant)	QRxPharma Ltd, Venomics P/L and University of Queensland
BH3-mimetic drugs, earlier developed as potential anticancer agents, also show promise in treating legionnaires' disease	Walter and Eliza Hall Institute, Melbourne, and Monash University Biomedicine Discovery Institute

Source: Adapted from [Harrison \(2000\)](#).