Pharmacology for Podiatrists

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To Janet and Lesley

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Preface

The increasing complexity of health care now demands that a multidisciplinary team of professionals work together for the benefit of patients. Podiatrists form an essential part of this provision and need to continually appraise their own practice and assess how it best fits with that of other members of the team. The most effective way to do this is to find out about the work of other members of the team and to educate these colleagues about the work of podiatrists.

The incidence of drug therapy of disease has increased dramatically in recent years, such that the proportion of the population who are receiving at least one drug is increasing annually. Furthermore, many older patients are regularly receiving more than one drug (polypharmacy) and it is not uncommon for some patients to be taking eight or nine different drugs at the same time. Clearly, the chance of patients suffering not only from the adverse effects of these drugs, but also potentially serious drug interactions, is high.

The nature of podiatrists' work means that not only do they probably spend more time with individual patients than most other members of the health care team, but also the majority of their patients will be in the older, high-risk category. In this situation, they are ideally placed to spot potential adverse drug effects and interactions and be able either to reassure the patient as to the nature of the adverse effect or to refer the patient back to their medical practitioner if necessary. In this way, podiatrists are now in a position to provide another valuable service to health care provision, that of monitoring long-term effects of commonly prescribed drugs.

Over the past ten years, the practice role of the podiatrist has expanded to incorporate specialist surgical provision, the treatment of sports injuries and, most recently, the profession has gained access to prescription only medicines (POM). It is likely that the number of POMs available to podiatrists will increase in future years, and we hope that this book will be invaluable to those practitioners who wish to develop their understanding of the mechanisms by which drugs produce their effects and the potential for the development of adverse effects and drug interactions.

The early chapters of this book address the basic principles of pharmacology and drug action. Later chapters cover the major organ systems of the body, giving a brief overview of the structure and control mechanisms of each. The major diseases affecting these organ systems are then considered, together with a survey of the drugs used to combat the diseases and a summary of their common adverse effects. In order to avoid undue complexity, drug dosage has not been addressed in this book. Students who wish for more details of this aspect of drug therapy are referred to the Further Reading section at the back of the book. Throughout the book, drugs are referred to by their generic names, rather than any proprietary names.

We hope that this text will be an aid both to undergraduate students studying pharmacology for the first time and to those practitioners following a postgraduate course in pharmacology to enable them to become accredited for prescription purposes.

Common Abbreviations

The following is a list of common abbreviations used throughout this book. More specific abbreviations are defined in the text.

5-HT	5-hydroxytryptamine (serotonin)
ACE	angiotensin-converting enzyme
ACh	acetylcholine
AChR	acetylcholine receptor
ADH	antidiuretic hormone (vasopressin)
ANS	autonomic nervous system
ATP	adenosine triphosphate
AV node	atrioventricular node
Ca^{2+}	calcium ion
cAMP	cyclic adenosine monophosphate
cGMP	cyclic guanosine monophosphate
Cl^-	chloride ion
CNS	central nervous system
COX	cyclo-oxygenase
COX I	cyclo-oxygenase I
COX II	cyclo-oxygenase II
CVS	cardiovascular system
DAG	diacylglycerol
DMARDs	disease-modifying antirheumatic drugs
DNA	deoxyribonucleic acid
ECG	electrocardiogram
FSH	follicle-stimulating hormone
GABA	γ-aminobutyric acid
GDP	guanosine diphosphate
GI	gastrointestinal
GnRH	gonadotrophin-releasing hormone
G-protein	trimeric protein which can bind GDP and GTP
GTP	guanosine triphosphate
HCl	hydrochloric acid
HDL	high-density lipoprotein
HIV	human immunodeficiency virus
H. pylori	*Helicobacter pylori*
HRT	hormone replacement therapy
i.m.	intramuscular(ly)
i.p.	intraperitoneal(ly)
IBS	irritable bowel syndrome
IP_3	inositol triphosphate
i.v.	intravenous(ly)
K^+	potassium ion
kDa	kilodalton (measure of molecular weight)
l	litre(s)
LDL	low-density lipoprotein
L-dopa	L-dihydroxyphenylalanine
LGIC	ligand-gated ion channel
LH	luteinising hormone
mAChR	muscarinic acetylcholine receptor
MAO-A	monoamine oxidase-A
MAO-B	monoamine oxidase-B
MAOI	monoamine oxidase inhibitor
mm Hg	mm of mercury pressure
mRNA	messenger RNA
Na^+	sodium ion
nAChR	nicotinic acetylcholine receptor
NANC	non-adrenergic non-cholinergic
NE	norepinephrine (previously called noradrenaline)
NO	nitric oxide
NSAIDs	non-steroidal anti-inflammatory drugs
PG(s)	prostaglandin(s)
PNS	peripheral nervous system
RNA	ribonucleic acid
SA node	sinoatrial node
s.c.	subcutaneous(ly)
SSRI	specific serotonin reuptake inhibitor
VGIC	voltage-gated ion channel
VLDL	very low-density lipoprotein
WHO	World Health Organisation

1

Introduction

WHAT IS PHARMACOLOGY?

The word *pharmacology* is derived from the Greek word *pharmakon* which means drug, and so the science of pharmacology is the study of the effects of biologically active chemicals (drugs) on living systems, cells, cell membranes and enzymes. These chemicals may be substances that occur naturally in the body such as epinephrine and insulin, everyday substances in our diet such as caffeine and alcohol, or therapeutically active drugs such as digoxin and aspirin.

Pharmacology also includes the study of the mechanisms by which natural chemicals exert their controlling effects in the body, as well as the origin of drugs, their structure, site(s) and mechanism(s) of action, adverse effects, metabolism and excretion. Consequently, the study of pharmacology can be undertaken at a number of different levels, namely the effect of drugs on:

- whole body systems, such as the cardiovascular system
- a whole organ, such as the heart
- individual cells, such as the conducting cells in the heart
- the subcellular components, such as the nucleus
- enzymes in the cell, such as phosphodiesterase.

The study of pharmacology is important not only in the treatment of human diseases, but also in the study of the toxic effects of harmful chemicals, whether they are drugs or chemicals in the environment. In many cases, the dividing line between a chemical being a useful drug or a poison is a very narrow one. All drugs will produce unwanted adverse effects if given to patients in too large a dose, or if used inappropriately. The aim of the treatment of diseases with drugs (*pharmacotherapy*) is to achieve as high a degree of *selectivity* in action for the drug as is possible and thus to reduce the adverse effects to an acceptable minimum.

We can see, therefore, that a knowledge of the pharmacology of the commonly used drugs is important for all professionals involved in the care of patients, especially to allow for the identification of the adverse effects produced by most drugs.

HISTORY OF PHARMACOLOGY

Pharmacology has its roots in the magic and folk medicine of many ancient civilisations. Throughout recorded history, a special place in society has been reserved for those people who knew about medicines and their use for the treatment of diseases. Mankind has used natural remedies to treat diseases for thousands of years and we can find references to recipes for these drugs in the written records of almost every ancient civilisation. Most of these ancient recipes were mixtures of substances taken from the plants and animals found locally.

One of the earliest pharmacopoeias was recorded in the Ebers papyrus, written in Egypt in about 1500 BC. It contains over 650 recipes for potions used for the treatment of common diseases and afflictions, including 'cures' for baldness, night blindness, worm infestations and many other common ailments afflicting the

people of the time – some of which still bother us today. Many of the concoctions were bizarre, such as the mixture of 'fat of lion, fat of hippopotamus and fat of ibex', to be used for baldness. Other preparations, such as opium, are still in use today.

Medicine, and the use of drugs, also developed in China and India, but few of the developments affected Western medicine, as there was no direct communication between the civilisations. The development of Western medicine and pharmacy owes a great deal to the Ancient Greek civilisation. The Greeks thought that disease was the result of an imbalance in the various 'humors' of the body – blood, phlegm, black bile and yellow bile – and that diseases could be treated by administering potions that restored the natural balance in the body. This doctrine was supported by Galen (AD 130–210) and led to the development of a large range of herbal remedies. During the time of the Roman civilisation, the teachings of the Greeks were organised into a number of different compendia of medicines (*materia medica*), the greatest of which was that written by Dioscorides in AD 57. This listed over 500 remedies derived from plants and gave details of how to prepare the medicines for administration to the patient.

During the Middle Ages, the practice of treating diseases with drugs spread throughout Europe, being mainly practised by monks who used the herbs grown in their gardens. One of the greatest contributors to the development of medicine during this period was a man known as Paracelsus. Paracelsus was born in Switzerland in the late fifteenth century; the son of a physician, he travelled throughout Europe collecting recipes and treating disease. He was the first person to postulate that diseases could be treated with chemicals (drugs), since he suggested that the major life functions are also chemical processes. He also taught that all substances are potentially poisons and that it is only the amount ingested that differentiates between a medicine and a poison.

The emergence of the systematic study of anatomy and physiology in the seventeenth and eighteenth centuries led to an understanding of the structure and function of animals and humans. This in turn led to the development of the sciences of experimental physiology and experimental pharmacology, in an attempt to elucidate not only the basic processes controlling the functions of the body systems, but also the sites and mechanisms of action of drugs.

Major developments during this period include:

- the discovery of the structure and function of the circulation by William Harvey (1578–1657)
- the postulation that diseases are caused by an imbalance in the body by Sylvius (1614–1672)
- the isolation of pure morphine by Serturner (1783–1841)
- the discovery of the role of proteins in life by Francois Magendie (1783–1855)
- the discovery of the principle of homeostasis by Claude Bernard (1813–1878).

Other examples of the discovery of therapeutically effective drugs from natural sources are vitamin C for the prevention of scurvy; quinine for the treatment of malaria; and digitalis for the relief of the symptoms of heart failure.

Further studies, carried out during the late nineteenth century and throughout the twentieth century, have led to the identification of the large number of chemicals that control normal bodily function. These studies also highlighted the fact that the way forward in the treatment of disease lay in the ability to either mimic or antagonise the actions of these chemicals in the body. Parallel developments in chemistry have led to the introduction of sophisticated techniques for the synthesis and analysis of many chemicals. Thus, the naturally occurring substances can provide a basis for the development of new drugs.

Some of the major discoveries during this period include:

- the suggestion that chemicals bind to specific parts of cells by Paul Erhlich (1854–1915)
- the introduction of the concept of drug receptors by Langley (1852–1926)
- the development of theories of drug action by Lockett, Bartlett and Paton
- the development of the theory of neurohumoral transmission and the identification of a large number of neurotransmitter chemicals that allow for interaction between nerves and other tissues

- the design of specific drug molecules (propranolol and cimetidine) by James Black
- the characterisation and expression of receptor proteins.

WHERE DO DRUGS COME FROM?

Modern drugs now come from a variety of different sources. Drug manufacturers often specialise in particular therapeutic areas, depending upon their particular range of expertise and a careful analysis of the potential market for the drug.

During the nineteenth and early twentieth centuries, many drugs came from natural sources, such as plants. Probably the most effective of these was digoxin, derived from the foxglove *Digitalis purpurea.*

A thorough knowledge of the receptor pharmacology of a disease allows for the design of drug molecules, which may be able to either moderate the activity of naturally occurring neurotransmitters in the body, or replace neurotransmitters that are not being produced in sufficient quantities for normal control of body processes. It is the job of the synthetic chemists to design and make new drug molecules based on this pharmacological knowledge and then to pass them on to pharmacologists for evaluation.

An example of this approach was the development of the β-adrenoceptor antagonists by Black and his colleagues. Their knowledge of the chemical structure of the naturally occurring agonist (norepinephrine) at the β_1-adrenoceptor in the heart enabled the development of a synthetic drug that was much more potent. Small changes in the structure of this molecule produced a compound that bound very strongly to the receptor, but which did not produce any direct effect. The first β-adrenoceptor antagonist (blocker) was born.

Some drugs arise from a fortuitous observation that a particular chemical has an unexpected effect on a body system, or that patients being treated with the chemical recover unexpectedly from an unrelated disease. Whilst the drug may not be sufficiently potent to be therapeutically useful itself, it may provide the chemists with a starting molecule from which they can produce more active derivatives. This approach has been used to develop a range of antibacterial drugs from parent molecules that have the desired effect, but which are not suitable for clinical use, either because they are not sufficiently potent or have too many adverse effects.

A lot of effort is now being put into searching for novel chemicals, in the flora of the great forests of the world. In fact, the development of drugs from natural sources has almost turned 'full circle' in that we are now looking to these sources, not for the finished drug, but for novel molecules with therapeutic actions, which may then be developed into clinically useful drugs.

More recently, the unravelling of the human genetic code (the human genome), and the identification of the links between some human diseases and genetic changes, has led to attempts to develop new drugs based on the genetic changes inherent within some diseases.

TERMINOLOGY AND DRUG CLASSIFICATION

One major stumbling block to an understanding of clinical pharmacology is the vocabulary used to describe both disease states and the adverse effects of drugs. In this section we will look at the derivation of some of the medical terms used and try to see how they are built up. Once this has been mastered, working out what the words mean becomes a lot easier.

The long words used in medical terminology are actually constructed by joining together a series of prefixes and suffixes with root words that describe a particular organ or process in the body. For example, let us consider the word *endocarditis*. This complex word consists of three parts, the *prefix* (endo), the *stem* (cardio) and the *suffix* (itis):

- endo – meaning inside
- cardio – meaning the heart
- itis – meaning inflammation

Literally, endocarditis means an 'inflammation inside the heart'. In fact the term means an inflammation of the endocardium, which lines the heart, but its literal derivation is not too far away from reality.

We can see, therefore, that a knowledge of the most commonly used prefixes and suffixes, together with a knowledge of the major stem words, would allow us to construct and understand quite complex medical terms.

Tables 1.1 to 1.3 list some of the more common prefixes, stems and suffixes used in medicine, together with examples of their use. Reference to these tables should allow you to decipher a large number of common medical terms. Perhaps you would like to try and decipher the following terms:

- supraventricular tachycardia
- myocardial ischaemia

Table 1.1 Common prefixes used in medical terminology.

Prefix	Meaning	Example
a-(an-)	without	aphasia (lack of speech), anuria (without urine)
ad-	near to	adrenal (near the kidney)
arthr-	joint	arthritis (inflammation of a joint)
brady-	slow	bradycardia (slow heart)
carcin-	cancer	carcinogenic (cancer producing)
cardio-	heart	cardiopathy (heart disease)
co-	with	coenzyme (molecule that functions with an enzyme)
cyto-	cell	cytoplasm (fluid inside the cell)
dys-	difficult	dysphagia (difficulty in eating/swallowing)
endo-	inside	endometrium (tissue inside the uterus)
erythro-	red	erythrocyte (red blood cell)
glyco-	sugar	glycolysis (breakdown of sugar)
hemi-	half	hemisectomy (to remove half)
hetero-	different	heterozygous (different genes for the same trait)
homo-	same	homozygous (same genes for a given trait)
hyper-	above, over	hypertension (high blood pressure)
hypo-	under, below	hypotension (low blood pressure)
inter-	between	intercostal (between the ribs)
intra-	within	intracerebral (inside the brain)
iso-	equal	isoenzyme (different forms of the same enzyme)
leuc(k)o-	white	leuc(k)ocyte (white blood cell)
lip-	fat	lipid (fat-like)
mal-	bad	malodorous (bad smell)
myo-	muscle	myocardium (heart muscle)
neuro-	nerve	neurology (study of nerve function)
oligo-	little, few	oligospermia (few sperm)
osteo-	bone	osteoporosis (disease forming porous bones)
phleb-	vein	phlebitis (inflammation of a vein)
pneumo-	air, gas	pneumothorax (air in the thorax)
pod-	foot	podiatry (treatment of foot disorders)
procto-	anus, rectum	proctoscopy (examination of the rectum)
steno-	narrow	stenosis (narrowing of vessel)
supra-	above, upon	suprarenal (above the kidney)
tachy-	fast	tachycardia (fast heart rate)
tox-	poison	toxicity (study of poisons)

Table 1.2 Common stem words used in medical terminology.

Stem	Meaning	Example
cardio-	heart	cardiomyopathy (disease of heart muscle)
cerebral	brain	cerebral oedema (accumulation of fluid in the brain)
renal	kidney	renal hypertension (hypertension due to renal dysfunction)
hepato-	liver	hepatotoxic (poisonous to the liver)
myo-	muscle	myalgia (muscle pain)
ophthalmo-	eye	ophthalmology (study of the eye)
oto-	ear	ototoxic (damaging to the ear)
viscer-	internal organ	visceral pain (pain associated with internal organs)

Table 1.3 Common suffixes used in medical terminology.

Suffix	Meaning	Example
-aemia	blood	anaemia (lack of blood)
-algia	pain	neuralgia (pain in a nerve)
-ary	associated with	urinary (associated with urine)
-blast	bud	fibroblast (fibre-producing cell)
-cide	kill	bactericide (substance that kills bacteria)
-ectomy	cut out	mastectomy (removal of breast tissue)
-gram	drawing	cardiogram (drawing of the heart)
-ia	condition	ischaemia (lack of oxygen)
-ic	state	ischaemic (state of tissue deprived of oxygen)
-itis	inflammation	gastritis (inflammation of the stomach)
-oid	similar to	arachnoid (like a spider)
-pathy	disease	nephropathy (disease of the kidney)
-phobia	fear of	agoraphobia (fear of open spaces)
-plegia	paralysed	quadriplegia (paralysed in all four limbs)
-rrhoea	flow	diarrhoea (flow of faeces)
-stomy	artificial opening	tracheostomy (artificial opening in the trachea)
-tropic	influencing	gonadotropic (influence on the gonads)
-uria	urine	anuria (no urine)

- analgesia
- haemorrhage
- haematuria
- hemiplegic
- proctalgia

Pharmacological terminology

Like most other scientific disciplines, pharmacology has a vocabulary of its own to describe the various properties of drugs and the processes by which they produce their effects in the body. Many of these terms will be used throughout this book but, for convenience, the major terms are listed here:

- *agonist* – a drug that produces a measurable biological effect.
- *antagonist* – a drug that does not produce a measurable biological effect itself, but which interferes with the ability of an agonist to produce an effect.
- *receptor* – a target molecule with which a drug interacts to produce its effect in the body.
- *parasympathomimetic* – a drug that mimics the action of stimulating the parasympathetic nervous system.
- *parasympatholytic* – a drug that produces an action to inhibit parasympathomimetic drugs.
- *sympathomimetic* – a drug that mimics the

action of stimulating the sympathetic nervous system.
- *sympatholytic* – a drug that produces an action to inhibit sympathomimetic drugs.
- *cholinergic* – a name given to nerves that release acetylcholine when stimulated.
- *adrenergic* – a name given to nerves that release norepinephrine when stimulated.
- *pharmacodynamics* – the study of what a drug does to the body. It includes a study of the drug–receptor interaction and the mechanisms producing pharmacological effects of the drug.
- *pharmacokinetics* – the study of what the body does to a drug. It includes a study of the absorption, distribution, metabolism and excretion of drugs.
- *pharmacotherapy* – the treatment of diseases by the use of drugs.
- *pharmacoepidemiology* – the effect of the use of drugs on the community.
- *selectivity* – the ability of a drug to produce a single pharmacological effect in the body. Complete selectivity does not exist for any drug currently on the market and, as a consequence, all drugs show a range of adverse effects.
- *adverse effect* – an effect produced by a drug which is not the required therapeutic effect. Adverse effects may be mild, sufficiently severe to require the cessation of treatment or they may be life-threatening.
- *selective toxicity* – the ability of a drug to affect the metabolism of a non-human, or abnormal, cell, rather than those of the patient. Selective toxicity is the property used in antibacterial and anticancer drugs.
- *therapeutic ratio* – the ratio of a drug dose that produces severe adverse (toxic) effects to that which produces the desired therapeutic effect. Therapeutic ratios vary between $> 10\,000 : 1$ and $2 : 1$.
- *risk–benefit ratio* – the balance between the advantages and disadvantages of using a drug. Assessment of the risk–benefit ratio must take into account such things as the quality of life the patient will experience with or without the drug, its adverse effects measured against the severity of the disease, and the cost of the drug. For example, an extremely expensive drug that had a large range of adverse effects would not be acceptable for the treatment of the common cold, but it may be acceptable for the treatment of a life-threatening cancer.
- *pharmacoeconomics* – the study of the costs of drug use.

Drug classification

We have seen above that the term *drug* may be used to describe any substance, whether natural or foreign, that produces a biological effect within the body. However, in order to make them therapeutically useful, most drugs have to be formulated into tablets, capsules, liquids or other formulations to make them palatable for the patient to take. In this form they are called *medicines*.

The classification of drugs has been a problem in pharmacology throughout the last 150 years. There are several approaches to the classification of drugs, and a drug may have a number of different descriptions according to the classification system used. In general, drugs may be classified according to one of the following parameters:

- its molecular mechanism of action
- the type of nerve with which it interferes
- the branch of the nervous system on which it works and the effect produced
- the chemical nature of the molecule.

For example, the drug atropine may be classified as follows:

- An *antagonist* at muscarinic acetylcholine receptors (a muscarinic antagonist), because of its molecular mechanism of action.
- An *anticholinergic drug*, because of its ability to block the effects of cholinergic transmission in the parasympathetic nervous system.
- A *parasympatholytic drug*, because of its ability to block the effects of stimulating the parasympathetic nervous system.
- An *alkaloid* of *Atropa belladonna*, because of its chemical structure and natural source.

All drugs may be described by three different names. The full *chemical* name is often extremely complex and describes the chemical structure of the drug molecule. The *generic* name is shorter

and usually indicates the class of drug to which the individual molecule belongs. The *proprietary* name is the name given to the drug by the manufacturer.

This naming scheme for drugs is illustrated in the following example:

Chemical Name:	1[(2S)-3-mercapto-2-methyl-proprionyl]-L-proline
Generic Name:	captopril (note the absence of a capital letter)
Proprietary Name:	Capoten®

Clearly, the chemical name is too complex to be used routinely, and there may be several manufacturers making and selling the drug under different proprietary names. Therefore, the generic names of drugs are used throughout this book. Proprietary names of drugs may be found in the *British National Formulary*, which is published twice a year by the British Medical Association and the Royal Pharmaceutical Society of Great Britain.

DRUG ADMINISTRATION

Introduction

Clearly, drugs cannot produce their effects unless they can be administered to the patient in such a way that they reach their site of action in a sufficient amount to produce the desired pharmacological action. In order for this to be achieved the drug must be given to the patient in an acceptable form and it must be absorbed from its site of administration into the blood. It must then be distributed throughout the body, in such a way that it gets to its site of action, and remains there long enough to produce a clinical effect.

Unfortunately the body regards most drug molecules as undesirable and tries to excrete them as rapidly as possible. Therefore the administration regimen for a drug must always attempt to maintain a constant concentration of the drug in the plasma, but must take into account the absorption, distribution, metabolism and excretion processes that the drug undergoes while it remains in the body.

To date, no drug is totally devoid of effects on the body other than the desired clinical effect. Therefore it is important when contemplating the administration of drugs to consider not only the desired clinical effect, but also the adverse effects that drug administration may have on the patient.

Adverse drug effects may be classified into two major groups:

- Augmented adverse effects. These arise as an extension of the pharmacological action of the drug that is producing the desired clinical effect. In theory, they may be predicted from knowledge of the pharmacological mechanism of action of the drug. An example is the dry mouth and blurred vision that accompanies the administration of atropine (atropine is an antagonist of acetylcholine and this action also causes dry mouth and a blurring of the vision).
- Bizarre adverse effects. These cannot be predicted from knowledge of the pharmacological mechanism of action of the drug. An example is the anaphylactic shock seen in some patients who are given penicillin.

Drug therapy must always be a balance between the therapeutic advantages to the patient of using the drug and the adverse effects that may be produced. The level of acceptability of adverse effects depends primarily on the severity of the disease to be treated. For example, while a drug that causes severe hair loss would not be acceptable for the treatment of the common cold, it may be tolerated for the treatment of a life-threatening cancer.

The ratio between the dose of drug that produces a toxic effect and that which produces the clinical effect is called the *therapeutic ratio*.

Common adverse effects of drugs

Throughout the later chapters of this book we will be looking at the adverse effects produced by drugs. Some of the more common adverse effects of drugs, and a brief explanation of their meaning, are listed in Table 1.4.

Table 1.4 Common adverse effects of drugs and their meaning.

Adverse Effect	Explanation
Acidosis	Disturbance of acid–base balance in the body resulting in too much acid
Agranulocytosis	Lack of granulocytes in the blood
Albuminuria	Excretion of albumin in the urine
Alkalosis	Disturbance of acid–base balance in the body resulting in too much alkali
Alopecia	Hair loss
Amnesia	Loss of memory
Anaphylaxis	Severe allergic reaction
Anorexia	Loss of appetite
Angioedema	Accumulation of fluid in the tissues of the heart
Arthralgia	Pain in the joints
Asthenia	Absence of strength, weakness
Ataxia	Uncoordinated muscle movement
Bradycardia	Decrease in heart rate
Bradykinesia	Slowness of movement
Carcinogenic	Agent capable of inducing cancer
Cirrhosis	Fibrous growth in the liver
Conjunctivitis	Inflammation of conjunctiva of the eye
Diplopia	Double vision
Dyscrasia	Abnormal composition of body fluids
Dyskinesia	Difficulty in movement
Dyspepsia	Indigestion
Dyspnoea	Difficulty in breathing
Erythema	Patchy redness of the skin
Euphoria	Sense of well-being
Floaters	Opaque bodies in the eye
Gynaecomastia	Breast development in males

Adverse effect	Explanation
Haemolysis	Breakdown of the cellular components of blood
Hepatotoxicity	Damage to the liver
Hypersensitivity reactions	Range from simple rashes to life-threatening anaphylactic shock
Hypertension	Increased blood pressure
Hypotension	Decreased blood pressure
Insomnia	Inability to sleep
Leucopenia	Decreased white blood cell count
Mania	State of emotional excitement
Neuropathy	Damage to nerves
Nystagmus	Involuntary movement of the eyes
Pancytopenia	Overall fall in cellular components of blood
Parasthesiae	Tingling sensations in extremities
Petechiae	Small spots of blood under the skin surface
Postural hypotension	Fall in blood pressure on standing up, causing fainting
Pruritus	Itching
Purpura	Disease characterised by purple patches under skin
Somnolence	Sleepiness
Tachycardia	Increased heart rate
Tardive dyskinesia	Stereotyped movements, expecially of the face and tongue
Thrombocytopenia	Decreased numbers of thrombocytes (platelets) in blood
Urticaria	Allergic reaction of skin characterised by development of weals

ROUTES OF DRUG ADMINISTRATION

Drugs may be administered by a number of different routes; they may be taken by mouth, inserted into the rectum, injected, inhaled or applied to the skin. The route chosen depends on a number of factors, such as:

- the desired site of action of the drug
- the desired duration of action of the drug
- the potential toxicity of the drug.

The term *bioavailability* is used to describe the fraction of the drug dose that is available to produce the pharmacological effect.

Oral administration

Oral administration is the most common and convenient route of drug administration. Drugs may be either retained in the mouth or swallowed.

If they are held in the mouth they may be absorbed either from the buccal cavity or from under the tongue (*sublingual*). In both cases, the drug passes directly into the systemic circulation, is rapidly carried around the body, and produces its pharmacological effect very quickly. An example of a drug that may be given in this way is glyceryl trinitrate, which is used to relieve the symptoms of the heart disease *angina pectoris*. Glyceryl trinitrate is formulated into small tablets that can either be placed under the tongue or allowed to dissolve on the gum. It may also be used as a fine spray.

Drugs that are swallowed first enter the stomach, where they may be retained for 1–2 hours before passing into the small intestine. Some drugs are absorbed from the stomach directly, but most are absorbed from the highly specialised absorption sites in the small intestine.

The contents of the stomach and small intestine may well affect the availability of drugs. The hydrochloric acid (HCl) present in the stomach destroys some drugs and the alkaline environment of the small intestine destroys others. The presence, or absence, of foodstuffs in the stomach or intestines may also significantly alter the availability of drugs administered by this route; for example, the presence of milk in the stomach can inhibit the absorption of some antibacterial drugs. Similarly, some drugs can alter the absorption of others; for example, iron preparations should not be taken at the same time as some antibacterial drugs.

Drugs that are absorbed from sites in the small intestine do not pass directly into the systemic circulation, but pass to the liver via the hepatic portal vein. Many drugs are metabolised (broken down) by the enzymes in the liver, so that only a small proportion of the administered dose enters the systemic circulation. This removal of drug as it passes through the liver for the first time is called the *first pass effect* and can be as high as 99% of the total drug dose. A proportion of metabolised drug is excreted, via the bile, back into the small intestine where it may be reabsorbed. This is called the *enterohepatic shunt*.

Rectal administration

The rectal mucosa has a good blood supply and fewer blood vessels in this area drain into the hepatic portal circulation. Thus it provides an ideal site for drug absorption, especially for those drugs that are irritant to the gastrointestinal tract and which may cause nausea and vomiting if taken by mouth. In order for drugs to be administered rectally they must be formulated into suppositories, which melt at body temperature.

Injection

Many drugs may be administered by direct injection into body tissues. This has the advantage that it avoids the gastrointestinal system but the disadvantage that it requires aseptic (sterile) techniques to avoid introducing infections into the body. The most common routes of injection are:

- intravenous (i.v.)
- intramuscular (i.m.)
- subcutaneous (s.c.).

Intravenous administration places the drug directly into the systemic circulation and is the

route of choice when an instantaneous effect is required. Drugs delivered by this route enter the blood as a bolus (single dose), and so it is possible that unusually high concentrations may be attained in certain tissues immediately after the injection, giving rise to toxic effects. Slow intravenous infusions of drugs may be used to deliver the required drug dose over a period of time. This route is also difficult for self-administration, as it requires complete sterility to avoid infections.

The intramuscular route allows for the drug to be injected directly into a muscle mass, such as the gluteus maximus muscle in the buttock. Variations in the formulation of the drug enable a depot effect to be attained by which a single injection may last for several weeks.

In subcutaneous injection, the drug is injected into the subcutaneous layer just under the skin. This is the most common route for the self-administration of insulin by insulin-dependent diabetics.

A more specialised route is intrathecal injection, which places the drug directly into the central nervous system (CNS). This route obviously requires complete sterility to avoid the introduction of infections into the CNS.

Inhalation administration

Recent advances in drug formulation have enabled the development of aerosols that produce a fine particulate suspension of the drug, which may be directly inhaled into the lungs. This is clearly an advantage if the lung is the site of action of the drug, for example the use of salbutamol in the relief of asthma, but may also provide an alternative and convenient route of administration of drugs that are destroyed in the gastrointestinal tract.

Topical application

Drugs may be formulated into ointments and creams for the treatment of skin diseases such as eczema, psoriasis and skin infections. An increasing number of drugs are now being formulated in such a way that they may be absorbed directly into the systemic circulation after application to the skin. Most people are familiar with the nicotine-containing patches used as an aid to giving up smoking. This route may also be used to administer other drugs, such as glyceryl trinitrate and hormone replacement therapy (HRT) preparations.

Drops and sprays

Some drugs may be administered in the form of eye drops or nasal drops/sprays. The administration of antibacterial drops for the treatment of eye infections is commonplace, but this route is also used for the administration of drugs for the treatment of glaucoma. Nasal drops and sprays are primarily used to administer drugs for the treatment of rhinitis and hay fever, but may also be used to administer some hormonal preparations.

It should always be noted that the administration of drugs by either of these routes may well result in the systemic absorption of sufficient quantities of drug to produce clinically significant adverse effects. An example is the administration of β-adrenoceptor antagonists in the treatment of glaucoma, which may result in the precipitation of an asthma attack in susceptible individuals.

The various routes of drug administration are summarised in Fig. 1.1.

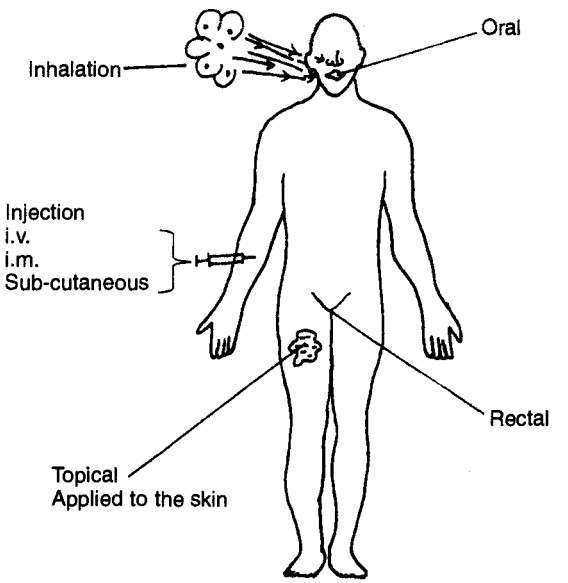

Fig. 1.1 The major routes of drug administration.

DRUG ABSORPTION

With the exceptions of intravenous and intrathecal administration, drugs given by all routes have to be absorbed across a lipid membrane before they can enter the systemic circulation. The mechanisms by which such drug absorption takes place depend upon the physical properties of the drug and the structure of the membrane. The major absorption processes are:

- aqueous diffusion
- passive diffusion
- carrier-mediated diffusion
- active transport.

Aqueous diffusion

Some drug molecules are small enough to pass through water-filled pores in cell membranes. However, this mechanism only applies to molecules with a molecular weight less than 100 Da, such as ethanol (molecular weight 46 Da) and urea (molecular weight 60 Da).

Passive diffusion

Passive diffusion accounts for the absorption of a large number of lipid soluble drugs and takes place as a result of there being a favourable concentration gradient across the cell membrane; the drug merely moving down the concentration gradient. Consequently drug absorption by passive diffusion will stop if the concentration of drug on each side of the membrane becomes equal.

Passive diffusion can only occur if the drug molecule is lipid soluble and able to dissolve in the lipids of the cell membrane. As most drugs are either weak acids or weak bases, they exist as a mixture of molecules without an electrical charge (un-ionised) and ions that carry either a positive or negative electrical charge (ionised). The degree of ionisation of the drug molecule is important in determining the effectiveness of this process in drug absorption.

The degree of ionisation of a drug molecule will depend on the physicochemical characteristics of the drug and of the environment in which it is located. In particular, it is the pKa of the drug molecule and the pH of the environment which are important. The pKa of a drug molecule is the pH at which the drug is 50% ionised.

The relationship between pH, pKa and percentage ionisation is given by the Henderson–Hasselbach equations. Weak acids ionise according to the following equation:

$$pKa = pH + \log_{10} (HA/A^-)$$

Weak bases ionise according to the following equation:

$$BH^+ \rightleftharpoons B + H^+$$

A convenient way of remembering the effect of pH on the degree of ionisation of a drug molecule is that acids are highly ionised in an alkaline environment and virtually un-ionised in an acidic environment. For weak bases, the reverse is true. Table 1.5 shows some examples of the variations in the pKa of commonly used drug molecules.

Drug	pKa
Frusemide	3.9
Phenobarbitone	7.2
Phenytoin	8.0
Morphine	8.0
Cimetidine	6.8
Diazepam	3.3

We can see from the discussion above that both the route of drug administration, and the site of absorption, contribute significantly to the amount of drug absorbed. For example, in the stomach the pH is approximately 2.0–2.5; consequently, weakly acidic drugs will be in a predominantly un-ionised form and absorption

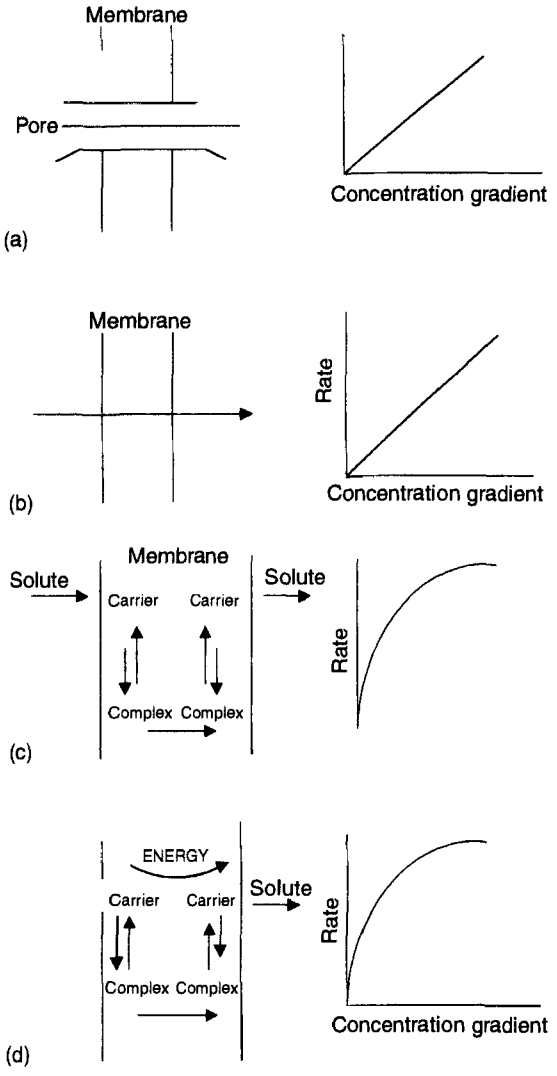

Fig. 1.2 The mechanisms and kinetics of drug absorption processes. (a) Aqueous diffusion, where the drug passes through an aqueous pore and the rate of diffusion is directly proportional to the concentration gradient. (b) Passive diffusion, where the drug dissolves in the membrane and the rate of diffusion is directly proportional to the concentration gradient. (c) Carrier-mediated diffusion, where the drug combines with a carrier and then diffuses across the membrane; availability of carrier is the rate-limiting step. (d) Active transport, similar to carrier-mediated systems, but an injection of energy (ATP → ADP) allows the system to transport against a concentration gradient.

virtually complete. Conversely, basic drugs will be almost completely ionised and absorption will be minimal. Factors that affect the pH of the stomach contents, such as foodstuffs or anti-ulcer drugs, can markedly alter the absorption characteristics of drugs from the stomach.

Carrier-mediated diffusion

Carrier-mediated diffusion accounts for the absorption of a number of drugs that are not lipid soluble. Lipid solubility is conferred on the drug by combination with a carrier, which then diffuses across the membrane as a drug–carrier complex; the drug dissociates on the other side of the membrane. It should be noted that, like passive diffusion, this process is diffusional and dependent on the existence of a concentration gradient across the membrane. In this case it is the concentration gradient for the drug–carrier complex which is important, and if the concentration gradient is abolished then drug absorption stops.

Active transport

Active transport is an energy-requiring process which is capable of bringing about the absorption of non-lipid-soluble drugs against a concentration gradient. Again, lipid solubility is conferred on the drug by combination with a carrier, but in this case the drug–carrier complex is moved against a concentration gradient by the injection of energy brought about by the breakdown of adenosine triphosphate (ATP).

The mechanisms and kinetic characteristics of these absorption processes are shown in Fig. 1.2.

DRUG DISTRIBUTION

Once the drug has entered the systemic circulation it must be carried to its site of action and pass out of the circulation into the extracellular fluid before it can produce its pharmacological effect. Most drug molecules are quite small and are able to pass out of the capillaries by a process of capillary filtration. However, while some drugs

are carried in simple solution in plasma, most are poorly soluble and become partially bound to plasma proteins (especially albumin), which act as carriers.

Plasma protein binding

It is important to note that when a drug is bound to a plasma protein it is therapeutically inactive and only drug molecules that are not bound to plasma proteins are available to produce their pharmacological effect.

The degree of plasma protein binding varies widely from drug to drug, but may be as high as 99% in some cases. This means that only 1% of the administered dose of the drug is 'free' and available to produce its therapeutic effect. Such high levels of plasma protein binding may have consequences for the patient. For example, if a drug is strongly bound to plasma protein, there will be a delay in attaining a suitable concentration of free drug in the plasma, as most of the early doses are bound up to the proteins. Conversely, if a patient stops taking such a drug, that amount bound to plasma protein acts as a depot and slowly dissociates into the plasma, producing the drug's effects for some days or weeks. Figure 1.3 illustrates this point.

It is also important to note the interaction between two drugs that are both bound to plasma proteins. The first point to consider is that there is a finite number of drug binding sites available on the plasma proteins and many of these are taken up by naturally occurring substances that are being transported around the body. The second point is that the binding of drugs to plasma proteins is a reversible process and that free and bound drug is in a dynamic equilibrium, as shown by the following equation:

$$\text{Free drug} + \text{protein} \underset{K_{-1}}{\overset{K_{+1}}{\rightleftharpoons}} \text{drug–protein complex}$$

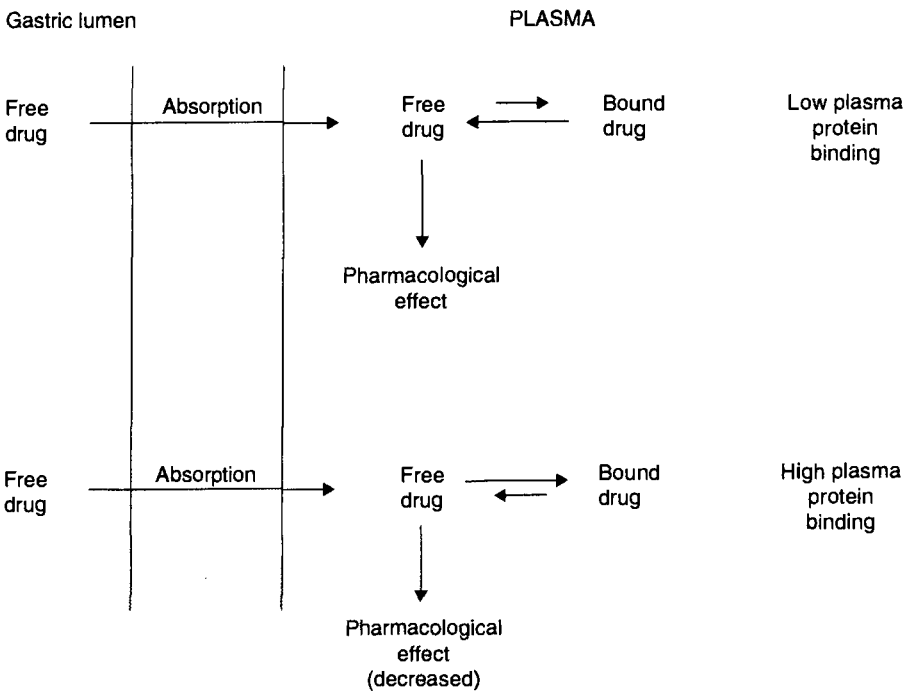

Fig. 1.3 The effects of plasma protein binding on the availability of free drug and pharmacological effect. Low plasma protein binding allows a high concentration of free drug in the plasma; high plasma protein binding allows only a low concentration of free drug in the plasma and therefore a reduced pharmacological effect.

where K_{+1} is the association rate constant and K_{-1} is the dissociation rate constant. This means that, if two drugs are introduced into the patient, the drug with the stronger binding affinity for the plasma protein will tend to displace the drug with the weaker binding affinity.

This interaction, and its consequences, may best be illustrated by considering the drugs warfarin and ibuprofen, both of which are highly plasma protein bound. Warfarin is an anticoagulant used to decrease the incidence of blood clots in susceptible patients. Ibuprofen is a commonly available anti-inflammatory drug, often used as a painkiller. Patients taking warfarin have their dosage carefully titrated against the tendency of the blood to clot. Once the correct dose is established it must be administered regularly to maintain control of blood clotting. The introduction of ibuprofen into such a patient will tend to displace some of the warfarin from its binding sites, and increase the amount of free warfarin in the blood, with potentially disastrous consequences for the patient. While it may not seem significant if the amount of warfarin bound to plasma protein is reduced, by the ibuprofen, from 99% to 98%, this means that the free warfarin has increased from 1% to 2% of the dose – and a doubling of the anticoagulant effect.

We have seen above that the pH of the environment in which a drug exists affects the degree of ionisation of the molecule. Therefore, if the pH of the biological fluids on either side of a cell membrane are different, this will alter the distribution pattern of the drug, even though it may be crossing the membrane by an equilibrating mechanism, such as passive diffusion.

This may be illustrated by considering the distribution of two drugs, one a weak acid (aspirin) and one a weak base (morphine), across the gastric mucosa, where the pH of the gastric contents is 2.5 and the pH of the plasma is 7.4. Aspirin has a pKa of 3.5 and morphine has a pKa of 8.0. Aspirin ionises according to the equation:

$$HA \rightleftharpoons H^+ + A^-$$

$$BH^+ \rightleftharpoons B + H^+$$

The effect of pKa on the absorption of aspirin and morphine from the stomach is shown in Fig. 1.4.

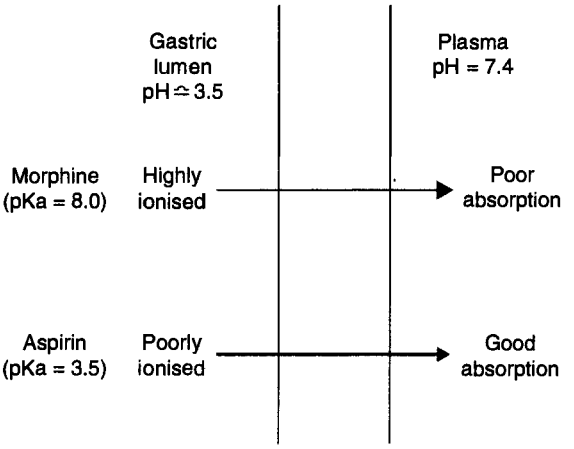

Fig. 1.4 The effect of pKa on the absorption of aspirin and morphine from the stomach. The basic drug, morphine, is highly ionised at gastric pH and so there is little absorption; the acidic drug, aspirin, is virtually unionised at gastric pH and so there is a high level of absorption.

The blood–brain barrier

A lipid layer, which provides a membrane between the blood and the cerebrospinal fluid in the CNS, surrounds the capillary endothelium in the brain. This is called the blood–brain barrier. Highly ionised molecules are unable to cross this lipid barrier and so do not penetrate into the brain in significant amounts. Conversely, molecules that are highly soluble in lipids cross the membrane easily and may attain high concentrations in the brain. The existence of the blood–brain barrier explains why some drugs are virtually devoid of CNS effects.

DRUG METABOLISM

Most drug molecules are metabolised to more water-soluble compounds in order to aid their

excretion from the body. Usually this results in a decrease in their pharmacological activity. However, in some cases the metabolism of a drug molecule may activate it, such that the clinical effectiveness of the parent drug is a property of the metabolite. Such drugs are called *prodrugs*. The majority of drug metabolism takes place in the liver, although some also occurs in the lungs, kidney, adrenal cortex and plasma.

In the liver, the process of drug metabolism normally takes place in two phases:

(1) *Phase I* reactions usually increase the water solubility of the drug by inserting a hydrophilic group (e.g. -OH). They usually decrease the pharmacological activity of the drug but in some circumstances drugs may be activated by these reactions.
(2) *Phase II* reactions are conjugation reactions in which the product from the phase I reaction is coupled together with a large molecule such as glucose to form a glucuronide derivative. Conjugation occurs at the site of a reactive group (such as -OH), which has often been inserted in the phase I reaction, and results in the production of a highly water-soluble, therapeutically inactive compound which may be readily excreted from the body.

Examples of phase I and phase II metabolic reactions are shown in Table 1.6.

Phase I drug metabolism

The most important phase I drug-metabolising process is oxidation, which is carried out by a family of enzymes called the cytochromes P-450. There are hundreds of different isoforms of the cytochrome P-450 enzymes, some of which are present all the time (constitutive enzymes) and some of which are synthesised in response to a chemical signal (induced enzymes), which may be the drug to be metabolised.

Thus, a number of different factors can affect the activity of the drug-metabolising enzymes and so alter the individual patient's response to a given drug. An increase in the activity of a drug metabolising enzyme is called *enzyme induction*. It is usually brought about by an increase in the rate of synthesis of the enzyme protein, probably as a result of changes in the nucleic acid transcription essential for protein synthesis. Enzyme induction may be brought about by environmental factors, such as smoking, the protein : carbohydrate ratio in the diet and drugs such as ethanol (alcohol) and phenobarbitone.

When two drugs compete as substrates for the same drug-metabolising enzyme there is a reduction in the rate of metabolism of both drugs, resulting in the phenomenon of *enzyme inhibition*. Inhibition of drug-metabolising enzymes can have serious consequences for the patient as it may result in either an increased concentration of unmetabolised drug in the plasma or a decreased ability to remove a toxic substance from the plasma. An example of the importance of enzyme inhibition is the interaction between the drug terfenadine and some antibacterial drugs that inhibit cytochrome P-450. Terfenadine is an antihistamine prodrug, which must be metabolised to an active metabolite, fexofenadine, by cytochrome P-450 before it can produce its pharmacological effect. The inhibition of cytochrome P-450 by antibacterial drugs such as erythromycin leads to a rise in the plasma levels of terfenadine and an increased risk of potentially fatal cardiac arrhythmias. This interaction has now led to the removal of terfenadine from the retail market.

Table 1.6 Examples of phase I and phase II drug metabolism.

Phase I metabolic reactions	Phase II metabolic reactions
Oxidation	Glucuronide formation
Reduction	Sulphate formation
Hydroxylation	Acetylation
Oxidative deamination	

Phase II drug metabolism

The conjugation (joining together) reactions of phase II drug metabolism occur in a wide variety of tissues, such as the lung and kidney, as well as in the liver. Conjugation reactions usually result

in an increase in the water solubility, and complete inactivation, of the molecule produced as a result of phase I metabolism. Only in a small number of situations does phase II metabolism result in activation of a prodrug, an example being minoxidil.

DRUG EXCRETION

The major route of drug excretion is via the kidneys (urine), although significant amounts of some drugs may be excreted via the faeces, exhaled air, breast milk and sweat. While urinary and faecal excretion are the most important routes for most drugs, it should be noted that some drugs are excreted in breast milk to such an extent that they are potentially toxic to the infant. These drugs should be avoided in nursing mothers.

In the kidney, drug molecules not bound to plasma proteins are filtered into the nephron by the process of glomerular filtration. Some drug is also excreted via either the acid-secreting or base-secreting pathways in the cells of the proximal convoluted tubule. The drug is then passed into the urine and voided via the bladder.

A number of factors serve to modify the amount of drug excreted through the kidneys. The pH of the urine determines the amount of drug that is in an ionised form in the lumen of the nephron. Highly ionised drug molecules are less likely to be reabsorbed by the cells of the nephron wall. For example, if the drug is a weak acid, then the normally acidic pH of urine may favour reabsorption. Making the urine alkaline, by the administration of sodium bicarbonate, may promote excretion of the drug. It should be noted that many drugs alter the pH of urine and, consequently, may alter the renal excretion of other drugs. An increase in the rate of urine flow may also increase drug excretion by reducing the time during which the drug is in the nephron and liable to be reabsorbed.

Faecal excretion

Drug excretion via the gastrointestinal tract results either from the excretion of unabsorbed drug following oral administration, or from secretion of drug into the g.i. tract with the bile. In the latter case, it is normally the products of phase II hepatic drug metabolism which are secreted into the bile and excreted by this route. It should be noted that some drug conjugates excreted by this route are subsequently hydrolysed back to the parent drug by gastrointestinal enzymes. The resultant drug molecule may then be reabsorbed and so the pharmacological effect is prolonged. This enterohepatic shunt is used in the administration of oestrogens in the contraceptive pill to allow for once-daily dosage.

Effects of age, sex and race

The processes of drug metabolism and drug excretion are both dependent upon the correct functioning of metabolising enzymes. Thus factors that affect the functional status of these enzymes can significantly alter the patient's response to drugs.

The expression of drug-metabolising enzymes in the fetus, and in premature babies, is less effective than in older children. Similarly, renal function in the neonate is not fully developed. These two factors serve to decrease the ability of newborn babies to metabolise and excrete drugs, leading to potential problems of drug toxicity.

At about two years of age, the expression of drug-metabolising (-oxidising) enzymes in children is complete and so young children can oxidise drugs faster than most adults. In elderly patients, a general decrease in hepatic and renal function usually results in a decreased capability for drug metabolism and excretion.

Data on sex differences on drug metabolism are incomplete. There is some evidence that females are less able to excrete amantadine than males, although the clinical significance of this is unclear.

There are several instances of racial variation in the ability to metabolise drugs. In particular, there are marked differences in the amounts of some of the cytochrome P-450 isoforms found in Caucasian, African and Asian patients. The most

marked example is the rate of acetylation of drugs.

Drug interactions

Whilst all drugs used to treat diseases will produce adverse effects if used inappropriately, it must also be borne in mind that many drugs will interact with other drugs to produce undesirable effects. Therefore, when two or more drugs are given together, the possibility of interactions between them must always be considered. Drug interactions may arise from either a *pharmacokinetic* or a *pharmacodynamic* interaction.

Pharmacokinetic interactions are usually the result of either interference with the metabolism of one drug by another, or changes in the amount of protein binding of one drug by another. Examples of these types of interactions have been discussed earlier in this chapter.

Pharmacodynamic interactions occur when two drugs have opposite effects on a particular body system. An example of this type of interaction is that between the decongestant drug phenylephrine and antihypertensive drugs such as prazosin. Prazosin is used to lower blood pressure in some patients suffering from an elevated blood pressure (hypertension), whereas phenylephrine causes a rise in blood pressure. Clearly, such an interaction is undesirable and may be potentially fatal.

It should be noted that while most drug interactions are undesirable, a small number may be clinically useful. For example, the clinical effectiveness of the anti-Parkinson drug L-dopa may be enhanced by the co-administration of another drug, carbidopa. Under normal circumstances, a large proportion of a dose of L-dopa is converted to dopamine in the peripheral circulation, rather than in the CNS. This process is catalysed by the enzyme dopa decarboxylase, and leads to a range of unacceptable side-effects arising from the release of large amounts of dopamine in the periphery. Carbidopa is an inhibitor of dopa decarboxylase and so its co-administration decreases the amount of dopamine released in the periphery and increases the amount of L-dopa entering the brain to produce the desired clinical effect. A list of the major drug interactions is included in Appendix I.

DRUGS IN THE ELDERLY

Elderly patients – those over 65 years of age – constitute a growing proportion of the population. Currently elderly patients represent about 18% of the population; however they consume nearly 50% of the drugs prescribed under the National Health Service. Nearly 70% of elderly patients receive regular medication and the majority are receiving more than one drug. In some cases, patients have been known to be receiving 11 different drugs on a regular basis. This multiple drugs prescribing (polypharmacy) not only gives rise to problems with patient compliance but also increases the risk of drug interactions and multiple adverse effects. The incidence of adverse effects in the elderly is nearly three times that in younger patients.

Changes in the apparent sensitivity of elderly patients to drugs arise from changes in their ability to absorb, metabolise and excrete drugs. The increase in gastric pH, decreased gastric motility and reduced splanchnic blood flow, associated with ageing, serve to decrease the rate of absorption of many drugs. Similarly, increased body fat and a fall in plasma albumin concentration often result in changes in drug distribution and plasma protein binding, both of which may give rise to apparent changes in sensitivity to the drug. Most elderly patients show a decrease in their ability to metabolise drugs, especially those metabolised by the microsomal oxidative enzyme systems, such as cytochrome P-450. This decrease in metabolising ability in elderly patients is thought to result from a decrease in blood flow through the liver and, consequently, there may be a decrease in the first pass effect in some drugs.

Probably the most important aspect of ageing is the decrease in renal function that occurs in elderly patients. In old age there is a fall in both renal blood flow and renal function, resulting in a severe decrease in the ability to excrete drugs via the kidneys. It is of prime importance, therefore, to ensure that dosing with drugs that are excreted through the kidney reflects this fall in renal function in order to prevent the development of toxic drug levels in the blood. The drug dose that

was suitable for the patient at the age of 55 years may be too high at 70 years of age.

DRUGS IN PREGNANCY AND BREAST FEEDING

Pregnancy

Nearly 40% of women take at least one drug during their pregnancy, excluding iron and folic acid supplements. Once these drugs enter the maternal circulation they are separated from the fetus only by the lipid membrane of the placenta and most drugs can cross this membrane and enter the fetal circulation. The effect of drugs during pregnancy can be divided into two aspects:

(1) the effect of the drug on the fetus
(2) the effect of the pregnancy on the drug.

Drugs can influence fetal development at three key stages and the consequences of drug toxicity are quite different at each stage. The three important stages are:

(1) fertilisation and implantation (the first 17 days after conception)
(2) the period of organ development (18–55 days after conception)
(3) the period of growth and development (56 days until full term).

Drugs that interfere with fertilisation or implantation will cause a failure of the pregnancy and produce abortion at a very early, subclinical stage. In this instance, there is little evidence of the effects of drugs, as most women would not know that they were pregnant at this stage.

Drugs that interfere with the process of organ development are the most dangerous drugs if administered during pregnancy. During the period 18–55 days after conception, the fetus is undergoing its major period of organ development, during which all the major organs of the body become differentiated and start to develop in their own right. It is at this stage that the fetus is at its greatest sensitivity to the possible teratogenic effects of drugs. A teratogen is any agent (virus, environmental toxin or drug) that can produce a deformity in a developing fetus. Examples of possible teratogenic drugs are phenytoin (craniofacial deformity), lithium (cardiac deformity) and warfarin (multiple organ deformity).

Drugs that affect growth and development do not necessarily cause major deformities in the fetus. However they may produce effects that have serious consequences for the developing fetus. For example, antithyroid drugs can produce the symptoms of hypothyroidism in the fetus, ACE inhibitors can cause fetal kidney malfunction and drugs of dependence (benzodiazepines and opiates) may cause withdrawal symptoms in the baby following delivery.

A small number of drugs, when given at the end of a pregnancy, may give rise to problems in the neonate (newborn baby). For example, aspirin can cause haemorrhage in the neonate, indomethacin can cause premature closure of the ductus arterious and pulmonary hypertension, and opiates can cause severe respiratory depression, hypotension and hypothermia.

Clearly, the ideal situation would be that pregnant women do not take any drugs during the period of their pregnancy. However, we can see from the comments above that many adverse drug effects may occur from drugs taken during a period when the woman does not know that she is pregnant. Similarly, there may be strong clinical reasons why a woman has to take certain drugs during her pregnancy, for example in the control of epilepsy. It is important, therefore, that drug therapy in all women of childbearing age is tempered with knowledge of the possible consequences to an unknown fetus. Furthermore, essential drug therapy during pregnancy must be carried out at the minimum dosage required to produce the desired clinical effect and bearing in mind the development stage of the pregnancy.

We have seen that drugs may have serious adverse effects on the developing fetus. However, it must also be borne in mind that pregnancy may alter the patient's ability to metabolise and excrete drugs. The plasma volume of the mother may increase by about 50% during the last trimester of the pregnancy and this can lead to a decrease in the plasma concentrations of many drugs. Similarly

there is a marked fall in plasma albumin levels during the same period and, at the same time, a rise in the levels of glycoprotein. This results in a decreased ability to bind acidic drugs and an increased ability to bind basic drugs in the plasma. The consequent rise in the free plasma levels of acidic drugs and the fall in free levels of basic drugs may have serious consequences for the patient. For example, diazepam and phenytoin are known to have significantly higher free drug concentrations during the last trimester of pregnancy.

The effective renal blood flow almost doubles during the third trimester of pregnancy and this can significantly increase the renal excretion of many drugs. Hepatic microsomal enzymes are also induced during pregnancy, leading to increased metabolism of drugs metabolised by this pathway.

Breastfeeding

The administration of drugs to nursing mothers may cause toxicity in the infant if the drug enters the breast milk at a pharmacologically active concentration. The factors that determine whether a drug enters breast milk are the same as those that determine its absorption and distribution. In general, acidic drugs enter breast milk to a lesser extent than do basic drugs, but this may only be regarded as a guide, as other factors may alter the distribution of specific drugs. Some drugs, such as phenobarbitone, inhibit the suckling reflex in the infant. For many drugs there is not sufficient evidence to establish the safety of their use in breastfeeding mothers and so it is advisable to avoid drug therapy in this situation if possible. A full list of drugs and their suitability for use in breastfeeding mothers is given in Appendix 5 of the *British National Formulary*.

SUMMARY

- Pharmacology is the study of drugs on the body.
- Pharmacology has its roots in the pharmacopoeiae of ancient civilisations.
- The major developments in pharmacology occurred during the twentieth century.
- Drugs may be obtained from a variety of sources, including plants.
- The complex words in medical terminology are made up from short terms that describe the tissue and the condition involved.
- Pharmacology has its own terminology that is used to describe drugs and their actions on the tissues and organs of the body.
- Drugs may be classified according to their molecular mechanism of action, the body system on which it acts or by its chemical nature.
- All drugs, when administered for their therapeutic effect, also produce a range of adverse effects, some of which may be predicted and some of which may not.
- Drugs may be administered to patients by a number of different routes, depending upon their pharmacological effects and the needs of the patient.
- Drug absorption may take place by aqueous diffusion, passive diffusion, carrier-mediated diffusion or active transport.
- A number of factors affect the distribution of drugs in the body, including their binding to plasma proteins, the chemical nature and the pH of the various body compartments.
- The major site of drug metabolism is the liver, although some metabolism may occur in the plasma, lungs and kidneys.
- Drug metabolism takes place in two stages and usually results in the inactivation of the drug and promotes its excretion.
- Drugs are excreted mainly via the kidneys, but may also be excreted in the faeces, exhaled air and sweat.
- Phase I drug metabolism is usually oxidation, reduction or hydrolysis.
- Phase II drug metabolism is usually a conjugation reaction.
- Drug interactions arise from either pharmacokinetic or pharmacodynamic interactions.
- Most drug interactions are undesirable, although some may be clinically useful.
- Elderly patients may be at greater risk of developing adverse drug effects as a result of their decreased ability to metabolise and excrete drugs.

- The most important aspect is the decrease in renal function that occurs in elderly patients.
- The administration of drugs to pregnant women and women of childbearing age must always take into account the possible effects on the developing fetus.
- Many drugs are teratogenic and some produce their effects during the period when the woman may not know that she is pregnant.
- The state of pregnancy may well affect the distribution and metabolism of many drugs.
- Administration of drugs to breastfeeding mothers may result in sufficient quantities of drug being passed to the infant to produce pharmacological effects.

2

How Drugs Work

INTERCELLULAR COMMUNICATION

Human beings are large multicellular organisms and, while most individual cells are capable of carrying out the basic life functions, it is essential to exert control over their activities for the benefit of the individual. In order to provide this control function, we have evolved three major control systems:

(1) the endocrine system
(2) the paracrine system
(3) the nervous system.

The endocrine system

The endocrine system has been developed to exert long-term control over a wide range of body functions, such as the control of glucose levels in the blood, bodily growth, sexual function and many others. Endocrine glands secrete chemicals called *hormones*, which travel around the body in the blood and exert their effects at distant sites. An example of endocrine control is the secretion of the hormone insulin, from the β-cells in the islets of Langerhans in the pancreas, in response to a rise in blood glucose level. The hormone is then carried in the blood and acts on cells all over the body to promote the uptake of glucose.

The paracrine system acts over relatively short distances. Stimulation of this system results in the release of locally acting hormones, called *autacoids*, which produce effects in the immediate area of their release. An example of paracrine control is the vascular effects occurring after tissue damage to the skin. If you exert a heavy scratch to the skin it produces a bright red flare, which rapidly turns dark red. Eventually, a weal is formed. This response is called the Lewis–Triple response and is due to the effects produced by the release of the autacoid histamine. Histamine is normally stored in mast cells and, when it is released by the physical damage caused by the scratch, it produces localised vasodilatation and an increase in the permeability of the capillaries. The bright red flare results from the localised vasodilatation, but the pooled blood rapidly turns dark red as it loses oxygen; the increased capillary permeability allows water to leak out of the capillaries and causes the weal.

The nervous system

The nervous system is an extremely complex sensory perception and control system, consisting of hundreds of thousands of interconnected nerves that form myriads of nerve–nerve, nerve–gland or nerve–muscle junctions. Messages are carried along the nerves by the propagation of electrical currents, resulting from movements of ions across the cell membrane of the nerve. However, at the many junctions there is no direct connection between the end of one nerve and the next nerve, gland or muscle cell. Therefore the electrical impulse, carried in the nerve, must be transmitted across the gap (synapse) by the release of a chemical called a *neurohumoral transmitter*, or *neurotransmitter*.

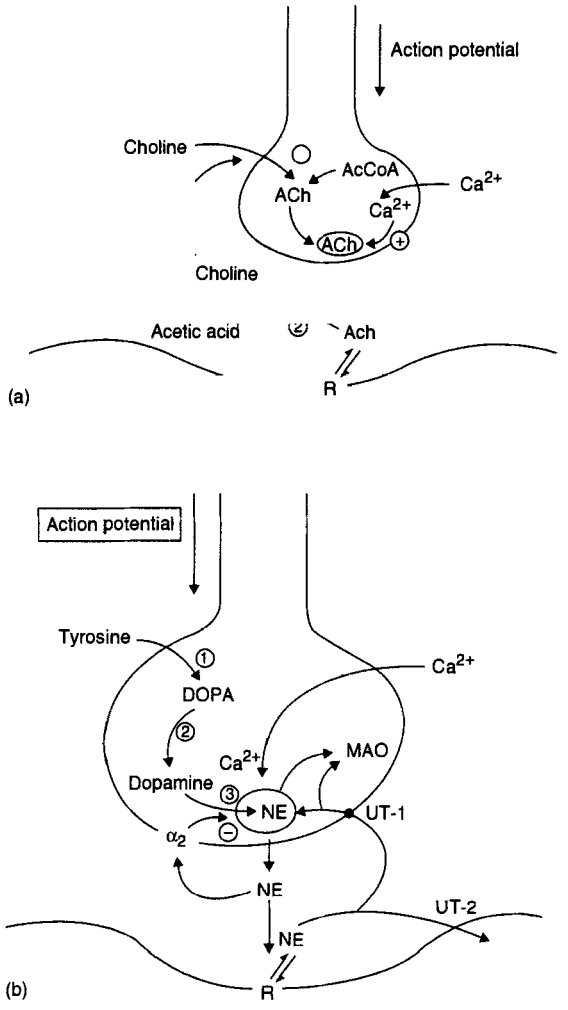

Fig. 2.1 The mechanisms of synthesis and storage of the neurotransmitters acetylcholine and norepinephrine. (a) Acetylcholine (ACh) is synthesised from choline and acetyl CoA by the action of the enzyme choline acetyltransferase (1). ACh in the synapse is broken down by the enzyme acetylcholinesterase (2). (b) Norepinephrine (NE) is synthesised from tyrosine, via dihydroxyphenylalanaine (DOPA) and dopamine; the enzymes involved are tyrosine hydroxylase (1), dopa decarboxylase (2), and dopamine-β-hydroxylase (3). NE is removed from the synapse by uptake 1 (UT-1) and uptake 2 (UT-2).

The process of neurohumoral transmission

Neurohumoral transmission is the process by which an action potential in a nerve is transmitted across the synapse. It consists of the release of a neurohumoral transmitter (neurotransmitter) which diffuses across the synapse to interact with a postsynaptic cell membrane to continue the transmission process. Over a hundred different chemicals have, so far, been identified as having a neurotransmitter function in the body, the most common being:

- acetylcholine (ACh)
- norepinephrine
- dopamine
- 5-hydroxytryptamine (5-HT, serotonin)
- histamine
- γ-aminobutyric acid (GABA)
- glycine
- nitric oxide (NO)

In order for a substance to act as a neurotransmitter it must first be synthesised and stored in the nerve ending of the presynaptic neurone. It must then be released, in response to the arrival of a nerve action potential, diffuse across the synapse and interact with a receptor on the postsynaptic membrane.

There must also be a mechanism for the termination of the action of the neurotransmitter. In some cases, such as acetylcholine, this is brought about by the enzymatic destruction of the neurotransmitter; in other cases, such as norepinephrine, the neurotransmitter is taken back into the presynaptic nerve ending to be used again.

The processes of synthesis, storage, release and termination of the action of acetylcholine and norepinephrine are shown in Fig. 2.1.

CELLULAR TARGETS FOR DRUG ACTION

In order for a drug to produce a pharmacological effect it must interact with a discrete target molecule which responds to produce a biological

effect. Thus, a drug-induced response may be considered to occur in three stages:

(1) combination of the drug with a target molecule
(2) a drug-induced change in the structure of the target molecule which produces a change in the electrical or molecular properties of the cell
(3) a biological effect.

Three main types of molecular target have been identified for drugs. These are:

(1) drug receptors
(2) enzymes
(3) carrier systems.

Drug receptors

Most drug receptors are found on the surface of cells, embedded in the cell membrane, although the receptors for some steroid hormones are located inside the cell. They are all proteins (or groups of proteins), which have the unique properties of being highly *specific* and *selective* for the drug. They are capable of responding to binding of the drug by changes in their shape, and are able to couple these events to biochemical and physiological events within the cell.

Three types of cell membrane receptor have been identified and they are termed *receptor superfamilies*. These are:

(1) ligand-gated ion channels (LGICs), including voltage-gated ion channels (VGICs)
(2) G-protein-coupled receptors
(3) kinase-linked receptors.

Ligand-gated ion channels

These are members of the group of transmembrane ion channels that are responsible for the passage of Na^+, K^+, Ca^{2+} and Cl^- ions across cell membranes. These receptors are large multi-subunit proteins which, when activated, open a channel in the membrane through which the ion may pass. LGICs are capable of very fast response times, often in the microsecond range.

LGICs are activated (*gated*) by the binding of a drug molecule (*ligand*) to a specific part of the protein on the outside of the membrane, the resulting open channel allowing passage of an ion into the cell. Because ions carry an electrical charge, their passage into a cell alters the potential difference across the cell membrane

Typically these receptors consist of four or five proteins packed tightly together into the cell membrane. Each individual protein is called a *subunit* and consists of a single amino acid chain that spans the membrane four times. The N-terminal and the C-terminal of the protein are both on the extracellular side of the cell membrane.

When the receptor is activated by the binding of a ligand to a site on the extracellular side of the membrane, there is a change in the shape of the protein subunits, which results in the opening of the ion channel through the cell membrane. The passage of ions through the membrane 'carries the message' into the cell and produces a measurable biological event.

Typical examples of ligand-gated ion channel receptors are the nicotinic acetylcholine receptor (nAChR) on skeletal muscle, which is a Na^+ ion channel, and the $GABA_A$ receptor in the brain, which is a Cl^- ion channel.

Voltage-gated ion channels (VGICs)

You should note at this point that there is another family of ion channels in the body which, although they have a structure similar to that of LGICs, are not gated by the binding of a ligand. These ion channels are gated by changes in the potential difference across the cell membrane and are called voltage-gated ion channels. Whilst these channels are not receptors in the strict pharmacological definition of the term, they are an important target for the action of drugs.

VGICs are multi-subunit ion channels in which the shape of the proteins that make up each subunit is dependent on the potential difference across the cell membrane (the membrane potential). When the membrane potential reaches a certain value, the gates in the ion channel open and the passage of ions takes place. VGICs are unusual in that they often have two or more voltage-dependent gates in the channel that open or close according to the membrane potential.

An example of a VGIC with two gates is the Na^+ ion channel found in cardiac muscle cells. The two gates in this channel are:

- the *m-gate*, which opens and closes quickly.
- the *h-gate*, which opens and closes slowly.

When the cardiac muscle cell is in diastole and the membrane potential is negative, the m-gate is closed and the h-gate is open. Consequently, the channel is closed and is said to be in the resting state. If the membrane potential becomes less negative (depolarisation), the m-gate opens quickly and, as both gates are now open, the channel is open for the passage of ions and is said to be in the activated state. Further changes in the membrane potential then cause the h-gate to close slowly and the channel becomes closed. As the membrane becomes more negative again, the m-gate closes but, as the h-gate is still closed, the channel is closed and is said to be in the inactive state. Provided that the membrane potential stays negative, the h-gate will open slowly and the channel is ready to respond to another depolarisation of the cell membrane by opening of the m-gate.

This sequence of events is summarised in Fig. 2.2.

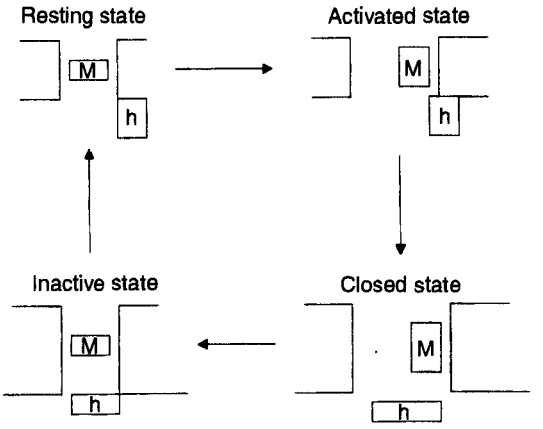

Fig. 2.2 The gating mechanism for a voltage-gated ion channel (VGIC). In the resting state the m-gate is closed and the h-gate is open; on activation, the m-gate opens allowing the influx of Na^+ ions; the channel is closed by the closing of the h-gate; the m-gate then closes and the channel enters its resting state before reopening of the h-gate primes the channel for action.

G-protein-coupled receptors

These are large single proteins, consisting of a chain of 450–700 amino acids, which have highly conserved structures. This means that, although over 100 G-protein-coupled receptors have been identified, they all have the same basic structure consisting of essentially the same amino acids. G-protein-coupled receptors typically have response times in the millisecond range.

The amino acid chain that makes up the receptor protein has seven areas called lipophilic domains. These are short portions of the amino acid chain, each containing 23–25 amino acids, that are predominantly lipid soluble. Consequently these domains preferentially enter the lipid environment of the cell membrane and so each lipophilic domain spans the cell membrane, and thus the receptor protein passes across the cell membrane seven times along its length. Sometimes, as a result of this structure, receptors in this superfamily are called 7-transmembrane receptors.

A G-protein is associated with the intracellular domains of the receptor protein. Each G-protein consists of three protein subunits, called the α-, β- and γ-subunits, which are joined together to form a structure called a trimer. The name G-protein derives from the fact that they are capable of binding guanosine nucleotides, such as guanosine diphosphate (GDP) and guanosine triphosphate (GTP). The trimeric G-protein is bound to two of the intracellular loops of the receptor protein. When the receptor is in the inactivated state, the α-subunit has a molecule of GDP attached to it. When the receptor is activated, by the binding of a ligand to the extracellular binding site on the receptor protein, there is a change in the shape of the receptor protein, which allows the G-protein to become activated. When the G-protein is activated, the α-subunit dissociates from the other subunits and, as a consequence of this separation, the α-subunit loses its GDP molecule and picks up a molecule of GTP.

The α-GTP molecule is able to move along the inner surface of the cell membrane and interacts with a target enzyme located in the cell membrane. The α-GTP molecule is able to either

activate or inhibit the target enzyme, and so regulate the intracellular level of the chemical product of the enzyme's action. An example of a target enzyme is adenylyl cyclase, which converts adenosine triphosphate (ATP) into cyclic adenosine monophosphate (cAMP). The cAMP produced by this enzyme is water soluble, can move freely around the cell and controls a large number of intracellular biochemical processes. It is called a *second messenger*.

The effects of activating the G-protein are terminated by the hydrolysis of the GTP molecule, back to GDP, and the resulting α-GDP molecule reassociates with the βγ-complex to re-form the trimeric G-protein.

The most common target enzymes and the second messengers they produce are listed in Table 2.1. An example of this type of receptor system is the β_2-adrenoceptor in the lungs, which is activated by the agonist salbutamol, used in some asthma inhalers.

Table 2.1 Examples of second messenger molecules produced from various target enzymes.

Target enzyme	Second messenger(s) produced
Adenylyl cyclase	Cyclic adenosine monophosphate (cAMP)
Guanylyl cyclase	Cyclic guanosine monophosphate (cGMP)
Phospholipase C	Inositol-1,4,5-triphosphate (IP_3) and diacyglycerol (DAG)

Kinase-linked receptors

Kinase-linked receptors are large single protein molecules embedded in the cell membrane. They often contain over 1000 amino acids, but have only one transmembrane domain. They have latent tyrosine kinase activity as an integral part of the intracellular domain of the receptor protein. This group of receptors has quite slow response times, often taking several seconds to produce a response. Currently there are few drugs that act on these receptors, but they are the targets for a large number of naturally occurring substances, such as insulin and many growth factors.

These receptors are quite different to other receptor superfamilies in that they act in pairs. Unlike the ligands that activate LGICs and G-protein-coupled receptors, the ligands that activate kinase-linked receptors are large polypeptides. Consequently they are capable of binding to two adjacent receptors at the same time to form a structure called a dimer. When this occurs, it triggers off a process called autophosphorylation, which results in the attachment of two phosphate groups to the intracellular domains of each receptor protein. The resultant region of the two receptors is able to bind a range of different proteins, called SH_2-proteins, and phosphorylate them. These phosphorylated SH_2-proteins are then able to move around the cell and control a range of intracellular biochemical processes, usually by changing the rate of synthesis of a protein.

An example of this type of receptor is the insulin receptor. The binding of a single insulin molecule to the extracellular domains of two adjacent receptors leads to the phosphorylation of an SH_2-protein, which controls the synthesis of the carrier molecule that promotes insulin uptake into the cell.

Steroid receptors

The receptors that respond to steroid hormones, such as the glucocorticoids, are large soluble proteins located in the cell nucleus. Consequently, they are only available to ligands that are lipid soluble and can penetrate the cell membrane and enter the nucleus.

When the steroid binds to the receptor protein it causes a change in the shape of the receptor, which allows the complex to bind to specific regions of DNA, causing a change in mRNA production. This results in an increase in the synthesis of a specific protein that is ultimately responsible for the action of the steroid in the cell. These responses are relatively slow and the effect of a steroid may take several hours, or even days, to become apparent.

The molecular structure and signal transduction mechanisms of each of the receptor superfamilies is summarised in Fig. 2.3.

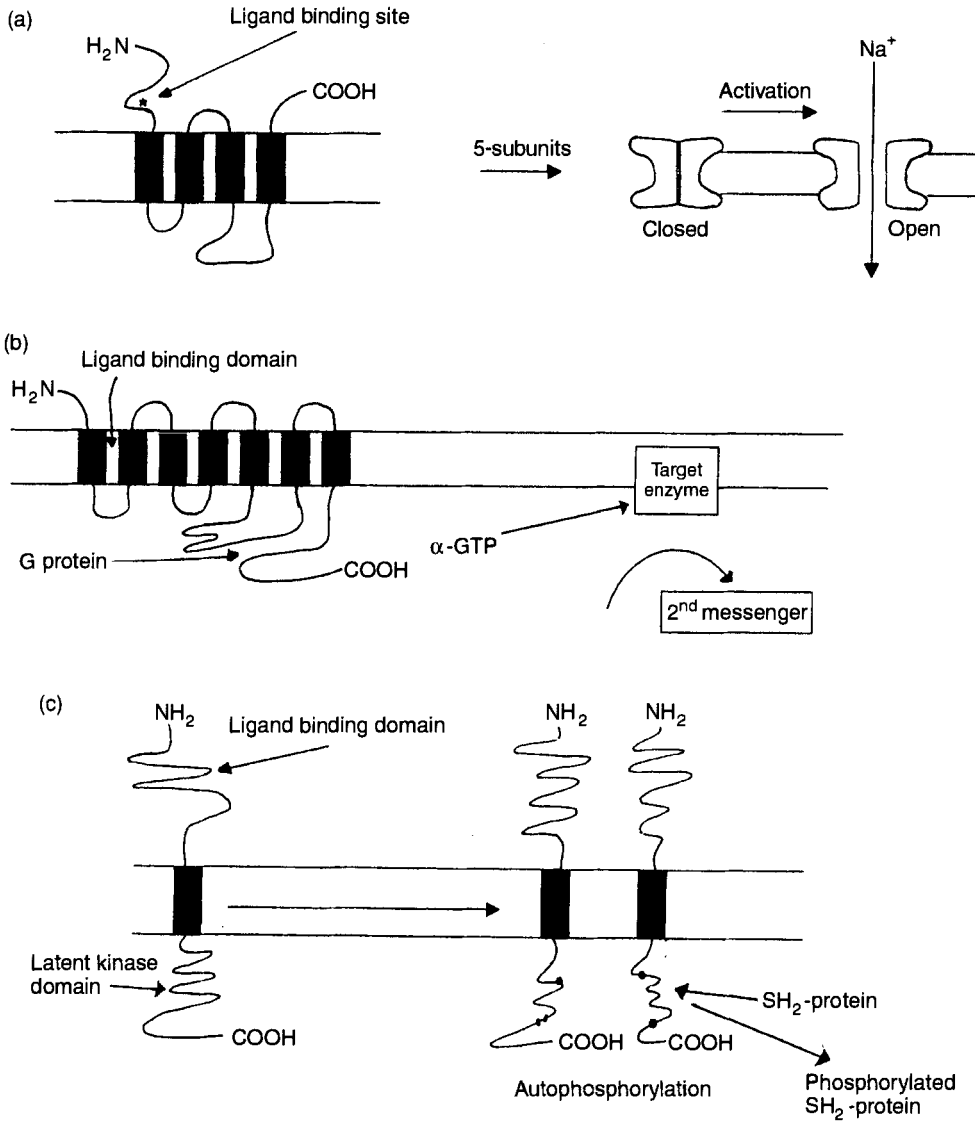

Fig. 2.3 The structures of the major membrane receptor superfamilies. (a) Ligand-gated ion channel, e.g. nAChR. Note the four transmembrane domains in each of the five subunits making up the multi-subunit receptor. (b) G-protein-coupled receptor. Note the seven transmembrane domains in the single receptor protein, the position of the G-protein and the actions of the α-GTP subunit on the target enzyme. (c) Kinase-linked receptor. Note the single transmembrane domain in the receptor protein, the functional dimer and the process of autophosphorylation.

Enzymes

Enzymes are the biological catalysts that control the myriad of reactions occurring in a living cell. It should not be too surprising, therefore, that many enzymes are the targets for the action of drugs. The majority of drugs that act on enzymes exert their action by inhibiting the enzyme. A common example of this is aspirin, which inhibits the enzyme cyclo-oxygenase (COX) and thus prevents the production of prostaglandins. Few drugs act by stimulating an enzyme; however, one example is glyceryl trinitrate, which causes vaso-dilatation by stimulating the enzyme guanylyl

Table 2.2 Examples of drugs acting on enzyme systems to produce clinical effects.

Enzyme	Drug	Action
Acetylcholinesterase	Neostigmine	Treatment of myasthenia gravis
Monoamine oxidase	Phenelzine	Antidepressant
Dihydrofolate reductase	Methotrexate	Anticancer drug

cyclase to produce the powerful vasodilator nitric oxide.

Inhibition of the enzymes responsible for the production of nucleic acids and proteins in the nucleus is a good target for anticancer drugs.

Table 2.2 summarises some of the common enzyme systems that are targets for drugs and the action for which they may be used.

Transport systems

The transport systems, such as active transport, responsible for moving many molecules between the different body compartments make very good targets for a number of drug molecules. The carriers are large proteins embedded in the cell membrane that normally function by binding the carried molecule to form a complex, which is then transported across the membrane.

Drugs that are similar in structure to the naturally carried molecule will be able to bind to the carrier and reduce the carriage (transport) of the correct molecule. There are many examples of drugs that act by inhibiting carrier molecules, including tricyclic antidepressants that inhibit norepinephrine uptake into neurones, and digoxin, which inhibits the Na^+/K^+ ATPase that constitutes the sodium pump in cell membranes.

PHARMACOKINETICS

Pharmacokinetics is the study of the behaviour of the drug once it is in the body, and is a study of the processes of absorption, distribution, metabolism and excretion. Once a drug enters the bloodstream it becomes subject to a number of physical processes that determine not only its therapeutic effectiveness, but also the period of time that it remains in the body. We have seen that plasma protein binding can greatly affect the way in which a drug behaves in the body and that only unbound drug molecules can pass out of the bloodstream into the surrounding tissues. Similarly, only unbound drug molecules can be filtered and excreted through the kidney.

The time it takes for the concentration of a drug in the blood to fall by 50% is called the *half-life* ($t_{1/2}$). Drugs that are rapidly removed from the bloodstream have short half-lives; drugs that are slowly removed from the blood have long half-lives. There is a great variation in drug half-lives, ranging from a few seconds to many hours.

If a drug is administered into the bloodstream by i.v. injection, then it is rapidly distributed throughout the whole blood volume. Taking serial blood samples will then allow us to monitor the behaviour of the drug and determine its half-life. Such an experiment would show that the concentration of drug in the blood would decrease as shown in Fig 2.4. A characteristic of

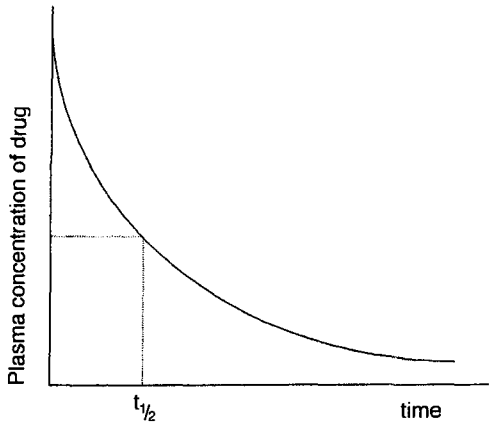

Fig. 2.4 The relationship between plasma concentration of drug and time. Note the determination of half life ($t_{½}$) from this relationship.

this curve is that the rate of decrease in the concentration of the drug in the blood (C) is proportional to the initial concentration of the drug (C_0). This is an exponential process and it may be converted to a linear relationship by plotting $\log_{10}$ drug concentration against time. Furthermore, the time taken for the concentration of drug to fall to half its initial value is always the same, namely ($t_{1/2}$), and this value is independent of the initial concentration of the drug.

The rate at which a drug is eliminated from the body is related to the half-life by the equation

$$t_{1/2} = 0.693/K_{el}$$

In this simple example we have ignored the effect of plasma protein binding. Drugs that are strongly bound to plasma proteins are less easily excreted through the kidney. Thus, plasma protein binding will tend to increase the half-life of the drug.

THE DRUG–RECEPTOR INTERACTION

Kinetics

The study of the drug–receptor interaction is called *pharmacodynamics*. The interaction between a drug molecule and its receptor is a dynamic equilibrium governed by the Law of Mass Action, which states that the rate of a physical or chemical reaction is dependent upon the concentrations of the reacting chemicals. This means that the drug molecule combines with its receptor to form a drug–receptor complex, but it then rapidly breaks down again to form drug molecule and free receptor. The process may then be repeated many times.

This interaction between a drug and its receptor may be represented by the following equation:

$$\text{Drug} + \text{receptor} \underset{K_{-1}}{\overset{K_{+1}}{\rightleftharpoons}} \text{drug–receptor complex} \quad (2.1)$$

where K_{+1} is the association rate constant and K_{-1} is the dissociation rate constant. When the system is in equilibrium the rate of forward reaction is exactly equalled by the rate of the backward reaction. Thus, the actual time for which a receptor is occupied by a drug molecule is very short. If we assume that $[D]$ is the initial molar concentration of drug, R is the total concentration of receptors, r is the concentration of receptors occupied by drug, and $R - r$ is the concentration of unoccupied receptors, then, by the Law of Mass Action:

$$\text{the rate of the forward reaction} = K_{+1} \times [D] \times (R - r)$$

$$\text{the rate of the backward reaction} = K_{-1} \times r$$

When the system is in equilibrium, these two rates are equal. Thus:

$$K_{+1} \times [D] \times (R - r) = K_{-1} \times r$$

Rearranging this equation we get:

$$K_{-1}/K_{+1} = K_d = [D] \times (R - r)/r$$

where K_d is the equilibrium dissociation constant. This equation may be rearranged and presented in terms of the receptor occupation (r):

$$r = ([D] \times R)/(K_d + [D])$$

This is the equation of a rectangular hyperbola, which is a curve relating two variables ($[D]$ and $(R - r)/r$) in such a way that their product (K_d) is constant. It can be shown that K_d is the concentration of drug ($[D]$) that causes 50% of the available receptors to be occupied (i.e. $r = R/2$).

A direct measurement of the occupancy of receptors by drug molecules may be achieved by radioligand binding, in which the binding of radioactively labelled drugs (ligands) to preparations of receptors is measured. From such an experiment, we can see that the relationship between drug concentration and the number of binding sites (receptors) occupied is also a rectangular hyperbola, exactly the same as that determined above. It should be noted that K_d is a reciprocal measure of the ability of the drug to bind to its receptor – this is called the *affinity* and is a measure of how well the drug binds to the receptor.

Types of response

The argument outlined above describes the physical process by which a drug interacts with its receptor. It does not, however, describe the con-

sequences of the interaction. Interactions between drug molecules may be of two types:

(1) interactions that produce a measurable biological effect (*agonist effect*)
(2) interactions that do not produce a measurable biological effect themselves, but which interfere with the actions of drugs that do (*antagonist effect*).

In the first case, the drug–receptor interaction produces a measurable biological response, such as muscle contraction. Drugs that interact with their receptor to produce a measurable response are called *agonists*. If we look at the range of responses that may be produced by a variety of agonists, we see that some appear to be able to produce much bigger responses than others. Agonists able to produce the maximum biological response that the tissue is capable of delivering are called full agonists. Those that can only produce a smaller response are called partial agonists. It should be noted that the apparent inability to produce a full biological response is not due to an inability of the drug to bind to the receptor, but an inability to trigger the response (intrinsic efficacy, see 'The dose–response relationship' below).

In the second case the binding of a drug molecule to its receptor does not produce a directly measurable biological response, but its binding may well prevent the binding of an agonist and thus reduce its effect. Such drugs are called *antagonists*. In the majority of cases antagonist drugs bind reversibly to the receptor and may be removed by washing or stopping dosage administration; such drugs are called reversible antagonists. It should be noted at this point that some antagonist drugs bind chemically to the receptor and cannot be easily removed; these drugs are called irreversible antagonists.

THE DOSE–RESPONSE RELATIONSHIP

We have seen above that drugs exert their effects in the body by interacting with highly specialised areas of cells called receptors. Some drugs (agonists) interact with these receptors to produce a measurable biological effect, whereas some (antagonists) interact with receptors to prevent the actions of agonist drugs, but do not produce a biologically measurable effect themselves. You should note that the ability of a drug molecule to bind to its receptor site does not, in itself, produce a response. Indeed, some antagonists bind much more strongly to their receptor than do agonists. Clearly, there must be another property possessed by the agonist, which enables it to produce a response, that is not possessed by the antagonist. This property of a drug to produce a measurable effect is called the *intrinsic efficacy*.

In order to quantify this relationship between drugs and their receptors we need to consider not only the concept of intrinsic efficacy, but also that of *potency*. The intrinsic efficacy of a drug is a measure of its ability to elicit a response once it has become bound to its receptor. It is arbitrarily measured on a scale of 0 to 1. Thus, full agonists have an intrinsic efficacy equal to 1 and antagonists have an intrinsic efficacy equal to 0. Partial agonist drugs have an intrinsic efficacy in between these limits.

The potency of a drug is a measure of the concentration that produces a given effect on a particular receptor. Potency is usually derived from the concentration of the drug that produces 50% of the maximal response of which the tissue is capable – this concentration is called the EC_{50}. Potency is the reciprocal of the EC_{50}. Thus, a highly potent drug has an extremely low EC_{50}, whereas a less potent drug has a higher EC_{50}.

The relationship between potency and intrinsic efficacy for agonists, partial agonists and antagonists is summarised in Fig. 2.5.

It would be reasonable to expect that the size of response produced by an agonist drug would be dependent on the concentration of drug actually at the receptor site. If the concentration of the drug is below a certain level there is no effect, but as the concentration is increased, the response increases until it reaches a maximum. In patients this will generally be proportional to the dose given.

If we plot the relationship between the concentration of an agonist and the size of the response that it produces, we get a rectangular hyperbola as shown in Fig. 2.6(a). By plotting

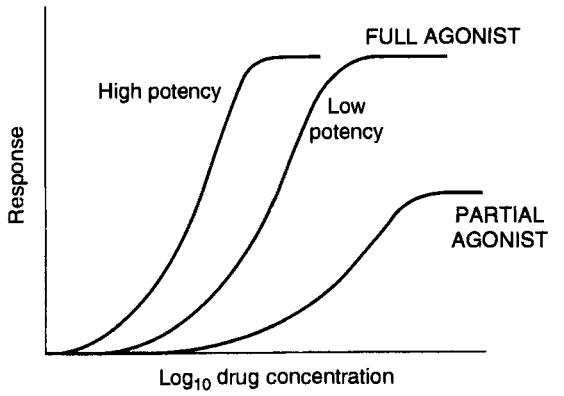

Fig. 2.5 The relationships between potency and intrinsic efficacy for agonists and partial agonists. Note the two lines for the full agonists, both have the same maximum effect (intrinsic efficacy), but the curve to the left is for a drug having a higher potency than that on the right; the curve for the partial agonist shows a low intrinsic efficacy and low potency.

the relationship between the $\log_{10}$ of the concentration of the drug against the size of the response we get a graded, sigmoidal relationship called the *dose–response curve*, as shown in Fig. 2.6(b). It should be noted that this curve is approximately linear over the range 20–80% of the maximum response and that the EC_{50} for the agonist can be derived graphically from this relationship.

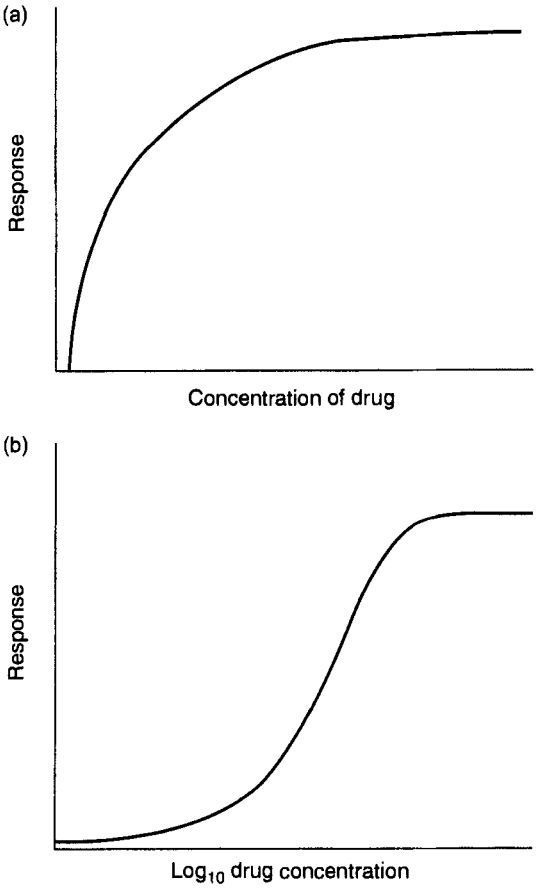

Fig. 2.6 The relationship between concentration of drug and response. (a) Rectangular hyperbolic relationship between drug concentration and response. (b) The sigmoidal relationship between $\log_{10}$ drug concentration and response.

ANTAGONISM

Pharmacological antagonism

Some drugs produce opposite effects on the same body system. This is called pharmacological antagonism. An example would be the co-administration drugs such as phenylephrine and captopril. Phenylephrine is often used in cold treatments, whereas captopril is used to lower blood pressure in hypertension. The co-administration of these two drugs would reduce the antihypertensive effect of captopril and may be dangerous for the patient.

Pharmacodynamic antagonism

We have seen that some drugs (antagonists), which have an intrinsic efficacy equal to 0, interfere with the action of agonist drugs at their receptors. It should be noted that, in many cases, the binding of an antagonist drug to its receptor is much more powerful than the binding of an agonist drug to the same receptor. The type of antagonism produced by an antagonist drug falls into two main categories, depending on the type of interaction between the antagonist and its receptor.

Reversible-surmountable antagonism

Most clinically useful antagonists interact with their receptor in a manner similar to the interaction between an agonist and the receptor, that is it forms a dynamic equilibrium similar to that shown in Equation (2.1). In this situation, when both agonist and antagonist are present, there is a two-way equilibrium in which agonist and antagonist molecules compete with each other for the receptor, as described in Equation (2.1), the agonist–receptor complex producing a response and the antagonist–receptor complex not producing a response. Figure 2.7 shows the effect of such an antagonist on the dose–response relationship for an agonist. Note that the dose–response curve for the agonist drug is shifted to the right and that the slope of the curve is not changed (parallel rightward shift). Note also that if sufficient agonist drug is used it is able to overcome the effect of the antagonist and produce the same maximum response as it did in the absence of antagonist.

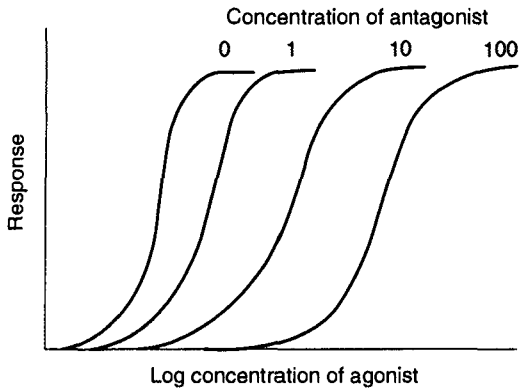

Fig. 2.7 The effect of increasing concentrations of a competitive antagonist on the $\log_{10}$ drug concentration : response curve for an agonist. Note that, with increasing concentration of the antagonist, the curves are moved to the right, but the slope is not altered and the same maximum response is achieved.

This type of antagonism is called reversible-surmountable antagonism. In reversible-surmountable antagonism there is an apparent increase in the EC_{50} for the agonist drug in the presence of increasing concentrations of antagonist. Furthermore, washing the drug away from its site of action can reverse the effects of the antagonist.

The pA_2 scale of Arunlakshana and Schild

Measurement of the potency of an antagonist is difficult, as it does not produce a direct effect. However, the potency of a reversible-surmountable antagonist may be measured by determining the size of the rightward shift in the dose–response curve for the agonist that is produced by a known concentration of the antagonist. The pA scale, first described by Arunlakshana and Schild, is such a measure of the potency of an antagonist drug against an agonist.

The most common measurement of antagonist potency is the pA_2, which may be defined as: $-\log_{10}$ of the molar concentration of antagonist that produces a twofold rightward shift of the dose–response curve of the agonist. Thus a potent antagonist has a high pA_2, whereas a less potent antagonist has a low pA_2. It should also be noted that, when quoting the value of a pA_2 for an antagonist, the agonist must also be defined, as it may be different against other agonists. Examples of pA_2 values for some antagonists are shown in Table 2.3.

Table 2.3 pA_2 values of some common antagonists.

Antagonist	Agonist	pA_2
Atropine	Acetylcholine	8.9
Atropine	Histamine	4.6
Diphenhydramine	Acetylcholine	4.0
Diphenhydramine	Histamine	9.5

Non-reversible antagonism

A small number of antagonists do not interact with their receptors in the manner described above. In many cases they form chemical bonds with the receptor and do not form a dynamic equilibrium. The most common antagonist in this group is phenoxybenzamine, which alkylates the receptor and renders it completely unavailable for

interaction with an agonist molecule. When agonist and antagonist drugs are present together in this situation there is no two-way dynamic equilibrium, and the effect of such an antagonist on the dose–response curve of the agonist is shown in Fig. 2.8. Note that the dose–response curve for the agonist is shifted to the right, but that the slope is not the same (non-parallel rightward shift). Note also that the maximum response produced by the agonist is decreased as a result of the destruction of the receptors. This type of antagonism is called non-reversible antagonism and, as the drug cannot be washed away, it cannot be reversed.

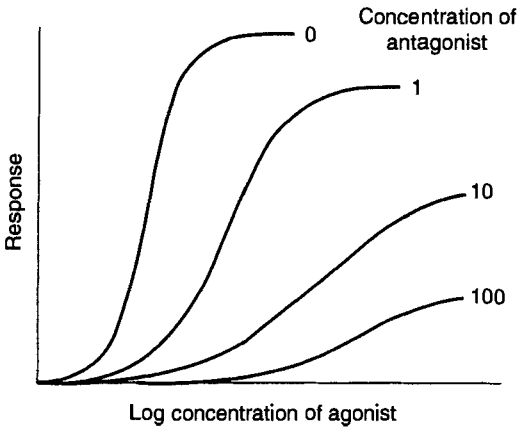

Fig. 2.8 The effect of increasing concentrations of a non-competitive antagonist on the $\log_{10}$ drug concentration : response curve for an agonist. Note that, with increasing concentration of the antagonist, the curves are moved to the right, the slope is decreased and the maximum response is reduced.

SUMMARY

- The main systems that allow for communication between cells are the endocrine, paracrine and nervous systems.
- The nervous system may be divided into the central nervous system (CNS; brain and spinal cord), the afferent nervous system (carrying messages into the CNS) and the efferent nervous system (carrying messages from the CNS).
- Neurohumoral transmission is the process by which an action potential in a nerve releases a neurotransmitter from the nerve ending. This diffuses across a synapse and interacts with the postsynaptic cell membrane.
- Drugs exert their effects by acting upon receptors, enzymes and carrier systems in the body.
- Cell membrane drug receptors may be divided into ligand-gated ion channels, G-protein-coupled receptors and tyrosine kinase-linked receptors.
- Steroid receptors are located close to the cell nuclei.
- Pharmacokinetics is the study of the behaviour of the drug in the body.
- Pharmacodynamics is the study of the drug–receptor interaction.
- Drugs that produce a measurable biological response are called agonists.
- Antagonists are drugs that do not, themselves, produce a measurable biological response, but which interfere with the actions of agonists.
- Antagonism is the effect produced by antagonists; it may be irreversible or reversible/surmountable.
- The potency of antagonists is measured on the pA_2 scale.

3

The Role of the Podiatrist in Patient Care

INTRODUCTION

In the UK, podiatry has its origins in the seventeenth century when, like dentistry, practice was carried out by street traders, particularly in London. Physicians, surgeons and even barbers regarded both abnormal excrescences of the feet and decayed teeth as neither medical nor surgical problems and the treatment of such was certainly considered beneath their dignity. Although the first published recognition of the foot in 1780 is credited to a Frenchman it was a London corn cutter in 1785 who first used the name *cheiropodist*, the word being derived from the Greek *kheir* meaning hand and *pous pod* meaning foot. As the name suggests, early practitioners were involved in the treatment of both the hand and the foot. So it was that 'corn cutters' became chiropodists and at about the same time 'tooth pullers' became dentists.

Throughout the late eighteenth and early nineteenth centuries the first learned textbooks dealing specifically with the foot were produced and royalty were frequently attended by a 'surgeon-chiropodist', as they were then known. Preceptor training developed but it was not until 1919 that the first school of chiropody was opened in London, offering a formal education system under the patronage of an eminent consultant of the time. This was quickly followed by courses being established in Edinburgh, Manchester and Glasgow. Closely associated with these schools, professional organisations also proliferated and these were finally grouped together to form the Society of Chiropodists in 1945.

From its earliest days the podiatry profession insisted on the highest standards and developed quite rapidly from a correspondence course to a two-year integrated training programme followed in the 1950s by the three-year diploma and finally to an all-graduate profession in the late 1980s. At this time the momentum for change in chiropody was accelerated and this was reflected in the title of degrees, becoming a BSc Hons in podiatric medicine or podiatry and the professional practitioner being known as a podiatrist. The Society of Chiropodists also changed its title to the Society of Chiropodists and Podiatrists (SOCAP). The general public and many members of the health care team are still not familiar with this relatively new terminology and so chiropodist and podiatrist are used synonymously in this chapter.

Early attempts were made to set up regulatory mechanisms for chiropody, other than SOCAP. The first of these was the Board of Registration of Medical Auxiliaries, under the auspices of the British Medical Association. This organisation ceased to function following the establishment of the professional boards, which were set up by the 1960 Professions Supplementary to Medicine Act. The Chiropodists Board has since that time maintained a register of practitioners eligible to be employed within the NHS but does not control entry to the private sector. Only those students who graduate from one of the 14 recognised schools of chiropody within the UK are eligible for state registration and can use the letters SRCh.

In 1999 there was a government review of the Professions Supplementary to Medicine Act of 1960 (PSM Act), with proposals to remove the profession's own statutory body and thereby its powers of self-regulation, replacing it with the Health Professions Council. The Bill received

Royal Assent and became the Health Act 1999 in June of that year with the repeal of the 1960 PSM Act. The drafting of Statutory Instruments (SIs), by which the PSM Act will be replaced, continues at the time of writing and it is planned that the new Statutory Regulatory mechanisms will be in place by autumn of 2001. Regulation of the profession will undoubtedly change following governmental consultation with representatives of the podiatry profession but the detail of such changes is not yet known.

CURRENT SCOPE OF PRACTICE OF THE PODIATRIST IN THE UK

The Professions Supplementary to Medicine Act 1960 through the Chiropodists Board defines the Scope of Practice for Chiropody such that:

> 'it comprises the maintenance of the feet in healthy condition, and the treatment of their disabilities by recognised chiropodial methods in which the practitioner has been trained'.

The Act further states that:

> 'Chiropodists should confine themselves to this field of work'.

It is recognised that ambulatory foot surgery is becoming a well-established procedure in chiropodial practice and this specialised field of work is further defined by the Chiropodists Board as:

> 'surgery performed by chiropodists at a level sufficiently minor as to be carried out on a day-case basis and which would not normally warrant in-patient admission, the patient being ambulant with or without assistance immediately after surgery. It should be subject to the limitations of the operator's skills and training, and the facilities available'.

In addition, the Statement of Conduct issued by the Chiropodists Board, as drawn up by its Disciplinary Committee as a requirement of the Professions Supplementary to Medicine Act 1960, coupled with the Society of Chiropodists and Podiatrists' own Code of Ethics, comments that:

> 'as regular practice, treatment of the hands is contrary to the Statement of Conduct. However, activities such as the cutting of normal fingernails may well arise in the course of a registrant's practice.
>
> 'Other complaints such as abnormal fingernails or amputation of calluses should only be treated if the patient has been referred by a registered medical practitioner'.

The current scope of practice is best illustrated by a description of the wide variety of activities in which the podiatrist engages in everyday situations in the clinic.

A podiatrist is able to recognise the interrelation between the function of the foot and the rest of the body and takes an holistic approach to the assessment and treatment of individuals. Patients may understandably become confused when the practitioner begins looking at the shoulders and hips in order to cure a painful foot. The podiatrist should therefore take care to explain the relevance of certain examination techniques to the patient to avoid such confusion for the patient and to increase compliance.

As research within the profession increases it provides further evidence to explain many foot problems on a scientific basis and the podiatrist can improve foot function using the principles of biomechanics in examination and treatment.

Podiatric management must involve an understanding of a broad range of medical and surgical conditions associated with the neuromuscular, peripheral vascular, musculoskeletal and endocrine systems and details of common signs and symptoms of conditions affecting these systems are discussed later in this chapter.

An increasingly important area of the podiatrist's work involves the maintenance or restoration of tissues to a viable state utilising clinical surgical skills and a thorough knowledge of appropriate dressings. This is particularly important as podiatrists become involved in team management of patients such as diabetics, rheumatoid arthritics, and those incapacitated by peripheral vascular diseases.

The clinical work of the podiatrist includes the use of local anaesthetics in the management of painful nail conditions, superficial soft tissue lesions and ambulatory foot surgery.

A key role of the podiatrist is in the promotion of good foot health practices and in the prevention of dysfunction. This involves teaching and advising individuals as patients, carers or others within the health care team, and the general public about optimal foot health and preventative measures.

From June 1999 the clinical practice of the podiatrist has been further enhanced with an amendment to the Prescriptions Only Medicines Act allowing state-registered podiatrists access to a limited list of drugs. Currently these include:

- ibuprofen 200 mg
- co-dydramol 10/500 mg
- paracetamol 500 mg
- amorolfine lacquer
- hydrocortisone cream 1%
- local anaesthetics with epinephrine 1 : 100 000 concentration.

In addition to the above scope of practice it is important to remember that in order to obtain the most effective clinical management of patients, the podiatrist must also take account of the appropriate cultural, psychosocial and economic factors influencing the delivery of treatment at that time. This involves the utilisation of good communication skills, a recognition of an individual's personal beliefs and identity and the recognition of the role of the podiatrist within a multidisciplinary environment.

PATIENT RECORDS

Clear, accurate and up-to-date records are mandatory and must be maintained by the podiatrist in practice. Case notes must be accessible to anyone with the right to see them and should set out, in unambiguous terms, what has been done, why, the basis on which it was done and what precautions were taken to guard against possible problems. SOCAP have published guidelines within the *Minimum Standards of Clinical Practice* document (Version 1.0, January 1999) to inform members of the minimum standards required in response to current legislation and issues related to 'best practice'. In general:

- Records must describe all elements of the consultation. This includes all professional services such as further referrals and advice given to patients.
- Records must be maintained in accordance with accepted procedures and current legislation.
- The practitioner must maintain written evidence of all assessments carried out, details of the treatment plan for the individual and the objectives of the management strategy.

Written documents

(1) The writing used in the document must be legible to any reader and done in black ink.
(2) A record must be made at the time of treatment, and any subsequent corrections to the entry must be signed and dated.
(3) A clear and logical format must be used.
(4) Where blank spaces appear, they should be scored through with a solid line.
(5) All attendances and entries must be dated and signed.
(6) It is a legal requirement that all patients' records are retained for a period of eight years after that patient's last appointment.
(7) Records relating to children and to young people must be kept until the patient's twenty-fifth birthday, or for eight years after the last entry, whichever is the longer.

Although not included in the guidelines provided by SOCAP, it is also considered good practice to:

- ensure that the patients' identifier number is on each page of the records;
- write out the details of the consultation (including the treatment) in full (i.e. in longhand), without the use of abbreviations. This avoids the risk of misinterpretation.

However, some health care professions do use agreed abbreviations and those acceptable to SOCAP are given in the published guidelines to practitioners. The standard abbreviations that are

considered acceptable for use within podiatry clinical records are given in Table 3.1.

Confidentiality

(1) Where patients' records are maintained on an electronic retrieval system, e.g. a computer, the practitioner must ensure that they comply with the requirements of the Data Protection Act 1998.

(2) 'Paper records' must be stored in a locked area, which does not allow access by unauthorised persons. It is recommended that metal storage facilities be used to minimise fire hazards and ensure safe storage of records in the event of a fire.

Table 3.1 Clinical abbreviations used in podiatry.

General terminology		**Skin pathologies**	
A/	Apex, e.g. A/2 (apex of second toe)	VP	Verruca pedis
B/F	Both feet	HD	Hard corn
C/O	Patient complains of	Hmill	Seed corn
O/E	On examination	H Molle	Soft corn
R/	Right foot	H Vasc	Vascular corn
L/	Left foot	HNV	Neurovascular corn
ID	Interdigital area, e.g. ID1/2	Pp	Pressure point
GHG	General health good	CPMA	Callus plantar metatarsal area
F/	Feet	CPD/1	Callus plantar digital area of first toe
H	Haemorrhage		
Anatomical terminology		**Padding**	
Ant.	Anterior	SCF	Semi-compressed felt
Post.	Posterior	SR	Sponge rubber
Superi.	Superior	FW	Fleecy web
Inf.	Inferior	PMP	Plantar metatarsal pad
Med.	Medial	Pl. Cush.	Plantar cushion
Lat.	Lateral	TG	Tube gauze
Pl.	Plantar	TF	Tube foam
Dor.	Dorsal	OCP	Oval cavity pad
J	Joint	IDW	Interdigital wedge
MTPJ	Metatarsophalangeal joint	Cres.	Crescent cut out
IPJ	Interphalangeal joint		
Met. Head.	Metatarsal joint		
Dist.	Distal		
Prox.	Proximal		
Nails		**Miscellaneous**	
O/H	Corn under the nail plate	HG	Hypergranulation tissue
O/C	Onychocryptosis	OA	Osteoarthrosis
O/G	Onychogryphosis	RhA	Rheumatoid arthritis
O/X	Onychauxis	IDDM	Insulin-dependent diabetes mellitus
O/P	Onychophosis	NIDDM	Non-insulin-dependent diabetes mellitus
PNA	Partial nail avulsion	>>	Condition improved
TNA	Total nail avulsion	<<	Condition deteriorated
Sub Ung.	Subungual	HAV	Hallux abductovalgus
		HL	Hallux limitus
		HR	Hallux rigidus

(3) Practitioners must be aware of patients' rights of access to treatment records in accordance with the Data Protection Act 1998 and the Access to Medical Records Act 1990, and should maintain records in an appropriate fashion. Judgemental statements of a personal or insensitive nature must not be made.
(4) Changes in patients' medical and personal information should be recorded on their records at regular intervals. These changes should be dated and signed.

EXAMINATION, ASSESSMENT AND DIAGNOSIS

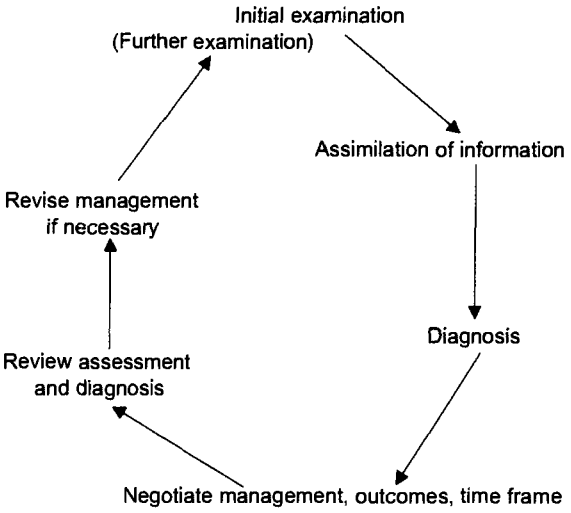

Fig. 3.1 Schematic diagram of patient assessment and diagnosis.

The profession of podiatry is dedicated to patient care within the NHS and in the private sector. Podiatrists are primary health care professionals who are responsible for the assessment, diagnosis and management of conditions affecting the foot and lower limb without referral from medical practitioners. Review of patient progress is undertaken solely by the podiatrist, which places a considerable measure of clinical responsibility on the practitioner.

An extensive range of assessments is undertaken by the podiatrist at the initial consultation and analysis of the information enables a diagnosis to be made before a management strategy is negotiated with the patient. The three elements already outlined, i.e. examination, assessment and diagnosis, should be regarded as a continual process of review to take account of changes in patient medical history, parenteral and topical medication, podiatric function or to refine the management in order to achieve a better outcome (Fig. 3.1).

This is particularly important with the increasing emphasis now being placed on evidence-based medicine (EBM). A patient record that shows constant repetition of treatments suggests that no re-evaluation has taken place to test the effectiveness of a particular strategy. If in fact the strategy requires repeated treatments the record should clearly indicate that an evaluation has taken place, periodically, and that continuation is indicated. Patient management is a dynamic process and the podiatrist needs to be fully aware of any changes, however minor, that have taken place since the last consultation. This involves not only physical measurement but careful questioning by the professional and in some cases even more careful listening so that vital clues are not missed. With the introduction of prescription-only medicines (POMs) the podiatrist needs to be fully appraised of the current medication used by patients to avoid contraindications if further medication is prescribed, and to recognise interactions and their manifestations in the lower limb. This is a most important part of the treatment as the podiatrist has time to examine the lower limb for abnormal reactions and listen to the patient, who may give information that can indicate an adverse reaction.

Similarly an indication of the psychosocial circumstances of the patient is necessary to deliver effective patient care. Certain groups of patients may possess characteristics which, if identified by the podiatrist, could influence the management plan that is proposed. The elderly are such a group and assessment may include the support offered to the patient from a spouse or close relatives. It has been shown that this support is important to the maintenance of a

positive physical and mental health state for the patient. With an increasing proportion of the very old (i.e. over 80 years) there are fewer spouses left alive and the children who could provide care are themselves in their late fifties and sixties. This has implications if the podiatrist requires help from close relatives in the management of the patient and the practitioner does need the information to either adjust the management plan or arrange for other sources of support for the patient.

It has been estimated that approximately 70% of the elderly have no mental health problems but that 15% exhibit functional disorders such as anxiety and depression. A further 10% demonstrate some organic brain syndrome, e.g. Alzheimer's disease, and the latter conditions increase substantially with increasing age.

Although a small proportion of the total population, the increased incidence of physical and mental illness in the elderly also leads to an increase in the levels of medication taken by these patients. All members of the health care team need to familiarise themselves with the possible effects of such medication, in relation to both the physical effects on the patient and the possible effect on the practitioner's assessment.

CLINICAL ASSESSMENT AND EXAMINATION

Routine clinical investigations include: visual assessment of the patient and in particular the skin and nails, taking note of the colour and texture of each; vascular assessment of the lower limb; neurological testing; biomechanical measurement; and a detailed medical and social history. Details of each are recorded in the patient records and an analysis of the details made to determine a diagnosis. In some circumstances the underlying problem lies outwith the expertise of the podiatrist and referral to the general practitioner (GP) or other parts of the health care team is necessary for further investigation.

Much can be learned from patients simply by looking at them when first entering the clinic. The human façade can give a good indication of robust general health and illness without the need for further investigation. A patient who is 'ill' or in pain often need say nothing to the practitioner, who will recognise the symptoms almost immediately. The facial and body characteristics that indicate internal illness and intense or prolonged pain are difficult to verbalise, but are recognised by the lay person as well as the professional. Words such as 'grey', 'drawn', 'lethargic', 'drowsy', 'sluggish', 'listless', 'weary', 'weak', 'strained', 'pinched', 'haggard' and 'tense' are all in everyday usage to give an impression that a person is somehow 'not well' and may have internal pain which is difficult for them to describe precisely. The podiatrist needs to use each of these key descriptive words to tease out further details from the patient which will help to localise the problem and give an indication of the diagnosis.

Lower limb problems are often easier to spot, as any pain in the leg will result in some alteration to the gait. The act of walking the patient into the surgery will alert the podiatrist to a problem before the patient speaks. A limp, for instance, may point to a problem in the foot, the knee, the hip or even the spine that can be localised by the podiatrist simply watching the patient's gait. Further and more precise examination can then determine the exact position and nature of the problem.

Visual examination of the skin and the appendages is important in order to recognise local signs and symptoms that may indicate more remote pathologies. Changes in the foot are often the first presenting sign of a more general condition that needs referral for appropriate specialist examination, e.g. ulceration, Bowen's disease, or cyanosis.

The skin should be examined to determine its overall texture, both locally on the lower limbs, and on other parts of the body that can be readily accessed. The podiatrist should note if the skin is normal in texture when compared to other parts or if it has become coarse, dull or shiny or if it appears thin and atrophic with a translucent quality to it.

The colour of the skin should be determined in good light, preferably natural, or with a colour-corrected lamp so that abnormal coloration is not distorted. The skin may show pallor, which is localised to one limb, or be the normal pale colouring of the individual. Erythema may be present as a manifestation of a local inflammation. Where cyanosis is present, the podiatrist should determine if this is confined to a small area of the skin (chilblain), the lower limbs in general (peripheral vascular disease) or if there is central cyanosis (cardiothoracic disease). Pigmentation may be various shades of brown, indicating haemosiderosis, or a range of different colours, indicating metal or chemical ingestion. A black discoloration with mummification of the tissues may indicate gangrenous changes, which should be referred for further medical investigation immediately.

The temperature of the skin can be determined using the back of the hand and comparing both limbs simultaneously, noting whether the tissues are hot, a normal warm temperature, cool or frankly chilled. It is not usual for the podiatrist to take precise measurements of skin temperature but to determine clinically if any abnormality is present.

An assessment of the humidity of the tissues is made by palpation and is described as dry or moist or hyperidrotic. Areas of distinct maceration should be recorded in the patient's notes with a diagram to locate the area precisely.

Other features to note about the skin include an assessment of its elasticity (movement and rebound) or induration (tethering or undue hardness), the presence or absence of hair growth and the state of the hair itself (fine or coarse). Superficial skin abnormalities should be noted and recorded appropriately, including, callosities, dermatoses such as eczema and psoriasis, discontinuity of the skin in fissures and ulcerations, any other manifestation which causes specific skin changes (congenital hyperkeratosis, AIDS, bullous dermatoses).

The nail unit can be a useful determinant of the general health of the patient but is also subject to disease itself. Disorders can be classified as surface defects, alterations in thickness and subungual.

(1) *Surface defects.* The normal nail plate is a smooth, slightly convex, translucent structure with a pink nail bed which is visible through the plate. With age the nail develops longitudinal ridges, thickens and becomes more opaque. Poor arterial circulation in a younger person may cause premature ridging which looks similar to that found in the elderly and longitudinal 'beading' has been noted more frequently in patients with rheumatoid arthritis or those individuals prone to develop the disease later in life. Transverse ridges occur with general illness (e.g. Beau's lines), with trauma and with repeated episodes of paronychia. There may be longitudinal splits in the plate affecting the free edge alone giving a crenellated appearance (onychorrhexis or trauma), or involvement of a greater proportion of the central area of the plate (pterygium). Surface roughness and friability may simply be a sign of ageing but could be an indication of onychomycosis, eczema or psoriasis. Pitting is characteristic of alopecia areata and psoriasis.

(2) *Alteration in thickness.* An increase in thickness of a single nail is often due to repeated minor or single major trauma. The thickened nail is accompanied by a slight brown colour change and exaggerated nail ridges. If more than one nail is affected fungal infection, eczema, psoriasis and poor peripheral circulation should all be considered as possible causes.

(3) *Subungual disorders.* Any abnormality occurring in the nail matrix or nail bed will have an effect on the nail plate. These abnormalities can be seen as alterations in shape, colour and sometimes the surface of the nail. A single nail that is noted to be painful and increasing in lateral curvature may be caused by an involution of unknown aetiology but should be investigated for the possible development of subungual exostosis. Soft tissue growth in the nail matrix or at the level of the proximal nail fold manifests as a depressed channel or separation from the nail bed. Of increasing importance is the early recognition of

changes due to subungual malignant melanoma occurring as a dark brown or black longitudinal band with spread of the pigmentation into the periungual tissues. The appearance of red subungual discoloration may indicate haemorrhage or the development of glomus tumour, which may need further investigation and treatment.

Vascular examination

The assessment of blood flow in the lower limb can be undertaken by clinical observation and palpation or with the use of instruments such as a vasoflow meter (Doppler), a plethysmograph and by calculation of the ankle brachial index.

Clinical observation should take note of the temperature and colour of the foot and lower limb. A pale, cool foot may indicate a relatively avascular situation, while a brick-red/cyanotic limb may indicate a dysvascular condition. Arterial pulses should be palpated with comparison of each limb and, if necessary, further elevation tests can be undertaken to differentiate between arterial and venous insufficiency. Oedema of the foot and ankle, particularly if it is 'pitting', may indicate a more generalised cardiovascular insufficiency.

In circumstances where it proves impossible to palpate the pedal pulses, e.g. when vessels lie deep in the tissues, the podiatrist may use a vasoflow meter (Doppler) to produce an audible signal of the arterial flow. It should be remembered that some patients feel uncomfortable hearing the pulse signal and in these instances headphones are useful.

A photoplethysmograph can be used to produce a visual, graphical trace of the blood flow through small digital vessels and is useful in determining whether surgery can be undertaken. A trace is also useful to monitor deterioration in peripheral circulation due to advancing disease (e.g. diabetes) or improvements in the circulation due to systemic therapy or cessation of smoking.

A further useful indicator of vascular status in the lower limb is the ankle brachial index, which compares the measured blood pressure in the arm with that in the ankles. This is usually expressed as a ratio of ankle pressure : arm pressure, with a ratio of 0.8 or less indicative of a compromised circulation. This ratio is often used as a determinant for nail surgery and may alert the podiatrist to problems requiring further investigation.

Neurological assessment

The neurological status of the lower limb is an important assessment undertaken by the podiatrist and most especially when involved in the care of diabetic patients and the elderly. Motor and sensory systems of both limbs should be examined and the results recorded and evaluated regularly to monitor any change or deterioration.

Motor power is assessed according to the Oxford (MRC) scale where:

0 = No muscle activity
1 = Muscle twitch without moving segment
2 = Segment moved with gravity eliminated
3 = Segment moved against gravity
4 = Segment moved against gravity and resistance
5 = Full power

In podiatric testing of motor power, muscles are usually examined in muscle groups, testing the strength of toe extension and flexion, foot invertors and evertors, and ankle dorsiflexors and plantarflexors. A defect in motor strength may result in structural deformity and limited joint movement and may be the first indication of motor disability.

Sensory assessment provides important information for the podiatrist to determine touch, proprioception, pain, temperature and vibration. Skin sensation is measured using Semmes Weinstein filaments and is a good indication of a loss of protective sensation. A single filament is pressed against the skin until it just begins to bend and a sense of pressure is felt. If no sensation is recorded using a filament of 6.10g there is judged to be a significant sensory deficiency. This is a particularly useful test in the initial assessment and continual care of diabetic patients.

Vibration sensation is determined using a tuning fork on several bony prominences or with a neurothesiometer, which can provide more precise information on the magnitude of the loss at different levels in the lower limb.

The ability to appreciate differences in temperature should be checked regularly and where a deficiency is recorded the podiatrist must advise the patient accordingly to prevent accidental burns.

Biomechanical assessment

An accurate assessment of the mechanical function of the foot and leg must be undertaken to reach a precise diagnosis in many patients. The podiatrist is an expert in the measurement of the range and direction of joint motion in the lower limb and much has been written in recent years on the 'normal' range of movements to be expected at specific joints. It is not necessary to have sophisticated equipment in order to make an accurate assessment, and visual observation together with simple measuring devices such as an orthogauge or goniometer may be all that is necessary. Ideally the whole of both limbs should be exposed and patients are often asked to wear shorts for the assessment or to roll trousers above the knee to ensure an unrestricted view of both knees and patellae.

Examination is carried out in a logical and methodical manner, beginning with the patient standing to assess head and shoulder tilt, spinal position, hip position and initial static evaluation of both feet. More precise measurements of each joint can then be made, as shown in Table 3.2.

Further measurements of leg length may be necessary by the podiatrist, or in cases where there is hypermobility (joint laxity) or hypomobility (joint stiffness) that prevents the practitioner from making accurate joint assessments, the patient may be referred for X-ray investigation.

Gait analysis

As well as the techniques employed by the practitioner in clinical examination of gait, a number of devices are available for static and dynamic evaluation of the foot in gait. Static evaluation can be carried out using a plantarscope which visually demonstrates weight distribution of the plantar surfaces by tissue blanching. Alteration of the position of the foot or leg by the practitioner may indicate the cause of the problem, which can then be managed by orthotics. A device called a podometer additionally indicates the foot size and calcaneal deviation. The pedobaroscope electronically projects a coloured image of weight distribution to a VDU screen which can then be photographed, stored on videotape or printed as hard copy for future reference. Small areas of pressure (2 mm × 3 mm) are recorded as different colours calibrated to a range of pressures.

A range of dynamic devices are available for gait analysis, from simple footprints on coloured paper using chalk or ink, to an inked rubber mat with variable raised ridges and squares (Harris and Beath mat). More sophisticated forceplate systems use transducers incorporated into floor mats or insoles (Musgrave, E Med, F-Scan) and produce a computer-generated pictorial record, which is useful to evaluate the success of orthotic treatment. Electrodynagrams utilise pressure transducers applied directly to the skin and videography is a useful tool when incorporated with a treadmill to enable the practitioner to examine the dynamics of the foot while the patient walks and runs at differing speeds and at different inclines.

Research has identified problems with each of

Table 3.2 Joint assessment.

Joint	Measurements
Ankle	Plantarflexion, dorsiflexion, rotational variations in lower limb
Subtalar (talocalcaneal)	Neutral position, inversion with adduction and plantarflexion
Midtarsal	Relationship of forefoot to hindfoot
Tarso-metatarsal	First and fifth ray plantarflexion and dorsiflexion
Metatarso-phalangeal	Quantify first and fifth ray motion, joint surface integrity, HAV, HL, HR, HF, subluxation, dislocation

the static and dynamic systems currently used in podiatric practice, but advances in technology will eventually produce a system that accurately records information about gait, and is easy to interpret.

Patients in high-risk categories

All professionals in the health care team need to be alert to the signs and symptoms that signal the patient 'at risk' and the importance of a detailed assessment and examination has been discussed earlier. The podiatrist is in the unique position of perhaps being the first member of the health care team to have contact with the patient. The evaluation and analysis of the results of the initial examination is the responsibility of the podiatrist and it is then encumbent upon the practitioner to take the appropriate action in the management of that patient. For a large percentage of the patients seen this is a relatively straightforward process of negotiation with the practitioner in the formulation of a management plan which is subsequently revised at regular intervals.

However, a number of pathologies may be identified during the examination, which places the individual in a special category known as 'high risk'. These patients may have a reduced healing potential, or an increased risk of developing infections, or may present at the initial consultation with areas that have ulcerated or can be identified as prenecrotic sites. Even those patients without frank pathologies are in a vulnerable position in the surgery and all clinical contacts must be dealt with in an atmosphere of stringent precautions. Some of these precautions are mandatory for the practitioner: instrument sterilisation must be carried out by autoclave, with a separate set of instruments for each patient contact; preparation of the skin prior to treatment must be carried out with an appropriate alcohol-based cleanser (the addition of an antiseptic has minimal added effect); and post-operative care should take careful account of the dressings and medicaments used. Patients within an identified 'at-risk' group should have added precautions, avoiding injudicious use of caustics and close monitoring if they are used, meticulous application of dressings with non-constrictive strapping or bandaging, and limited use of surgical procedures and only after consultation with the GP. Whatever the clinical status of the patient, good patient education also needs to be in evidence to promote self-care.

THE PODIATRIST'S ROLE IN PREVENTION OF COMPLICATIONS

The importance of a detailed and accurate examination and assessment of all patients was emphasised earlier, and with the high-risk patient this is particularly so. Investigation of the vascular and neurological systems offers information that can determine the effective management of the patient and may indicate the need for further investigations. The detection of impaired sensory function together with a history of polyuria and continuing thirst may lead the podiatrist to perform a simple urinalysis or estimation of blood glucose levels using a glucometer. A raised glucose level in the urine or blood may be indicative of diabetes mellitus and so referral for further medical examination would be intimated with a letter outlining the clinical findings made by the podiatrist. It is increasingly expected that the podiatrist then continues with regular interventions to prevent complications or manage any developing wounds.

Diabetic complications that can affect the feet are numerous with secondary disorders associated with atherosclerosis, motor, sensory and autonomic nerve dysfunction, an increased susceptibility to infection, retinopathy, kidney disease and poor healing due to glycosylation of tissues. The podiatrist's skill in tissue debridement and the use of desloughing and cleansing agents with appropriate dressings is recognised as a major factor in the reduction of complications leading to hospitalisation of diabetic patients, and the current emphasis on a multidisciplinary approach is invaluable.

Other conditions leading to the identification of patients as 'high risk' are:

- Vascular disorders involving the arterial and venous systems (including ischaemic compli-

cations of both the macrovasculature and microvasculature). Disorders of the lymphatic system are also important to recognise as is the differentiation of oedema associated with venous insufficiency or chronic cardiac failure.

- Neurological dysfunction in any modality resulting in loss of protective sensation, structural deformity due to reduced motor function and alterations in gait or disorders of the central nervous system affecting communication skills.
- The arthritides and in particular the inflammatory arthritides, e.g. rheumatoid arthritis and seronegative spondarthritides; diffuse connective tissue diseases producing an inflammatory reaction directed against the body's own tissues, e.g. systemic lupus erythematosis (with Raynaud's phenomenon), progressive lupus erythematosis (with avascular necrosis), and polyarteritis nodosa (ulceration and neuropathy).
- Immunosuppression and patients with compromised immunity, e.g. AIDS, diabetes mellitus, transplant recipients, secondary to drug therapy.
- Malnutrition/malabsorption which reiterates the importance of a thorough medical and social history. Diet peculiarities, poverty and a history of pernicious anaemia may all result in poor healing.
- Psychological and mental disturbances such as depression, anxiety and Alzheimer's may make it difficult for patients to care for themselves or understand the instructions for patient self-care given by the podiatrist.

All of the conditions outlined may involve drug therapy and the podiatrist should record precise details of all drugs taken by the patient, which should then be checked in the latest edition of the *British National Formulary* (BNF). With an increasing elderly population, a heightened awareness of health care in general, and a prodigious rise in self-medication with homeopathic remedies there has been a significant increase in the levels of medication taken by patients of all ages. Without the discipline of checking and rechecking medications the practitioner may be faced with seemingly erroneous and confusing results to assessments. Drug actions must be considered in the holistic approach to diagnosis and assessment of patients and direct communication with the GP or even a local pharmacist may be necessary to establish the possible effects on psychological and physiological functions being measured in the podiatrist's clinic.

It should be remembered that the metabolic changes that occur with advancing age can cause a variety of unusual effects when drugs are prescribed, in particular in the renal system. Similarly, the side-effects of some commonly prescribed psychotropic drugs are very much increased in the elderly, but may only become apparent when psychological tests are carried out for some other reason, such as determining the ability of the patient to carry out simple instructions for podiatry care in the home.

Self-medication raises different problems, as the patient may be reluctant to admit to their use. Conversation during treatment often alerts the podiatrist to a cocktail of remedies taken alongside prescribed medication. Again these must be recorded and advice sought about possible interactions and side-effects.

PATIENT EDUCATION

Patients need to be able to contribute to their own care and be actively involved in the development of the management proposed for them. This is the basis of the negotiated management plan adopted by most health care professionals today in the care of patients. The introduction of the Patient's Charter, recommendations from the World Health Organisation and the specific aims of the St Vincent Declaration in the treatment of diabetics has raised awareness of the need to provide better information to patients about their conditions to ensure quality in patient care. As well as informing patients about their illness it is therefore also necessary to educate them about how to maintain a healthy lifestyle and to provide them with the opportunity to make informed choices about the treatment available.

The terms 'health education', 'health promotion' and 'patient education' are often used interchangeably with the assumption that there is little or no difference between them. Although very closely linked, there are distinct differences which separate the three.

By definition 'health education' is the improvement of health literacy through the provision of information to encourage changes in an individual's attitude and behaviour. This is probably appreciated best in health advice leaflets and advertising campaigns, e.g. anti-smoking. 'Health promotion' on the other hand is concerned with providing equal opportunities for members of the public, regardless of their state of health. It is more targeted towards prevention of disease in individuals, and within communities, by forming health policies to ensure that individuals reach their fullest health potential. It can be dictated by governments to redirect health service provision.

More recently the term 'patient education' has been used which involves more than providing information about diseases or promoting health policies to prevent disease. It is directed towards those individuals who are in receipt of health care and is more specific to the individual's condition. It educates the patient about the disease or condition and the likely consequences. This allows the patients to become actively involved in their own treatment and to make optimal choices about treatment alternatives.

As the time involved in a podiatry treatment is usually longer than that allowed for other forms of treatment, the podiatrist is in a strong position to deliver advice directly to the patient. This can be general promotion of health or the prevention of foot problems or an educational role in promoting self-care. Podiatrists have previously referred to the practice of educating patients as foot health education rather than patient education, but it is not a new concept in podiatric practice.

Several examples of patient education can be identified in the profession, with information given on well-fitting footwear, general foot hygiene, care of the diabetic foot, the children's foot, advice on the treatment of verrucas and guidelines on postoperative dressings. Good practice in patient education would involve giving the patient:

- information about the cause of their disease or condition
- details on how the condition may develop over time
- an explanation of the available treatment options
- guidance on the steps the patient can take to prevent the condition
- advice on what is likely to make the condition worse or make it recur
- an explanation of the likely outcome, the effect it may have on the individual's lifestyle and how the patient can help in the monitoring of the condition.

Each disease is different, and as the same disease may present and behave differently in each individual, so patient education must be given on an individual basis. If incorporated fully into everyday practice it forms part of the assessment, examination and diagnosis routine familiar to the podiatrist and is accepted by the patient as part of the management. It is important that the patient understands the information being given (both verbal and written) and is provided with an opportunity to ask for clarification or further explanation in order to gain facts that are helpful for their own needs. This may be a slow process, as the information may need to be explained in several different ways, using very simple language, before full understanding is achieved. Perseverance does have rewards in that it has been shown that effective patient education:

- improves patient compliance
- improves the health of the patient
- ensures co-operation with the management plan
- prevents further ailments
- relieves symptoms more quickly
- improves the relationship between the patient and carer
- increases satisfaction with received treatment
- increases the chance of patients completing a course of therapy.

Once they are confident that they can use the information effectively in their home environment, patients can begin to control their own health care.

The evidence suggests that podiatrists have recognised the value of patient education as an important aspect of patient care but that it is limited to specific groups perceived as 'high risk'. It should be adopted in all spheres of podiatric care and podiatrists should use their specialised knowledge to improve the care and maintenance of foot health by encouraging the patient to take an active role in their treatment.

FUTURE ROLE OF THE PODIATRIST AS A MEMBER OF THE MULTIDISCIPLINARY HEALTH CARE TEAM

To discuss the role of a 'multidisciplinary health care team' we should first understand what is meant by this commonly used phrase. By definition 'multi' means many or more than one, and 'a discipline' is a branch of instruction or learning or a speciality, and can be used to imply behaviour, conduct and attitude. These basic words in themselves give a good indication of what is meant and once combined in the context of health care the sense of 'shared care' and 'joint' or 'collective responsibility' can be clearly appreciated. Many areas of patient care now incorporate a range of individuals with particular specialities who combine their expertise for the benefit of the patient. This 'cross-boundary' method of working is a high priority in the government's aims for the NHS, which are centred on:

- improving the health of the nation and reducing inequalities
- raising clinical and management standards and responsiveness
- providing integrated treatment and care
- improving performance and cost-effectiveness
- raising public confidence.

Medical and 'professions allied to medicine' (PAMs) specialists working together to provide integrated treatment and care are more responsive to the needs and concerns of patients, are more aware of the contribution of each speciality to overall care, and this can have a very positive effect in raising clinical and management standards. As a result the 'team' is able to reduce the time taken to reach the treatment outcome thereby improving the cost-effectiveness of the management and increasing the satisfaction of the patient.

Those areas where the multidisciplinary approach, involving a podiatrist, has been shown to be most effective are in the care of diabetic and rheumatology patients. However, there is also a steady increase in the number of combined medical and paramedical teams who are involved with vascular disease, sports injuries, rehabilitation centres and in the care of the ageing patient. For care to be effective the members of the team need to communicate regularly and transparently, not only between themselves, but also with the patient. This is best achieved in the forum of a full team member meeting, where individual patients are discussed to ensure that common aims are identified and adhered to. This planned episode of care must be communicated to the patient so that there is full awareness of the strategies to be employed and the means by which the outcome will be reached. This may involve some input from the patient or carer, working with the multidisciplinary team, to continue part of the treatment at home, e.g. exercise regimes, dressings, diet.

The multi-team meeting also provides an opportunity to share all information gathered from the patient during several separate interventions. This is a most important part of multidisciplinary care to ensure that no piece of vital information is lost; what seems trivial or of no consequence to one speciality may be crucially important to another and can signal the need to change the management for the benefit of the patient. This effectively means that all team members need to understand the work of colleagues and to appreciate how the parts combine to create the whole. Often this involves a series of educational seminars or lectures, which builds professional respect and confidence between the differing medical strands. It also contributes to shared learning from, and about, each other and the respective disciplines. In this respect the podiatrist has a full contribution to make in demonstrating the particular role that can be

played and in answering the many questions other health care professionals may have.

The composition of the multidisciplinary team is entirely dependent upon the medical disorder on which it is centred. Most are under the direction of a medical consultant with a nurse specialist who acts as a liaison between all the other disciplines and coordinates the interventions. Other team members can vary and may include a dietician, social worker, physiotherapist, occupational therapist, podiatrist, pharmacist, patient and carer, or orthotist. For example, the multidisciplinary team in a hospital rheumatology department could consist of:

- consultant rheumatologist
- rheumatology nurse specialist
- appliance officer/orthotist
- dietician
- occupational therapist
- patient and carer
- pharmacist
- physiotherapist
- psychologist
- podiatrist
- social worker

whereas the diabetic team may be composed of:

- consultant diabetologist/endocrinologist
- vascular surgeon
- diabetes nurse specialist
- podiatrist
- dietician
- consultant in pain management
- orthotist
- physiotherapist
- radiologist
- orthopaedic surgeon.

Although the involvement of the podiatrist in the multi-care team is increasing it is by no means automatic. It is, therefore, important that the podiatrist takes every opportunity to make known to the other relevant medical and paramedical professionals the role that he or she can take in patient care. Other members of the multidisciplinary health care team will then utilise the expertise of the podiatrist to maximise the care available for all groups of patients.

SUMMARY

- Podiatry has its roots in the practice of 'corn cutters' in the late eighteenth century.
- The profession is controlled by an accrediting body called the Society of Chiropodists and Podiatrists.
- The scope of practice of the profession is defined in the Professions Supplementary to Medicine Act 1960.
- Recent changes in legislation mean that podiatrists now have access to a range of prescription medicines.
- Accurate patient records are essential in the maintenance of acceptable standards of clinical practice.
- Effective clinical assessment of patients must include visual examination, vascular examination, neurological assessment, biomechanical assessment, gait analysis and the identification of patients in a 'high-risk' category.
- The podiatrist has an important role to play in the prevention of complications in the patient's treatment as well as educating the patient as to the treatments they are receiving.
- As a member of the multidisciplinary health care team, the podiatrist must work to ensure the highest standards of patient treatment.

4

Drugs Affecting the Peripheral Nervous System

INTRODUCTION

The peripheral nervous system (PNS) provides for the conscious and subconscious control of all basic sensory and motor functions of the body. It may be divided into two functional units:

(1) The *afferent* nervous system, which is responsible for the detection of external stimuli and the transmission of messages from the sensory organs in the periphery into the spinal cord and the brain.
(2) The *efferent* nervous system, which controls the activity of all peripheral tissues by carrying messages from the brain to the peripheral tissues.

The efferent nervous system may be further subdivided into:

(a) the *somatic* nervous system, which controls skeletal muscle
(b) the *autonomic* nervous system, which controls the visceral functions of the body such as blood pressure, digestion and function of the endocrine glands and is responsible for maintaining a constant internal environment in the body.

The autonomic nervous system maintains the internal environment of the body and may be subdivided both structurally and functionally into the *sympathetic* branch and the *parasympathetic* branch. The sympathetic branch of the autonomic nervous system prepares the body for action (the so-called 'fright and flight' syndrome), while the parasympathetic branch is associated with the processes of digestion and other functions carried out at rest.

The major branches of the nervous system are shown in Fig. 4.1.

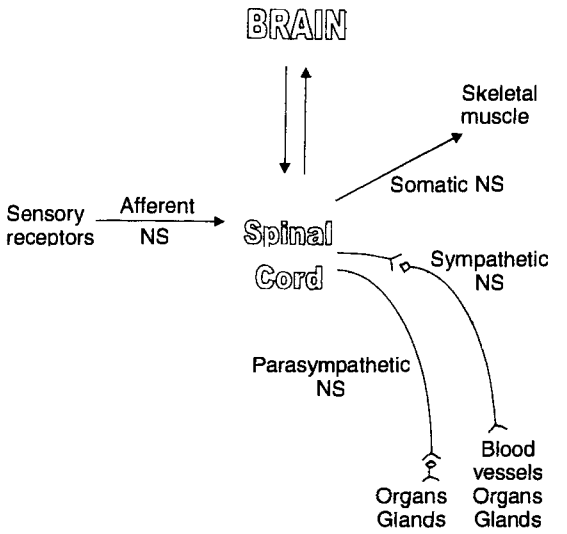

Fig. 4.1 The main branches of the nervous system. Afferent nerves transmit impulses from the sensory receptors into the spinal cord and brain; efferent somatic nerves innervate the skeletal muscles, and the sympathetic and parasympathetic branches of the autonomic nervous system innervate the organs, glands and blood vessels.

THE NEURONE

The neurone is the basic functional unit of both the PNS and the central nervous system (CNS). The human body contains about 10^{10} neurones, each of which are composed of four parts:

(1) The *cell body* contains the nucleus and other structures associated with the functioning of the cell.
(2) The *axon* conducts nerve impulses, in the form of an action potential, to a distant site in the body.
(3) The *dendrites* transmit impulses to their own nerve cell body.
(4) The *synapse* is the small gap either between adjacent nerves or between a nerve and another tissue.

There are many different types of neurone, but they may be classified into three basic forms (Fig. 4.2.). *Bipolar* neurones are often the interneurones that bridge between other neurones, particularly in the CNS. *Unipolar* neurones are predominantly sensory neurones in the afferent branch of the PNS and *multipolar* neurones are usually motor neurones.

In peripheral nerves the axons are long, whereas in the CNS the axons of the interneurones are short. In both cases they are covered by a myelin sheath, which is derived from Schwann cells in the periphery and from neuroglial cells in the CNS.

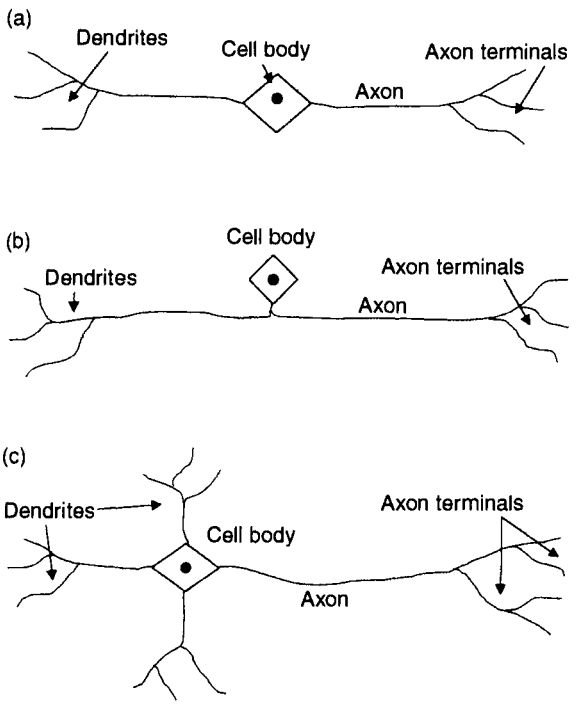

Fig. 4.2 The different types of neurone found in the nervous system. (a) Bipolar neurone; (b) unipolar neurone; (c) multipolar neurone.

The synapse is the point of connection between a neurone and another component of the nervous system. It is made up of the following:

- the terminal portion of the presynaptic neurone (the *presynaptic membrane*)
- the small gap, called the *synaptic cleft*
- the membrane of the cell being innervated (the *postsynaptic membrane*).

Neurotransmitters, which are synthesised and stored in the terminal of the axon, are released from the presynaptic membrane, diffuse across the synaptic cleft and interact with receptors on the postsynaptic membrane.

THE NEURONAL ACTION POTENTIAL

When a neurone is at rest it has a transmembrane potential difference (membrane potential) of about −65 mV. This membrane potential is due to the unequal distribution of ions across the cell membrane, as a result of the action of various ion pumps and ion channels. The most important ions that contribute to the generation of this resting membrane potential are Na^+, K^+, Ca^{2+} and Cl^-.

Impulses, and hence messages, are carried along the neurone by a wave of depolarisation, which may be recorded as the neuronal action potential (NAP). The NAP is initiated by a rapid influx of Na^+, through fast-acting channels, which is self-propagating and travels along the axon of the neurone. When the NAP reaches the end of the neurone it causes a depolarisation of the presynaptic membrane and the opening of voltage-gated Ca^{2+} channels, which allow Ca^{2+} ions to enter the neurone. This calcium initiates the release of neurotransmitter at the ends of the neurone and also promotes the outflow of K^+ ions, which terminates the NAP. The ion fluxes

and changes in transmembrane potential associated with the NAP are summarised in Fig. 4.3.

Whether a neurone depolarises or not, and whether it triggers a NAP, is dependent upon the resting membrane potential of the neuronal membrane in the dendrites. This, in turn, is dependent upon the ion distribution across the neuronal cell membrane in the region of the dendrites. This membrane contains receptors for neurotransmitters that have been released from other neurones and the actual membrane potential is dependent upon the relative actions of these

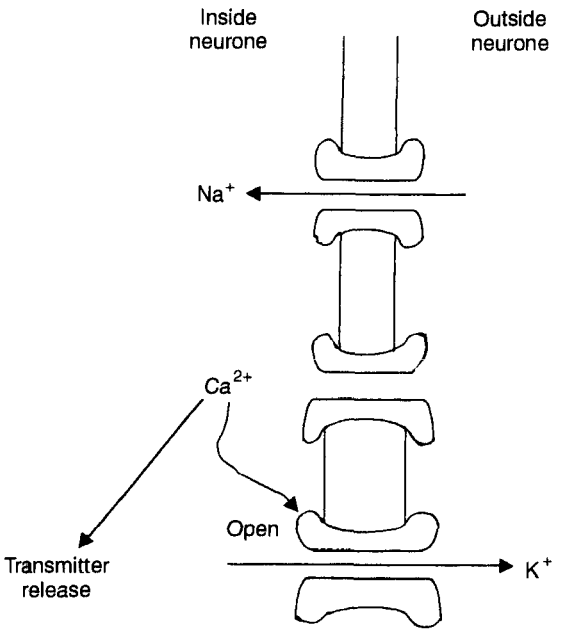

Fig. 4.3 The movement of ions during the passage of a nerve action potential. On the arrival of the nerve action potential, Na^+ channels open and allow the influx of Na^+ to depolarise the cell membrane; subsequent opening of voltage-gated Ca^{2+} and K^+ channels; the Ca^{2+} is used to promote release of neurotransmitter from the nerve ending.

For example, a neurotransmitter that promotes depolarisation of the cell membrane, by the opening of a Na^+ ion channel, will increase the likelihood of a NAP being triggered. Conversely, a neurotransmitter which hyperpolarises the cell membrane, by the opening of a Cl^- ion channel, will decrease the likelihood of a NAP occurring.

THE SOMATIC NERVOUS SYSTEM

The endings of sensory neurones in the periphery are a complex network of receptors that are sensitive to a range of different stimuli, including mechanical deformation, heat and light. Impulses from these receptors are transmitted as action potentials via sensory neurones into the spinal cord, where they enter via the dorsal root. Some neurones terminate in the spinal cord, while others pass up into the brain stem and the thalamus. Thus the incoming signal information may be acted upon immediately (reflexes) or integrated into the nervous activity in the brain.

This branch of the nervous system is responsible for our ability to detect, and react to, changes in our environment.

THE SOMATIC NERVOUS SYSTEM

Motor neurones of the somatic nervous system arise in the ventral horn of the spinal cord and synapse with motor neurones descending from the motor cortex in the brain. They leave the spinal cord via the ventral root and each myelinated α-neurone innervates a group of skeletal muscle fibres called a motor unit. The neurotransmitter released at the ends of these motor neurones is ACh, which acts upon nAChRs to produce muscle contraction. The junction between a somatic nerve and a skeletal muscle cell is called the neuromuscular junction (NMJ).

THE SYMPATHETIC NERVOUS SYSTEM

The preganglionic neurones of the sympathetic nervous system leave the spinal cord in the thoracolumbar regions and pass a short distance to a series of sympathetic ganglia, which are

groups of nerve–nerve junctions lying on either side of, and close to, the spinal cord. Long postganglionic neurones then pass to the tissue to be innervated. The neurotransmitter released in the sympathetic ganglia is ACh, whereas the neurotransmitter released at the postganglionic nerve ending is norepinephrine.

THE PARASYMPATHETIC NERVOUS SYSTEM

Preganglionic fibres in the parasympathetic nervous system leave the spinal cord in the craniosacral regions. Each preganglionic fibre is long and passes to a ganglion that is close to, or sometimes on, the tissue being innervated. The postganglionic fibres are short. The neurotransmitter released at ganglia in the parasympathetic nervous system is ACh. This neurotransmitter is also released at the postganglionic nerve ending in this system, but at this site it acts upon muscarinic acetylcholine receptors (mAChRs).

The anatomical details of the sensory, somatic, sympathetic and parasympathetic nervous systems are summarised in Fig. 4.4.

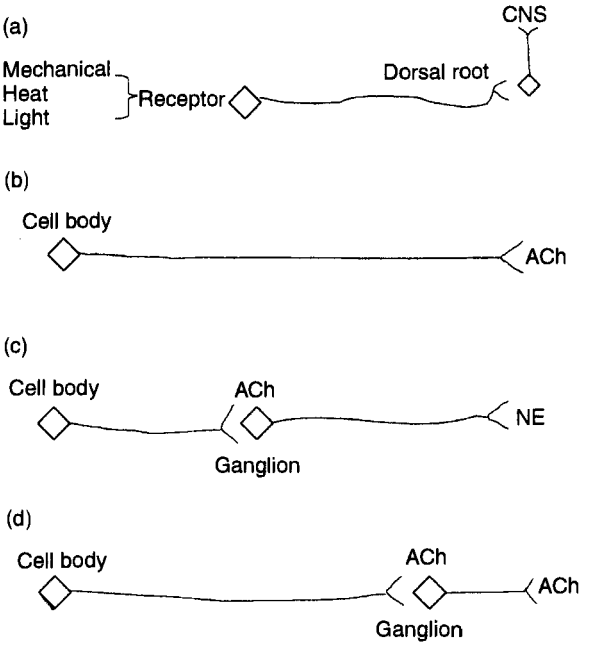

Fig. 4.4 The anatomical details of the sensory, somatic, sympathetic and parasympathetic nervous systems. (a) Sensory neurone. Note the single neurone passing to the spinal cord and neurones passing up into the central nervous system. (b) Somatic neurone. Note the single neurone passing from the spinal cord to the innervated muscle. (c) Sympathetic neurone. Note the short preganglionic neurone (releasing ACh) and the long postganglionic neurone (releasing NE). (d) Parasympathetic neurone. Note the long preganglionic neurone (releasing ACh) and the short postganglionic neurone (releasing ACh).

DISEASES OF THE PERIPHERAL NERVOUS SYSTEM

Somatic nervous system

The control of skeletal muscle is brought about by the activity of somatic nerves, modified by the influence of input from appropriate sensory receptors on muscles and tendons. The major diseases associated with abnormal function of the somatic nervous system are:

- myasthenia gravis
- myasthenia syndrome (Lambert–Eaton syndrome)
- muscle spasticity.

Myasthenia gravis

Myasthenia gravis is a disease that affects the NMJ. It is an autoimmune disease, characterised by muscle weakness and fatigue after even a brief period of activity. Patients report a generalised feeling of weakness, especially of the eyelids, extraocular muscles, neck and diaphragm. The clinical symptoms of the disease arise from a decrease in the number of nAChRs in the NMJ area, which results from the autoimmune response. Myasthenic patients often have antibodies to nAChRs in their blood.

In normal patients, the ACh released from the nerve endings diffuses across the synaptic cleft and interacts with the nAChRs on the postsynaptic membrane. This causes a depolarisation

of the postsynaptic membrane (an end-plate potential), which is self-propagated across the muscle cell and brings about muscle contraction. In the myasthenic patient, the decreased availability of nAChRs leads to a poorly generated end-plate potential and an inability to maintain muscle contraction.

Drugs used in the treatment of myasthenia gravis

Anticholinesterases:	neostigmine, pyridostigmine, edrophonium
Immunosuppressant drugs:	prednisolone, azathioprine, cyclosporin

Anticholinesterases

ACh, which is the neurotransmitter at the NMJ, cannot be given as a drug because it is hydrolysed very quickly by esterase enzymes in the blood. However, drugs which inhibit the enzyme acetylcholinesterase, which is the enzyme responsible for destroying ACh at the NMJ, cause an increase in the concentration of neurotransmitter in the synapse and a reversal of the clinical symptoms of the disease. Neostigmine and pyridostigmine both cause a prolonged reversal of the symptoms of myasthenia gravis. However, it should be noted that these drugs will increase the activity of cholinergic systems elsewhere in the body and so they are contraindicated in patients who have bradycardia, who have suffered a heart attack, or who suffer from peptic ulcer disease, renal impairment or Parkinson's disease.

Adverse effects include nausea, vomiting, increased salivation, diarrhoea and abdominal cramps. Increased bronchial secretions, sweating, bradycardia, miosis and involuntary defecation or micturition are signs of overdose. The use of anticholinesterase drugs is contraindicated in the presence of urinary or intestinal obstruction.

Immunosuppressant drugs

The effectiveness of anticholinesterase therapy often decreases after several weeks' treatment and so more aggressive therapy is required. Immunosuppressant drugs seek to reduce the autoimmune response and so prevent the destruction of the nAChRs in the neuromuscular junction.

Prednisolone may increase muscle weakness in the early stages of treatment; however, as muscle strength returns, the dose of the glucocorticoid can be reduced to avoid adverse effects.

Azathioprine suppresses the formation of antibodies to the nAChR protein by inhibiting T-lymphocyte activity. Its therapeutic effectiveness can take up to 1 year to develop. Adverse effects include nausea, vomiting, dermatitis, bone marrow depression and a 'flu-like' syndrome.

Its adverse effects limit the usefulness of cyclosporin, which acts by inhibiting the action of T helper cells. These include renal toxicity, hypertension and tremor.

Myasthenia syndrome

Myasthenia syndrome resembles myasthenia gravis in its clinical symptoms; however, it does not respond to treatment with anticholinesterase drugs, such as those described above. It arises from a decrease in the excitability of the skeletal muscle cells to the normal stimulation by the somatic nervous system. It is commonly associated with lung cancer. The treatment of myasthenia syndrome is based upon the use of Ca^{2+} salts to increase the release of neurotransmitter.

Muscle spasticity

Muscle spasticity is characterised by an increased level of tone (hypertonia) in the skeletal muscles and may also involve uncontrolled muscle contractions. It usually occurs as a symptom of an underlying pathological disease, such as cerebral palsy, multiple sclerosis or stroke, but may also occur as a result of displacement damage to the skeleton. The hypertonia of muscle spasticity usually arises from excessive tendon reflexes, spasm of the flexor muscles or a combination of both.

If possible, the treatment of muscle spasticity should seek to identify and eliminate the underlying cause of the problem. However, in many cases this is not possible and so the drug treatment of muscle spasticity is aimed at reducing excessive stimulation of the motor neurones that innervate the skeletal muscles.

Drugs used in the treatment of muscle spasticity

Muscle relaxants:	baclofen, dantrolene
Benzodiazepines:	diazepam
α_2-Adrenoceptor agonist:	tizanidine

Muscle relaxants

Baclofen is an analogue of GABA, which can cross the blood–brain barrier easily. It is of greatest benefit in the treatment of muscle spasms in flexor and extensor muscles. The primary site of action for baclofen is to inhibit neuronal transmission in the spinal cord, by an action on the $GABA_B$ receptor. This leads to a decrease in the influx of Ca^{2+} into the cells, decreased release of excitatory neurotransmitters and inhibition of the spinal reflexes causing the spasticity.

Baclofen is more effective in the treatment of muscle spasticity arising from lesions in the spinal cord and those arising from multiple sclerosis. It is less effective in spasticity arising from stroke. Adverse effects include drowsiness, motor incoordination, mental confusion, parasthesias, insomnia, respiratory depression, cardiovascular depression, hypotension, gastrointestinal disturbances and nausea. Overdose may produce seizures and its use is not recommended in patients suffering from epilepsy.

Treatment with baclofen should not be withdrawn abruptly as this may cause anxiety and tachycardia. Care must be taken in the treatment of patients who suffer psychiatric illness, epilepsy, cerebrovascular disorders, hepatic or renal impairment. Its use in pregnancy must be balanced against the benefits to the patient. Baclofen treatment is contraindicated in peptic ulcer disease.

Dantrolene has a direct action on the skeletal muscle cell, in which it interferes with the excitation–contraction coupling mechanism by reducing the release of Ca^{2+} from the sarcoplasmic reticulum. It is a hydantoin derivative and is of major benefit in the relief of spasticity associated with paraplegia and hemiplegia. Adverse effects of dantrolene include muscle weakness (which may limit its therapeutic usefulness), a transient drowsiness on commencement of treatment, dizziness, fatigue, anorexia, nausea, headache, visual disturbances, insomnia, chills and fever, increased urinary frequency, constipation and/or diarrhoea. Long-term treatment may result in liver toxicity. The use of dantrolene in patients suffering from impaired cardiac or respiratory function requires extra caution.

Benzodiazepines

The benefit of using benzodiazepines, such as diazepam, derives from their action on the $GABA_A$ receptor, probably in the spinal cord. The resultant increase in Cl^- influx hyperpolarises the cell membrane and inhibits neuronal firing in the motor nerves. Diazepam is more effective in the treatment of muscle spasticity arising from spinal cord lesions, but is not very effective in the treatment of spasm of flexor muscles. The adverse effects of benzodiazepines, which include drowsiness and the development of dependence, are discussed in Chapter 5.

α_2-Adrenoceptor agonists

Tizanidine is a recently introduced α_2-adrenoceptor agonist, which has been licensed for the treatment of the muscle spasticity associated with multiple sclerosis. It is thought to act upon presynaptic α_2-adrenoceptors to reduce neurotransmitter release in the spinal cord and so decrease the activity in motor neurones. Adverse effects of tizanidine include drowsiness, fatigue, dry mouth, nausea, gastrointestinal disturbances, bradycardia, insomnia and hallucinations. Its use is contraindicated in hepatic impairment.

Autonomic nervous system

Drug interventions in the autonomic nervous system (ANS) fall into two main categories:

(1) Drugs that are used to alter normal ANS function for therapeutic purposes, especially the peripheral control of pain.
(2) Drugs that are used to treat diseases associated with functional abnormalities of the ANS.

Peripheral control of pain

Pain is a normal occurrence of everyday life and serves to provide an essential defence mechanism

against potentially dangerous external stimuli. It is also indicative of many pathological disorders, such as rheumatoid arthritis or some cancers. Pain may be subdivided into two main forms:

(1) Acute pain, usually short term in duration and resulting from physical damage to a tissue; it ceases when the healing processes are completed.
(2) Chronic pain persists after the normal healing processes following surgery have been completed, or may result from serious underlying pathological disease and last for months, or even years.

The detection of pain is a three-stage process:

(1) Stimulation of pain receptors (nociceptors) in the peripheral tissues.
(2) Transfer of 'pain message' to the spinal cord.
(3) Onward passage of the 'pain message' to the brain and the perception of pain.

Stimulation of nociceptors

Unlike most other receptors in the body, nociceptors do not have a well-defined anatomical structure. They are thought to be simple bare nerve endings distributed throughout the skin, muscle and various organs of the body. It should be noted that some areas of the body, such as the heart, are relatively devoid of nociceptors and so 'pain' is not detected directly in these areas.

The mechanism by which these nociceptors are stimulated is not fully understood. However, it is well documented that many substances that are released at the sites of tissue damage are able to stimulate pain receptors, including:

- histamine
- 5-hydroxytryptamine
- bradykinin
- prostaglandins
- lactic acid
- ATP.

Transfer of 'pain message' to the spinal cord

Once the nociceptors have been activated, two types of sensory neurones transmit the pain message to the spinal cord. Myelinated neurones (Aδ fibres) carry impulses at about 15 m/s and are thought to give rise to the sensation of sharp, intense pain. Non-myelinated neurones (C fibres) carry impulses at about 1 m/s and are thought to give rise to the sensation of less focused pain, such as a headache or the visceral pain associated with cancer.

A variety of neurotransmitters are released by the Aδ fibres and C fibres that transmit impulses into the spinal cord, the most important of which are glutamate, neurokinin A and substance P. The action of these neurotransmitters is to stimulate neurones that transmit the impulse up the spinal cord to the brain. An important step in this process is the production of NO, which acts as a positive-feedback transmitter to increase the release of glutamate and substance P from the presynaptic neurones. This gives rise to the phenomenon of 'spinal wind-up' and serves to increase the electrical activity in the spinal neurones and reinforce the pain message.

The neurotransmitter activity at these sites in the spinal cord is modulated by the release of opioid peptides from descending neurones in the spinal cord. The most important of these peptides are met-enkephalin and β-endorphin, which act to control the natural perception of pain. It is thought that one reason why individuals appear to have different pain thresholds is the amount of these natural analgesic peptides produced.

Transmission and perception of pain by the brain

There are usually a large number of neuronal inputs feeding information into the spinal cord from nociceptors throughout the body. It would appear that the neurones of the spinal cord are able to process this information such that it is 'gated' and only pain sensation above a certain level is passed up to the brain. In this way, low-level pain stimuli may be controlled and are not perceived by the brain. Whilst this gating mechanism is beneficial in that it prevents over-reaction to low-level painful stimuli, it may mask pain arising from pathological causes.

Drugs used in the peripheral treatment of pain

NSAIDs:	aspirin, paracetamol, ibuprofen, mefenamic acid, naproxen, piroxicam, fenoprofen

The peripheral treatment of pain by drugs is centred upon attempting to decrease the sensitivity of the nociceptors to painful stimuli and so to decrease the number of impulses passing up to the brain via the spinal cord. In the discussion above, we have seen that nociception (detection of pain) is increased by substances such as histamine and prostaglandins. In fact, it is probably the prostaglandins produced at the site of tissue injury that are the greatest contributor to the stimulation of nociception.

The role of prostaglandins in nociception can best be illustrated by considering the pain resulting from two different types of skin injury. If you cut yourself with a sharp knife or the edge of a piece of paper, the level of pain resulting from the injury is quite low, even though the cut may be quite deep. On the other hand, if you fall and graze your knee, the resultant level of pain is high, even though the depth of the injury is only small. In the latter case, there is a larger amount of tissue damage resulting from the injury and hence an increased production of prostaglandins to stimulate the nociceptors in the skin.

NSAIDs

Non-steroidal anti-inflammatory drugs (NSAIDs) are the main therapeutic group used for the peripheral control of pain. NSAIDs such as ibuprofen, fenoprofen and piroxicam act by inhibiting the activity of the cyclo-oxygenase (COX) enzyme system and so decrease the amount of prostaglandins produced and the degree of nociception. They are of benefit in the control of pain arising from diseases such as rheumatoid arthritis. Their pharmacology is discussed in more detail in Chapter 13.

Diseases of the autonomic nervous system

Diseases of the autonomic nervous system are called dysautonomias. They are usually the result of familial, or disease-induced, malfunctions of the autonomic nervous system. The three most common dysautonomias are:

- Familial dysautonomia (Riley–Day syndrome)
- Shy–Drager syndrome
- Horner's syndrome.

Familial dysautonomia

Familial dysautonomia is an inherited disorder, which shows a complex group of symptoms, including an inability to control body temperature, absence of tears, hypertension and uncontrolled perspiration. Pathologically, patients show decreased myelination of nerves and a smaller number of nerve fibres in tracts of the autonomic nervous system. Treatment of this disease is symptomatic, as no cure is available and patients usually die in early infancy.

Drugs used in the treatment of familial dysautonomia

carbachol, norepinephrine, phenothiazines, antibacterial drugs

Treatment of this disease state is centred on attempts to relieve the symptoms and to control the development of respiratory tract infections, particularly pneumonia. Autonomic drugs, such as carbachol and norepinephrine, may be of transient benefit and phenothiazines are used to control the gastrointestinal and behavioural symptoms. Antibacterial drugs are used to control pneumonia.

Shy–Drager syndrome

This syndrome is again the result of a failure of the autonomic nervous system to control body function. It is characterised by a complex set of symptoms including severe postural hypotension, urinary incontinence, erectile dysfunction in males, tremor and muscle rigidity. Pathologically, patients show a loss of preganglionic sympathetic nerve fibres and there is also CNS involvement.

Drugs used in the treatment of Shy–Drager syndrome

fludrocortisone, epinephrine, ephedrine

Again, the treatment of this disease is symptomatic. Fludrocortisone increases Na^+ and water retention and so offsets the postural hypotension. The use of sympathomimetic drugs, such as epinephrine and ephedrine, also combat the postural hypotension, but may render the patient hypertensive when lying down.

Horner's syndrome

Horner's syndrome results from the loss of sympathetic control of the head. It is characterised by the loss of pupillary dilation, drooping of the eyelids, facial vasodilatation and a loss of the ability to perspire. The symptoms may only affect one side of the body and often result from disease-induced damage, such as a tumour, of the cervical ganglion or preganglionic sympathetic nerves on the affected side. A common cause of this syndrome is lung cancer, which can metastasise into the cervical ganglion.

Drugs used in the treatment of Horner's syndrome

Sympathomimetics:	phenylephrine, cocaine, ephedrine

Sympathomimetics

Drugs that mimic the actions of the sympathetic nervous system are of some benefit in the treatment of Horner's syndrome. The drug used depends upon an accurate determination of the site of the disease-causing lesion. If it is in the preganglionic fibres, then both directly acting and indirectly acting drugs, such as phenylephrine and ephedrine, will be of benefit. If the lesion is associated with postganglionic fibres then only directly acting drugs, such as phenylephrine, will be of use.

SUMMARY

- The peripheral nervous system (PNS) provides for the conscious and subconscious control of all sensory and motor functions of the body.
- The PNS is subdivided into the afferent (sensory) and efferent (motor) branches.
- The efferent branch of the PNS is divided into the somatic and the autonomic branches.
- The autonomic branch of the PNS is further divided into the sympathetic and parasympathetic branches.
- The basic functional unit of the nervous system is the neurone.
- Messages are transmitted along neurones by the generation and propagation of a neuronal action potential (NAP).
- Diseases of the somatic nervous system include myasthenia gravis, myasthenia syndrome and muscle spasticity.
- Myasthenia gravis is an autoimmune disease of the skeletal neuromuscular junction (NMJ) that may be treated with either anticholinesterases or immunosuppressants.
- Muscle spasticity results from increased activity in skeletal muscles (hypertonia) and may be treated with muscle relaxants, benzodiazepines and α_2-adrenoceptor agonists.
- Acute and chronic pain is detected by nociceptors, which may be stimulated by mechanical or chemical stimuli.
- The peripheral control of pain may be attained by the use of non-steroidal anti-inflammatory drugs.
- Diseases of the autonomic nervous system include familial dysautonomia, Shy–Drager syndrome and Horner's syndrome.
- Familial dysautonomia may be treated with cholinomimetics, sympathomimetics, phenothiazines and antibacterial drugs.
- Shy–Drager syndrome may be treated with steroids and adrenergic agonists.
- Horner's syndrome is treated with sympathomimetic drugs.

5

Drugs Affecting the Central Nervous System

INTRODUCTION

The mammalian CNS comprises the vast number of nerve cells and neurones that make up the brain and the spinal cord. It receives information from the peripheral tissues via the afferent branch of the peripheral nervous system and, following processing within the CNS, sends messages out to the peripheral tissues via the efferent branches of the peripheral nervous system. Thus, the CNS acts as the major integrative and interpretive centre for neuronal impulse processing in the body.

Structure of the central nervous system

Anatomically, the CNS comprises the brain and the spinal cord. The spinal cord consists of large numbers of neuronal tracts, which either pass information up into the brain (ascending tracts) or pass information down from the brain to the periphery (descending tracts). The tracts are interconnected, at numerous levels, by short interneurones, which allow for both integration and control of sensory input at the spinal level.

At the top of the spinal cord is the *medulla oblongata*, which is the first structural area of the brain stem. The area between the medulla oblongata and the *midbrain* is called the *pons*. The pons contains the areas that control respiration and the cardiovascular system and acts as a relay station between the higher centres of the brain and the PNS.

The *cerebellum*, which lies immediately behind the pons, has connections with both the ascending and descending tracts of the spinal cord. Although its function is not fully understood, it is thought that the cerebellum exerts fine control over motor coordination and integrates sensory input to allow for the performance of complex tasks. The midbrain (mesencephalon), lying immediately above the pons, is the most primitive part of the brain. It contains two large bundles of nerve fibres, termed the *cerebral peduncles*, which carry fibres to and from the *thalamus* and the *cerebral hemispheres*.

The central core of the *cerebrum* (diencephalon) contains four distinct anatomical and functional units:

(1) The *hypothalamus* regulates the autonomic nervous system, the secretion of endocrine hormones and the control of hunger, thirst and fatigue.
(2) The *subthalamus* has connections to the basal ganglia and the substantia nigra and is involved in motor function.
(3) The *epithalamus* integrates the sensory input from olfactory and somatic afferent fibres. The pineal gland, which is part of this area, is thought to control day–night function (circadian rhythm).
(4) The *thalamus*, the largest part of the diencephalon, is an integration centre for information carried in ascending fibres before they are passed to the cerebral hemispheres for processing.

The *basal ganglia* are areas of grey matter that have both afferent and efferent connections with the cerebral cortex, thalamus and brain stem. They are thought to exert an influence on the cerebral hemispheres to control motor function.

The *cerebral hemispheres* (telencephalon) are the largest and most complex parts of the brain.

They are thought to be responsible for the control of consciousness, complex thought and the ability to learn. The cerebral hemispheres may be divided into:

(1) the *frontal* lobe, which appears to control speech, formation of personality, higher reasoning and intellectual capacity
(2) the *occipital* lobe, which is associated with the processing of visual input
(3) the *temporal* lobe, associated with memory and hearing
(4) the *parietal* lobe, which controls motor function and sensory function.

The structure of the CNS is summarised in Fig. 5.1.

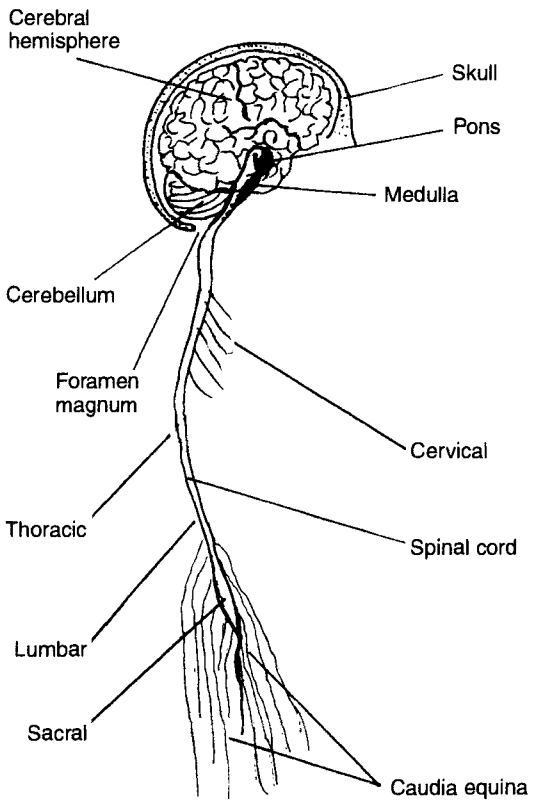

Fig. 5.1 The anatomical structure of the central nervous system.

Neurotransmitters in the central nervous system

A large number of neurotransmitters have been identified in the CNS. The actions of these neurotransmitters are summarised below:

(1) *Glutamate* is an amino acid and is the major excitatory neurotransmitter. It acts on NMDA (*N*-methyl-D-aspartate) and non-NMDA receptors and is found in the thalamus, the pyramidal cells and the hippocampus. Some drugs produce psychoses by acting on the NMDA receptor and so it is thought that disorders of glutamate transmission may be the cause of psychotic illness.
(2) *GABA* is an amino acid (γ-aminobutyric acid) and is the major inhibitory neurotransmitter. It acts on $GABA_A$ and $GABA_B$ receptors. $GABA_A$ receptors are LGICs and are found on 40–50% of neurones, $GABA_B$ receptors are G-protein-coupled receptors. Most anti-anxiety drugs act on $GABA_A$ receptors.
(3) *Glycine* must be present for glutamate to have an effect on its receptor; it also acts on a glycine receptor, which is an LGIC.
(4) *Acetylcholine* acts on both nAChRs and mAChRs. It is thought to be associated with the control of motor function, awareness and memory.
(5) *5-Hydroxytryptamine* is widely distributed, and is associated with control of mood and depressive illness.
(6) *Norepinephrine* is widely distributed, and is associated with control of mood and vasomotor control.
(7) *Dopamine* plays a role in motor coordination, prolactin release and psychotic illness.
(8) *Peptides.* A large number of peptides (> 250) are thought to play a neurotransmitter role in the CNS. These include endorphins, enkaphelins and dynorphins, which control stress and mood; vasopressin and oxytocin, which control mood; substance P and neurokinin, which are important in affective disorders; and cholecystokinin and neurotensin, which may be important in schizophrenia.

Most drugs that affect the CNS do so by altering the processes of neurotransmission responsible for the interactions between the millions of nerve cells that make up the brain. Some act presynaptically to alter the synthesis, storage or release of neurotransmitters, and some act postsynaptically, to either activate receptors or inhibit the actions of natural agonists at receptors located on other nerve cell bodies.

The basic functions of neurones in the CNS are similar to those in the PNS in that neurotransmitter molecules are released from presynaptic nerve endings and interact with postsynaptic receptors on nerve cell bodies, to either promote or inhibit firing of the neurone. However, in the CNS, the interconnections between the neurones are much more complex and there are powerful networks of inhibitory neurones which act constantly to control the rate of neurotransmitter release.

Many of the receptors found in the CNS are coupled to ion channels, and the activation of these receptors results in the opening of an ion channel and the passage of ions across the cell membrane of the nerve cell body. The effect of this action is dependent on the type of ion that is transported, but may be recorded electrically as a postsynaptic potential.

If the opening of the ion channel results in the influx of Na^+ ions then the cell membrane will become depolarised and the chances of the nerve cell body discharging to produce an action potential will be increased. Such an event will give rise to an excitatory postsynaptic potential (EPSP). On the other hand, if the ion channel carries Cl^- ions, then the cell membrane will become hyperpolarised and the chances of the nerve cell depolarising will be decreased. Such an event will give rise to an inhibitory postsynaptic potential (IPSP).

Drug interventions in the CNS fall into two main categories:

- drugs that are used to alter normal CNS function for therapeutic purposes
- drugs that are used to treat diseases associated with functional abnormalities of the CNS.

ALTERATION OF NORMAL CNS FUNCTION

The CNS functions normally to coordinate and control the multitude of bodily functions and to ensure that the internal environment is maintained in a suitable state for health. However, in a number of situations, it may be deemed necessary to alter the normal functioning of the CNS either to produce a hyperexcited state or, more commonly, to depress CNS function. Typical situations are:

- CNS stimulation
- anaesthesia
- control of pain.

CNS stimulation

Drugs that stimulate the CNS have been used for centuries in attempts to increase human performance, or to alter perception of the environment. Some drugs, such as caffeine, are normal constituents of food and drink, while others, such as cocaine, have been used to increase endurance. The therapeutic use of CNS stimulant drugs is now limited to the treatment of narcolepsy.

Drugs used to stimulate the CNS

Psychomotor stimulants:	theophylline, caffeine, nicotine, cocaine, methylphenidate, modafinil, dexamphetamine
Hallucinogens:	lysergic acid diethylamide (LSD), phencyclidine

Psychomotor stimulants

CNS stimulant drugs can be divided into two categories, namely psychomotor stimulants, which cause excitement, euphoria, decreased fatigue and increased motor activity, and hallucinogens, which produce profound changes in perception and mood.

Theophylline and caffeine, which are found in tea and coffee respectively, both act by increasing the levels of intracellular cAMP and cGMP. Patients ingesting large quantities of these drugs experience a loss of fatigue and increased mental alertness, increased heart rate and urine loss. Even moderate doses can cause insomnia, anxiety and agitation in some patients.

Nicotine, the active ingredient in tobacco, causes stimulation of ganglia at low doses, followed by blockade of ganglionic transmission at larger doses. Similar effects are seen at nicotine receptors in the CNS. Nicotine is a powerful CNS stimulant producing euphoria, arousal, improved attention and reaction times. However, higher doses can produce respiratory paralysis and hypotension. The peripheral effects of nicotine are complex. Stimulation of sympathetic ganglia increases blood pressure and heart rate, whereas stimulation of parasympathetic ganglia can produce bradycardia and diarrhoea. Ganglionic blockade produced by high doses of nicotine causes severe hypotension and paralysis in gastrointestinal and bladder smooth muscle.

Cocaine acts by blocking the reuptake of norepinephrine, 5-HT and dopamine (by uptake 1) into presynaptic nerve endings in the CNS. This action produces a powerful stimulation of the CNS, increasing mental awareness, euphoria, delusions and paranoia. Peripherally, the prolonged effect of amine transmitters caused by the blockade of their reuptake results in tachycardia, hypertension, dilation of the pupils and peripheral vasoconstriction. Cocaine is addictive.

The clinical effects of dexamphetamine are similar to those of cocaine; however, the mechanism by which the increase in amine levels is produced is different. Dexamphetamine promotes the release of norepinephrine and dopamine from their storage granules in the presynaptic nerve endings, resulting in increased levels of these transmitters in the synapses of the CNS. Dexamphetamine causes stimulation of the whole cortex, brain stem and medulla resulting in increased alertness, decreased appetite and insomnia. Adverse effects include insomnia, restlessness, dizziness, weakness, night terror episodes, tremor, dependence, anorexia, hyperactivity, cardiac arrhythmias, angina, convulsions and circulatory collapse. The use of dexamphetamine is contraindicated in patients suffering hypertension, cardiovascular disease, hyperthyroidism, agitation, glaucoma and in pregnancy.

Methylphenidate is used as part of a programme to treat the hyperactivity in children who suffer from attention-deficit hyperactivity disorder (ADHD). Adverse effects are similar to those described for dexamphetamine.

Modafinil may be used for the treatment of narcolepsy. It should only be used for short periods as dependence develops rapidly at therapeutic doses. Adverse effects include insomnia, anorexia, abdominal pain, euphoria, nervousness, personality disorders, palpitations, dry mouth, hypertension, nausea, gastrointestinal discomfort and tachycardia. Its use is contraindicated in pregnancy and in breastfeeding mothers.

Hallucinogens

LSD affects many sites within the CNS. It is an agonist at presynaptic 5-HT receptors in the midbrain causing hypertension, pupillary dilation and increased body temperature. Low doses of LSD produce bizarre hallucinations and severe mood changes. Higher doses can produce severe psychotic changes that are difficult to reverse.

Phencyclidine inhibits amine reuptake in the CNS. Adverse effects include numbness of extremities, staggered gait, slurred speech and muscular rigidity. Phencyclidine is an analogue of the anaesthetic ketamine.

Anaesthesia

General anaesthesia

Anaesthesia is a state in which there is an absence of the sensation of pain. General anaesthesia is a state of unconsciousness with an absence of the sensation of pain over the whole of the body, whereas local anaesthesia is a state in which there is an absence of the sensation of pain in a particular part of the body. Thus anaesthetic drugs may be divided into two major groups, *general* anaesthetics and *local* anaesthetics.

The depth of anaesthesia produced by general anaesthetics can be divided into four stages characterised by the degree of CNS depression. The four stages of anaesthesia are:

- Stage 1 – *analgesia*: the patient loses the sensation of pain, but remains conscious.
- Stage 2 – *excitement*: the patient becomes delirious and violent; there is an increase in blood pressure and respiratory rate. This stage can be avoided by using a rapidly acting intravenous anaesthetic, such as thiopentone, to induce the anaesthesia.
- Stage 3 – *surgical anaesthesia*: respiration is regular and skeletal muscle is relaxed; eye movement ceases and pupils become fixed. Surgery may be performed at this level.
- Stage 4 – *medullary paralysis*: there is severe depression of respiration and medullary function; death can occur rapidly.

The time-course of anaesthesia may also be divided into three different stages. These are:

- *Induction* is defined as the time from the initial administration of the anaesthetic to the attainment of stage 3 anaesthesia. This depends on the speed with which the anaesthetic drug enters the CNS. For gaseous anaesthetics this will be determined by the solubility of the gas, which determines how fast it crosses the alveolar membrane of the lungs to enter the blood. For intravenous anaesthetics it will depend on the lipid solubility of the drug.
- *Maintenance* is defined as the time during which the patient remains at the stage 3 level of anaesthesia. Gaseous anaesthetics are usually used for the maintenance of anaesthesia as they give good, flexible control of the patient.
- *Recovery* is the opposite of induction and is defined as the time it takes for the patient to recover consciousness after the cessation of administration of the anaesthetic drug. Typically, drugs that have a rapid rate of induction also have a short recovery period.

Drugs used to induce general anaesthesia

Inhalation general anaesthetics:	halothane, enflurane, nitrous oxide, ether
Intravenous general anaesthetics:	thiopentone, propofol, ketamine

The mechanism by which general anaesthetics produce their effect is not clear. They are all capable of decreasing the permeability of cell membranes to Na^+ ions, probably by altering the physical state of the membrane, which prevents opening of the Na^+ ion channels.

The inhalation general anaesthetics are the drugs most commonly used for the maintenance of anaesthesia. They have the advantage that changing the concentration of the gas in the patient's air supply can alter the level of anaesthesia. Halothane is the most potent of the gaseous anaesthetics, but has been reported to cause liver damage. Isoflurane is less potent than halothane, but does not induce cardiac arrhythmias.

The most commonly used intravenous anaesthetic is thiopentone. It is a barbiturate with a very short duration of action. Following i.v. administration it rapidly enters the CNS producing anaesthesia within 5–6 seconds. Conversely, thiopentone is rapidly distributed out of the CNS into skeletal muscle and fat. Thus the duration of anaesthesia is extremely short. Propofol has a similar action.

Ketamine is a short-acting non-barbiturate anaesthetic that induces a state of dissociation in which the patient appears to be awake but is unconscious and does not feel any pain. It can produce postoperative hallucinations.

Local anaesthetics

Local anaesthetics are applied peripherally to inhibit conduction of sensory impulses from the extremities into the CNS. They produce a loss of the sensation of pain in a limited area of the body without the loss of consciousness seen with general anaesthetics.

Drugs used to induce local anaesthesia

Local anaesthetics:	procaine, lidocaine, bupivacaine

The pharmacology of these drugs is discussed in Chapter 15.

Central control of pain

Opioid agonists and antagonists

Strong opioid agonists:	morphine, heroin, methadone, fentanyl
Moderate opioid agonists:	codeine, dextropropoxyphene, dihydrocodeine
Mixed agonist/ antagonists:	buprenorphine, pentazocine
Opioid antagonists:	naloxone, naltrexone

Opioid agonists

The opioid analgesics are a group of naturally occurring and synthetic compounds that produce a morphine-like analgesia, characterised by a feeling of dissociation from the pain. Their primary use is in the treatment of the intense pain resulting from surgery or disease. All drugs in this group produce their clinical effects by an action on a group of opioid receptors found in the CNS. These agonists act on these receptors to mimic the actions of a group of naturally occurring peptide neurotransmitters called endorphins and enkephalins. Unfortunately, it is not possible to separate the analgesic actions of the opioids from their euphoric effects and this has led to their widespread abuse.

Opioid drugs act on four different types of receptor, termed the δ-, μ-, κ- and σ-receptors, all of which are G-protein-coupled receptors. In the CNS, opioid receptors are found in five main areas:

- brain stem, where they are involved in the control of respiration, cough, nausea, blood pressure and pupillary diameter
- medial thalamus, where they are involved in the perception of deep pain
- spinal cord: receptors in the substantia gelatinosa of the spinal cord are associated with the receipt of incoming sensory perceptions of pain
- hypothalamus: control of endocrine secretion
- limbic system: probably associated with emotional behaviour rather than pain.

The analgesic property of the opioid analgesics is primarily due to their action upon the μ-receptors in the CNS, although κ-receptors also contribute to this effect. Binding of opioids to the σ-receptors is probably responsible for the hallucinogenic effects of these compounds.

Strong opioid agonists, such as morphine and methadone, interact primarily with μ-receptors, but will also bind to κ-receptors in the CNS and δ-receptors in the periphery. They produce strong analgesia, euphoria, respiratory depression and inhibition of the cough reflex as a result of their actions in the CNS, and also inhibit gastrointestinal motility by virtue of an action on peripheral receptors. Adverse effects include nausea, vomiting, constipation, drowsiness, respiratory depression, dry mouth sweating, difficulty of micturition, facial flushing, bradycardia, tachycardia, euphoria, postural hypotension, mood changes and dependence.

Moderate agonists, such as dextropopoxyphene, dihydrocodeine and codeine, are less potent than morphine and produce less euphoria than the strong agonists. The adverse effects are similar to those produced by morphine, but they are less pronounced.

The mixed agonist/antagonist drugs, such as pentazocine and buprenorphine, have actions that depend on the patient's previous exposure to opioid drugs. In patients who have not received opioid agonists, they show agonist activity and produce significant levels of analgesia. However, in patients who have been recently exposed to the more powerful agonists, they act as antagonists and produce withdrawal symptoms. Adverse effects are similar to those produced by morphine.

The opioid antagonists, naloxone and naltrexone, are strong antagonists at opioid receptors. In patients not previously exposed to opioid drugs, they are virtually without effect. However, in patients who have been exposed to the opioid agonists, they produce very strong symptoms of withdrawal. This latter action makes them extremely useful in reversing the effects of an overdose of a strong opioid agonist such as heroin.

DISEASES OF THE CENTRAL NERVOUS SYSTEM

Diseases of the CNS give rise to a wide variety of clinical symptoms, ranging from mild anxiety states to chronic psychotic disorders (schizophrenia) and movement disorders such as Parkinson's disease. The major diseases of the CNS are:

- anxiety
- depression
- psychotic disorders
- Parkinson's disease
- epilepsy.

Anxiety

Anxiety is an extremely unpleasant state of tension and apprehension, characterised by fears that arise from an unidentifiable source. The symptoms of anxiety are similar to those of fear, namely tachycardia, sweating and tremor, and may range in severity from the mild 'butterflies in the stomach' syndrome to a debilitating form, in which the patient is unable to function normally. Anxiety is a common symptom in a number of mental illnesses and is predominant in phobias, panic attacks and some compulsive disorders.

The treatment of anxiety depends upon its severity. Brief episodes of mild anxiety are often self-limiting and do not require treatment. However, the symptoms of prolonged, debilitating anxiety are usually treated by one of a range of anxiolytic/hypnotic drugs, most of which have considerable sedating action as well.

Drugs used in the treatment of anxiety

Norepinephrine/5-HT reuptake inhibitors:	venlafaxine
MAO inhibitors:	phenelzine, tranylcypromine, moclobemide
Mood stabilisers:	lithium, carbamazepine, sodium valproate
β-adrenoceptor antagonists:	propranolol, oxprenolol
Azapirones:	buspirone

Anxiolytic benzodiazepines

The most common drugs used for the treatment of anxiety are the benzodiazepines, such as diazepam and chlordiazepoxide. These act on the $GABA_A$ receptor in the CNS to increase hyperpolarisation of cell membranes. The binding of GABA to its receptor on the cell membrane causes the opening of a Cl^- ion channel that leads to an increased influx of Cl^- ions. Anxiolytic benzodiazepines bind to a site close to the GABA binding site on the receptor and increase the affinity of the GABA binding site for its agonist.

The action of benzodiazepines on the GABA receptor is shown in Fig. 5.2.

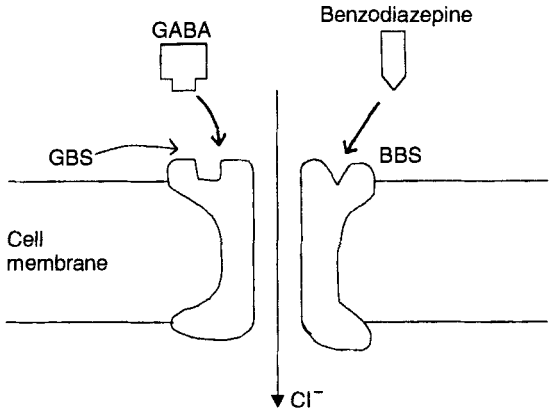

Fig. 5.2 The mechanism of action of benzodiazepines at the $GABA_A$ receptor in the central nervous system. Note the GABA binding site (GBS) and the benzodiazeine binding site (BBS).

Hypnotic benzodiazepines

Hypnotic benzodiazepines, such as nitrazepam and temazepam, are used to induce sleep and they are beneficial for the short-term treatment of insomnia, especially that resulting from anxiety states.

The clinical effects of the benzodiazepines is dependent on their action on the $GABA_A$ receptor, variations in clinical effect being derived

from differences in the amount of binding and metabolism of the various examples. At low doses, all benzodiazepines are anxiolytic and most are sedative at higher doses and many have a hypnotic action. Adverse effects of benzodiazepines include drowsiness, lightheadedness, confusion, ataxia, amnesia and dependence. Their use is contraindicated in patients suffering from respiratory depression, hepatic impairment, myasthenia gravis and sleep apnoea syndrome.

β-Adrenoceptor antagonists

β-Adrenoceptor antagonists, such as propranolol and oxprenolol, are of considerable use in the treatment of anxiety states, either used alone or in combination with an antidepressant drug. They do not affect the psychological symptoms of anxiety (worry and tension), but are of benefit in the control of the autonomic symptoms, such as tachycardia and tremor. They are of most benefit in patients whose symptoms are predominantly autonomic, rather than psychological. The adverse effects associated with these drugs include bradycardia, hypotension, cold fingers and toes (peripheral vasoconstriction), fatigue, sleep disturbances and a worsening of any existing psoriasis. They are contraindicated in asthmatic patients due to their tendency to cause bronchoconstriction.

Azapirones

Buspirone is a new drug that acts as a partial agonist on inhibitory 5-HT_{1A} receptors in the brain, and so decreases the rate of firing of 5-HT neurones, leading to an alleviation of the symptoms of anxiety. It does not have any action on the $GABA_A$ receptor and so does not cause sedation or dependence. Typically, the beneficial effect of buspirone may take several weeks to develop. Adverse effects of buspirone include nausea, dizziness, headache, excitement, tachycardia, confusion and dry mouth. It is contraindicated in epilepsy and pregnancy.

Affective disorders

Affective disorders are disease states in which the patient suffers changes in mood. There are two major types of affective disorder:

(1) depression
(2) bipolar disorder.

Depression

Depression is a major alteration of mood, which affects energy, sleep patterns, appetite, libido and general functional ability. The symptoms of depression are manifold, but are characterised by feelings of sadness, hopelessness, despair and an inability to derive enjoyment from normal activities. Many patients also report changes in sleep patterns, either finding difficulty in getting to sleep, or waking up early in the morning, decreased appetite and weight loss, loss of libido and poor concentration.

The exact causes of depression are difficult to identify. Two types of depression have been identified:

(1) Reactive depression may be defined as depression that results from an identifiable change in the environment, such as stress, redundancy or loss of a loved one.
(2) Endogenous depression is defined as depression that occurs without a clearly identifiable external cause.

The underlying neurological changes that occur in the brain of a patient suffering from depression have not been fully elucidated. There is some evidence that depression may have a genetic component, although this evidence is not as strong as that for schizophrenia. A large number of studies have shown that there are changes in the levels of some neurotransmitters in the brains of depressed patients and this has led to the suggestion that, in part, depression may result from changes in neurotransmitter activity in the hypothalamus and pituitary gland.

Monoamine theory of depression

The major biochemical changes in the CNS associated with depression are a decrease in the levels of the neurotransmitters norepinephrine, 5-HT and dopamine, all three of which are important neurotransmitters at many areas of the CNS. This correlation between mood and the levels of amine transmitters in the CNS has led to the

development of the monoamine theory of depression, which suggests that the changes in mood associated with depression are the result of a decrease in the levels of these neurotransmitters. Indeed, the vast majority of antidepressant drugs appear to act by increasing the availability of, particularly, norepinephrine and 5-HT in the CNS. Conversely, drugs that decrease the availability of these transmitters often produce depression as an adverse effect.

The involvement of dopaminergic pathways in the aetiology of depression is supported by the observation that a reduction in dopamine levels in the CNS can also give rise to the development of depression in susceptible patients. Other neurotransmitters in the brain, such as GABA, vasopressin and the opioid peptides, may also play a role.

Bipolar disorder

Bipolar disorder, sometimes called manic depression, is a form of depressive illness characterised by violent mood swings between depression and mania. The symptoms of the depressive phase are similar to those described above; the manic phase is characterised by hyperenthusiasm, rapid thought and speech, extreme self-confidence and impaired judgement.

Drugs used in the treatment of affective disorders

Tricyclic antidepressants:	amitriptyline, clomipramine, dothiepin, nortriptyline, imipramine, lofepramine, trimipramine, protriptyline
TCA-related antidepressants:	maprotiline, mianserin, trazodone
5-HT reuptake inhibitors:	fluoxetine, paroxetine, fluvoxamine, sertraline, citalopram
Norepinephrine/5-HT reuptake inhibitors:	venlafaxine
MAO inhibitors:	phenelzine, tranylcypromine, moclobemide
Mood stabilisers:	lithium, carbamazepine, sodium valproate

Tricyclic/polycyclic antidepressants

Tricyclic and polycyclic antidepressant drugs, such as amitriptyline and dothiepin, act by inhibiting the reuptake process that terminates the action of norepinephrine, 5-HT and dopamine at synapses in the CNS. The inhibition of this removal mechanism results in an increase in the concentration of the neurotransmitter in the synapse and a reversal of the symptoms of depression. The mechanism of action of these drugs is shown in Fig. 5.3.

The relative potency of these drugs varies markedly, as does their effectiveness in depressed patients. Furthermore many drugs in this group are metabolised to pharmacologically active

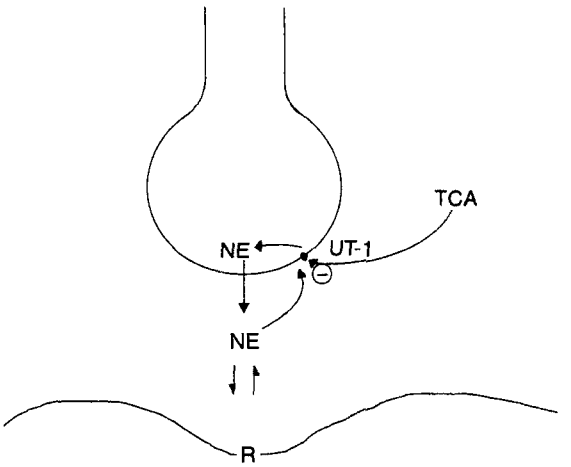

Fig. 5.3 The major site of action of antidepressant drugs. The action of norepinephrine in the synapse is terminated by reuptake back into the nerve ending (UT-1). Inhibition of this uptake process by the antidepressant (TCA) leads to an increase in the levels of NE in the synapse and reversal of the symptoms of depression.

metabolites. For example, amitriptyline is metabolised to nortriptyline in the liver. Therefore their effects are prolonged and they have a high potential for fatal overdose.

These drugs also have an affinity to bind to other receptors and produce a number of other pharmacological actions that can result in the development of unpleasant adverse effects, which may require the cessation of treatment. These adverse effects include blurred vision, dry mouth, constipation and urinary retention (resulting from a blockade of mAChRs), orthostatic hypotension (due to blockade of α_1-adrenoceptors), cardiac arrhythmias (blockade of mAChRs in the heart) and sedation (blockade of histamine H_1 receptors in the CNS). Their use is contraindicated in patients who have established heart disease or epilepsy.

TCA-related antidepressants

Drugs that are related to the tricyclic antidepressants, and which have essentially the same mechanism of action, include mianserin and trazodone. These drugs have a similar mechanism of antidepressant action to that described for the tricyclic drugs; however, they show a lower incidence of the antimuscarinic adverse effects of dry mouth, blurred vision and cardiac toxicity.

Selective 5-HT reuptake inhibitors

The selective 5-HT reuptake inhibitors (SSRIs), such as fluoxetine and paroxetine, are a new group of drugs that selectively inhibit the reuptake of 5-HT, rather than norepinephrine. Consequently they show fewer adverse effects than the tricyclic antidepressants and are almost devoid of anticholinergic and cardiac adverse effects.

Adverse effects include nausea, diarrhoea, insomnia, anxiety, agitation and sexual dysfunction. They are contraindicated in patients who have recently been treated with monoamine oxidase (MAO) inhibitors, and at least two weeks must elapse between stopping treatment with an SSRI and starting treatment with MAO inhibitors (see below).

Norepinephrine/5-HT reuptake inhibitors

The only drug currently available which specifically inhibits the reuptake of norepinephrine and 5-HT is venlafaxine. Its spectrum of activity is similar to that of the tricyclic antidepressants, but it is devoid of the anticholinergic and antihistaminic activity seen with the older drugs. Adverse effects are similar to those produced by SSRIs, but the frequency of their occurrence is lower. Care must also be taken in patients with hypertension as *venlafaxine* causes a rise in systemic blood pressure.

MAO inhibitors (MAOIs)

Monoamine oxidase is a mitochondrial enzyme found in the presynaptic nerve endings of aminergic nerves. It is responsible for the destruction of cytosolic amine transmitters, such as norepinephrine, 5-HT and dopamine, in the nerve endings. MAO exists in two isoforms: MAO-A occurs predominantly in the gut; MAO-B occurs in the presynaptic nerve endings of the CNS. Inhibition of this enzyme will, of course, result in a build-up of the levels of the amine neurotransmitters in the CNS and hence a reversal of the symptoms of depression. The original MAOIs used as antidepressants produce an irreversible inhibition of both MAO-A and MAO-B. Moclobemide is the first member of a new series of MAOIs, which produces a reversible inhibition of MAO-A.

Monoamine oxidase inhibitors, such as phenelzine and tranylcypromine, produce a reversal of the symptoms of depression coincident with a rise in the levels of monoamine neurotransmitters in the CNS. The use of MAOIs as antidepressant drugs is limited by the serious, unpredictable adverse effects seen with these drugs.

The most dangerous, and life-threatening, problem is the severe hypertension that results following the release of norepinephrine from its storage sites in the presynaptic nerve ending. In the absence of MAO activity, due to the MAO inhibitor, there is a decreased ability to terminate the actions of norepinephrine, giving rise to tachycardia, severe hypertension and death due to subarachnoid haemorrhage. Whilst some drugs can cause this release of norepinephrine, the main problem results from the presence of tyramine in foodstuffs.

Tyramine is normally inactivated by MAO-A found in the gastrointestinal tract. Patients who are being treated with a MAOI do not have this

defence mechanism, and so large amounts of tyramine enter the systemic circulation and displace norepinephrine from its binding sites. The resultant headache, tachycardia, cardiac arrhythmias and stroke are often fatal. Therefore it is *essential* that patients receiving MAO inhibitors are counselled against eating foodstuffs containing tyramine. The following foodstuffs have been reported to cause problems with MAOIs:

- mature cheeses
- yeast and protein extracts, such as Marmite, Oxo and Bovril
- beer
- Chianti and some oaked wines
- degraded protein, such as well-hung meat and game
- pickled herrings
- broad bean pods.

Several groups of drugs and medicines also produce a similar reaction if taken at the same time as MAOIs, including:

- opiates
- SSRIs
- sympathomimetics, such as pseudoephedrine and phenylephrine, used in cough and cold remedies
- some antihistamines, such as terfenadine.
- L-dopa.

It should also be noted that sufficient time must be allowed between stopping MAOI treatment and the introduction of other antidepressant drugs in order to avoid this interaction. In particular, a period of 6 weeks must be allowed between the use of an MAOI and an SSRI in order to avoid a life-threatening 'serotonin syndrome' resulting from the release of large amounts of 5-HT.

MAOI drugs also produce other adverse effects including drowsiness, orthostatic hypotension, blurred vision, insomnia, headache, weakness and fatigue, dry mouth, sweating, cardiac arrhythmias, difficulty in micturition and constipation.

Mood stabilisers

Lithium salts, such as lithium carbonate, are mood stabilisers used to treat the symptoms of mania in manic-depressive (bipolar) patients. They are successful in about 70% of patients. It is thought that lithium may produce its action by increasing the levels of the second messenger IP_3 in cells; however, how this increase produces the clinical effect is not clear. Lithium salts are given orally and are excreted through the kidney.

Lithium is extremely toxic and care must be taken to ensure that the plasma lithium concentration does not rise into the toxic level. In particular, it is most important to check both renal function and thyroid function before starting lithium therapy. Once treatment with a low dose of lithium has commenced the plasma lithium concentration should be monitored after 5 days to ensure that it has not risen above 1 mmol/l. Any subsequent increases in dosage require reassessment of the plasma levels of lithium after 5 days. During long-term treatment with lithium, the plasma level of the ion and renal function should be checked every 3 months and thyroid function should be checked every 6 months.

The adverse effects of lithium include thirst, nausea, diarrhoea, fine tremor and polyuria. Signs of lithium toxicity include anorexia, vomiting, coarse tremor, mental confusion, muscle twitching and convulsions. Coma and death eventually follow. A number of drugs interfere with the normal metabolism and excretion of lithium and their concomitant administration can lead to the development of lithium toxicity. These include:

- antipsychotic drugs, such as haloperidol
- NSAIDs (except aspirin)
- diuretics
- cardioactive drugs, such as digoxin and angiotensin-converting enzyme (ACE) inhibitors.

Carbamazepine is almost as affective as lithium in the stabilisation of the mood swings associated with bipolar disorder and in the treatment of acute mania in patients who do not respond to lithium. It is of particular benefit in patients who are switching rapidly between the manic and the depressive phases of bipolar disorder. Carbamazepine is a GABA agonist, which acts to stabilise neuronal cell membranes and to depress

conduction through voltage-gated Na^+ channels and Ca^{2+} channels.

Carbamazepine is an inducer of metabolising enzymes in the liver and so prolonged treatment with this drug may interfere with other drugs, such as tricyclic antidepressants, which are metabolised by this organ. Adverse effects of carbamazepine include nausea and vomiting, confusion, headache, ataxia, anorexia, diarrhoea or constipation, agranulocytosis and rash. Patients should be advised to report any sudden fever or infections, as these may be indicative of blood disorders resulting from the use of carbamazepine.

Sodium valproate, although normally used in the treatment of epilepsy, is effective as a mood stabiliser in bipolar disorder. The mechanism by which sodium valproate exerts its effect in bipolar disorder is not fully understood, but it is thought to increase the turnover of GABA in the brain. Adverse effects include nausea, vomiting, diarrhoea, sedation, ataxia and tremor.

Psychotic disorders

Psychotic disorders are mental states in which the patient appears to lose touch with the reality of the surrounding world. Typically patients may describe changes in their perception of the world, thought processes and ideas. Psychotic disorders are a group of mental illnesses, the most common of which is schizophrenia.

Schizophrenia is a mental disorder characterised by delusions, auditory hallucinations, and disturbances of thought and speech patterns. It usually shows initial symptoms in adolescence and progresses to a chronic, disabling disorder which requires constant monitoring and therapy. There is strong evidence that schizophrenia has a genetic component and probably results from a disturbance in dopamine metabolism in the CNS.

Schizophrenia usually develops in patients between 15 and 45 years of age, although it can develop in some older patients. Epidemiological evidence suggests that schizophrenia is more prevalent among persons living in inner cities and those from lower social classes. However, this is probably due to the fact that schizophrenic patients tend to lose their jobs, and drift down the social ladder, before their illness is diagnosed and they are admitted onto a treatment programme.

Typically, pre-schizophrenic patients may be described as emotionally detached 'loners', who have few friends and who tend to indulge in solitary pursuits and to shun company. Their behaviour is often thought to be 'eccentric' and they are not affected by praise. As the disease develops, patients become more withdrawn and introverted and often drift away from their home, family and friends. This increases their sense of loneliness and they begin to fail in their work.

Eventually, after a period ranging from several weeks to years, the 'florid' (positive) symptoms of schizophrenia appear, including delusions, hallucinations and altered perception. In addition, the patient may display a catatonic state of mind in which thought processes and motor activity are suppressed.

Once chronic schizophrenia has been diagnosed, it may follow one of four courses:

(1) It may regress completely and not recur (pattern A schizophrenia; 10–20% of patients).
(2) It may recur, repeatedly, with a full recovery between episodes (pattern B; 30–35% of patients).
(3) It may recur, repeatedly, without recovery between episodes and the patient's symptoms get worse with each episode (pattern C; 30–35% of patients).
(4) It may pursue a downward course from the outset (pattern D; 10–20% of patients).

Drugs used in the treatment of psychotic disorders

Phenothiazines:	chlorpromazine, methotrimeprazine, promazine, pericyazine, pipothiazine, thioridazine, fluphenazine, prochlorperazine, trifluoperazine
Butyrophenones:	haloperidol, benperidol, droperidol
Diphenylbutylpiperidines:	pimozide

Benzamides:	sulpiride
Thioxanthenes:	flupenthixol, zuclopenthixol
Dibenzodiazepines:	clozapine, olanzapine
Benzisoxazoles:	risperidone

The drugs used to treat psychotic disorders are called *antipsychotics* or *neuroleptic drugs*. They are sometimes called major tranquilisers, although this is not good terminology. Neuroleptic drugs can be divided into four major categories, namely phenothiazines, butyrophenones, thioxanthenes and dibenzoxapines. All drugs in these groups are potent antagonists at dopamine D_1 and D_2 receptors, both in the CNS and in the periphery. However, it is the ability of the drugs to bind to the dopamine D_2 receptor in the mesolimbic system of the brain that correlates most closely with their neuroleptic actions. This observation supports the hypothesis that schizophrenia results from a malfunction of dopaminergic tracts of this area of the CNS. This hypothesis is further supported by the observation that drugs that increase the activity of dopamine in the mesolimbic system, such as L-dopa and amphetamine, reverse the activity of neuroleptic drugs.

Whilst the major site of action of neuroleptic drugs is now thought to be the dopamine D_2 receptor in the mesolimbic system, they are not devoid of actions at other sites in the body, giving rise to a wide range of adverse effects. The adverse effects produced by neuroleptic drugs occur in the majority of patients and may result in the patient failing to continue with the medication, with serious consequences.

The most important groups of adverse effects arising from the use of neuroleptic drugs are the so-called *extrapyramidal effects*. Extrapyramidal effects include abnormal movements of the body and face (dystonia), tremor (parkinsonian symptoms), clenched jaw muscles and open mouth. These occur to different degrees with all neuroleptic drugs, however their incidence may vary from patient to patient.

The majority of neuroleptic drugs act as antagonists at the mAChRs producing blurred vision, dry mouth, sedation constipation and urinary retention. Symptoms of Parkinson's disease, such as muscle restlessness, tardive dyskinesia and changes of gait, result from their actions at dopamine receptors. Blockade of dopamine D_2 receptors in the pituitary gland leads to an increase in prolactin release. Postural hypotension results from a blocking action at α_1-adrenoceptors.

We have seen that the major therapeutic use of neuroleptic drugs is in the treatment of schizophrenia. However, their actions on dopamine D_2 receptors in the chemoreceptor trigger zone of the medulla makes them useful in the treatment of nausea and vomiting, especially that resulting from cancer chemotherapy and radiation therapy.

Phenothiazines

Phenothiazines, such as chlorpromazine, thioridazine and fluphenazine, are dopamine D_2 receptor antagonists. They may be subdivided into three major groups:

- *Group 1* – chlorpromazine and promazine – both have a pronounced sedative effect, some antimuscarinic effects and some extrapyramidal effects.
- *Group 2* – pipothiazine and thioridazine – have a moderate sedative effect, marked antimuscarinic effects and fewer extrapyramidal effects.
- *Group 3* – fluphenazine and trifluoperazine – do not cause excessive sedation and have very few antimuscarinic effects; however, they produce marked extrapyramidal effects.

In addition to the extrapyramidal effects discussed above, the adverse effects of phenothiazines include drowsiness, hypothermia, pallor, nightmares, insomnia, agitation, convulsions, nasal congestion, gynaecomastia and impotence. Their use is contraindicated in patients suffering CNS depression, bone marrow depression and phaeochromocytoma (an epinephrine-secreting tumour).

Butyrophenones

Butyrophenones, such as haloperidol and droperidol, are effective in the treatment of schizophrenia, but produce less sedation than the

phenothiazines. The adverse effects of butyrophenones are essentially similar to those described above for phenothiazines.

Piperidines
Piperidines, such as pimozide, are less sedating than the phenothiazines. Adverse effects are similar to those produced by the phenothiazines, but they have an increased tendency to produce severe cardiac arrhythmias. They are secreted in breast milk and so are contraindicated in breast-feeding mothers.

Benzamides
Sulpiride is a neuroleptic drug that produces little sedation. At low doses it is effective in reversing the apathy and withdrawal symptoms seen in many schizophrenic patients. At high doses, it is more effective in the control of the florid symptoms of schizophrenia. Adverse effects are similar to those described for the phenothiazines.

Thioxanthenes
Thioxanthenes, such as flupenthixol and zuclopenthixol, are particularly effective against the apathy and withdrawal seen in many schizophrenic patients, but they are of little benefit in the control of mania. The adverse effects are, again, similar to those described for the phenothiazines, but they produce less sedation and more extrapyramidal effects. Their use is contraindicated in senile dementia.

Dibenzodiazepines
Dibenzodiazepines, such as clozapine and olanzapine, have a low affinity for the dopamine D_2 receptor, but bind strongly to both D_1 and D_4 receptors. They are used to treat schizophrenic patients who do not respond to treatment with phenothiazines or butyrophenones. Initial treatment must be in hospitalised patients, under close medical supervision, due to the likelihood of severe hypotension and cardiovascular collapse. The use of clozapine is restricted due to the severe adverse effects, which include drowsiness, anxiety, confusion, fatigue, blurred vision, urinary incontinence and hypersalivation. More serious adverse effects include life-threatening neutropenia and agranulocytosis. Their use is contraindicated in cardiac failure or liver failure.

Benzisoxazoles
Benzisoxazoles, such as risperidone, are effective in the treatment of psychoses that show both positive and negative symptoms. It has a high affinity for 5-HT_2 receptors. Adverse effects include extrapyramidal effects, insomnia, agitation, headache, drowsiness, blurred vision, abdominal pain, sexual dysfunction, urinary incontinence, tachycardia and hypertension.

PARKINSON'S DISEASE

Parkinson's disease is a progressive neurological disorder of muscle movement, which is characterised by tremor (particularly in the hands), muscular rigidity, slowness of movement (bradykinesia) and changes in posture and gait. The actual cause of Parkinson's disease is unknown in the majority of patients, but it correlates with a reduction in the activity of inhibitory dopaminergic neurones in the *substantia nigra* and *corpus striatum* – areas of the brain that are associated with the control of movement.

Dopaminergic neurones arising in the substantia nigra fire continuously and make many connections with nerve cell bodies of cholinergic neurones in the corpus striatum. In turn, these neurones act to inhibit nerve cell bodies giving rise to inhibitory GABAergic neurones terminating in the substantia nigra. This circular pathway results in a control of skeletal muscle movement. Destruction of the dopaminergic neurones results in an imbalance of this control system, producing the clinical symptoms of Parkinson's disease.

Voluntary movement is controlled by nerve tracts that pass from the motor cortex down the spinal cord to activate lower motor neurones, which directly control the skeletal muscles via the somatic nervous system. Subsidiary pathways, which feed into these descending tracts from the basal ganglia, smooth out these voluntary movements and allow for fine motor control. Malfunction of these subsidiary pathways gives rise to the symptoms of Parkinson's disease. This control of motor coordination is shown in Fig. 5.4.

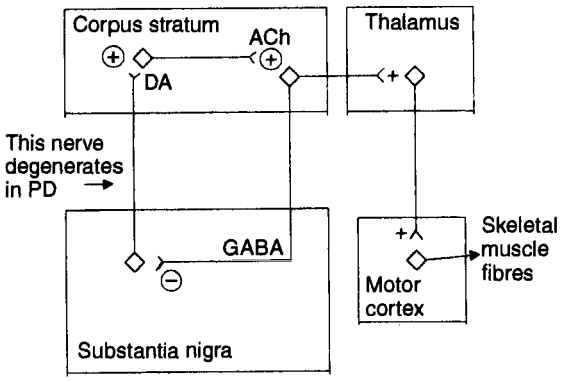

Fig. 5.4 The neural control of motor coordination in the central nervous system. Note how the output from the corpus striatum to the thalamus is modulated by the activity of the feedback system through the substantia nigra, mediated via GABA and dopamine. Degeneration of the nerve tracts from the substantia nigra to the corpus striatum gives rise to the symptoms of Parkinson's disease (PD).

It should be noted that while Parkinson's disease usually results from a decrease in the activity of the dopaminergic pathways in the CNS, drugs which act as dopamine receptor antagonists (such as haloperidol) may well produce Parkinson's-like symptoms as an adverse effect.

Drugs used in the treatment of Parkinson's disease

Dopamine precursors:	L-dopa, L-dopa/carbidopa
Dopamine receptor agonists:	bromocriptine, ropinirole, pergolide, apomorphine
Dopamine-releasing drugs:	amantadine
Antimuscarinic drugs:	benzhexol, orphenadrine, benztropine, procyclidine
MAO-B inhibitors:	selegiline

The drug treatment of Parkinson's disease is not able to reverse the degenerative process resulting in the failure of dopaminergic control of the corpus striatum. It merely offers temporary relief from the symptoms. Therefore treatment is aimed at either increasing the levels of, or the effectiveness of, dopamine in the substantia nigra and/or inhibiting cholinergic activity in the corpus striatum.

Dopamine precursors

The neurotransmitter dopamine is unable to cross the blood–brain barrier. However, its immediate precursor, L-dopa, can enter the brain readily and its administration to early parkinsonian patients restores the levels of dopamine in the substantia nigra to near normal, thus relieving the symptoms of the disease. It is more effective in relieving the bradykinesia and rigidity of Parkinson's disease rather than the tremor.

Unfortunately the effectiveness of L-dopa depends on the availability of functional dopaminergic neurones to convert it into dopamine by the action of the enzyme dopa decarboxylase in the nerve endings. Therefore, as the disease progresses, the number of dopaminergic neurones becomes so reduced that not enough L-dopa can be converted into dopamine to relieve the symptoms. In this situation the patient experiences inconsistent control of motor function and complains that the effect of the drug 'wears off'. They may experience sudden 'switching-on' and 'switching-off' of the effect of the drug, and experience sudden changes in their motor control.

Another problem with the use of L-dopa is that it is effectively metabolised by the enzyme dopa decarboxylase, located in the gastrointestinal tract. This results in not only a decreased availability of L-dopa to the CNS, but also the release of large amounts of dopamine in the peripheral circulation causing nausea, vomiting, cardiac arrhythmias and hypotension. This problem can be partially overcome by the co-administration of carbidopa, which does not enter the brain but inhibits the peripheral dopa decarboxylase in the gut. The concurrent use of L-dopa and carbidopa thus allows for the use of smaller doses of L-dopa and a decrease in the peripheral adverse effects of the drug.

Adverse effects of treatment with L-dopa, either alone or in combination with carbidopa, include anorexia, nausea and vomiting, postural hypo-

tension, dizziness, tachycardia, development of glaucoma, reddish discoloration of the urine, flushing, sweating, depression and drowsiness. It is contraindicated in patients suffering from glaucoma.

Dopamine receptor agonists

The dopamine released from the dopaminergic neurones terminating in the corpus striatum acts upon dopamine D_2 receptors. Thus administration of dopamine receptor agonists, such as bromocriptine, mimics the effects of dopamine release in the corpus striatum and is of benefit in patients who no longer have the ability to synthesise dopamine themselves. Ropinirole is a new drug which is thought to be more specific for the dopamine D_2 receptor than bromocriptine.

The use of bromocriptine and ropinirole is limited by the adverse effects produced by their actions on other dopaminergic pathways in the brain. These adverse effects include hypotension, hallucinations, mental confusion, nausea and vomiting, constipation, headache, cold fingers and toes (peripheral vasoconstriction), dry mouth and leg cramps. The use of bromocriptine and ropinirole is contraindicated in pregnancy.

Apomorphine is a potent agonist at both dopamine D_1 and D_2 receptors in the CNS. It is effective in the treatment of the swings in motor control, the 'off' episodes that occur in patients who are inadequately controlled by L-dopa. Apomorphine is normally given by s.c. injection or infusion and the dose must be carefully tailored to the patient's response. Adverse effects include dyskinesia, postural instability, slurred speech, confusion and hallucinations. Its use is contraindicated in respiratory or CNS depression.

Dopamine-releasing drugs

The antiviral drug amantadine has been shown to have anti-Parkinson effects in some patients. It acts by increasing the rate of synthesis and release of dopamine in the dopaminergic neurones, thus restoring the balance of dopaminergic activity in the CNS. It is only effective in patients who are still able to synthesise dopamine in the dopaminergic pathways of the brain. Amantadine is more effective against the rigidity and bradykinesia of Parkinson's disease and has little effect on the tremor. Adverse effects include anorexia, nausea, dry mouth, orthostatic hypotension, urinary retention, hallucinations, feelings of detachment, restlessness and agitation. Its use is contraindicated in epilepsy and if the patient has a history of gastric ulceration.

Antimuscarinic drugs

Antimuscarinic drugs, such as benztropine and orphenadrine, are much less effective than L-dopa in relieving the symptoms of Parkinson's disease. However, they play an important role as adjunct therapy to L-dopa, as they serve to restore the balance between dopaminergic and cholinergic activity in the CNS.

Benztropine is usually the drug of choice in most patients, producing its effects by blocking the actions of acetylcholine on mAChRs in the CNS. Adverse effects include blurred vision, dry mouth, constipation, dizziness, urinary retention, tachycardia and an increase in intraocular pressure. Antimuscarinic drugs are contraindicated in patients suffering from glaucoma, urinary retention or gastrointestinal obstruction.

MAO-B inhibitors

The enzyme monoamine oxidase (MAO) exists as two isoenzymes, MAO-A and MAO-B. MAO-B selectively metabolises dopamine, so that inhibition of this isoenzyme would be expected to relieve the symptoms of Parkinson's disease with fewer adverse effects than with drugs that inhibit both MAO-A and MAO-B.

Selegiline is a specific inhibitor of MAO-B and causes a rise in dopamine levels in the CNS of parkinsonian patients. It is sometimes used alone in the early stages of the disease, but can also be used as an adjunct to treatment with L-dopa in the later stages. Due to its selective action on MAO-B, selegiline has less effect on systemic blood pressure than other MAO inhibitors. Adverse effects include nausea and vomiting, hypotension, confusion, agitation, dry mouth, sleep disturbances and difficulty in micturition. Selegiline should be used with care in patients who have cardiac arrhythmias, uncontrolled hypertension or peptic ulceration.

EPILEPSY

Epilepsy, in its many forms, affects about 1% of the total population in the UK. It is not a single disease but a family of diseases characterised by sudden, uncontrollable and disorderly electrical discharges in neurones of the cerebral cortex. These electrical discharges result in a range of clinical consequences, dependent on the area of the brain affected. For example, if the discharge is in the motor cortex, then the patient will experience the uncontrollable muscular convulsions typical of an 'epileptic fit'. If other areas of the cerebral cortex are affected then the patient may experience visual, auditory or olfactory hallucinations.

The processes leading to the development of epilepsy are complex, but the neuronal discharges that occur usually result from the uncontrolled firing of a small area of the brain called the *primary focus*. This area of brain tissue may appear anatomically normal. In most cases there is no obvious, identifiable cause for this primary focus to develop. However, in some cases it may result from damage to the brain, such as hypoxia or physical trauma resulting from head injuries in an accident.

Primary epilepsy is diagnosed when there is no identifiable anatomical cause for the epileptic discharge. *Secondary* epilepsy occurs when the discharge is the result of an identifiable cause, such as physical injury, hypoglycaemia or meningeal infections.

The seizures that occur in epilepsy may be classified into two main groups, termed *partial* seizures and *general* seizures. Drug treatment of epilepsy depends upon the type of seizure diagnosed.

In partial epileptic seizures, the clinical consequences depend upon the area of the brain affected and the extent to which the electrical activity spreads across the brain.

- Simple partial seizures are confined to a specific location in the brain; the patient does not lose consciousness and the effect is seen only in a specific limb or muscle group.
- Complex partial seizures produce hallucinations, mental distortion and loss of consciousness; stimulation of motor areas may produce complex chewing movements of the mouth, diarrhoea and urinary incontinence.

Generalised seizures arise from a localised focus but then spread rapidly, producing electrical discharges in both hemispheres of the brain. These seizures may be convulsive or non-convulsive, but the patient suffers an immediate loss of consciousness and often has little recollection of the event when consciousness is restored. Again, there are several different forms of generalised seizure:

- Tonic-clonic (grand mal) seizures are the most common form of epilepsy and are responsible for the classical 'epileptic fit'. Seizures result in a loss of consciousness, severe jerking movements of all skeletal muscles and often excessive salivation. On cessation of the seizure, the patient is confused, disorientated and completely exhausted.
- Absence (petit mal) seizures produce a brief, self-limiting loss of consciousness. Typically these seizures occur in young patients and the patient shows rapid eye blinking which lasts about 5 seconds.
- Myoclonic seizures consist of short periods of muscle contraction (twitches) which last for several minutes. This type of seizure is rare, but often results from physical damage to the brain.
- Febrile seizures occur in children under 5 years of age and can occur in illnesses accompanied by a high temperature. They consist of short-duration tonic-clonic seizures but are benign and self-limiting on control of body temperature.
- Status epilepticus is a life-threatening form of epilepsy in which the patient suffers repeated tonic-clonic seizures without any intervening period of calm. It requires immediate medical attention.

Drugs used in the treatment of epilepsy

phenytoin, carbamazepine, phenobarbitone, primidone, sodium valproate, ethosuximide, gabapentin, lamotrigine, vigabatrin, benzodiazepines

We have seen that all types of epilepsy arise as a result of an increase in the excitability of nerve cell membranes in the CNS, giving rise to uncontrolled electrical discharges across the brain. It follows, therefore, that treatment of epilepsy is centred on depressing the excitability of nerve cell membranes that will either inhibit the development of an epileptic focus, or prevent its spreading to adjacent areas of the brain. Careful adjustment of dosage must be undertaken to ensure that the level of drug in the plasma is sufficient to prevent development of breakthrough seizures.

The initial treatment to control the development of the seizures depends on the specific type of seizure occurring. A number of antiepileptic drugs may be equally effective and the choice of drug used depends upon the response of the individual patient.

A list of preferred and alternative drugs used for each type of seizure is shown in Table 5.1.

Phenytoin

Phenytoin is usually the drug of choice for initial treatment, especially in adults. It is particularly effective in the control of tonic-clonic seizures and partial seizures, but may make absence seizures worse. It stabilises the neuronal cell membranes by inhibiting the influx of Na^+ ions, both in the resting state and during depolarisation. A secondary effect of phenytoin is inhibition of the influx of Ca^{2+} during depolarisation and thus it prevents repetitive firing of the neurones and the propagation of abnormal electrical impulses.

Phenytoin is not a generalised CNS depressant drug, however some depression does occur in the cerebellum and vestibular system producing nystagmus and ataxia. Nausea and vomiting are common adverse effects in patients who take this drug and the gums can grow over the teeth, especially in children. The inhibition of vitamin B_{12} metabolism by phenytoin may lead to the development of megaloblastic anaemia. Confusion, hallucinations and drowsiness are common CNS adverse effects. Inhibition of antidiuretic hormone (ADH) release, hyperglycaemia and decreased insulin secretion have also been reported.

Phenytoin is metabolised by the microsomal hydroxylation system in the liver. At low doses, the half-life is approximately 24 hours; however, at higher doses saturation of the hydroxylation enzyme system leads to an increase in the apparent half-life of the drug. Thus small increases in dosage produce disproportionate increases in plasma levels of the drug, with associated toxicity.

Phenytoin is notorious for producing interactions with other drugs. Repeated administration of phenytoin induces the cytochrome P-450 drug-metabolising system in the liver. The consequence of this is an increase in the metabolism of a large range of drugs including other antiepileptics, anticoagulants, oral contraceptives, some antibiotics and many others. Conversely, inhibition of the metabolism of phenytoin may be brought about by drugs such as cimetidine and so repeated use of these drugs leads to an increase in the plasma levels of phenytoin.

Carbamazepine

Carbamazepine, as with phenytoin, inhibits the propagation of electrical impulses in the CNS by blocking Na^+ channels on nerve cell membranes. It is extremely effective in controlling all types of partial seizure as well as tonic-clonic convulsions. Adverse effects include nausea and vomiting, drowsiness, headache, respiratory depression, visual disturbances, ataxia, cardiac arrhythmias

Table 5.1 Drugs used in the treatment of epilepsy.

Type of seizure	Preferred drugs	Alternative drugs
Generalised tonic-clonic seizures (partial) and generalised)	Phenytoin, carbamazepine	Phenobarbitone, primidone, sodium valproate
Absence seizures	Ethosuximide, sodium valproate	Clonazepam
Myoclonic seizures	Sodium valproate	Primidone

and constipation. The use of carbamazepine is contraindicated in patients with conduction defects in the heart, or who have a history of bone marrow depression.

Phenobarbitone
The antiepileptic actions of phenobarbitone are probably due to its ability to potentiate the inhibitory actions of GABA at the $GABA_A$ receptor in the CNS. Phenobarbitone binds to a site adjacent to the GABA binding site, increasing the influx of Cl^- ions and hence hyperpolarising the cell membrane.

Phenobarbitone is effective in the control of simple partial seizures and recurrent tonic-clonic seizures, but is less effective in the control of complex partial seizures. It has been used as the drug of choice in the treatment of seizures in children, however its prolonged use may decrease cognitive function. Adverse effects include sedation, ataxia, nystagmus and psychotic reactions on prolonged use. Rebound seizures can occur if the drug is withdrawn rapidly.

Primidone
Primidone is a derivative of phenobarbitone and has a similar mechanism of action. It is metabolised to phenobarbitone and phenylethylmalonamide in the body. Phenobarbitone produces effects as detailed above and phenylethylmalonamide is effective in the control of complex partial seizures. Adverse effects are similar to those described for phenobarbitone.

Sodium valproate
Sodium valproate reduces the propagation of abnormal electrical impulses across the brain, possibly by enhancing the activity of GABA. It is the most effective agent for the control of myoclonic seizures and absence seizures and it reduces the frequency of tonic-clonic seizures. However, its potential hepatotoxicity means that its use must be closely monitored and it is contraindicated in patients who suffer from liver disease.

The adverse effects of sodium valproate include sedation, nausea and vomiting, tremor and ataxia. A rise in marker enzymes in the plasma can occur as a result of liver damage and platelet aggregation may be inhibited, resulting in an increase in bleeding time. Sodium valproate inhibits the metabolism of phenobarbitone.

Ethosuximide
Ethosuximide is the drug of choice in the treatment of absence seizures. It is thought to inhibit Ca^{2+} movement in the thalamus and so prevent the development of absence seizures, which may arise from this area of the brain. The major adverse effects are gastrointestinal upset, drowsiness, lethargy, dizziness, weight loss, hiccup, photophobia, headache, depression and agitation.

Gabapentin
Gabapentin is a GABA analogue, which mimics the actions of GABA in the CNS. Its major use is as an adjunct therapy in patients with partial seizures that are not satisfactorily controlled by other antiepileptic drugs. Adverse effects include drowsiness, fatigue, ataxia, nausea and vomiting, rhinitis, dyspepsia, amnesia and weight gain. Gabapentin should not be withdrawn abruptly as there may be increased epileptiform activity.

Lamotrigine
Lamotrigine is the first of a new group of antiepileptic drugs that inhibit the release of glutamate and aspartate and block Na^+ channels. Consequently it prevents repetitive firing and is of use in the control of complex partial seizures and generalised tonic-clonic seizures. Adverse effects include influenza-like syndrome, malaise, insomnia, headache, irritability and aggression.

Vigabatrin
Vigabatrin is effective in chronic epilepsy, especially in tonic-clonic seizures and partial seizures. It is of particular effect in the treatment of infantile spasms. Adverse effects include drowsiness, confusion, headache, depression, agitation, tremor and possible psychotic episodes.

Benzodiazepines
The antiepileptic actions of benzodiazepines derives from their ability to enhance the inhibitory action of GABA by binding to the benzodiazepine binding site associated with the $GABA_A$ receptor in the brain. Diazepam, administered by i.v. injection, is the drug of choice for the control

of status epilepticus. Clonazepam suppresses the spread of seizures from the focus and is effective in all types of epilepsy except tonic-clonic seizures. When used at doses capable of inhibiting epileptic seizures the benzodiazepines are probably the safest group of antiepileptic drugs currently available. However, all are capable of producing drowsiness, ataxia and mood changes.

SUMMARY

- The central nervous system (CNS) consists of the brain and the spinal cord.
- The spinal cord is a complex series of neuronal tracts that carry impulses up into the brain and down from the brain to the periphery. There are many interconnections between these neuronal tracts.
- The brain is the major integrative area of the nervous system and may be subdivided into the medulla oblongata, pons, midbrain, cerebellum, cerebrum and cerebral hemispheres.
- A large number of neurotransmitters have been identified in the CNS, including, acetylcholine, norepinephrine, dopamine, 5-hydroxytryptamine, GABA, glutamate and many peptides.
- Drugs may be used to alter the normal function of the CNS to produce stimulation, anaesthesia or for the central control of pain.
- Psychomotor stimulants and hallucinogens may bring about stimulation of the CNS.
- Anaesthesia may be produced by either inhalation or intravenous general anaesthetics; local anaesthetics are used to produce localised anaesthesia.
- Central control of pain may be effected by opioid agonists and their effects reversed by opioid antagonists.
- Diseases of the CNS include anxiety, affective disorders (depression), psychotic disorders, Parkinson's disease and epilepsy.
- Anxiety may be treated with benzodiazepines, β-adrenoceptor antagonists or azapirones.
- Affective disorder may be divided into depression and bipolar disorder.
- Depression may be related to the levels of monoamine neurotransmitters (norepinephrine, 5-hydroxytryptamine or dopamine) in the CNS.
- Depression may be treated with tricyclic antidepressants, SSRIs, selective norepinephrine/serotonin reuptake inhibitors (SNSRIs) or MAO inhibitors.
- Bipolar disorder is treated with mood stabilisers.
- The major psychotic disorder is schizophrenia, which may be treated with phenothiazines, butyrophenones, piperidines, benzamides, thioxanthenes, dibenzodiazepines or benzisoxazoles.
- Parkinson's disease is a progressive neurological disorder that results in tremor, muscle rigidity, bradykinesia and changes in posture and gait.
- Parkinson's disease may be treated with dopamine precursors, dopamine receptor agonists, dopamine-releasing drugs, antimuscarinic drugs or MAO-B inhibitors.
- Epilepsy is a complex group of diseases characterised by uncontrolled neuronal discharge in the CNS resulting in convulsions or absence syndrome.
- Epilepsy may be treated with membrane-stabilising antiepileptic drugs.

6

Drugs Affecting the Gastrointestinal System

INTRODUCTION

The gastrointestinal (GI) tract is a muscular tube that extends from the mouth to the anus and performs a number of basic functions, including:

- ingestion of foods
- digestion of foods – the breakdown of complex molecules into simple molecules
- absorption of the products of digestion
- elimination of waste products
- water and electrolyte balance.

The gastrointestinal tract may be divided into the *mouth*, *oesophagus*, *stomach*, *small intestine* and *large intestine* and has a total length of about 30 feet. The type of muscle responsible for the propulsion of food through the gastrointestinal tract is smooth muscle, which receives innervation from both the parasympathetic and sympathetic branches of the autonomic nervous system. Acetylcholine, released from parasympathetic (cholinergic) neurones, causes contractions of the gastrointestinal smooth muscle, and norepinephrine, released from sympathetic (adrenergic) neurones, causes the muscles to relax. Usually it is the propulsive action of the parasympathetic nervous system that predominates. The basic structure of the gastrointestinal tract is shown in Fig. 6.1.

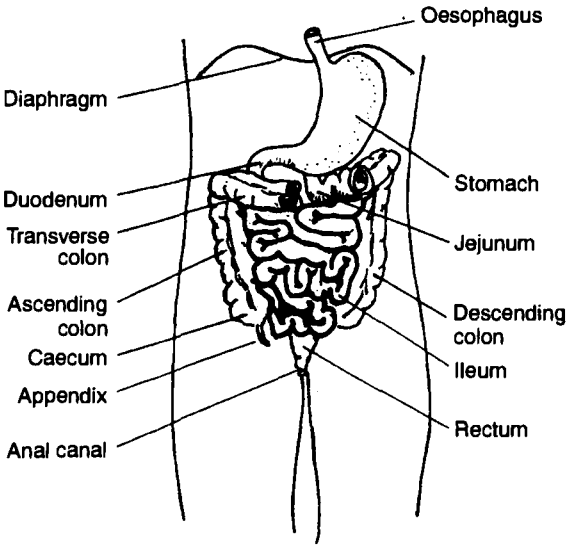

Fig. 6.1 The anatomical structure of the gastrointestinal tract. Note the relative positions of the oesophagus, stomach, duodenum, jejunum, ileum and colon.

The buccal cavity and oesophagus

The inner surfaces of the cheeks, tongue and the hard and soft palates form the mouth (buccal cavity). It provides the reception area for foodstuffs and is the site of the initial breakdown of large food particles (chewing) before their passage through the oesophagus to the stomach. The mouth receives saliva from a number of salivary glands that aid in initial digestion of carbohydrates, as well as providing lubrication as an aid to swallowing.

The oesophagus is a simple tube, about 25 cm in length, which transfers food to the stomach. The upper third of the oesophagus consists of skeletal muscle, whereas the lower parts of the oesophagus consist of smooth muscle.

The stomach

The stomach carries out three major functions: it stores food, digests food and delivers it to the

small intestine at a suitable rate to ensure efficient absorption. Hydrochloric acid (HCl) and pepsin are both secreted by cells in the wall of the stomach and carry out digestion of the stomach contents.

Secretion of HCl and pepsin

HCl is secreted directly from the parietal cells, which are located in the oxyntic glands of the stomach wall, by the so-called proton pump. The production of HCl is stimulated by gastrin, histamine and acetylcholine and inhibited by prostaglandin E_2 (PGE_2).

- Gastrin is a peptide hormone that is secreted from the G cells of the stomach wall, in response to both the anticipation of food (smell, taste, etc.) and the presence of food in the stomach. Gastrin also stimulates the enterochromaffin cells to release histamine.
- Histamine is an autacoid (paracrine hormone) that is stored in the enterochromaffin cells, which lie close to the parietal cells.
- Acetylcholine is the neurotransmitter released from the postganglionic nerve endings of the parasympathetic nerves innervating the stomach. It acts upon mAChRs (M_3 subtype) on the parietal cells. Acetylcholine also acts on M_2 mAChRs on the enterochromaffin cells to promote the release of histamine.
- PGE_2 acts on prostaglandin receptors on the parietal cells to inhibit acid secretion. The proton pump of the parietal cells is an H^+/K^+ ATPase system that is activated by the effects of the three stimulatory chemicals, and secretes H^+ ions into the lumen of the stomach. Cl^- ions are transported on another carrier.

The mechanisms that control the secretion of HCl in the stomach are summarised in Fig. 6.2.

Pepsinogen, secreted by the chief cells, is converted into pepsin by HCl in the lumen of the stomach. The combined effect of hydrochloric acid and pepsin in the stomach is to break down proteins to peptides, which are molecules consisting of short chains of amino acids. The proteolytic action of pepsin and HCl is potentially dangerous if they are allowed to come into contact with the stomach wall. Therefore under normal circumstances a layer of mucus protects the stomach wall. However, if this protective layer becomes damaged, ulcers may be produced.

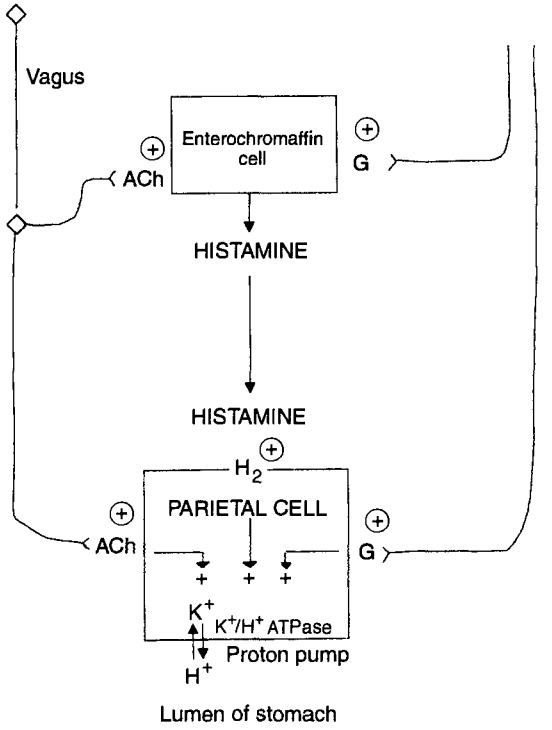

Fig. 6.2 The control of gastric acid secretion in the stomach. Gastric acid is secreted from the parietal cells of the stomach by the action of the proton pump. Gastrin (G) and ACh both stimulate the parietal cell directly as well as having an action on the mast cell to release histamine. Histamine also stimulates the parietal cells.

The small intestine

The small intestine is the major site of absorption for foodstuffs. It is about 22 feet long and the inner wall consists of a large number of finger-like projections called villi which results in there being a very large surface area to the inner layer of the organ. The small intestine may be divided into the following subsections:

- The *duodenum*, the first portion which receives secretions from the gall bladder, liver and pancreas.
- The *jejunum* and the *ileum*, which are the major absorption sites.

The large intestine

The large intestine comprises the *caecum*, *ascending colon*, *transverse colon*, *descending colon*, *sigmoid colon* and *rectum*. The main function of the large intestine is to convert the liquid contents of the small intestine into a solid waste material (faeces). This is brought about predominantly by reabsorption of large amounts of water and electrolytes from the lumen of the large intestine. The secretion of mucin aids the passage of the solid faeces along the large intestine.

DISEASES OF THE GASTROINTESTINAL TRACT

Diseases of the gastrointestinal tract often develop as a result of the highly specialised nature of the various organs which comprise the system. The high acidity associated with the stomach is controlled within the stomach by the secretion of mucus to protect the stomach wall. However, the overproduction of acid can lead to ulceration and its escape into other parts of the gastrointestinal tract can cause serious problems. Similarly malfunction of the large intestine can lead to water and electrolyte imbalance and the production of over-solid or extremely loose (watery) faeces. The following diseases of the gastrointestinal tract have been identified:

- peptic ulcer disease
- gastro-oesophageal reflux
- constipation
- diarrhoea
- inflammatory bowel disease
- irritable bowel syndrome

Peptic ulcer disease

Peptic ulcer disease is a chronic state that affects about 10% of the population. It is characterised by recurrent pain, which is affected by the ingestion of food. The pain is often located at the base of the sternum (breast bone) and patients often report severe pain during the night. Recent research has shown that about 70–80% of the adult population is infected by the organism *Helicobacter pylori*, which is present in the stomach and small intestine. It would appear that this organism might play an important role in the development of peptic ulcer disease. However, the picture is not completely clear as not all patients with *H. pylori* develop peptic ulcer disease and, conversely, not all patients who develop peptic ulcer disease carry *H. pylori* in their stomachs.

In its early stages, patients usually present with 'gastritis' and self-medicate with antacids to reduce the effects of oversecretion of stomach acid. However, in its later stages, peptic ulcer disease requires treatment with drugs. Failure to treat peptic ulcer disease often leads to severe erosion of the wall of the stomach at the site of the ulcer and serious, possibly life-threatening, loss of blood. Treatment is aimed at decreasing the overproduction of gastric acid, increasing the protection for the stomach wall and, if appropriate, eliminating *H. pylori*.

Gastric acid (HCl) is produced by the parietal cells of the gastric mucosa. These cells contain a unique acid pump, called the proton pump, which is responsible for the movement of H^+ ions from the cells into the lumen of the stomach. Secretion of gastric acid is stimulated by three main receptor-mediated systems:

(1) Activation of gastrin receptors which are sensitive to the hormone gastrin secreted from the antrum of the stomach.
(2) Activation of histamine H_2 receptors which respond to histamine secreted from the enterochromaffin-like cells close to the parietal cells.
(3) Activation of M_3 AChRs on the parietal cells which respond to ACh released from parasympathetic nerves innervating the stomach wall.

The secretion of gastric acid is inhibited by activation of prostaglandin receptors by PGE_2.

Drugs used in the treatment of peptic ulcer disease

Antacids:	sodium bicarbonate, aluminium hydroxide, magnesium trisilicate, magnesium hydroxide
Histamine H_2 receptor antagonists:	cimetidine, ranitidine, famotidine
Proton pump inhibitors:	omeprazole, lansoprazole
Antimuscarinic drugs:	pirenzepine
Prostaglandin analogues:	misoprostol
Others:	sucralfate, bismuth chelate
Triple therapy:	omeprazole plus metronidazole plus amoxycillin

Antacids

As their name suggests, antacids are drugs that neutralise the HCl produced by the parietal cells of the stomach. Most antacids currently available are salts of sodium, aluminium or magnesium, such as sodium bicarbonate, aluminium hydroxide and magnesium trisilicate. They may be used for the symptomatic management of the pain associated with overproduction of HCl, or its retrograde passage into the oesophagus (reflux oesophagitis). They are weak bases that act by neutralising the HCl such that the pH in the lumen of the stomach rises above 4. This also has the effect of inactivating pepsin.

Antacids have a number of adverse effects that may limit their use. Sodium bicarbonate, when it neutralises HCl in the stomach, releases large amounts of carbon dioxide, sometimes causing severe flatulence. Aluminium salts cause constipation and magnesium salts are laxatives. Antacids have a short duration of action because they are rapidly removed from the stomach. Another problem is that, because they cause a rise in gastric pH, this may stimulate acid production and make the situation worse. It should also be noted that the change in gastric pH brought about by antacids might well alter the absorption of drugs that are normally absorbed from the stomach. Remember that the degree of ionisation of a drug molecule, and hence the rate of absorption, is dependent on the pH of the fluid in which it is found (see Chapter 2).

Histamine H_2 receptor antagonists

Histamine H_2 receptor antagonists, such as cimetidine, ranitidine and famotidine, are potent inhibitors of gastric acid secretion, as histamine stimulation is the common pathway in the production of HCl by the parietal cells of the stomach. These drugs cause a reduction in both the basal (fasting) and food-stimulated rate of gastric acid production. Adverse effects include headache, rash, fatigue, altered bowel habit and confusion. Cimetidine, but not ranitidine or famotidine, inhibits the cytochrome P-450 enzyme system in the liver and so inhibits the metabolism of many other drugs. Cimetidine has been reported to produce breast tenderness and enlargement (gynaecomastia) in males.

Proton pump inhibitors

Drugs that inhibit the proton pump, such as omeprazole and lansoprazole, act by inhibiting the H^+/K^+ ATPase (proton pump) in the wall of the parietal cells, which is responsible for the secretion of H^+ to form HCl in the stomach. Proton pump inhibitors are capable of inhibiting gastric acid secretion by about 90% and, consequently, are more effective in patients who are infected with *H. pylori*, as the high pH inhibits growth of the organism. They have a long duration of action and may be given once daily. Adverse effects include headache, rashes, dizziness, diarrhoea, nausea and vomiting, flatulence, abdominal pain and bronchospasm. Their use in pregnancy and in patients with liver disease requires extra caution.

Antimuscarinic drugs

Antimuscarinic drugs, such as pirenzepine, antagonise the actions of acetylcholine on M_3 AChRs on the parietal cells of the stomach and so inhibit the production of both gastric acid and pepsin. Adverse effects include dry mouth

and blurred vision. The more powerful H_2 receptor antagonists and proton pump inhibitors have now superceded the use of anti-muscarinic drugs for the treatment of peptic ulcer disease.

Prostaglandin analogues
Misoprostol is a stable analogue of prostaglandin E_1 (PGE_1) and is effective in overcoming the ulcer-forming effects of NSAIDs. The production of the protective mucus that is secreted from the wall of the stomach is stimulated by prostaglandins synthesised in the cells of the stomach. NSAIDs are known to inhibit the production of this mucus in the stomach by inhibiting COX I, thus resulting in the formation of ulcers. The administration of misoprostol can overcome this effect of NSAIDs. Adverse effects include diarrhoea, abdominal pain, nausea and vomiting, flatulence, vaginal bleeding and dizziness. The use of misoprostol is contraindicated in women of childbearing age.

Other drugs
Sucralfate is an aluminium/sucrose compound that produces a protective layer over the ulcer and prevents further erosion by gastric acid. The main adverse effects are constipation, diarrhoea, nausea, dry mouth, gastric discomfort, dizziness, headache and vertigo.

Bismuth chelate binds to the base of an ulcer and provides a protective layer that shields the ulcer from gastric acid, and so promotes ulcer healing. The main adverse effect is a dark discoloration of the tongue and a blackening of the faeces.

Triple therapy
The bacterium *H. pylori* is sensitive to the antibacterial drugs amoxycillin, tetracycline and metronidazole. The use of a 'triple therapy' regimen has been shown to be of benefit for the treatment of peptic ulcer disease in patients who carry the *H. pylori* bacterium. A typical treatment regimen uses omeprazole, amoxycillin and metronidazole, in combination, for about 2 weeks, after which *H. pylori* should have been eradicated and the ulcer healed. Further treatment with other anti-ulcer drugs may then be required.

Gastro-oesophageal reflux

Gastro-oesophageal reflux affects about 10% of the population and occurs when the acidic contents of the stomach are regurgitated into the base of the oesophagus. As the oesophagus has no protective mucus layer, this results in inflammation of the oesophageal wall and considerable pain. If untreated, the repeated exposure of the oesophageal wall to high levels of acid may result in the development of a precancerous condition.

Patients often complain of a burning sensation, located at the base of the sternum, which follows the ingestion of food or sometimes after bending down. Treatment for gastro-oesophageal reflux depends on the severity of the symptoms. In mild cases, treatment with antacids or alginic acid is sufficient. More developed cases require treatment with drugs which either inhibit acid secretion (cimetidine or omeprazole) or promote motility (metoclopramide or cisapride).

Drugs used in the treatment of gastro-oesophageal reflux

Antacids:	sodium bicarbonate, aluminium hydroxide, magnesium trisilicate, magnesium hydroxide
Histamine H_2 receptor antagonists:	cimetidine, ranitidine, famotidine
Proton pump inhibitors:	omeprazole, lansoprazole
Motility promoters:	metoclopramide, cisapride

Antacids, H_2 receptor antagonists and proton pump inhibitors
The treatment of gastro-oesophageal reflux aims to prevent the damage caused by the passage of gastric acid retrogradely into the base of the oesophagus. Drug treatments that reduce the amount of acid produced, such as H_2 receptor antagonists and proton pump inhibitors, will be of benefit in this respect as will the administration of antacids. The use of these drugs is dis-

cussed under the treatment of peptic ulcer disease.

Motility promoters
Drugs that promote the motility of the gastrointestinal tract, such as metoclopramide, are useful adjuncts to treatment with H_2 receptor antagonists and proton pump inhibitors. Metoclopramide is a dopamine D_2 receptor antagonist and an agonist at 5-HT_4 receptors. It is thought that the stimulant action on 5-HT_4 receptors on interneurones in the stomach promotes the release of ACh, which serves to increase tone in the lower oesophageal sphincter and increase gastric motility. Thus the acid is prevented from moving retrogradely and passes into the intestines faster than normal. Adverse effects include extrapyramidal effects, tardive dyskinesia, drowsiness, diarrhoea and depression.

Cisapride is a 5-HT_4 receptor agonist which acts in a manner similar to that of metoclopramide. Adverse effects include diarrhoea, abdominal cramps, headache, extrapyramidal effects and urinary frequency.

Constipation

Constipation may arise from a number of different causes, but ultimately it is due to an absence of peristaltic activity in the colon. The normal regulation of smooth muscle activity in the colon is under the control of the CNS, the peripheral nervous system and gastrointestinal hormones. Factors that interfere with the normal functioning of any of these control systems may well produce constipation. Consequently constipation often occurs as an adverse effect following the administration of a number of different drugs that interfere with CNS or peripheral nervous system activity, such as the opioid analgesics morphine and codeine. Table 6.1 lists drugs that often produce constipation as a major adverse effect.

The normal frequency of defecation varies considerably between individuals and ranges from three times a day to once every 3–4 days. This leads to a problem in the diagnosis of constipation, as many people believe that they must defecate at least once a day to remain healthy. This misconception often leads to problems, especially in elderly patients, as an inadequate diet may produce apparent constipation. The subsequent ingestion of a powerful laxative may well produce the desired effect in the short term, but often produces rebound constipation, due to overemptying of the colon. This triggers the ingestion of more laxatives and so the cycle is repeated.

Table 6.1 Drugs that often cause constipation.

Aluminium salts
Antidepressants
Iron preparations
Opiates
Ca^{2+} channel-blocking drugs
Sympathomimetic drugs
Anticholinergic drugs

In many cases, regularity of bowel habit may be promoted by attention to the diet. If the constipation is not the result of any blockage, or if it is not the result of drug therapy, the inclusion of fibre (fruit and bran) into the diet often promotes a gentle increase in stool formation and relieves the constipation. Only in the most severe cases of constipation should the use of stimulant laxatives be used on a regular basis as they may produce damage to the endothelial lining of the gastrointestinal tract.

Drugs used in the treatment of constipation

Stimulant laxatives:	senna, bisacodyl, danthron
Osmotic laxatives:	lactulose
Faecal softeners:	docusate, arachis oil, liquid paraffin

Stimulant laxatives
Stimulant laxatives, such as senna and bisacodyl, produce a direct stimulatory effect on gastrointestinal smooth muscle and so produce a purgative effect. The use of such drugs often results in a decrease in bowel activity after the laxative effect and can trigger off a cycle of purging and constipation that the patient finds difficult to break. They should not be used for long-term treatment, except under strict medical super-

vision, and should never be used if there is any evidence of gastrointestinal obstruction. Adverse effects include abdominal pain and irritation.

Osmotic laxatives
Osmotic laxatives, such as lactulose, act by retaining water in the lumen of the large intestine, thus increasing the bulk and stimulating the reflexes which result in defecation. Their use is to be preferred over the directly acting stimulant laxatives but their onset of action is much slower. Adverse effects include abdominal discomfort, cramps and flatulence.

Faecal softeners
Faecal softeners, such as docusate, act by virtue of their detergent properties to increase intestinal secretion of fluid, although there may also be a direct stimulant action. This results in a gradual softening of the stool and an increase in the volume. The resultant stimulation of peristalsis aids evacuation. The use of arachis oil or liquid paraffin is not now recommended.

Diarrhoea

Diarrhoea is characterised by the frequent passage of loose watery stool. In the majority of cases diarrhoea results from either a bacterial or viral infection of the gastrointestinal tract, although it can occur as an adverse effect of many drugs which interfere with the normal control mechanisms of the colon. Psychological factors may well play an important role in some cases of diarrhoea and it may also be indicative of more serious underlying bowel disease. Table 6.2 lists drugs that cause diarrhoea as a major adverse effect.

Diarrhoea resulting from acute infections is usually self-limiting and only lasts one or two days. Diarrhoea lasting longer than this is indicative of a more serious problem. One of the major problems with diarrhoea, especially in children and the elderly, is dehydration and loss of electrolyte balance. In many cases acute diarrhoea may be treated by the administration of electrolyte solutions such as Dioralyte®. Opiate-like drugs, such as loperamide and diphenoxylate, may be used to treat more persistent diarrhoea. However, it should be borne in mind that, in the majority of cases, diarrhoea is symptomatic of underlying disease and the treatment of chronic, recurrent diarrhoea should focus upon the identification and treatment of the underlying disease state.

Table 6.2 Drugs that often cause diarrhoea.

Magnesium salts
Antibacterial drugs
Iron preparations
β-adrenoceptor antagonists
Parasympathomimetics

Drugs used in the treatment of diarrhoea

The choice of drugs for the treatment of diarrhoea depends upon identification of the underlying cause. However, in cases where the diarrhoea is an isolated incident, it is sufficient to treat the symptoms.

Electrolyte rehydration therapy:	proprietary preparations – Dioralyte
Antidiarrhoreal drugs:	loperamide, diphenoxylate, morphine, codeine

Diarrhoea can result from a number of different causes. It may result from the introduction of foreign bacteria or viruses into the gastrointestinal tract (poor food hygiene, direct infection) or may be the result of an upset in the balance of the bacterial flora by drugs (antibiotics). The symptoms may range from mild to severe.

Electrolyte rehydration therapy
The primary aim in the treatment of diarrhoea is to prevent dehydration and to replace lost electrolytes, especially in young children and the elderly. To this end, most transient forms of diarrhoea may be treated by the administration of electrolyte solutions to replace Na^+, K^+ and bicarbonate. Proprietary preparations, such as Dioralyte®, are available as sachets of powder, which may be mixed with freshly boiled and

cooled water, and given to the patient as required. Prompt rehydration therapy is of prime importance in young children and the elderly.

Antidiarrhoeal drugs
In more severe cases of diarrhoea, drugs that reduce gastrointestinal smooth muscle motility may be required. Loperamide, diphenoxylate and morphine may all be used as they decrease the peristaltic activity of the gut and reduce the passage of watery stool. They act on μ-opioid receptors in the gastrointestinal tract, to modulate the release of ACh, and so reduce motility. Adverse effects include abdominal cramps and bloating.

Inflammatory bowel disease

Inflammatory bowel disease includes ulcerative colitis and Crohn's disease. It is characterised by the sudden onset of bloody diarrhoea, accompanied by abdominal cramps. These flare-ups of the disease are interspersed with periods when the patient is asymptomatic, but may be anaemic and prone to other infections. The exact causes of inflammatory bowel disease are not known, but infections by microbes from the genus *Mycobacterium* have been implicated in some cases. There is also considerable evidence to support the hypothesis that, in some patients, genetic and/or environmental factors may play a role.

Drugs used in the treatment of inflammatory bowel disease

Aminosalicylates:	balsalazide, mesalazine, sulphasalazine, olsalazine
Glucocorticoids:	budesonide, hydrocortisone, prednisolone
Immunosuppressants:	azathioprine, 6-mercaptopurine

Aminosalicylates
Aminosalicylates, such as sulphasalazine and mesalazine, are used widely in the treatment of inflammatory bowel disease and can be of major benefit in the maintenance of the disease in remission. Sulphasalazine is broken down in the gut to an active component, 5-aminosalicylic acid (5-ASA) and sulphapyridine. The mechanism of action of 5-ASA is not known. Adverse effects include nausea, epigastric discomfort, headache, oligospermia and haematological abnormalities. Mesalazine produces fewer adverse effects than sulphasalazine, but can still cause nausea, headache, abdominal cramp and diarrhoea.

Glucocorticoids
Their systemic adverse effects limit the use of glucocorticoids in the treatment of inflammatory bowel disease. They are of benefit in the treatment of major relapses, but are of limited use in maintaining remission. The most commonly used drugs are budesonide, hydrocortisone and prednisolone. The adverse effects of these drugs are discussed in Chapter 10.

Immunosuppressants
Immunosuppressant drugs, such as azathioprine and 6-mercaptopurine, have been reported to be beneficial in the treatment of inflammatory bowel disease. These drugs reduce the need for glucocorticoid therapy, but their effect is not seen for several months. The adverse effects of immunosuppressant drugs are discussed in Chapter 17.

Irritable bowel syndrome

Irritable bowel syndrome (IBS) usually presents with periods of diarrhoea and accompanying abdominal pain. The bouts of diarrhoea may be infrequent or may occur on a daily basis. In the early stages, paying attention to the diet and increasing the amounts of dietary fibre may treat the disease. Antidiarrhoeal drugs, such as loperamide, may be used to control the diarrhoea, but antispasmodic drugs are required to control the abdominal pain.

Drugs used in the treatment of irritable bowel syndrome

Antispasmodics:	hyoscine, dicyclomine, alverine, mebeverine

Spasm of the gastrointestinal smooth muscle is responsible for a range of clinical effects, ranging from mild discomfort to severe abdominal pain. The use of antispasmodic drugs serves to alleviate this pain and is of benefit in the treatment of diseases varying in severity from non-ulcer dyspepsia to IBS.

Antimuscarinic drugs, such as hyoscine and dicyclomine, act by inhibiting the parasympathetic drive to the gut. They are competitive antagonists of acetylcholine at the mAChR in gastrointestinal smooth muscle. Their action results in relaxation of the smooth muscle and relief of the painful symptoms. Adverse effects include tachycardia, cardiac arrhythmias, dry mouth, urinary retention, blurred vision and photophobia.

Other antispasmodic drugs include alverine and mebeverine, both of which are thought to have a direct relaxant effect on gastrointestinal smooth muscle. They are of particular benefit in the treatment of IBS. Adverse effects include nausea, headache, pruritis and dizziness.

SUMMARY

- The gastrointestinal tract extends from the mouth to the anus; it is the major route for the intake, digestion and absorption of foodstuffs.
- Apart from the upper part of the oesophagus, the gastrointestinal tract consists of smooth muscle, which is stimulated (contracted) by the parasympathetic nervous system and inhibited (relaxed) by the sympathetic nervous system.
- Hydrochloric acid and pepsin are secreted in the stomach to aid digestion of foodstuffs.
- Acid secretion in the stomach is stimulated by gastrin, histamine and acetylcholine, and is inhibited by prostaglandin E_2.
- The small intestine is the major site of food absorption; it is divided into the duodenum, jejunum and ileum.
- The large intestine comprises the caecum, ascending colon, transverse colon, descending colon, sigmoid colon and rectum. It converts the liquid leaving the small intestine into solid waste material by the reabsorption of water. Major diseases of the gastrointestinal tract are peptic ulcer disease, gastro-oesophageal reflux, constipation, diarrhoea, inflammatory bowel disease and irritable bowel syndrome.
- Peptic ulcer disease may be treated with antacids, histamine H_2 receptor antagonists, proton pump inhibitors, antimuscarinic drugs, prostaglandin analogues and drugs such as sucralfate and bismuth chelate. Triple therapy with an antibacterial drug is often used to eradicate *H. pylori*.
- Gastro-oesophageal reflux may be treated with antacids, histamine H_2 receptor antagonists, proton pump inhibitors and drugs that promote motility of the gastrointestinal tract.
- Constipation may result from dietary factors, or may be the result of drug therapy. It is relieved by stimulant laxatives, osmotic laxatives or faecal softeners.
- Diarrhoea is characterised by the passage of loose, watery stools. It may occur as a result of infections, drug therapy or psychological factors. Electrolyte treatment is most appropriate in many cases (especially children) although antidiarrhoeal drugs may also be used.
- Inflammatory bowel disease includes ulcerative colitis and Crohn's disease. Treatment includes aminosalicylates, glucocorticoids and immunosuppressant drugs.
- Irritable bowel syndrome usually presents as bouts of diarrhoea with abdominal cramps. Antispasmodic drugs are the most common form of treatment.

7

Drugs Affecting the Cardiovascular System

INTRODUCTION

- It acts as a transport system, ensuring that every cell in the body is supplied not only with the oxygen and nutrients it requires to perform its normal functions but also that waste products of cellular metabolism are taken away to excretion sites elsewhere in the body.
- It provides a defence mechanism against infectious organisms and in repairing damaged tissues; it plays an important role in maintaining acid–base balance.
- It helps regulate body temperature.

- the *heart* acts as a pump
- the *blood* is the transport medium
- the *blood vessels* radiate throughout the body and convey blood to and from the tissues.

The heart

The heart is a powerful, muscular pump that develops sufficient pressure within the vascular system to ensure that the blood is pushed through the blood vessels and reaches all metabolising tissues. Beating at about 70 beats/min, the heart is located in the thoracic cavity between the lungs. It consists of four chambers, two *atria* on the top of the heart and two *ventricles* below. The atria have relatively thin walls, but the ventricles have extremely thick muscular walls. The pumping action of the heart is derived from rhythmical contraction (*systole*) and relaxation (*diastole*) of the cardiac muscle, which takes place in a well-coordinated manner, to ensure efficient movement of blood.

The right atrium receives deoxygenated blood from the *superior vena cava* and the *inferior vena cava*, which are the major veins that drain the body, and delivers it to the right ventricle. The backflow of blood from the right ventricle to the right atrium is prevented by the *tricuspid valve*. The right ventricle passes the blood to the lungs, via the *pulmonary artery*, where it becomes oxygenated. A *semilunar valve* prevents backflow of blood from the pulmonary artery to the right ventricle.

Oxygenated blood from the lungs is returned, via the *pulmonary veins*, to the left atrium, which delivers it to the left ventricle. Backflow of blood from the left ventricle to the left atrium is prevented by the *bicuspid valve*. The left ventricle passes oxygenated blood to the body via the *aorta*. A semilunar valve prevents backflow of blood into the left ventricle. Figure 7.1 shows the anatomical structure of the mammalian heart and valves and the direction of blood flow through the heart.

The heart consists of cardiac muscle, which is inherently rhythmic, and conducting tissue. The basic rhythm of the heartbeat is initiated by the *sinoatrial node* (SA node), which acts as the pacemaker. When the cells of the SA node depolarise, they trigger off a wave of depolarisation, which spreads across the atria, closely followed by a wave of contraction called *atrial systole*. The wave of depolarisation then enters the ventricles by way of the *atrioventricular node* (AV node), which slows down the impulse before passing it to the *bundle of His*.

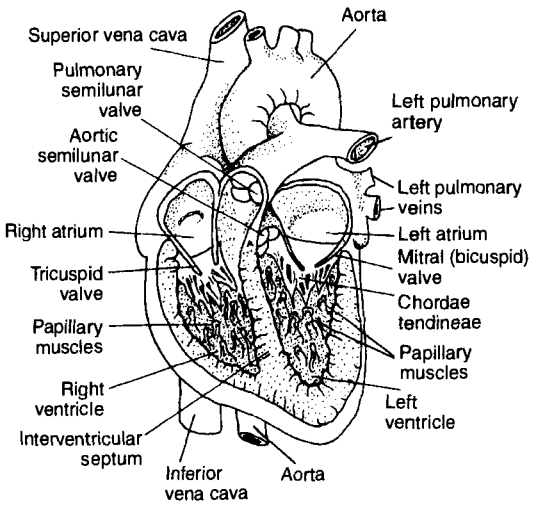

Fig. 7.1 The anatomical structure of the mammalian heart. Note the positions of the right and left atria, the right and left ventricles and the major blood vessels entering and leaving the heart.

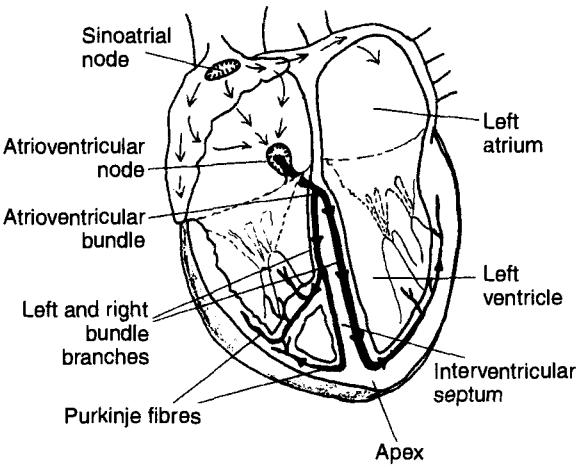

Fig. 7.2 The conducting tissues of the mammalian heart. Note the positions of the SA node, AV node, bundle of His and the Purkinje fibres.

The cells of the bundle of His are electrically insulated from the cardiac muscle cells of the ventricles and so the impulse travels down to the apex of the heart without causing any contraction. When the wave of depolarisation reaches the apex of the heart it emerges from the bundle of His into the *Purkinje tissue* which then triggers off *ventricular systole*. Thus ventricular systole starts at the apex of the heart and spreads upwards towards the atrioventricular border, and so the blood is pushed up into either the pulmonary artery or the aorta.

Details of the conducting system in the heart and the passage of the electrical impulse are shown in Fig. 7.2.

Electrical activity in the heart

The processes of initiation and propagation of the action potential in the heart, and the contraction that results from them, are dependent on changes in the distribution of various ions across the cell membranes of the cardiac muscle cells and conducting tissues. The distribution of Na^+, K^+, Ca^{2+} and Cl^- across the cell membranes, at rest, results in the generation of a resting membrane potential of -85 to -90 mV.

A cardiac action potential is generated when the membrane potential decreases to about -75 mV, at which point voltage-gated Na^+ channels open and allow the rapid movement of Na^+ ions into the cell. As the membrane potential falls, other voltage-gated ion channels open for K^+, which allow K^+ ions to leave the cell and so repolarise the membrane. During this depolarisation and repolarisation phase, L-type voltage-gated Ca^{2+} channels are also opened, which allow the influx of Ca^{2+} ions that are used to initiate muscle contraction. Therefore, the cardiac action potential can be resolved into three different ion movements:

(1) rapid influx of Na^+ ions
(2) efflux of K^+ ions
(3) slow influx of Ca^{2+} ions.

These ion movements result in the typical cardiac action potential shown in Fig. 7.3. They can be categorised into five phases:

- Phase 0 is the rapid influx of Na^+ ions.
- Phase 1 is the start of repolarisation due to efflux of K^+ ions.
- Phase 2 represents the influx of Ca^{2+} ions.
- Phase 3 is continued K^+ efflux.
- Phase 4 is the slow drift of the membrane potential back towards the trigger potential.

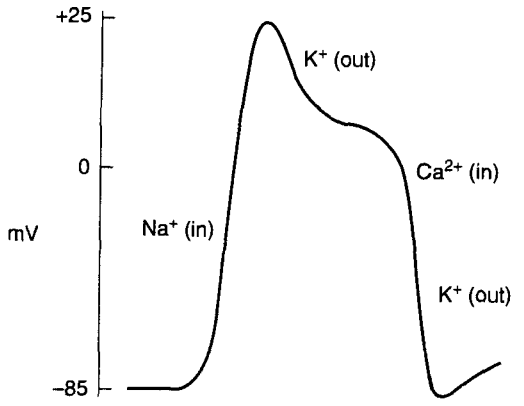

Fig. 7.3 The movement of ions during the passage of a cardiac action potential. At the trigger potential (−85 mV) the opening of the voltage-gated Na^+ channel allows the influx of Na^+ ions and depolarisation of the membrane; subsequent opening of K^+ channels allows for the efflux of K^+ and repolarisation of the membrane; the opening of L-type Ca^{2+} channels allows for the influx of Ca^{2+} for muscle contraction and a slowing of the rate of repolarisation (plateau effect).

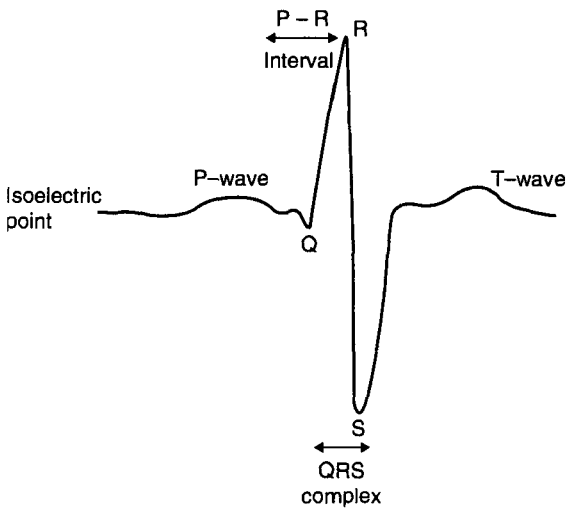

Fig. 7.4 A typical electrocardiogram (ECG). The P wave represents atrial systole, the QRS complex represents ventricular systole, the P-R interval is a measure of the time taken for the impulse to be conducted from the atria to the Purkinje fibres of the ventricles.

We can see that the depolarisation of the cardiac cell membrane is coupled to contraction of the muscle cell as a result of the influx of Ca^{2+} ions that occurs during the repolarisation phase. Therefore, the sequence of events that take place during a single heartbeat can be summarised as follows:

- depolarisation of the SA node, leading to depolarisation of the atria
- contraction of the right atrium and movement of blood into the right ventricle
- contraction of the left atrium and movement of blood into the left ventricle
- passage of the wave of depolarisation through the AV node and bundle of His into the Purkinje tissue
- contraction of the left ventricle and movement of blood into the aorta
- contraction of the right ventricle and movement of blood into the pulmonary arteries.

These events can be monitored on the surface of the skin, to produce an electrocardiogram (ECG), which gives a picture of the electrical activity occurring in the heart during the cardiac cycle. A typical ECG is shown in Fig. 7.4.

Control of cardiac output

We have seen that the rhythmical contraction (systole) and relaxation (diastole) of the heart is an inherent property of cardiac muscle and that the result of this activity is the pumping of blood out into the aorta. The volume of blood pumped into the aorta each minute is called the cardiac output. The cardiac output is dependent on two parameters: the volume of blood pumped for each heartbeat (stroke volume) and the number of beats per minute (heart rate), as described in the equation:

$$\text{Cardiac output} = \text{stroke volume} \times \text{heart rate}$$

Cardiac output is not constant, rather it is continuously being adjusted to meet the changing demands of the body. Altering one, or both, of the constituent parameters can change the cardiac output.

The force with which cardiac muscle contracts during systole determines the stroke volume. An increase in the force of contraction will increase

the stroke volume; conversely, a decrease in the force of contraction decreases the stroke volume. The most important parameter that determines the force of contraction is the volume of blood in the ventricles at the end of ventricular diastole, immediately before the start of ventricular systole. This is called the *end-diastolic volume*. This relationship between the end-diastolic volume and the force of muscle contraction results from the fact that, up to a certain limit, the force of contraction in cardiac muscle is proportional to the length of the muscle fibres, as described by Starling's law of the heart.

Starling's law states that the force of contraction of cardiac muscle is directly proportional to the initial length of the muscle fibres. Clearly this is proportional to the end-diastolic volume as, if this volume increases, the muscle fibres must be stretched to enclose the blood in the ventricular chamber.

The stroke volume is also influenced by both neuronal and hormonal factors. For example, the sympathetic nerves to the heart release norepinephrine, which increases the force of cardiac muscle contraction, as does the circulating hormone epinephrine.

The heart rate depends primarily on the rate of depolarisation of the SA node. However, this resting rate of depolarisation can also be influenced by both neuronal and hormonal factors. The sympathetic nerve fibres, which innervate the whole muscle mass, release norepinephrine, which increases the rate of contraction. A similar effect is produced by the hormone epinephrine. The parasympathetic nerves to the heart, which innervate primarily the nodal tissue, release acetylcholine, which slows the heart rate down. Thus the actual rate at which the heart beats is dependent on the natural rate of the SA node, sympathetic and parasympathetic nerve activity and the levels of epinephrine circulating in the blood.

The control of cardiac output is summarised in Fig. 7.5. In a normal resting adult the cardiac output is about 5 l/min. During exercise this can rise to about 25–30 l/min.

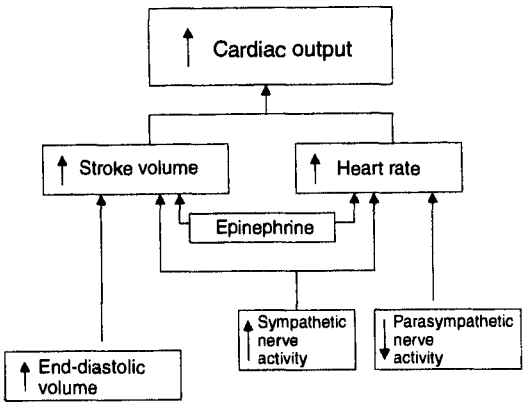

Fig. 7.5 Factors controlling cardiac output. Stroke volume and heart rate both serve to determine cardiac output. Stroke volume is dependent upon the end-diastolic volume, sympathetic nerve activity and the levels of circulating epinephrine; heart rate is determined by sympathetic and parasympathetic nerve activity and circulating epinephrine.

The blood vessels

There are four major types of blood vessel:

- arteries
- arterioles
- capillaries
- veins.

Arteries convey blood from the heart and distribute it throughout the body. The wall of the arteries is designed to withstand the high pressure of the blood leaving the heart and consists of three basic layers:

- tunica intima
- tunica media
- tunica adventitia.

The *tunica intima* consists primarily of a single layer of endothelial cells that provide not only a smooth surface over which the blood flows, but also a source of the vasodilator substance nitric oxide (NO) and other substances that affect blood flow and coagulation. In some larger arteries there is a considerable amount of elastic tissue.

The *tunica media* is the thickest of the three layers and contains large amounts of elastic tissue and smooth muscle. The smooth muscle receives innervation from the sympathetic nervous system. When this muscle contracts it decreases the diameter of the blood vessels (*vasoconstriction*); when it relaxes the diameter of the blood vessel is

increased (*vasodilatation*). Vascular smooth muscle is always kept in a state of partial contraction, thus allowing for the diameter of the blood vessel to be adjusted by either increasing or decreasing the sympathetic drive.

The *tunica adventitia* consists mainly of fibrous connective tissue that gives added strength to the arterial wall.

The smallest arteries are called *arterioles*. They have a similar structure to that of the arteries, but they contain less elastic tissue and more smooth muscle in the tunica media. These blood vessels are the major control gates for the distribution of blood, as vasoconstriction in arterioles can decrease blood flow to a particular organ. Conversely, vasodilatation in arterioles can increase blood flow to an organ. For example, after a meal there is a requirement for more blood to be diverted to the gastrointestinal tract to aid absorption of foodstuffs. Consequently the arterioles supplying blood to the gastrointestinal tract are dilated, and those to other areas of the body, such as the brain and skeletal muscle, are constricted. This is why you may feel drowsy, and should not go undergo strenuous exercise, after a heavy meal.

Capillaries are the sites of exchange of gases, nutrients and waste products between blood and cells. The walls of capillaries consist only of the single layer of endothelial cells of the tunica intima. This extremely thin wall allows for the easy passage of substances smaller than proteins, usually by diffusion. However, it should be noted that the efficient exchange of substances at the capillaries is dependent on there being an adequate blood pressure in the capillaries.

Veins are responsible for returning blood from the tissues to the heart and their walls contain the same three basic layers found in arteries. However, they contain very little elastic tissue and smooth muscle and cannot withstand high pressure and are easily distended. Many veins, especially those in the lower extremities, contain valves that assist in the return of blood to the heart against the pull of gravity.

Blood pressure

The pumping action of the heart moves blood around the blood vessels under considerable pressure. Blood pressure is dependent upon both the cardiac output and the resistance to flow through the blood vessels (peripheral resistance), as shown in the equation:

$$\text{Blood pressure} \propto \text{cardiac output} \times \text{peripheral resistance}$$

Cardiac output is determined by the rate and force of contraction of the heart (see above) and the resistance to flow is dependent upon the diameter of the blood vessels, their elasticity and the viscosity of the blood. The control of these parameters is discussed below.

Two values may be determined for blood pressure:

(1) Systolic pressure – the pressure in the arteries at the peak of ventricular systole. This is the maximum pressure to which the system is subjected.
(2) Diastolic pressure – the pressure in the arteries at the end of ventricular diastole. This is the pressure to which the system is exposed continuously.

Blood pressure is usually expressed as systolic pressure/diastolic pressure, and a typical value is 120/80 mm Hg. The difference between the two values (40 mm Hg) is called the pulse pressure.

Control of blood pressure

The pressure of blood circulating in the blood vessels is extremely important not only to ensure an adequate distribution of blood throughout the body, but also to ensure effective capillary exchange. Thus we have evolved an extremely sensitive and reactive control system to ensure that blood pressure remains within closely defined limits, but at the same time can be varied rapidly in response to external stimuli. The pressure of blood in the blood vessels is derived from the pumping of blood into the closed blood vessels and the resistance to flow through these vessels. Thus we can see that blood pressure is dependent on both cardiac output and the diameter of the blood vessels and the maintenance of a constant blood pressure can be brought about by changes in either, or both, of these parameters.

The nervous control of blood pressure

The nervous control of blood pressure is brought about by the baroreceptor reflex system. Basically, this consists of a pressure-sensitive detector system (*baroreceptors*) which continuously monitor the blood pressure, an integrating centre in the brain (*vasomotor centre*) and an effector system (heart and blood vessels). Afferent nerve fibres transmit information from the baroreceptors to the vasomotor centre and efferent fibres transmit messages from the vasomotor centre to the effector organs.

Baroreceptors are situated in the carotid sinuses and the aortic arch; essentially they are stretch receptors which generate impulses at a rate proportional to the degree of stretch in the arterial wall. An increase in blood pressure will result in an increase in the number of impulses passed to the vasomotor centre, situated in the medulla.

The vasomotor centre integrates the information received from the baroreceptors and adjusts the impulse traffic in the efferent nervous pathways to the heart and blood vessels accordingly. Thus if the vasomotor centre receives a decrease in afferent impulses from the baroreceptors (fall in blood pressure), it initiates responses that will bring about an increase in blood pressure. Conversely, if it receives information that the blood pressure is too high, then it will reduce these responses so that blood pressure falls.

Efferent nerves from the vasomotor centre innervate the heart, arterioles, veins and adrenal medulla. Sympathetic nerves to the heart increase the force and rate of contraction of cardiac muscle and so increase blood pressure. Parasympathetic nerves to the heart decrease the force of contraction and so lower blood pressure. Sympathetic nerves to arteries and veins cause vasoconstriction and so their stimulation will increase blood pressure. The sympathetic nerves to the adrenal medulla increase the secretion of epinephrine, thus increasing blood pressure. Sympathetic nerves to the kidney also increase the release of renin (see below).

The renin-angiotensin-aldosterone system

A more long-term control of blood pressure is brought about by the renin-angiotensin-aldosterone system. Renin is an enzyme that is released from the juxtaglomerular cells of the kidney, in response to either a fall in blood pressure or stimulation of the sympathetic nerves to the kidney. The action of renin is to convert a circulating polypeptide called *angiotensinogen* into *angiotensin I*. Angiotensin I acts as a substrate for the enzyme angiotensin converting enzyme (ACE), which is found in the lung, and is converted by this enzyme into *angiotensin II*. Angiotensin II is a very potent vasoconstrictor and is also a stimulator of aldosterone release from the adrenal cortex. Angiotensin II acts directly on receptors on vascular smooth muscle cells to cause vasoconstriction; aldosterone promotes sodium and water retention by the kidney. Thus a fall in blood

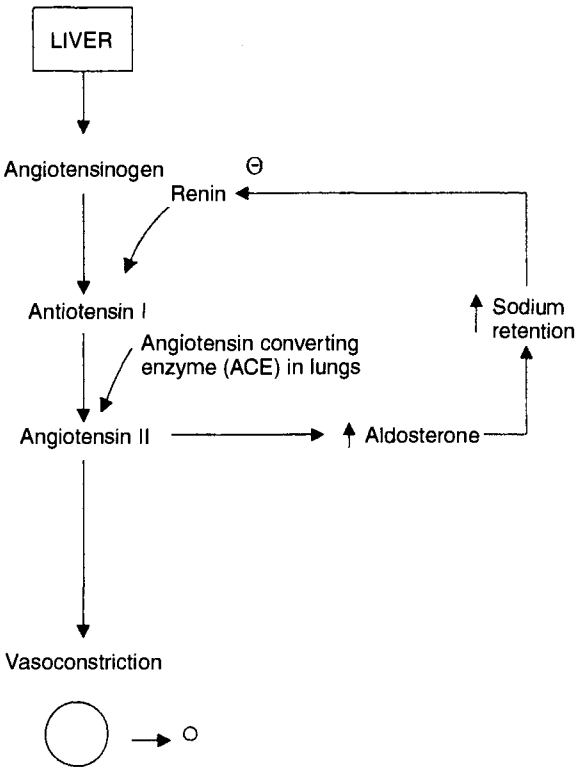

Fig. 7.6 The renin-angiotensin-aldosterone system. Renin is released from the juxtaglomerular cells of the kidney in response to a decrease in renal blood flow; renin catalyses the conversion of angiotensinogen to angiotensin I which, in turn, is converted to the potent vasoconstrictor agent angiotensin II by ACE found in the lungs; release of aldosterone ultimately leads to a decrease in renin release.

pressure leads to the release of a substance (renin), the effect of which is to increase blood pressure. Figure 7.6 summarises the renin-angiotensin-aldosterone system.

The mechanisms that control blood pressure are summarised in Fig. 7.7.

The blood

Blood is a thick, viscous fluid composed of cells, proteins, water and dissolved solutes. Normally, it comprises about 8% of total body weight and the normal blood volume is about 5.0–5.5 l.

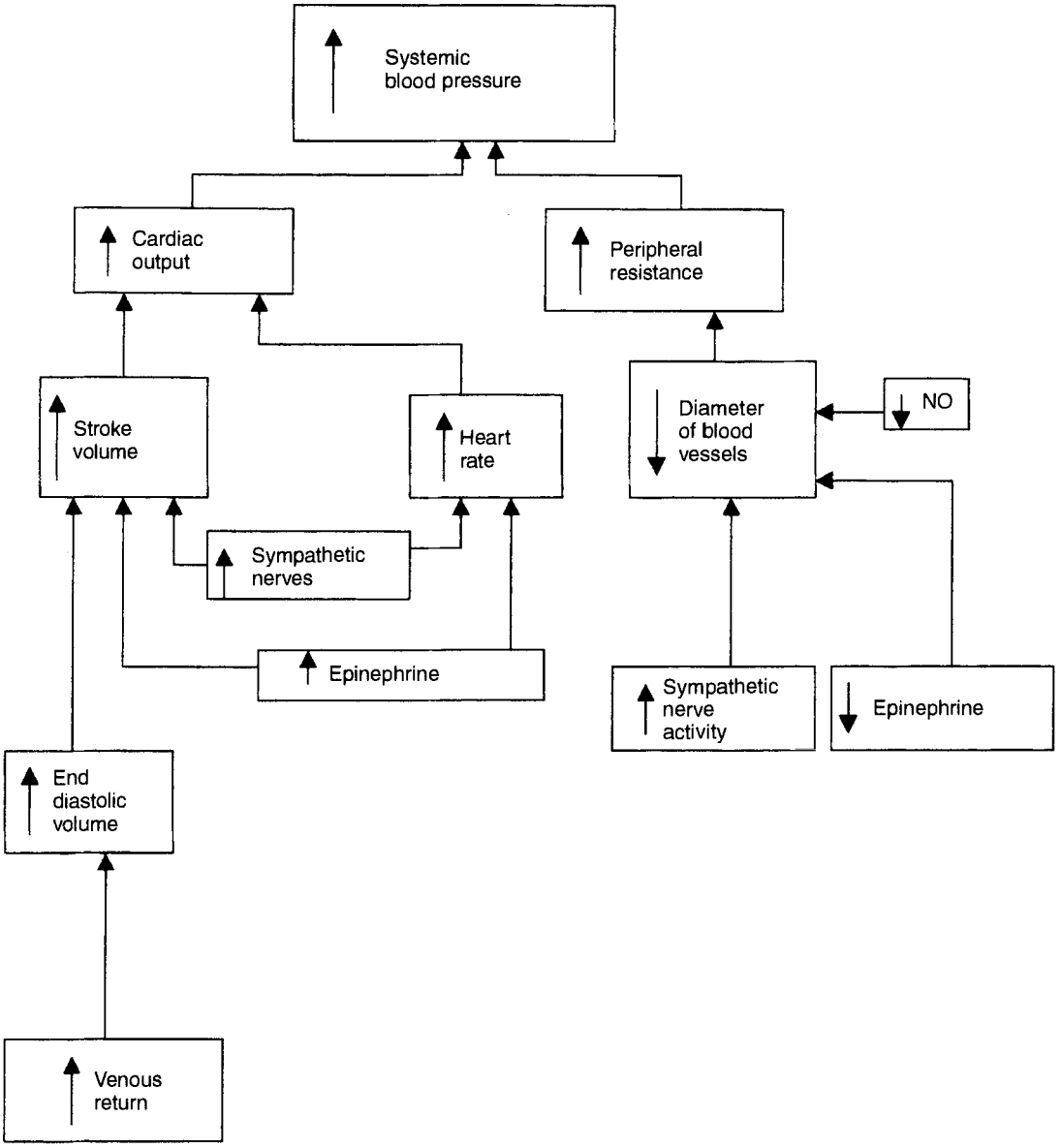

Fig. 7.7 A summary of the mechanisms controlling blood pressure. Blood pressure is determined by cardiac output and peripheral resistance to blood flow. Cardiac output is dependent upon stroke volume and heart rate; peripheral resistance is determined by sympathetic nerve activity and circulating epinephrine.

There are three basic types of cell in blood:

(1) *Erythrocytes* (red blood cells) are the most numerous (4.5–5.5 × 10^6/mm^3); they are biconcave, non-nucleated discs that contain large amounts of haemoglobin, which is responsible for the carriage of oxygen and carbon dioxide.
(2) *Leucocytes* (white blood cells) are less numerous (4000–8000/mm^3); they have multilobed nuclei and are part of the body's defence mechanism against bacteria.
(3) *Thrombocytes* (platelets) are cell fragments which perform an important role in the initiation of blood clotting in response to physical damage to blood vessels.

The aqueous fluid matrix that comprises blood after the cellular constituents have been removed is called *plasma*. Plasma is about 92% water but it contains large amounts of plasma proteins, which are present in solution. These include:

- Albumin, which supplies the majority of the osmotic pressure of plasma (and thus controls water movement into and out from the vascular compartment) and sites for the plasma protein binding of drugs.
- α-Globulins and β-globulins, which act as carrier molecules for substances that do not easily dissolve in plasma.
- γ-Globulins, which are involved in the production of antibodies for defence against invading organisms. Fibrinogen and prothrombin are two plasma proteins that are important in the control of blood clotting.

With the exception of γ-globulins, all plasma proteins are synthesised in the liver. The γ-globulins are formed in the plasma cells of the lymph nodes.

DISEASES OF THE CARDIOVASCULAR SYSTEM

Introduction

We have seen from the summary above that efficient functioning of the cardiovascular system is absolutely essential for the well-being of the individual. It is essential that cardiac output and blood pressure are both maintained within the close limits necessary for efficient distribution of blood to all tissues of the body and for capillary exchange. Failure of efficient cardiovascular function is extremely serious, as its effects ramify throughout the whole body and may well be life-threatening.

The major diseases affecting the cardiovascular system are:

- congestive heart failure
- cardiac arrhythmias
- angina pectoris
- hypertension
- errors of blood clotting
- anaemias
- hyperlipidaemias and atherosclerosis

Congestive heart failure

In health, the cardiac output varies considerably, depending on the metabolic needs of the body, both at rest and when undertaking exercise. The healthy heart has a considerable reserve capacity, such that it can respond to the increased demands put upon it, by increasing its work rate to ensure that the rate of venous return is matched by the cardiac output. However, if the workload put upon the heart increases beyond certain limits, it cannot respond by increasing its force of contraction and so begins to fail. Initially, this may only be apparent during exercise, but gradually the symptoms (oedema, breathlessness and lethargy) appear under more normal conditions, giving rise to the disease known as congestive heart failure (CHF).

As the heart begins to fail the cardiac output decreases and the major organs do not receive an adequate blood supply. The kidney is one of the

organs most sensitive to a decrease in blood flow and it responds by activation of the renin-angiotensin-aldosterone system. This increases the amounts of angiotensin II circulating in the blood and leads to retention of sodium and water and the development of oedema, especially in the lungs and lower extremities. The clinical symptoms of CHF depend upon whether it is acute or chronic failure.

- Acute CHF gives rise to tachycardia, shortness of breath and poor exercise tolerance.
- Chronic CHF gives rise to cardiac arrhythmias, hypertension and oedema.

The severity of CHF depends upon the scale of damage to the heart tissues, the particular area of the heart that has been affected and the ability of the heart to compensate for the damage.

In its initial stages, CHF is characterised by a small increase in the size of the heart and a fall in both cardiac output and blood pressure. Compensatory mechanisms are brought into play, which increase the force of contraction of the heart and attempt to restore the efficiency of the system and to return the cardiac output to normal. As the disease progresses, the reliance on these compensatory mechanisms increases until they are no longer able to cope, cardiac output begins to fall and tissue perfusion decreases. Eventually the progression of the disease is such that the fall in cardiac output results in a generalised decrease in circulation and eventually circulatory collapse.

Drugs used in the treatment of congestive heart failure

The treatment of CHF aims to remove accumulated water and restore the cardiac output towards normal values. There are four main types of drug used in the treatment of congestive heart failure:

(1) *Positive inotropic drugs* act by increasing the force of contraction of the failing heart, thus restoring cardiac output and organ perfusion.
(2) *Diuretics* cause an increase in sodium and water excretion by the kidney and so reduce systemic blood pressure and the workload placed on the heart.
(3) *ACE inhibitors* inhibit the production of angiotensin II and so reduce blood pressure, aldosterone production and cardiac workload.
(4) *Vasodilators* reduce the preload on the heart by decreasing peripheral resistance.

Positive inotropic drugs

Cardiac glycosides:	digoxin, ouabain
β_1-Adrenoceptor agonists:	dobutamine, dopamine, dopexamine
Phosphodiesterase inhibitors:	amrinone, milrinone

The most effective drug in this class is digoxin, which acts by inhibiting the Na^+/K^+ ATPase that constitutes the sodium pump found in the cell membrane of cardiac muscle cells. Digoxin binds to the sodium pump, preventing the exchange of K^+ for Na^+. As a consequence of this action, there is an increase in the intracellular concentration of Na^+, which inhibits the Na^+/Ca^{2+} exchange pump that normally removes Ca^{2+} from the cell. The direction of this exchange pump is eventually reversed by the rise in the intracellular concentration of Na^+ and Ca^{2+} is pumped into the cell. These effects of digoxin eventually result in an increase in the intracellular concentration of Ca^{2+} ions and an increase in the force of muscle contraction (see Fig. 7.8).

Digoxin has an extremely small therapeutic ratio (1.9) and so the development of adverse effects is common. Adverse effects of digoxin include anorexia, nausea and vomiting, headache, fatigue, drowsiness, diarrhoea, abdominal pain, visual disturbances, cardiac arrhythmias and heart block.

β_1-Adrenoceptor agonists, such as dobutamine and dopamine, act on the β_1-adrenoceptor in cardiac muscle cells, in a manner similar to that of the naturally occurring substances norepinephrine and epinephrine. The β_1-adrenoceptor is a G-protein-coupled receptor that is positively coupled to its target enzyme adenylyl cyclase. Activation of this enzyme leads to an increase in the intracellular levels of the second messenger cAMP and an increase in the efficiency of the voltage-gated Ca^{2+}

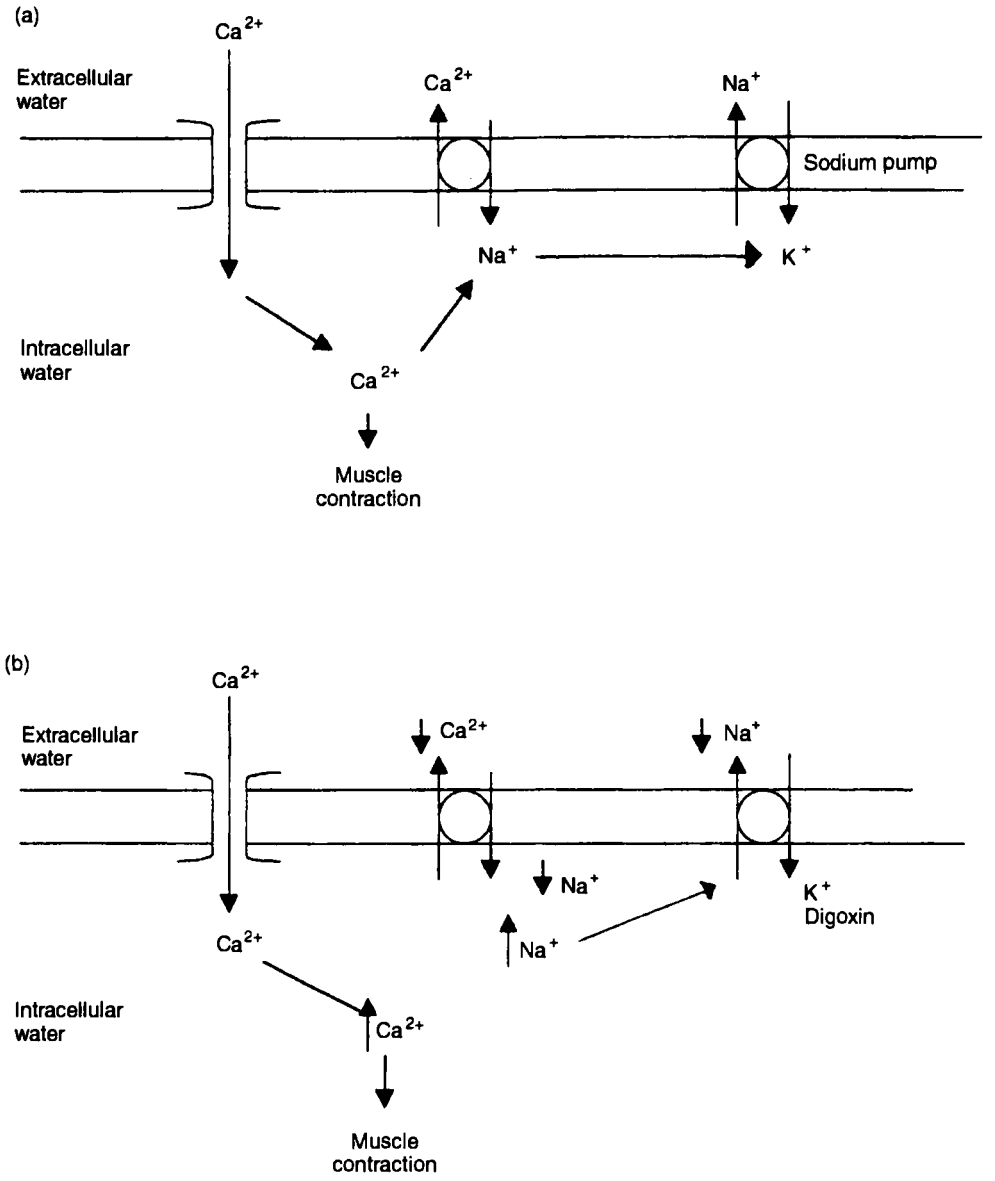

Fig. 7.8 The effect of digoxin on the distribution of ions in the heart. (a) Under normal conditions the sodium pump maintains a low concentration of Na^+ ions inside the cell; this allows for the efficient removal of Ca^{2+} by Ca^{2+}/Na^+ exchange. (b) In the presence of digoxin, the sodium pump is inhibited; this allows the intracellular Na^+ concentration to rise and inhibits Ca^{2+} efflux. Eventually, the Ca^{2+}/Na^+ exchange is reversed and intracellular Ca^{2+} rises dramatically, causing an increase in the force of muscle contraction.

channel responsible for the influx of Ca^{2+} into the cell. The resultant rise in intracellular Ca^{2+} concentration leads to an increase in the force of contraction of the heart. The major adverse effects are tachycardia and hypertension.

Amrinone and milrinone are inhibitors of the enzyme phosphodiesterase type 3 (PDE3), which is responsible for the breakdown of cAMP in cardiac muscle cells. Inhibition of this enzyme leads to an increase in the levels of cAMP in the

cell and an effect similar to that produced by stimulation of the β_1-adreneoceptor. Adverse effects include nausea, headache, insomnia, the generation of ectopic foci, ventricular tachycardia and hypotension

The mechanisms of action of positive inotropic drugs are summarised in Fig. 7.9.

Diuretics

Thiazides:	bendrofluazide, chlorthalidone, metolazone, indapamide, hydrochlorothiazide, chlorothiazide, xipamide
Loop diuretics:	bumetanide, frusemide
Potassium-sparing diuretics:	amiloride, spironolactone, triamterene

Diuretics are drugs that produce an increase in sodium and water excretion by a direct action on the kidney. The reabsorption of water by the renal nephron is osmotic and is dependent on the reabsorption electrolytes, especially Na^+, K^+, HCO_3^- and Cl^-. The most commonly used diuretic drugs are thiazides, loop-acting diuretics and potassium-sparing diuretics.

Thiazides, such as bendrofluazide and chlorothiazide, act on the nephron to inhibit the reabsorption of Na^+ and water. The resultant reduction in circulating plasma volume reduces the preload on the heart and so relieves the symptoms of CHF. These drugs are very well tolerated.

The loop diuretics, frusemide and bumetanide, act on the ascending limb of the loop of Henle to inhibit the generation of the medullary osmotic pressure gradient. Again the reduction in circulating plasma volume relieves the oedema of CHF. The major adverse effect is hypokalaemia, and extra care must be taken if digoxin is also being used.

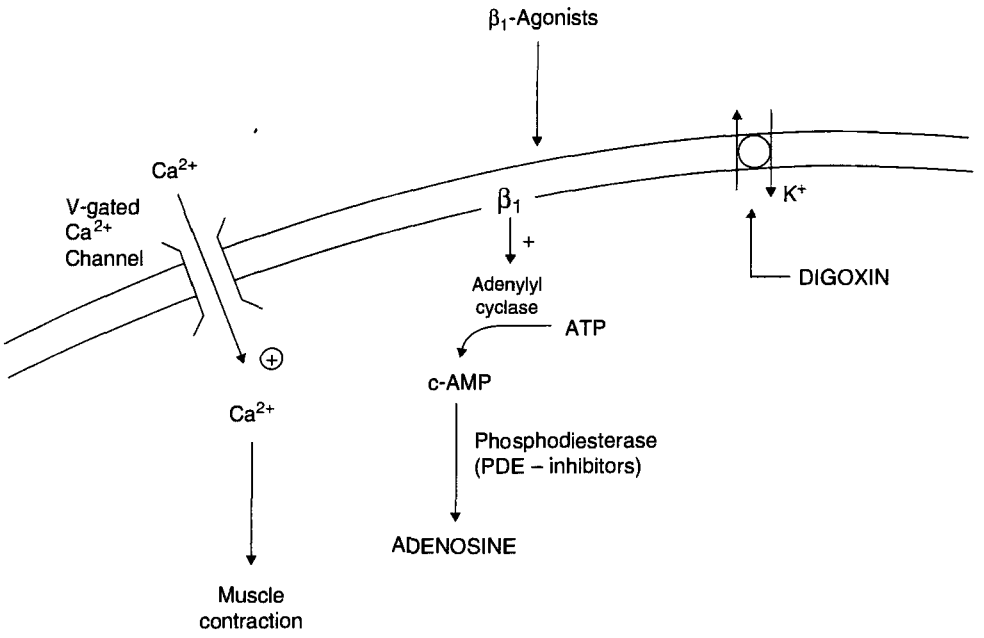

Fig. 7.9 The mechanisms of action of positive inotropic drugs on the heart. A positive inotropic effect on the heart is brought about by an increase in the intracellular Ca^{2+} levels. This is brought about by increased Ca^{2+} influx through the Ca^{2+} channel, effected by a rise in cAMP levels in the cell. β_1-Adrenoceptor agonists (dobutamine) increase the rate of conversion of ATP to cAMP and phosphodiesterase inhibitors inhibit the breakdown of cAMP. The actions of digoxin are described in the legend to Fig. 7.8.

Potassium-sparing diuretics, such as amiloride, provide a small diuretic effect, which is beneficial in CHF. They also combat the hypokalaemia produced by other diuretics. The major adverse effect is hyperkalaemia.

Drugs affecting the renin-angiotensin system

ACE inhibitors:	captopril, cilazapril, enalapril, lisinopril, fosinopril, perindopril
Angiotensin II receptor antagonists:	losartan, valsartan, candesartan, irbesartan

ACE inhibitors, such as captopril and enalapril, act by decreasing the production of angiotensin II by the renin-angiotensin-aldosterone system. The decrease in circulating angiotensin II leads to not only a decrease in vasoconstriction (vasodilatation), but also a reduction in the secretion of aldosterone from the adrenal cortex. Both of these effects will lead to a decrease in blood pressure and hence a relief of the symptoms of CHF.

The major adverse effects of these drugs are flushing, nausea, chest pain, tachycardia and the development of a persistent dry cough. The cough results from an inhibition of the breakdown of a peptide called bradykinin, which stimulates the cough reflex. Their use is contraindicated in patients with angio-oedema, renal disease or stenosis (narrowing) of the aorta.

Angiotensin II receptor antagonists, including losartan and valsartan, act by inhibiting the actions of angiotensin II at its receptor in vascular smooth muscle. This inhibits the vasoconstrictor action of angiotensin II and allows the blood vessel to dilate. Angiotensin II receptor antagonists are devoid of many of the adverse effects of ACE inhibitors, therefore they provide a useful alternative to the ACE inhibitors in patients for whom the side-effects are too great. Adverse effects of losartan include hypotension, hyperkalaemia, diarrhoea, dizziness, alterations in taste perception and migraine headache.

Vasodilators

The vasodilators, such as nitroprusside and glyceryl trinitrate, are of benefit in the treatment of severe CHF, as they cause a significant vasodilatation and reduction in the workload of the heart. Nitroprusside, given by i.v. injection, is the treatment of choice in acute CHF. It reduces the filling pressure of the left ventricle by allowing pooling of the blood into the veins. Adverse effects include flushing, headache and hypotension.

Cardiac arrhythmias

Cardiac arrhythmias arise from either disorders of impulse generation, impulse conduction or a combination of both. In a normal healthy heart, the site at which the cardiac impulse is generated (the pacemaker) is the SA node and impulses generated there are conducted throughout the heart by the specialised conducting tissues.

Disorders of impulse generation

The most common type of arrhythmia is the development of an *ectopic focus*, a group of cells that take over the normal pacemaker activity of the SA node. This may occur as a result of damage to the cells from a heart attack, the adverse effects of some drugs, or metabolic disturbances such as hyperthyroidism. Arrhythmias arising from such causes may be subdivided into two categories:

(1) *Supraventricular* arrhythmias arise from ectopic foci in the atria or the AV node.
(2) *Ventricular* arrhythmias arise from ectopic foci in the ventricles.

Supraventricular arrhythmias cause an increase in ventricular beating rate, a reduced stroke volume and an increase in the workload on the heart. They may be divided into three types:

- *Atrial flutter* arises from a single, atrial ectopic focus. It is characterised by an atrial beating rate of 150–300 beats/min. The AV node cannot transmit impulses at these high rates, however the ventricular rate does increase. The ECG shows multiple P waves for each QRS complex, typically 2 : 1 or 3 : 1.
- *Atrial fibrillation* arises from multiple atrial ectopic foci, giving atrial beating rates in the range 300–600 beats/min. There are no normal

P waves on the ECG and the ventricular beating rate is high but less than that of the ventricles. There is a marked decrease in cardiac output.

- *Supraventricular paroxysmal tachycardia* occurs as a result of the intermittent appearance of an atrial ectopic focus.

Ventricular arrhythmias may be divided into two groups:

- *Ventricular fibrillation* is caused by the emergence of ventricular ectopic foci leading to a rapid, uncoordinated ventricular beat and a severe fall in cardiac output. This type of arrhythmia is rapidly fatal and requires immediate electrical treatment by the application of a d.c. current to the chest wall.
- *Ventricular paroxysmal tachycardia* arises from the intermittent emergence of a ventricular ectopic focus. The ECG shows more QRS complexes than P waves.

Disorders of impulse conduction

It must be remembered that, even if the process of impulse generation is operating satisfactorily, a rhythmical heartbeat is also dependent upon the correct functioning of the conducting tissues of the heart. Disorders of the impulse conducting tissues of the heart can arise from either physical damage to the tissues, such as a heart attack or a bacterial infection, or from the adverse effects of some drugs. Two major groups of arrhythmias have been identified as resulting from disorders of impulse conduction:

(1) *Heart block* occurs mainly in the AV node or the bundle of His and usually results from a decrease in the transmission capability of damaged cells. However, it can occur as a result of treatment with cholinomimetic drugs. Typically there is a separation of atrial and ventricular beating rates in the ratio 2:1, 3:1 or 4:1. The result of this is that the patient has little reserve capacity to increase cardiac output in the event of exercise.

(2) *Re-entrant tachycardia* occurs as a result of either severe physical damage to the heart tissue, as a result of a heart attack, or the action of drugs such as dobutamine, digoxin or quinidine, which alter the excitability of the cell membrane of the heart cells. In such situations the cells may not be able to conduct impulses in the normal direction, but will be able to pass them in the 'wrong' direction (see Fig. 7.10). A single impulse entering the damaged region may result in the generation of many impulses as a result of this 're-entry circuit' and give rise to multiple muscle contractions. A rare version of re-entrant tachycardia occurs in Wolff-Parkinson-White syndrome, in which there is an abnormal electrical connection between the atria and the ventricles, which bypasses the AV node. As a consequence, the ventricular impulse may re-enter the atria, trigger off a short-circuit current and produce very high beating rates in excess of 500 beats/min.

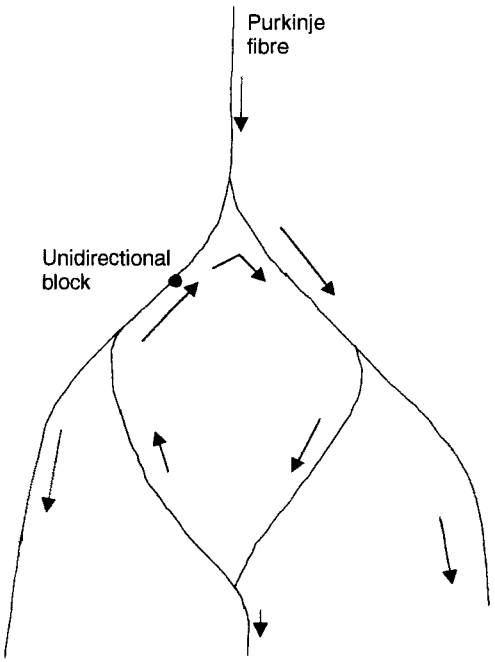

Fig. 7.10 Details of impulse blockade and antidromic conduction in re-entrant tachycardia. Small impulses cannot pass the blockade site. However, the larger 'antidromic' impulse can pass the damaged site and trigger off a series of circular impulses, which result in re-entrant tachycardia.

Drugs used in the treatment of cardiac arrhythmias

Na^+ channel-blocking drugs:	quinidine, lignocaine, procainamide, disopyramide, flecainide, phenytoin
β_1-Adrenoceptor antagonists:	propranolol, atenolol, metoprolol, pindolol
K^+ channel-blocking drugs:	amiodarone, sotalol, bretylium
Ca^{2+} channel-blocking drugs:	verapamil, diltiazem
Other drugs:	adenosine, digoxin

We can see from the comments above that most cardiac arrhythmias arise from an increase in the excitability of either cardiac muscle cells or conducting cells. Thus the main aim of treatment must be to stabilise the cell membranes of these cells to reduce the likelihood of extraneous depolarisations. Vaughan-Williams has classified drugs used in the treatment of cardiac arrhythmias according to their primary mechanism of action. The classification is as follows:

- Class I – Na^+ channel-blocking drugs
- Class II – β-Adrenoceptor antagonists
- Class III – K^+ channel-blocking drugs.
- Class IV – Ca^{2+} channel-blocking drugs.

Class I anti-arrhythmic drugs may be further subdivided into:

- Class IA – drugs which slow phase 0 depolarisation
- Class IB – drugs which shorten phase 3 repolarisation
- Class IC – drugs which have a pronounced effect on slowing phase 0 depolarisation.

Na^+ channel-blocking drugs (class I)

These drugs act by inhibiting the influx of sodium ions through the rapidly acting Na^+ channels which are open during phase 0 depolarisation of the cell membrane. Their action is 'state dependent', meaning that they are more effective on the rapidly opening and closing channels found in ectopic foci rather than those in other areas of the cardiac tissue. Consequently these drugs become preferentially bound to areas of high electrical activity and so smaller doses may be used, while still achieving the desired clinical effect.

- Class IA drugs slow the rate of rise of the cardiac action potential and so slow the rate of conduction of the action potential through the heart and increase the refractory period.
- Class IB drugs have a lesser effect on the rate of depolarisation. They interact rapidly with the sodium channels and cause a decrease in the duration of the cardiac action potential.
- Class IC drugs markedly depress the rate of rise of the cardiac action potential and so slow the rate of conduction.

However, it must be stressed that the Vaughan-Williams classification is not absolute and that many drugs show effects which may be attributed to more than one classification. For example sotalol, whilst classified as a class III drug, shows some effects typical of class I, class II and class IV drugs.

Quinidine is the prototype drug in class IA. It binds to both open and closed sodium channels, thus reducing the influx of the Na^+ ions that cause membrane depolarisation. It is particularly effective in the control of a wide range of arrhythmias arising from ectopic foci in both the atria and the ventricles, and exerts effective control over re-entrant tachycardia by decreasing the responsiveness of conducting tissues and prolonging the effective refractory period.

Perversely, high doses of quinidine can cause cardiac arrhythmias as a consequence of its cardiodepressant actions. In particular, quinidine may cause SA node and AV node block. Toxic levels may induce tachycardia. The more common adverse effects seen in patients treated with quinidine are nausea and vomiting, diarrhoea, blurred vision, myocardial depression, heart failure, cardiac arrhythmias and headache.

Procainamide is also a class IA anti-arrhythmic drug, derived from the local anaesthetic procaine. Its mechanism of action is essentially similar to

that of quinidine. Adverse effects include depression, hallucination and psychotic episodes in susceptible patients.

Disopyramide is probably the most commonly used class IA anti-arrhythmic drug. The mechanism of action of disopyramide is similar to that of quinidine, although it has a greater negative inotropic effect than the other class IA drugs. Consequently care must be exercised in its use in patients who have impaired left ventricular function, as its use may possibly lead to heart failure. The adverse effects of disopyramide derive mainly from its anticholinergic effects and include tachycardia, ventricular fibrillation, myocardial depression, dry mouth, blurred vision, constipation, psychotic episodes and urinary retention. The use of disopyramide is contraindicated in patients who have heart block or heart failure.

Lignocaine is a class IB anti-arrhythmic drug. It associates with, and dissociates from, the Na^+ channel extremely rapidly and so has a primary effect in areas of tissue that are depolarising frequently. Lignocaine is a local anaesthetic that shortens the duration of phase 3 repolarisation and decreases the duration of the action potential. It is of particular benefit in the treatment of the ventricular arrhythmias that often arise during a heart attack. Lignocaine is well tolerated by most patients. Adverse effects include drowsiness, slurred speech, paraesthesiae and convulsions.

Flecainide is an example of a class IC anti-arrhythmic drug. It dissociates slowly from both open and closed Na^+ channels and, therefore, exerts considerable effects even at slow rates of cardiac muscle contraction. Flecainide causes a marked decrease in the rates of impulse conduction in all areas of the heart, the reduction in automaticity occurring as a result of an increased threshold potential. Flecainide is of use in the treatment of ventricular arrhythmias that do not respond to other anti-arrhythmic drugs. However, its use in heart failure is contraindicated due to the negative inotropic effect of the drug. Adverse effects of flecainide include dizziness, blurred vision, cardiac arrhythmias, nausea and vomiting and photosensitivity.

β_1-Adrenoceptor antagonists (class II)

Antagonism of the β_1-adrenoceptor in the heart leads to a decrease in the levels of phosphorylation of the L-type Ca^{2+} channel (c.f. dobutamine under 'Positive inotropic drugs' earlier in this chapter). Thus drugs such as propranolol, atenolol, metoprolol and pindolol inhibit cardiac arrhythmias by reducing cardiac automaticity and the rate of phase 4 repolarisation, therefore prolonging the refractory period. They reduce the rate of atrial and ventricular flutter and are of particular use in the treatment of both re-entrant tachycardia and the arrhythmias produced by epinephrine and digoxin. They may also be used to combat 'sudden arrhythmic death', a phenomenon seen following heart attacks.

The use of a selective β_1-adrenoceptor antagonist, such as atenolol, metoprolol or pindolol, is preferable to propranolol in sensitive patients as these drugs are less likely to produce the bronchospasm and cold fingers/toes resulting from the β_2-adrenoceptor blockade produced by propranolol.

The adverse effects of propranolol include bronchospasm, peripheral vasoconstriction, increased sodium retention and changes in glucose metabolism. Its use in sensitive asthmatic patients and insulin-dependent diabetics is, therefore, contraindicated. The cardioselective β_1-adrenoceptor antagonists show a reduced incidence of adverse effects, thus making their use in asthmatic and diabetic patients more acceptable. However, it must be noted that the cardioselectivity of these drugs is relative and not absolute. It is good practice to monitor all susceptible patients who are taking β_1-adrenoceptor antagonists for evidence of bronchospasm or interference with glucose metabolism.

K^+ channel-blocking drugs (class III)

The movement of K^+ ions through K^+ channels in cardiac muscle cells is important in terminating the action potential and effecting repolarisation of cardiac cells during the action potential. Thus, the blockade of these K^+ channels decreases the outflow of K^+ ions and lengthens both the repolarisation time and refractory period.

Amiodarone is an iodine-containing compound that acts as a non-selective blocker of K^+ channels. It is effective in the treatment of both supraventricular and ventricular tachyarrhythmias. Amiodarone also shows class I, class II and class IV anti-arrhythmic activity. The therapeutic

usefulness of amiodarone is limited by the incidence of adverse effects that can be sufficiently serious to warrant cessation of treatment in about 50% of patients. Adverse effects include gastrointestinal disturbance, tremor, ataxia, dizziness, hyperthyroidism, hypothyroidism, photosensitivity, liver damage, neuropathy, muscle weakness and a blue discoloration of the urine and skin.

Sotalol is a class III anti-arrhythmic drug which also has marked β_1-adrenoceptor antagonist action (class II). It reduces the rapid efflux of K^+ ions and so prolongs the duration of the action potential and the refractory period. Sotalol is of benefit in the treatment 'sudden arrhythmic death'. Adverse effects include those associated with its β_1-adrenoceptor antagonist action. Also, prolongation of the Q-T interval by this drug may precipitate the potentially fatal torsade de pointes in susceptible patients.

Bretylium prolongs the refractory period and increases the threshold potential in Purkinje tissue. The major adverse effect is postural hypotension.

Ca^{2+} channel-blocking drugs (class IV)

Opening of the voltage-sensitive L-type Ca^{2+} channel brings about the influx of Ca^{2+} into the cardiac cell. The current flow, which results from this influx, is seen as the plateau phase of repolarisation during the cardiac action potential. Thus the reduction in Ca^{2+} influx brought about by class IV anti-arrhythmic drugs results in a prolongation of the repolarisation phase, prolongation of the phase 4 depolarisation and a decrease in the rate of impulse conduction.

Verapamil and diltiazem directly block the L-type Ca^{2+} channel and are, therefore, effective in pacemaker cells in which Ca^{2+} plays an important role in the upstroke of the action potential. Thus they are effective in blocking AV conduction and controlling supraventricular tachycardia. Both verapamil and diltiazem bind preferentially to open, depolarised Ca^{2+} channels and so prevent the repolarisation of the cell membrane until the drugs dissociate from their binding sites. They exhibit the phenomenon of 'state dependence'. These drugs are more effective in the treatment of supraventricular arrhythmias, rather than ventricular arrhythmias, and are of special benefit in the control of re-entrant supraventricular tachycardia and in reducing the ventricular rate in both atrial flutter and atrial fibrillation.

The adverse effects of verapamil and diltiazem are similar, including bradycardia, headache, peripheral vasodilatation, flushing and hypotension. The negative inotropic effect produced by these drugs contraindicates their use in patients with pre-existing depressed cardiac function.

Other anti-arrhythmic drugs

Adenosine is an agonist at adenosine receptors located on ATP-sensitive K^+ channels in cardiac cells. Its action is to open these channels, allow hyperpolarisation of the cell membrane, and prevent the opening of the Ca^{2+} channels. When given by i.v. injection, adenosine is effective in the treatment of paroxysmal ventricular tachycardia, especially Wolff-Parkinson-White syndrome. Adverse effects include facial flushing, chest pain, bronchospasm, lightheadedness, severe bradycardia and a choking sensation. Its use is contraindicated in asthmatic patients.

Digoxin acts by inhibiting the Na^+/K^+ pump in the cardiac cell membrane. This results in a decrease in the refractory period in both atrial and ventricular muscle cells, but an increase in the effective refractory period in the cells of the Purkinje tissue. Consequently digoxin is of benefit in the treatment of atrial flutter and atrial fibrillation as it prevents the rise in ventricular rate seen in these conditions. Digoxin has an extremely low therapeutic ratio and adverse effects include the generation of ectopic foci in the ventricles and the production of ventricular tachycardia. Other adverse effects of digoxin include cardiac arrhythmias, nausea, vomiting, diarrhoea and abdominal pain.

Angina pectoris

Cardiac muscle is dependent on a continuous supply of oxygen from the blood flowing through the coronary arteries. Unlike other types of muscle found in the body, cardiac muscle cannot function on an oxygen debt, as it cannot store oxygen inside the cells. Under normal conditions, the amount of oxygen supplied to the cardiac muscle cells by the coronary arteries is more than enough to supply the oxygen requirements

throughout the full range of cardiac workload. If, however, the coronary arteries become occluded, by the deposition of atheromatous plaques, then their ability to supply oxygenated blood may fall below that required to maintain cardiac muscle function. In this situation, the cardiac muscle cells become *ischaemic* and their anaerobic metabolism results in the release of a number of substances which cause pain.

Angina pectoris is the clinical syndrome that results from such cardiac ischaemia. It may initially be noticed as a shortness of breath, on exercise, but eventually progresses to a crushing pain around the chest and radiating down the left arm. It is more severe during exercise and may become completely debilitating, resulting in the patient being bedridden. A number of diseases may trigger the development of angina pectoris, including:

- coronary artery atherosclerosis
- coronary artery thrombosis
- coronary artery spasm (Prinzmetal's angina)
- accumulation of pain mediators at the site of damage to the endothelial lining of the coronary blood vessels.

The most common cause of angina is the development of atheromatous plaques in the coronary arteries supplying blood to the heart. In this situation, two types of angina pectoris may be identified:

(1) Stable angina. There is a stable plaque formation in the coronary artery and the degree of inhibition of coronary blood flow is constant. In this situation it is possible for the patient to predict the degree of exertion that will cause clinical symptoms of angina pectoris.
(2) Unstable angina. The atheromatous plaque may be fissured, or begin to break up. In this situation the patient is not able to predict the circumstances under which an anginal attack will develop.

The treatment of angina pectoris depends upon correct identification of the type of disease present. Furthermore, treatment must be aimed at not only aborting an anginal attack, but also preventing their development. Therefore treatment must be designed for both acute attacks and prophylaxis (prevention) of the development of angina attacks.

The treatment of stable angina pectoris centres on two strategies, either increasing the coronary blood flow by dilatation of the coronary arteries or decreasing the cardiac muscle oxygen requirements by reducing its workload. In unstable angina, prevention of platelet aggregation is used, in addition to standard treatment, in order to prevent the development of emboli, which may lodge in a coronary blood vessel and precipitate an attack.

Drugs used in the treatment of angina pectoris

Organic nitrates:	glyceryl trinitrate, isosorbide mononitrate, isosorbide dinitrate
β_1-Adrenoceptor antagonists:	propranolol, atenolol, metoprolol
Ca^{2+} channel-blocking drugs:	nifedipine, verapamil, diltiazem, isradipine, nicardipine
Antiplatelet drugs:	aspirin, clopidogrel, dipyridamole

Organic nitrates

The organic nitrates are esters of nitric or nitrous acids with alcohols. Some are gaseous at room temperature, whereas others are liquids or solids. They produce a rapid relief of the symptoms of angina, by relaxing vascular smooth muscle and hence increasing blood flow to the heart. This is brought about by the rapid metabolism of the nitrate (NO_3^-) ion, first to nitrite (NO_2^-) and then to nitric oxide (NO). NO is a potent stimulator of the enzyme guanylyl cyclase, which produces an increase in the intracellular levels of cGMP and relaxation of the circular smooth muscle of the blood vessels.

The effects of glyceryl trinitrate on the cardiovascular system are twofold. Firstly, it produces dilatation of the large veins, causing pooling of

blood in the venous system and a decrease in the venous return to the heart. Second, the dilatation of the coronary arteries increases blood flow and oxygen supply to the heart muscle. The consequent decrease in workload on the heart also reduces the oxygen demand of the cardiac muscle and further improves the patient's situation. Glyceryl trinitrate may be given in a number of different forms:

- sublingual tablets – placed under the tongue for the rapid treatment of an anginal attack
- slow-release tablets – placed on the gum for the prophylactic treatment of angina
- spray – for the rapid treatment of an anginal attack
- skin patches – placed on the skin to allow slow penetration of drug for prophylactic treatment.

Isosorbide mononitrate and isosorbide dinitrate are compounds that act in essentially the same way as glyceryl trinitrate, but which have a slower onset of action. However, they also have a more prolonged duration of action and may be used in the prophylactic treatment of angina.

One major problem with the use of nitrates for the treatment of angina pectoris is the development of the phenomenon of 'nitrate tolerance'. This develops over a period of weeks, if the patient is exposed to nitrates continuously, and results in a decreased clinical response to a given dose of the nitrate. Consequently, larger doses of nitrate have to be used in order to gain a clinically effective response, and the problem of adverse effects becomes important. Nitrate tolerance can be avoided by careful planning of the dosage to ensure that plasma levels of the drug vary over a 24-hour period and, ideally, the patient is free of nitrates for approximately 8 hours in each 24-hour period.

The adverse effects of organic nitrates derive from their pharmacological actions. The most common are a throbbing headache, facial flushing, dizziness, tachycardia and postural hypotension. Their use is contraindicated if the patient is hypersensitive to nitrates, or if the patient suffers from glaucoma.

β_1-Adrenoceptor antagonists

The β_1-Adrenoceptor antagonists produce their beneficial effects in the treatment of angina pectoris by antagonising the actions of norepinephrine and epinephrine on the β_1-adrenoceptor in the heart. This reduces both the heart rate and the contractile force of the heart, and hence its workload. A decrease in cardiac output and a slight fall in systemic blood pressure, both of which serve to further decrease the workload, improve these beneficial effects further. Metoprolol and propranolol are both examples of β_1-adrenoceptor antagonists that are of benefit in the treatment of angina pectoris.

The adverse effects associated with the use of β_1-adrenoceptor antagonists stem from their pharmacological mechanism of action. The major adverse effect is the development of airways constriction and the possible onset of asthma in susceptible patients. This results from the antagonist action of these agents on β_2-adrenoceptors in the airways, which are responsible for dilatation of the bronchioles. Propranolol is equipotent on both β_1- and β_2-adrenoceptors and is therefore contraindicated in susceptible patients. The other drugs in this group are cardioselective. However, they are not cardiospecific and their use in asthmatic patients must be carefully monitored.

Other adverse effects of β_1-adrenoceptor antagonists include hypotension, cardiac conduction disorders, peripheral vasoconstriction, sleep disturbances, fatigue and exacerbation of psoriasis.

Ca^{2+} channel-blocking drugs

Ca^{2+} channel-blocking drugs prevent the influx of Ca^{2+} ions into cardiac and smooth muscle cells, thus causing a decrease in muscular contraction and vasodilatation. They also decrease the influx of Ca^{2+} into myocardial cells and so decrease the velocity of impulse conduction in the heart.

Nifedipine acts predominantly on vascular smooth muscle and so decreases arteriolar resistance. It is of major benefit in the treatment of angina resulting from coronary artery spasm. Verapamil slows cardiac contraction, thus decreasing heart rate and cardiac muscle oxygen demand. It is contraindicated in patients with evidence of depressed cardiac function. Diltiazem reduces both heart rate and blood pressure, although the effect is less than that seen with

verapamil. Diltiazem also relieves coronary artery spasm and so is of benefit in the treatment of patients with variant angina.

Adverse effects resulting from the use of Ca^{2+} channel-blocking drugs include flushing, headache, hypotension and cardiac depression. Their use in patients with depressed cardiac function, or conduction abnormalities, is contraindicated.

Treatment of unstable angina

Patients who suffer from unstable angina have the additional problem of the generation of emboli that may precipitate an anginal attack without warning. An embolus is a small fragment of fibrin clot that breaks off from a thrombus and is carried in the blood. In order to decrease the likelihood of platelet aggregation triggering off the production of an embolus, these patients require additional therapy to prevent platelet aggregation.

Antiplatelet drugs

Aspirin is a potent, irreversible inhibitor of COX I, and so prevents the aggregation of platelets and the subsequent release of a number of vasoconstrictor agents, which would worsen the clinical situation. Low doses of aspirin, typically 75–150 mg/day, are sufficient to prevent platelet aggregation and decrease the incidence of heart attacks in patients suffering from unstable angina. Adverse effects of aspirin treatment include gastrointestinal bleeding, gastric ulceration and bronchospasm in susceptible patients. It should be used with care in asthmatics.

Clopidogrel and dipyridamole are both of benefit in the prevention of embolus formation in unstable angina. Adverse effects include an increased incidence of gastrointestinal bleeding, abdominal discomfort, nausea, vomiting, headache, dizziness, flushing, vertigo and paraesthesiae.

Treatment of Prinzmetal's angina

Prinzmetal's angina (variant angina) results from an unpredictable spasm of the coronary arteries. In the majority of patients nifedipine used alone is sufficient to produce dilatation of the coronary arteries and prevent the anginal attack. Newer Ca^{2+} channel-blocking drugs, such as isradipine and nicardipine, are also of benefit in this situation. The use of β_1-adrenoceptor antagonists is contraindicated in Prinzmetal's angina, as they may increase the frequency and severity of the spasms.

Hypertension

In the healthy adult the systolic and diastolic blood pressures are 120 mm Hg and 80 mm Hg respectively. This is usually reported as 120/80 and the blood pressure is kept within this normal range by the control systems described earlier in this chapter.

In many individuals, the blood pressure is considerably above these normal values, a situation termed *hypertension*. In the majority of people there is no identifiable reason for this elevation in blood pressure – this is called primary essential hypertension. More rarely, the hypertension may be due to epinephrine-secreting tumours or kidney malfunction – this is called secondary hypertension. Unless it is severe, the elevation in blood pressure may not produce any overt symptoms. However, the increase in the systolic blood pressure may lead to rupture of capillaries (stroke) and elevation of the diastolic blood pressure increases the workload on the heart and may precipitate heart failure.

In 1993, the Joint National Committee attempted to define the grades of hypertension in relation to the values for the blood pressure measured in individuals. Table 7.1 summarises the Joint National Committee's definitions of the various grades of hypertension.

Table 7.1 Joint National Committee definitions of grades of hypertension.

Blood pressure description	Systolic pressure (mm Hg)	Diastolic pressure (mm Hg)
Normal	<130	<85
High normal	130–139	85–89
Mild hypertension	140–159	90–99
Moderate hypertension	160–179	100–109
Severe hypertension	180–209	110–119
Very severe hypertension	>210	>120

The treatment of hypertension presents a series of problems:

(1) In many cases, hypertension is asymptomatic until the patient has suffered a cardiovascular accident, such as a stroke.
(2) All drugs that are used to treat hypertension have a range of adverse effects, some of which are especially severe for the patient.
(3) Patients who felt quite well before the hypertension was diagnosed, now feel considerably unwell due to the drugs. This causes problems with patient compliance as many patients stop taking their antihypertensive drugs, with potentially disastrous consequences.

It is desirable, therefore, to attempt to treat patients whose blood pressure is in the high normal range in ways that do not produce these problems. Patients may be advised to change their lifestyle, such that they avoid activities that might lead to an elevated blood pressure. The three most important parameters are:

(1) exercise
(2) reduction of body weight
(3) reduction of salt intake in the diet.

In many patients in the high normal range, these measures may be sufficient to reduce the diastolic blood pressure to a value < 90 mm Hg, a satisfactory response. Drug therapy should only be introduced if such measures are insufficient to reduce blood pressure to the desired range.

Drugs used in the treatment of hypertension

Diuretics:	thiazides, loop diuretics, potassium-sparing diuretics
β_1-Adrenoceptor antagonists:	propranolol, acebutolol, atenolol, betaxolol, bisoprolol, carvedilol, celiprolol, esmolol, metoprolol, nadolol, pindolol, oxprenolol, sotalol, timolol, labetalol
Centrally acting antihypertensives:	inhibitors of transmitter synthesis and release
Peripherally acting antihypertensives:	α_1-adrenoceptor antagonists, direct-acting vasodilators, adrenergic neurone-blocking drugs, potassium channel activators, calcium channel-blocking drugs
Drugs affecting the renin-angiotensin-aldosterone system:	ACE inhibitors, angiotensin II receptor antagonists

Diuretics

Thiazides:	chlorothiazide, mefruside, hydrochlorothiazide
Loop diuretics:	frusemide, bumetanide, torasemide, ethacrynic acid
Potassium-sparing diuretics:	amiloride, triamterene, spironolactone

Diuretics, either used alone or in combination with a β-blocker, are the first line of drug treatment for the control of mild hypertension. Low-dose diuretic therapy is relatively safe and is well tolerated in the majority of patients. The use of a diuretic drug reduces the chances of the hypertensive patient suffering stroke, myocardial infarction or heart failure, all of which are possible consequences of untreated hypertension.

Thiazides Thiazides, such as chlorothiazide and hydrochlorothiazide, inhibit the reabsorption of Na^+ ions from the cortical diluting segment and

the last third of the proximal convoluted tubule of the renal nephron. This results in a decrease in reabsorption of water, a decrease in extracellular fluid volume and circulating plasma volume, and a fall in blood pressure. At higher doses they also have a direct relaxant effect on the smooth muscle of blood vessels, further contributing to their antihypertensive effect. Long-term treatment with thiazide drugs, therefore, results in a gradual return of the plasma volume to normal values and peripheral resistance decreases.

Thiazides are extremely well tolerated in the majority of patients. Hyperglycaemia can occur in susceptible patients and so these drugs should not be used to treat diabetic patients who have developed hypertension. The major adverse effect is a decrease in plasma K^+ levels (hypokalaemia), resulting from an increase in the activity of the Na^+/K^+ exchange pump in the distal convoluted tubule of the nephron. Whilst this fall in plasma K^+ levels does not cause too many problems in otherwise healthy patients, it is clinically important in elderly patients and those receiving digoxin therapy. The consequences of uncontrolled hypokalaemia are cardiac arrhythmias and heart failure.

Loop diuretics Loop (high ceiling) diuretics, such as frusemide, act to inhibit the Cl^-/Na^+ reabsorption system in the ascending limb of the loop of Henle. This causes a reduction in the medullary osmotic pressure gradient and a consequent decrease in water reabsorption from the collecting ducts. The subsequent decrease in circulating plasma volume causes a marked fall in blood pressure. Adverse effects of frusemide include hypokalaemia, which is much more pronounced than that produced by the thiazides. Therefore patients under treatment with this drug should have their plasma K^+ levels monitored regularly. Other adverse effects include alkalosis, increased Ca^{2+} excretion, nausea, gastrointestinal disturbances, gout, hyperglycaemia, tinnitus, bone marrow depression and elevated plasma cholesterol. Their use is contraindicated in patients suffering cirrhosis of the liver or renal failure.

Potassium-sparing diuretics Potassium-sparing diuretics, such as amiloride, triamterene and spironolactone, produce their diuretic effect by inhibiting the Na^+/H^+ and Na^+/K^+ exchange pumps in the distal convoluted tubule of the nephron. Spironolactone acts by inhibiting the synthesis of the K^+-carrying protein responsible for the secretion of K^+ at this site. Consequently, there is decrease in Na^+ reabsorption, a small diuretic effect and a fall in blood pressure. Amiloride blocks the movement of Na^+ ions through ion channels in the cell membranes of the distal convoluted tubular cells, again causing a small diuretic effect and fall in blood pressure. Potassium-sparing diuretics are not usually used as the sole treatment for hypertension, but their inhibition of K^+ ion secretion can be used to offset the hypokalaemia produced by thiazides and loop-acting diuretics.

Adverse effects of amiloride and triamterene include dry mouth, gastrointestinal disturbances, confusion, postural hypotension and hyperkalaemia. Spironolactone may also cause impotence and gynaecomastia in the male and menstrual irregularities in the female. Their use is contraindicated in renal failure and hyperkalaemia. Spironolactone should not be used in pregnancy or Addison's disease.

The diuretic effects of thiazides, loop diuretics and potassium-sparing diuretics are summarised in Fig. 7.11.

β_1-Adrenoceptor antagonists

β_1-Adrenoceptor antagonists (β-blockers) block the β_1-adrenoceptors in the heart as well as β_2-adrenoceptors in the bronchi, blood vessels and liver. The exact mechanism by which these drugs lower blood pressure is not fully understood, but they reduce cardiac output, alter the sensitivity of the baroreceptors in the peripheral vasculature and reduce renin secretion in the kidney.

Propranolol is the prototype β-adrenoceptor antagonist and is equally active at both β_1- and β_2-adrenoceptors, whereas newer drugs, such as atenolol, bisoprolol and metoprolol, are more active on the β_1-adrenoceptors in the heart. Lipid-soluble drugs may also enter the CNS and produce an additional antihypertensive effect by reducing the activity in the sympathetic nerves innervating the heart and possibly reducing renin release from the kidneys. Pindolol is a partial

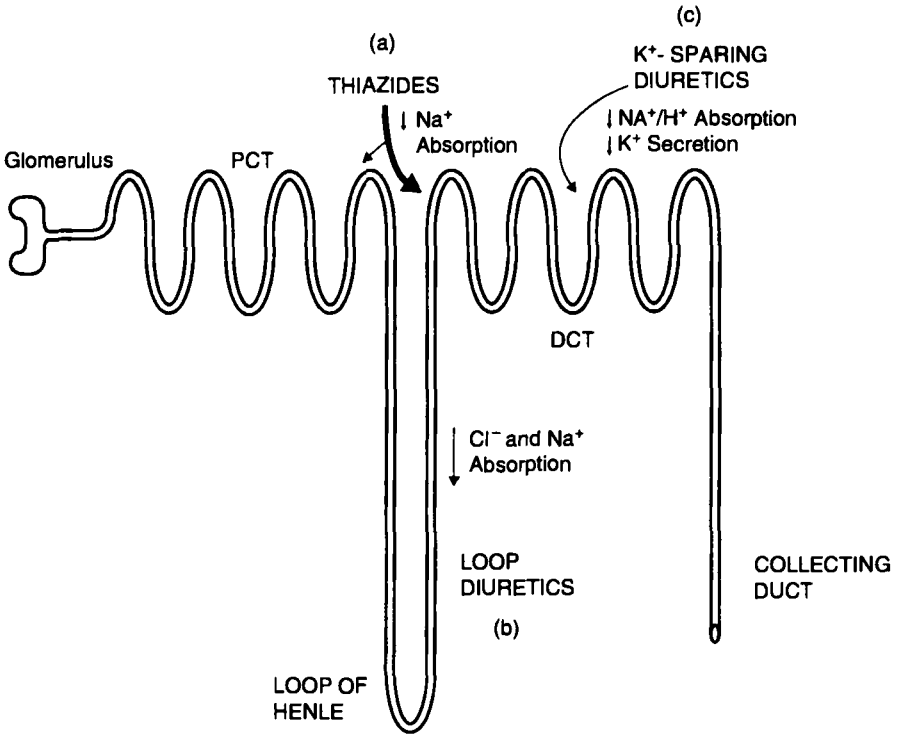

Fig. 7.11 The sites and mechanisms of action of diuretic drugs. (a) Thiazides inhibit Na^+ reabsorption in the cortical diluting segment and the proximal convoluted tubule (PCT). (b) Loop diuretics inhibit Cl^- and Na^+ reabsorption in the ascending limb of the loop of Henle. (c) Potassium-sparing diuretics inhibit Na^+/H^+ absorption and K^+ secretion in the distal convoluted tubule (DCT).

agonist at β_1-adrenoceptors and does not increase heart rate. Labetalol and carvedilol are also antagonists at the α_1-adrenoceptors in blood vessels and so lower peripheral resistance in addition to their β-blocking effect.

The β_1-adrenoceptor antagonists are generally well tolerated. Adverse effects include bradycardia, heart failure, hypotension, cardiac arrhythmias, peripheral vasoconstriction, gastrointestinal disturbances and fatigue. Those that penetrate the blood–brain barrier may cause sleep disturbances and hallucinations. Non-selective β_1-adrenoceptor antagonists are contraindicated in asthmatic patients and even the so-called cardioselective drugs must be used with extreme caution in such patients. All β_1-adrenoceptor antagonists are contraindicated in patients suffering from heart failure, Prinzmetal's angina, heart block or bradycardia.

Centrally acting antihypertensive drugs

Inhibitors of transmitter synthesis:	α-methyldopa
Inhibitors of transmitter release:	clonidine, moxonidine

Inhibitors of transmitter synthesis Centrally acting antihypertensive drugs act by inhibiting the sympathetic outflow from the CNS and thus cause a decrease in cardiac output and vasodilatation. α-Methyldopa is a substrate for the enzyme dopa decarboxylase, which is found in the nerve endings of the vasomotor centre. This enzyme is a key enzyme in the synthetic pathway for norepinephrine in these nerves, and is responsible for the conversion of dopa into dopamine.

Consequently, α-methyldopa is converted by the enzyme into α-methyldopamine which, in turn, is converted by the enzyme dopamine-β-hydroxylase into the false transmitter α-methylnorepinephrine. This substance is stored in the norepinephrine storage granules and is released on nerve stimulation. α-Methylnorepinephrine is less potent than norepinephrine on the post-synaptic α_1-adrenoceptors, but is more potent than norepinephrine on the inhibitory, presynaptic, α_2-adrenoceptors. Thus it inhibits further transmitter release.

Treatment with α-methyldopa produces a slow fall in blood pressure, which remains stable over a prolonged period of time. The adverse effects of α-methyldopa treatment include dry mouth, sedation, drowsiness, diarrhoea, depression, liver damage and sodium retention. It should also be borne in mind that α-methyldopa may well inhibit dopamine synthesis in dopaminergic neurones and so produce a Parkinson-like syndrome in susceptible individuals. The use of α-methyldopa is considered safe in pregnancy and in asthmatic patients, but it is contraindicated in patients suffering from depression or liver failure.

Inhibitors of transmitter release Clonidine is an agonist at the inhibitory presynaptic α_2-adrenoceptor and so inhibits transmitter release in adrenergic neurones and a consequent fall in blood pressure. The onset of action of clonidine is much quicker than that seen with α-methyldopa. Adverse effects include depression, dry mouth, bradycardia, fluid retention, nausea, constipation and rash.

Clinical depression is a common adverse effect seen with clonidine. This is often of sufficient severity to warrant cessation of treatment. However, great care should be taken on cessation of treatment, as rapid withdrawal of the drug will cause the release of large amounts of norepinephrine and a life-threatening rise in blood pressure. Death is usually due to a large subarachnoid haemorrhage. Therefore, clonidine must be withdrawn slowly.

Peripherally acting antihypertensive drugs

β_1-Adrenoceptor antagonists:	doxazosin, indoramin, prazosin, terazosin
Direct-acting vasodilators:	sodium nitroprusside, hydralazine
Adrenergic neurone-blocking drugs:	bethanidine, guanethidine, debrisoquine
Potassium-channel activators:	minoxidil
Calcium channel-blocking drugs:	amlodipine, diltiazem, felodipine, isradipine, lacidipine, nicardipine, nifedipine, nimodipine, nisoldipine, verapamil

α_1-Adrenoceptor antagonists Prazosin, doxazosin and indoramin are selective antagonists of norepinephrine at peripheral α_1-adrenoceptors in the blood vessels. They cause a rapid decrease in peripheral blood pressure, due to the vasodilatation that results from a reduction in the sympathetic drive to blood vessels. The major adverse effect is postural hypotension, especially after the first dose, and patients should be counselled to take their drug either at night, or while sitting down. Additional adverse effects include dizziness, drowsiness, weakness, headache, palpitations, urinary frequency, incontinence and priapism in males. Their use is contraindicated in patients who have heart failure.

Direct-acting vasodilators Sodium nitroprusside and hydralazine are directly acting vasodilators that produce a large fall in blood pressure. Their use is reserved for the management of hypertensive crises. Sodium nitroprusside is usually given by i.v. injection and is metabolised to NO. Nitric oxide acts by stimulating guanylyl cyclase and so increasing the intracellular levels of cGMP and hence relaxation of the vascular smooth muscle. Adverse effects include headache, dizziness,

nausea, retching, perspiration, palpitations and abdominal pain.

Hydralazine is used to treat mild to moderate hypertension that does not respond to other treatments. Again, hydralazine acts by increasing the levels of cGMP in the vascular smooth muscle cells, following activation of guanylyl cyclase. Adverse effects include fluid retention, tachycardia, nausea, vomiting, headache, rash and fever.

Adrenergic neurone-blocking drugs Adrenergic neurone-blocking drugs, such as bethanidine, debrisoquine and guanethidine, prevent the release of norepinephrine from the postganglionic nerve endings of the sympathetic neurones innervating the blood vessels. They enter the presynaptic nerve ending on the uptake 1 pathway and then bind to the inner surface of the neuronal membrane to prevent release of the neurotransmitter. They are now used primarily in the treatment of hypertension that is resistant to other drugs. Adverse effects include postural hypotension, fluid retention, nausea, headache, nasal congestion and failure of ejaculation in males. Their use is contraindicated in phaeochromocytoma, renal failure and heart failure.

Potassium-channel activators Minoxidil is an activator of ATP-sensitive K^+ channels in vascular smooth muscle. It causes a marked fall in blood pressure and is used in the treatment of severe hypertension. The opening of the K^+ channels by minoxidil hyperpolarises the cell membrane, and so reduces the influx of Ca^{2+} through the voltage-gated L-type Ca^{2+} channels in the cell membrane. Consequently, the vascular smooth muscle relaxes and blood pressure falls. Adverse effects include sodium and water retention, weight gain, peripheral oedema, tachycardia and increased hair growth. Its use is contraindicated in phaeochromocytoma.

Ca^{2+} channel-blocking drugs The entry of the Ca^{2+} for smooth muscle contraction can be reduced by the use of Ca^{2+} channel-blocking drugs, such as verapamil, diltiazem and nifedipine. The responsiveness of patients to Ca^{2+} channel-blocking drugs varies widely, elderly patients being most responsive. These drugs are of benefit in the treatment of a wide range of hypertensive patients, producing a well-controlled even fall in blood pressure. Adverse effects include headache, palpitations, sweating, tremor, flushing, gastrointestinal disturbances, dyspnoea and hypotension. Their use is contraindicated in pregnancy, unstable angina and heart block. They should not be used within 1 month of a heart attack.

Drugs affecting the renin-angiotensin-aldosterone system

ACE inhibitors:	captopril, enalapril, lisinopril, fosinopril, perindopril, quinapril, ramipril, trandolapril
Angiotensin receptor antagonists:	losartan, valsartan, candesartan

ACE inhibitors

ACE inhibitors are effective antihypertensive drugs in the treatment of moderate hypertension. The decrease in the production of angiotensin II, as a result of inhibition of the enzyme, leads to a direct fall in blood pressure as a result of a decrease in the amount of vasoconstriction. These drugs also inhibit the release of aldosterone from the adrenal cortex which, in turn, increases sodium loss from the kidney and so a diuresis.

Captopril, enalapril and fosinopril are examples of ACE inhibitors that are effective in the treatment of mild to moderate hypertension, especially when thiazides and/or β-adrenoceptor antagonists are contraindicated. They are of particular benefit in the treatment of hypertension in insulin-dependent diabetics. The first dose of an ACE inhibitor drug may cause a sudden fall in blood pressure and patients should be counselled accordingly. Adverse effects include angio-oedema, persistent dry cough, sinusitis, rhinitis, tachycardia, chest pain, flushing and photosensitivity. Their use is contraindicated in pregnancy and renovascular disease.

Angiotensin receptor antagonists

Losartan and valsartan are antagonists of angiotensin II at its receptor in vascular smooth

muscle. The administration of losartan causes a prolonged fall in blood pressure, similar to that produced by ACE inhibitors. However, their mechanism of action means that they have fewer adverse effects than ACE inhibitors and are better tolerated by sensitive patients. Adverse effects include hypotension and hyperkalaemia, and they should not be used in pregnant women.

Errors of blood clotting

Under normal circumstances, blood flowing through the blood vessels is a viscous liquid. However, if the blood vessels become damaged the blood will coagulate (clot) in order to restrict blood loss and arrest bleeding. The mechanism by which blood coagulates is complicated and depends on the activation of various factors present in the blood, by chemicals released at the site of tissue injury. This cascade results in the production of *fibrin*, which forms a blood clot and stops further blood loss.

Platelet activation

Normal blood clotting requires not only activation and aggregation of the platelets, which normally circulate in an inactive form, but also the subsequent production of *thrombin*, which catalyses the production of the fibrin clot. Under normal circumstances, circulating platelets contain a large number of granules that contain both 5-HT and ADP. The surface of the platelet has a number of receptors, the activation of which affects the ability of the platelet to store these granules. The process of emptying these storage granules in the platelets is termed *platelet degranulation*.

Prostacyclin is a prostaglandin derivative that is released from the endothelial lining of the blood vessel wall. Activation of a prostacyclin receptor on the platelet inhibits platelet degranulation. *Thromboxane A_2* is another prostaglandin-like compound that is released from activated platelets. Activation of the thromboxane A_2 receptor on the wall of the platelet leads to the release of more thromboxane A_2 and promotion of platelet degranulation. This forms a positive feedback loop which, if activated, leads to massive platelet aggregation and degranulation. When this occurs as the result of damage to a blood vessel, the platelets clump together to form a *platelet plug*, which prevents blood loss through the damaged wall of the blood vessel.

Thus we can see that the activation status of circulating platelets in normal blood is a balance between the inhibitory role of prostacyclin and the stimulatory role of thromboxane A_2. Thus, any factors that may alter this balance in favour of the thromboxane A_2 pathway will increase the chances of unwanted clot formation. In particular, physical damage to the endothelial lining of the blood vessels will both decrease the synthesis of prostacyclin and expose the underlying collagen, and so promote clot formation.

The process of platelet activation is summarised in Fig. 7.12.

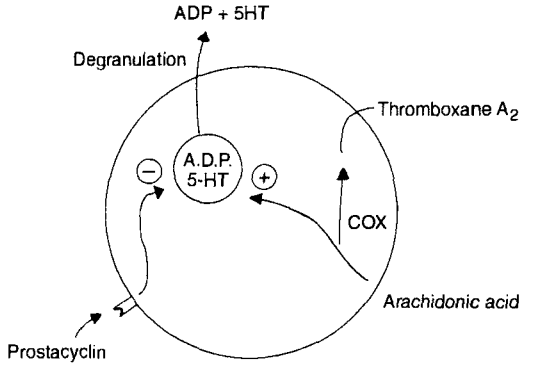

Fig. 7.12 The process of platelet activation. The release of ADP, 5-HT (platelet degranulation) and thromboxane A_2 all lead to platelet activation by positive feedback. Under normal conditions, platelet degranulation is inhibited by prostacyclin, but promoted by the products of arachidonic acid metabolism. Inhibition of COX by aspirin is the basis for the use of this drug to prevent thrombus formation following a heart attack.

Blood clotting

Localised stimulation of the coagulation cascade, by the factors released from both the damaged walls of the blood vessel and degranulated platelets, results in the production of thrombin (factor II). Thrombin is a serine protease enzyme that converts circulating *fibrinogen* into *fibrin*, which becomes deposited in the platelet plug to form the final clot. The clot is finally stabilised by the formation of cross-linkages between adjacent fibrin molecules.

Fibrinolysis

Fibrinolysis is the process by which fibrin is broken down. Activation of the clotting pathway described above also activates the fibrinolytic pathway. Inactive *plasminogen* is converted to the enzyme *plasmin*, which destroys fibrin. This mechanism serves to limit the production of unwanted fibrin clots and to dissolve formed clots following wound healing.

The coagulation cascade is summarised in Fig. 7.13. It is possible for this coagulation cascade to be triggered in undamaged blood vessels, usually by increased platelet aggregation. If this occurs, the blood vessel will become blocked by a blood clot (thrombosis) with potentially serious consequences for the patient.

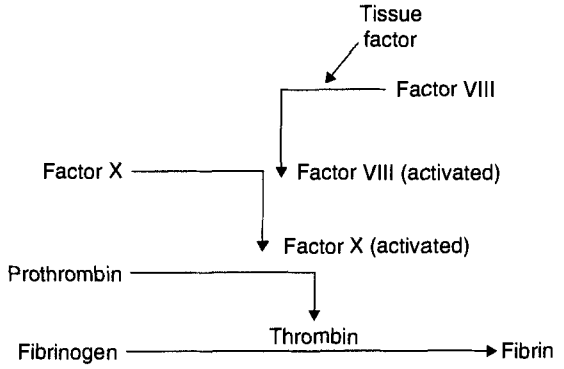

Fig. 7.13 The coagulation cascade. Activation of the various coagulation factors ultimately leads to the conversion of fibrinogen to fibrin.

Thrombus production in arteries and veins occurs by two different mechanisms:

(1) *Venous thrombosis* usually occurs in the deep veins of the legs and results from stagnation of blood, usually as a result of prolonged inactivity after an operation. The danger here is that part of the thrombus may break off, to form an embolus, which may then become lodged in the lung with fatal consequences.

(2) *Arterial thrombosis* usually occurs as a result of damage to the endothelial cells with age, often as a result of the deposition of atheromatous plaques. The subsequent non-laminar flow of blood around the plaque results in platelet activation and a triggering of the coagulation cascade. The resulting thrombus may then break up to form emboli, which can become lodged in small arteries, especially those in the brain.

Drugs used in the treatment of errors of blood clotting

Anticoagulants:	heparin, warfarin, phenindione
Platelet inhibitors:	aspirin, dipyridamole, clopidogrel
Thrombolytic drugs:	alteplase, anistreplase, reteplase, streptokinase, urokinase

Anticoagulants

Heparin is a rapidly acting anticoagulant which is usually given by s.c. or i.v. injection to prevent the formation of thrombi. Although it occurs naturally in combination with histamine, the heparin used commercially is usually produced from either porcine (pig) intestine or bovine (cow) lung. Heparin acts by binding to antithrombin III to produce an almost instantaneous anticoagulant effect, which is maximal within minutes of i.v. administration. It is the drug of choice for the treatment of deep vein thrombosis and pulmonary embolism and its prophylactic use decreases significantly the incidence of thromboembolisms in susceptible patients. Adverse effects include excessive bleeding, hypersensitivity reactions and thrombocytopenia.

Vitamin K is a fat-soluble vitamin that is essential for the synthesis of several factors in the coagulant cascade including factors II, VII, IX and X. Warfarin and phenindione are vitamin K antagonists that have a marked anticoagulant effect by inhibiting the clotting cascade at points where these factors act. Warfarin is the most widely used drug for the treatment of deep vein thrombosis and in patients who have suffered a heart attack, or who have undergone major cardiac surgery. These patients are often at risk of the spontaneous formation of emboli. The anticoagulant effect of warfarin takes 48–72 hours to become fully established.

The dose of warfarin must be monitored carefully, to ensure that haemorrhage does not occur and this is usually affected by monitoring the 'one-stage prothrombin time' or international normalised ratio (INR). This should be determined every 2–3 days at the start of treatment, and then every 10–12 weeks once the patient has been stabilised. In most clinical situations the INR should be in the range 2.0–3.0 to prevent the development of unwanted thrombi or emboli.

Great care should be taken in the administration of warfarin for two reasons:

(1) It is very highly bound to plasma proteins and so the administration of other protein-bound drugs may well displace sufficient warfarin to cause a major haemorrhage.
(2) Warfarin is metabolised by the cytochrome P-450 system in the liver, therefore the co-administration of drugs that alter the activity of this enzyme system will produce potentially serious changes in the availability of warfarin.

The major adverse effect of warfarin is excessive bleeding. Other adverse effects include hypersensitivity, rash, alopecia, diarrhoea, skin necrosis and jaundice. The use of warfarin is contraindicated in pregnancy, because it is teratogenic, peptic ulcer disease and severe hypertension.

Platelet inhibitors

Aspirin is the most commonly used drug for the prophylactic control of blood clotting, especially following a heart attack. It blocks the formation of thromboxane A_2 in platelets by irreversibly acetylating the enzyme COX I, the key enzyme in the synthetic pathway. The effect of aspirin on this system is rapid, most of it occurring in the hepatic portal system following absorption of the drug from the gastrointestinal tract. The aspirin-induced inhibition of thromboxane A_2 production lasts for the complete life of the platelet (7–10 days). The major adverse effect is an increase in gastrointestinal bleeding.

Dipyridamole is a coronary vasodilator normally used in the prophylactic treatment of angina. It acts by inhibiting the enzyme phosphodiesterase, which is responsible for the breakdown of cAMP in the cardiac cells, producing a rise in the intracellular concentration of this second messenger molecule. However, the ability of dipyridamole to increase cAMP levels in the platelets by the same mechanism also inhibits platelet degranulation, thus inhibiting the process of platelet activation. Adverse effects include gastrointestinal disturbances, dizziness, headache, tachycardia, hypotension, hot flushes and a worsening of the symptoms of coronary heart disease.

Clopidogrel is a recently introduced antiplatelet drug that is particularly effective in the prevention of atherosclerotic degeneration in patients who have a history of ischaemic stroke, heart attack or peripheral vascular disease. Adverse effects include haemorrhage, abdominal discomfort, constipation, nausea, vomiting, gastric ulceration, vertigo and paraesthesiae.

Thrombolytic drugs

Thrombolytic drugs are used to break down fibrin clots (thrombi and emboli) that have formed at sites within the cardiovascular system. They are of particular benefit if given to patients immediately following a heart attack, in the treatment of large pulmonary embolism and in the treatment of life-threatening deep vein thrombosis.

Streptokinase is the drug most commonly used in the treatment of life threatening venous thrombosis or in pulmonary embolism, but is likely to trigger hypersensitivity reactions. Urokinase may be used for thrombolysis in the eye and has the advantage of not causing hypersensitivity reactions. Adverse effects include nausea, vomiting and excessive bleeding.

Anaemias

Anaemias arise as a consequence of decreased oxygen-carrying capacity of the blood. Oxygen is normally carried in combination with haemoglobin inside the red blood cells (erythrocytes), however malfunctions of this oxygen carrying system will result in the symptoms of anaemia, such as shortness of breath and fatigue. There are several types of anaemia:

- *Iron-deficiency anaemia* is the most common type of anaemia. Iron is an essential con-

stituent of the haem part of the haemoglobin molecule and so a deficiency of iron results in decreased haemoglobin synthesis. Iron deficiency can arise from dietary failure, excessive excretion of iron, menstruation in women or pathological blood loss. In the latter case the anaemia may be symptomatic of a more serious underlying disease.

- *Megaloblastic anaemia* results from a deficiency of vitamin B_{12} (cobalamin) or folic acid, both of which are essential for the synthesis of DNA. Vitamin B_{12} is found in most animal products and is readily absorbed from the gastrointestinal tract, provided that an intrinsic factor is secreted from the stomach. Therefore, vitamin B_{12} deficiency is unusual in healthy patients who eat a normal diet. However, deficiency may arise as a result of some vegetarian/vegan diets and, in elderly patients, from a deficiency in intrinsic factor. This is sometimes called *pernicious anaemia*. Folic acid is found in a wide range of fresh foods, but it is destroyed rapidly by cooking. Folic acid deficiency can arise if food is overcooked, or the patient eats an inadequate diet. It may also arise in pregnancy, when the demand for folic acid is greater than normal, and as a result of alcohol abuse.
- *Anaemia of renal failure* usually arises as the result of a decreased production of erythropoietin by the cells of the kidney. Erythropoietin is an important factor that controls the growth and development of erythrocytes, as it stimulates cell proliferation and differentiation. In its absence, stem cells do not mature into erythrocytes and there results a decreased oxygen-carrying capacity in the blood.

Drugs used in the treatment of anaemias

Iron deficiency anaemias:	ferrous sulphate, ferrous gluconate, ferrous fumarate
Megaloblastic anaemias:	hydroxocobalamin, folic acid
Renal failure anaemia:	erythropoietin

Iron-deficiency anaemias

Iron-deficiency anaemias are treated by supplementing the dietary iron intake with the use of drugs such as ferrous sulphate and ferrous gluconate. Treatment should be aimed at increasing the haemoglobin content of blood by 1–2 g/l and treatment should be continued for at least 3 months to ensure replenishment of the body's iron stores. Adverse effects include gastrointestinal disturbances, constipation, diarrhoea and worsening of the symptoms of irritable bowel syndrome. It should be noted that excessive iron intake is potentially dangerous and so dietary supplements containing iron should not be taken unless there is a proven clinical necessity for them.

Megaloblastic anaemias

Anaemia resulting from a deficiency in vitamin B_{12} may be treated by the i.m. administration of hydroxocobalamin. In elderly patients this produces a rapid reversal of the fatigue and confusion seen as a result of their pernicious anaemia. Adverse effects include itching, fever, chills, flushes, nausea and hypokalaemia. Folic acid deficiency is treated by the administration of folic acid. It is extremely well tolerated.

Anaemia of renal failure

The administration of erythropoietin is of benefit in the treatment of the anaemia resulting from chronic renal failure. Adverse effects include hypertension, hyperkalaemia and convulsions.

Hyperlipidaemia and atherosclerosis

What is hyperlipidaemia?

Hyperlipidaemia is a complex group of diseases, all of which are characterised by there being an elevated level of lipids (fats) in the circulating blood. Hyperlipidaemias may be designated as primary or secondary, depending upon the underlying cause of the disease:

- *Primary hyperlipidaemia* may arise from two basic causes, either a defect in a single gene or, more commonly, a combination of genetic defects and environmental factors.

- *Secondary hyperlipidaemia* arises from an number of different causes. These include other disease states, such as diabetes mellitus and hypothyroidism, and cirrhosis of the liver, usually resulting from excessive intake of alcohol or other liver disease.

Normal lipid metabolism

Ingested lipid is the body's main source of stored fuel. The lipids that are consumed in our normal diet, and the compounds synthesised from them, form the major structural components of cell membranes, bile, steroid hormones, prostaglandins and leukotrienes.

Dietary lipids are absorbed in the form of free fatty acids and are converted into triglyceride–protein complexes by combination with the apoprotein apo B48 in the wall of the small intestine. These triglyceride protein complexes are then covered with a phospholipid monolayer to form *chylomicrons*, which then pass into the blood. Similarly, the liver is able to synthesis triglycerides and combine them with another apoprotein (apo B100) to form *very low-density lipoprotein* (VLDL), which is released into the blood.

These triglyceride-rich lipoproteins acquire the apoprotein apo C from *high-density lipoprotein* (HDL) particles and this acts as a co-factor for the enzyme lipoprotein lipase. Lipoprotein lipase is found in the cells of the vascular endothelium and catalyses the breakdown of the triglycerides in both chylomicrons and VLDL to release free fatty acids, which are then taken up into the metabolising cells. The breakdown of VLDL by lipoprotein lipase also leads to the production of *low-density lipoprotein* (LDL). The remnants of the chylomicrons, and LDL resulting from the breakdown of VLDL, are absorbed into the liver to re-form VLDL. This process is summarised in Fig. 7.14.

We can see from Fig. 7.14. that fatty acids from our diet are moved around the body as *triglycerides* incorporated into *lipoproteins*, and that

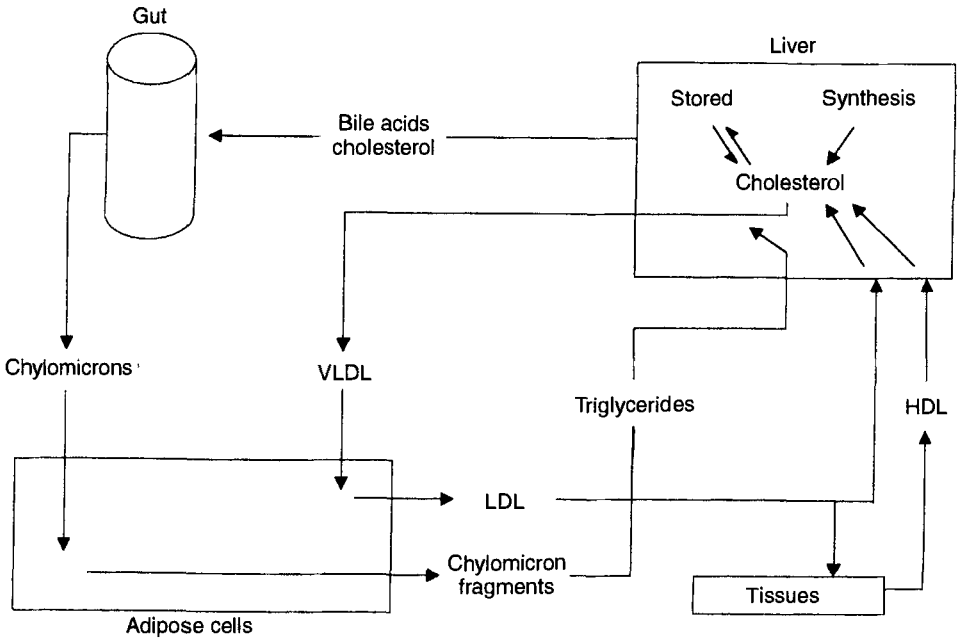

Fig. 7.14 The carriage of lipids and triglycerides in the blood. Fats are absorbed from the gut and carried to adipose cells as chylomicrons. Chylomicron fragments and LDLs are transported to the liver to be synthesised into cholesterol. HDL is also transported from tissues to the liver for conversion to cholesterol. Cholesterol may also be synthesised *de novo* in the liver as well as being stored for future use. VLDL is used to transport cholesterol to adipose cells. Some cholesterol is excreted into the gut together with a range of bile acids.

the most important constituent is *cholesterol*. Therefore the levels of cholesterol in the blood at any one time are of prime importance in the satisfactory functioning of this system. Too much cholesterol can lead to the deposition of fatty deposits on the walls of major blood vessels (see atherosclerosis below) and major cardiovascular disease.

What is atherosclerosis?

Atherosclerosis is a disease of the cardiovascular system that usually results from an elevation in the levels of cholesterol in the blood (see hyperlipidaemias above) and is one of the major clinical consequences of hyperlipidaemia. In the early stages of the disease excess cholesterol is laid down on the inner surface of the walls of blood vessels as 'fatty streaks'. Eventually, these fatty streaks develop into *atheromatous plaques*, which are large deposits of fatty tissue protruding into the lumen of the blood vessel.

The consequences to the patient of the formation of atheromatous plaques are many and especially affect the circulating blood and the cardiovascular system. These may be summarised as follows:

(1) The decrease in the diameter of the blood vessel means that there is a decrease in the flow of blood through the vessel, possibly causing ischaemia in the tissues which receive their blood supply from the affected vessel. This is of major importance in the heart and the brain.
(2) The flow of blood past the plaque is turbulent, thus increasing the chances of platelet activation and increased formation of blood clots (thrombi and emboli).
(3) Damage to the endothelial cells decreases the production of prostacyclin and nitric oxide, thus causing an increase in platelet aggregation and blood pressure.
(4) Damage to the wall of the blood vessel decreases the elasticity of the wall and results in an increase in both systolic and diastolic blood pressures, resulting in an increased workload on the heart and possibility of stroke.

Drugs used in the treatment of hyperlipidaemias and atherosclerosis

Resins:	cholestyramine, colestipol
Fibrates:	bezafibrate, ciprofibrate, clofibrate, fenofibrate, gemfibrozil
HMG-CoA reductase inhibitors:	atorvastatin, cerivastatin, fluvastatin, pravastatin, simvastatin
Nicotinates:	acipimox, nicotinic acid
Fish oils:	omega-3 marine triglycerides

Resins

The resins, cholestyramine and colestipol, are anion-exchange resins that are particularly effective in the treatment of hyperlipidaemia resulting from excessive fat absorption from the gastrointestinal tract, although they are also effective against other types of hyperlipidaemias. They both act by binding to the bile acid which is essential for lipid absorption from the gastrointestinal tract, thus allowing the cholesterol in the gut to be excreted in the faeces. As a consequence of this decrease in cholesterol absorption, more is taken up by the liver, to be converted into bile, and so there is a decrease in the levels of LDL in the blood.

Neither of these resins is absorbed from the gastrointestinal tract and so they show very few adverse effects. However, some adverse effects do occur and include gastrointestinal discomfort, constipation, diarrhoea, nausea and vomiting. It should be noted that these resins might also decrease the absorption of other anions from the gastrointestinal tract and, in particular, they reduce the absorption of fat-soluble vitamins, such as vitamin K, causing a potential decrease in the effectiveness of the coagulation cascade in blood.

Fibrates

The fibrate drugs, such as bezafibrate and clofibrate, are derivatives of fibric acid. They act primarily to increase the activity of lipoprotein lipase in the periphery and so promote the clearance of the triglycerides in chylomicrons and VLDL from the blood, by increasing their transfer into metabolising cells. The result of this action is to promote the transfer of cholesterol esters from HDL to triglyceride-rich particles and this, in turn, increases the cholesterol content of HDL. These drugs are especially effective in the treatment of the hypertriglyceridaemia associated with diabetes mellitus. Adverse effects include gastrointestinal disturbances, nausea, gastric pain, headache, dizziness, vertigo, fatigue and pruritis. They are contraindicated in severe renal or hepatic failure.

HMG Co-A reductase inhibitors

The enzyme 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase is responsible for the synthesis of mevalonic acid, the immediate precursor of cholesterol. Inhibition of this enzyme by drugs such as atorvastatin and pravastatin leads to a decrease in cholesterol synthesis in the liver and an increased uptake of cholesterol from the blood. These drugs produce a fall in the cholesterol content of LDL, HDL and VLDL and produce the greatest fall (35–40%) in LDL-cholesterol. These drugs have now been reported to produce a number of effects on muscle, especially myalgia (muscle pain), myopathy (decreased muscle mass) and muscle weakness. Other adverse effects include insomnia, headache, abdominal pain, fatigue, nausea and vomiting. They should be used with caution in patients with impaired liver function and a high intake of alcohol. Their use is contraindicated in pregnancy.

Nicotinates

Nicotinic acid and acipimox both cause a marked decrease in the levels of VLDL, by reducing the transfer of fatty acids from adipose tissue to the liver. The lowered level of VLDL results in a transfer of cholesterol into HDL and a decrease in LDL-cholesterol. Adverse effects include flushing, vasodilatation, headache, epigastric pain, heartburn, dry eyes, bronchospasm, urticaria, itching and rashes. Their use is contraindicated in pregnancy and peptic ulcer disease.

Fish oils

Omega-3 triglycerides, such as eicosapentaenoic acid, are an essential constituent of cell membranes. Ingestion of fish oils reduces VLDL synthesis. Adverse effects are rare, but include nausea and flatulence.

SUMMARY

- The cardiovascular system (CVS) is a highly specialised transport system, consisting of the heart, blood vessels and blood.
- The heart consists of two atria and two ventricles.
- The right atrium receives deoxygenated blood from the venae cavae and passes it to the right ventricle; the right ventricle delivers blood to the lungs.
- The left atrium receives oxygenated blood from the lungs and passes it to the left ventricle; the left ventricle delivers blood to the aorta and the systemic circulation.
- Backflow of blood in the heart is prevented by valves.
- The pumping action of the heart is achieved by alternating contraction (systole) and relaxation (diastole) of the cardiac muscle.
- The heart beat is initiated by a depolarisation in the sino-atrial node, which spreads across the atria, through the atrioventricular node into the bundle of His and the Purkinje tissue. The sinoatrial node acts as the pacemaker for the heart.
- Electrical activity in the heart results from the movement of Na^+, K^+ and Ca^{2+} ions across the cell membrane of the cardiac muscle cells; these ion movements take place through ion channels.
- Electrical activity in the heart can be monitored on an ECG.
- The force and rate of contraction of the heart are modified by both neuronal and hormonal factors, such as the sympathetic and parasympathetic branches of the autonomic nervous system and the hormone epinephrine.

- Blood vessels may be classified into arteries, arterioles, capillaries and veins.
- With the exception of capillaries, all blood vessels have a trilaminar wall; arteries and arterioles have large amounts of smooth muscle.
- Capillaries are the sites of exchange of gases, nutrients and metabolites between blood and the tissues.
- Blood pressure may be expressed as systolic/diastolic pressure; the normal value is 120/80 mm Hg.
- Blood pressure is controlled by the baroreceptor reflex system and by the renin-angiotensin-aldosterone system.
- Blood consists of plasma plus erythrocytes, leucocytes and thrombocytes (platelets).
- Erythrocytes carry oxygen to the tissues, leucocytes are part of the body's defence mechanisms and platelets are associated with the formation of blood clots.
- Plasma contains large amounts of protein, especially albumin, which binds many drugs and renders them unavailable to the body.
- Major diseases of the CVS include heart failure, cardiac arrhythmias, angina pectoris, hypertension, errors of the blood clotting mechanism, anaemias, hyperlipidaemias and atherosclerosis.
- Heart failure occurs when the heart muscle fibres become overstretched and can no longer contract with their normal force. This results in a decreased cardiac output and renal function, together with the accumulation of fluid (oedema) in the lower limbs and lungs.
- Heart failure may be treated with positive inotropic drugs, diuretics, ACE inhibitors and vasodilator drugs.
- Cardiac arrhythmias arise from disorders of either impulse generation or impulse conduction in the heart. They are debilitating and may be life-threatening.
- Arrhythmias arising from disorders of impulse generation are atrial flutter, atrial fibrillation, ventricular fibrillation and ventricular paroxysmal tachycardia.
- Disorders of impulse conduction give rise to heart block and re-entrant tachycardia.
- Cardiac arrhythmias are treated with drugs that depress electrical activity in the heart. The major drugs are Na^+ channel blockers, β_1-adrenoceptor antagonists, K^+ channel blockers and Ca^{2+} channel-blocking drugs.
- Adenosine and digoxin may also be used to treat certain types of arrhythmia.
- Angina pectoris is the tight, crushing pain felt around the chest and in the arms when the oxygen demand of the cardiac muscle exceeds the ability of the coronary circulation to deliver oxygenated blood in sufficient quantities.
- Angina may arise from coronary artery atherosclerosis (stable and unstable angina), or from coronary artery spasm (Prinzmetal's angina).
- Angina may be treated with organic nitrates, β_1-adrenoceptor antagonists or Ca^{2+} channel-blocking drugs.
- Hypertension is the name given to a state of elevated blood pressure; it may be graded from mild to very severe.
- Primary essential hypertension is the name given to hypertension arising from no identifiable cause.
- Untreated hypertension leads to an increased workload on the heart, leading to heart failure, and an increased risk of cardiovascular accident (stroke).
- Hypertension may be treated with diuretics, β_1-adrenoceptor antagonists, centrally acting drugs, peripherally acting drugs and drugs that inhibit the renin-angiotensin-aldosterone system.
- The formation of blood clots serves to prevent blood loss at sites of injury; it is triggered by the process of platelet activation and aggregation.
- The clotting cascade consists of a series of inactive clotting factors that are activated in turn, finally resulting in the formation of a fibrin clot.
- Excessive blood clot formation may lead to the development of arterial thrombosis and deep vein thrombosis, both of which are capable of blocking the vessel in which they are formed. Emboli are floating clots that may lodge in distant blood vessels.

- Excessive clot formation may be treated with anticoagulants, inhibitors of platelet activation or thrombolytic drugs.
- Anaemias arise as a consequence of decreased oxygen-carrying capacity in the blood.
- Common anaemias are iron-deficiency anaemia, megaloblastic anaemia and the anemia of renal failure; they may be treated by replacement therapy.
- Hyperlipidaemias (particularly raised cholesterol levels) and atherosclerosis are closely linked disease states.
- Hyperlipidaemias may be classified as primary or secondary, according to the underlying cause.
- Atherosclerosis is a disease of the blood vessels in which there is deposition of atheromatous plaques that may block the lumen of the vessel.
- Atherosclerosis can give rise to angina, hypertension, stroke and an increased workload on the heart.
- Hyperlipidaemias and atherosclerosis may be treated by anion exchange resins, fibrates, HMG CoA reductase inhibitors, nicotinates or fish oils.

8

Drugs Affecting the Respiratory System

INTRODUCTION

The mammalian respiratory system is the primary mechanism by which the cells of the body receive oxygen for their many metabolic processes and by which the large amounts of carbon dioxide produced by this metabolism are excreted. Air is drawn into the respiratory tract, by the process of *inspiration*, and passes through the nasopharynx, trachea and the lungs. The air then passes through a series of smaller and smaller bronchioles before entering the alveoli. The alveoli are the site of gaseous exchange between the inhaled air and the blood passing through the lungs:

- Oxygen passes from the alveolar air into the blood where it combines with haemoglobin in the erythrocytes to form oxyhaemoglobin.
- Carbon dioxide passes in the reverse direction from the blood into the alveolar air. The air is then expelled from the lungs by the process of *expiration*.

Each lung contains thousands of alveoli and the surface area available for gas exchange is about $80\,m^2$.

Respiration is the rhythmical cycle of inspiration and expiration that ensures the alveoli are adequately aerated with air containing a high concentration of oxygen and that the air containing carbon dioxide is efficiently expelled. It is controlled by spontaneous rhythmical discharges from the respiratory centre in the medulla of the brainstem. The respiratory centre is, in turn, influenced by higher centres in the brain and by vagal afferent nerve fibres coming from the lungs.

Inspiration occurs as a result of contractions of both the diaphragm and the intercostal muscles between the ribs. This causes an increase in the volume of the thorax and expansion of the lungs. The resultant decrease in air pressure in the lungs allows air to flow in from the atmosphere down a pressure gradient. Under normal conditions,

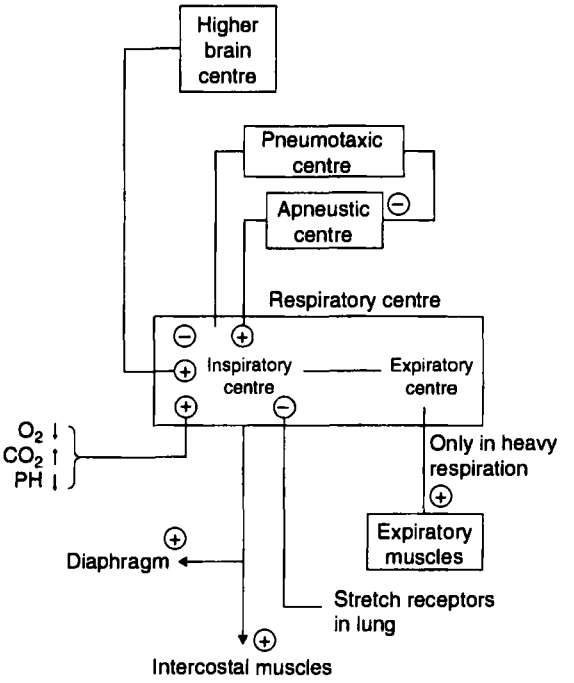

Fig. 8.1 The mechanisms controlling respiration. The inspiratory centre is stimulated by the apneustic centre, higher centres in the brain and by changes in the levels of oxygen (O_2), carbon dioxide (CO_2) and hydrogen (H^+) ions in the blood. It is inhibited by the pneumotaxic centre, expiratory centre and afferent fibres running from stretch receptors in the lungs. Inspiration is brought about by contraction of both the diaphragm and the intercostal muscles. Expiratory muscles are only activated during forced expiration.

expiration is brought about by relaxation of the diaphragm and intercostal muscles, which allows the thorax to return to its original volume, and so air is pushed out of the lungs. The control of respiration is summarised in Fig. 8.1.

The airways leading to the alveoli contain large amounts of smooth muscle in their walls and their diameter is controlled by a number of different influences. These are:

(1) *Parasympathetic innervation* via the vagus nerve releases ACh, which interacts with mAChRs to cause smooth muscle contraction.
(2) *Non-adrenergic non-cholinergic (NANC) innervation* releases neurotransmitters, some of which are inhibitory (NO) and some of which are excitatory (substance P) on bronchial smooth muscle.
(3) *Circulating epinephrine*, synthesised in the adrenal medulla, acts on β_2-adrenoceptors to relax bronchial smooth muscle.

Therefore the tone and degree of contraction of airway smooth muscle is the sum total of parasympathetic, NANC and circulating epinephrine influences and, as a result, the smooth muscle of the airways is normally partially contracted. The control of airway smooth muscle is summarised in Fig. 8.2.

DISEASES OF THE RESPIRATORY SYSTEM

Adequate functioning of the respiratory system is dependent not only on the ease with which air can enter and leave the system, but also on the ability of the alveoli to effect efficient and adequate exchange of oxygen and carbon dioxide in the short time interval between inspiration and expiration. Diseases of the respiratory system can arise if the patient's airways become constricted, or if the lining of the respiratory tract becomes inflamed, giving rise to symptoms such as coughing, wheezing, shortness of breath and abnormalities of gaseous exchange.

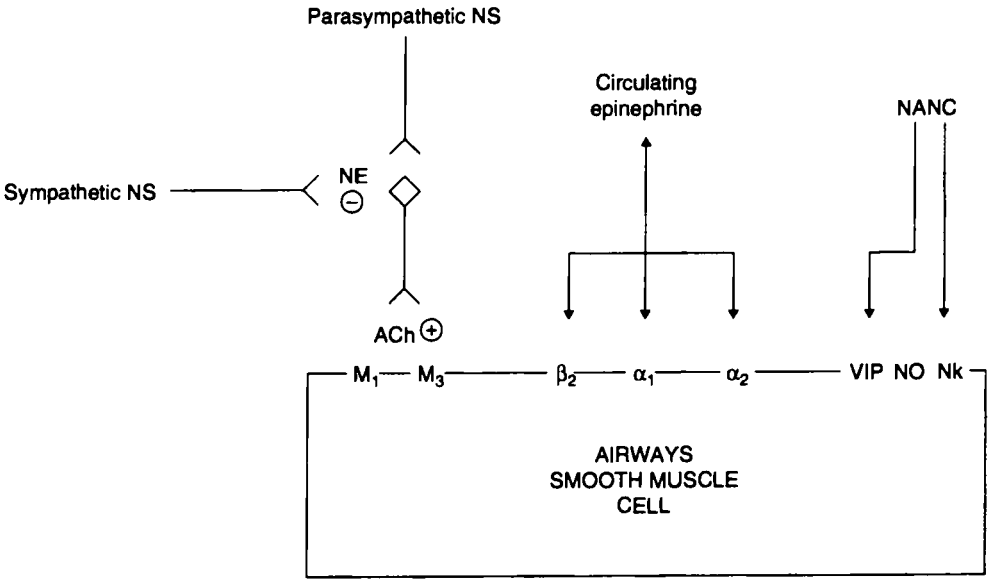

Fig. 8.2 The control of airways smooth muscle. Contraction of airways smooth muscle is mediated via a variety of receptors and natural spasmogens; ACh acts upon M_1 and M_3 mAChRs and its release is modulated by norepinephrine (NE). Circulating epinephrine acts on α_1-, α_2-, and β_1-adrenoceptors; there is considerable NANC innervation of airways smooth muscle. VIP, vasoactive intestinal peptide; Nk, neurokinin A.

The major diseases of the respiratory system are:

- bronchial asthma
- chronic bronchitis
- cough
- cystic fibrosis
- rhinitis and rhinorrhoea
- respiratory tract infections.

Bronchial asthma

Bronchial asthma is a chronic inflammatory disease characterised by constriction of the airways leading to a decrease in respiratory function and respiratory distress. This is the result of constriction of the airways smooth muscle, oedema of the mucosal lining and an increase in the secretions of the cells lining the airways. It affects about 20% of the population and is particularly prevalent in children.

Bronchial asthma is usually mediated via IgE antibodies bound to mast cells in the mucosal lining of the airways. There is usually a family history of the disease. When challenged by re-exposure to the antigen an antigen–antibody reaction takes place which results in the release of mediators such as histamine and leukotrienes, which are stored in the mast cells. These agents then diffuse throughout the airways and cause the bronchoconstriction and oedema typical of asthma. Figure 8.3 summarises the processes that occur during the development of bronchial asthma.

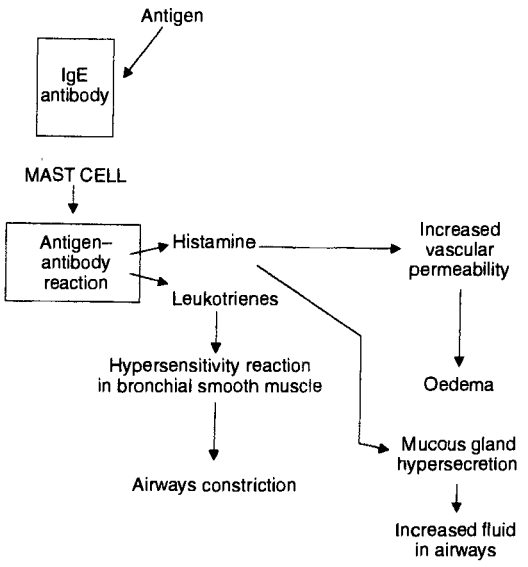

Fig. 8.3 Factors leading to the development of bronchial asthma. Bronchial asthma is usually an IgE-mediated response to exposure to an antigen. The release of histamine and leukotrienes leads to an increased vascular permeability, mucous gland hypersecretion and constriction of the bronchioles.

Drugs used in the treatment of bronchial asthma

β_2-Adrenoceptor agonists:	salbutamol, bambuterol, terbutaline, reproterol, salmeterol
Xanthines:	aminophylline, theophylline
Antimuscarinic drugs:	ipratropium, oxitropium
Leukotriene receptor antagonists:	montelukast, zafirlukast
Membrane stabilisers:	sodium cromoglycate, nedocromil sodium
Corticosteroids:	beclomethasone, budesonide, fluticasone, prednisolone

β_2-Adrenoceptor agonists

β_2-Adrenoceptor agonists, such as salbutamol and salmeterol, produce their beneficial effect by stimulating the β_2-adrenoceptors found on airways smooth muscle and mast cells. They are effective against all types of bronchoconstriction, irrespective of the mediator, and they are the most common drugs used to alleviate the bronchoconstriction associated with bronchial asthma. Relaxation of the smooth muscle is mediated via an increase in the concentration of intracellular cAMP. These drugs are usually given by inhalation, thus enabling the use of a low dose, which avoids the systemic adverse effects.

Adverse effects include tachycardia (an action on β_1-adrenoceptors on the heart), peripheral vasodilatation, tremor, nervous tension and hypokalaemia.

Antimuscarinic drugs

Antimuscarinic drugs, such as ipratropium and oxitropium, can be given by inhalation and produce bronchodilatation by inhibiting the bronchoconstrictor action of the ACh released from cholinergic nerves. They are effective against bronchoconstriction mediated via the cholinergic pathway, but are less effective against that resulting from other mediators. The size of the response is usually less than that obtained with β_2-adrenoceptor agonists, but their effect is a useful adjunct to other treatments. Adverse effects include dry mouth, blurred vision, constipation and urinary retention. They are contraindicated in patients suffering from glaucoma.

Xanthines

Xanthines, including theophylline and aminophylline, have been used for many years to relieve the symptoms of asthma. They are usually given orally and act to produce a rise in the intracellular levels of cAMP because they inhibit the enzyme phosphodiesterase, which is responsible for the breakdown of the cyclic nucleotide in the cell. The major problem with xanthines is that they have a low therapeutic ratio and a wide range of adverse effects including nausea, tachycardia, cardiac arrhythmias, headache, insomnia and convulsions.

Leukotriene antagonists

Leukotriene antagonists, such as montelukast and zafirlukast, represent the newest approach to the management of bronchial asthma. The role of leukotrienes in the development of asthma has only recently become fully established. Leukotrienes are formed from arachidonic acid, by the action of the enzyme 5-lipoxygenase, and leukotriene D_4 is a potent bronchoconstrictor agent. It is now thought that the release of leukotriene D_4 is one of the main contributory factors to the severe bronchoconstriction characteristic of bronchial asthma.

Montelukast is now used as additional treatment for asthmatic patients who do not respond adequately to other treatments. Zafirlukast is effective in the prophylaxis of bronchial asthma. Adverse effects include abdominal pain, headache, diarrhoea, dizziness and infections of the upper respiratory tract.

Membrane stabilisers

Membrane stabilisers, such as sodium cromoglycate and nedocromil, do not cause bronchodilatation. They act partially by stabilising the mast cell membranes and so prevent the release of the chemicals, such as histamine, prostaglandins and leukotrienes, which produce bronchoconstriction. They are used prophylactically in the treatment of bronchial asthma. Adverse effects include coughing, transient bronchospasm (due to the dry powder inhaler), headache, nausea and vomiting (nedocromil).

Corticosteroids

Corticosteroids, such as beclomethasone and prednisolone, are glucocorticoids that act by reducing the mucosal oedema associated with bronchial asthma, thus reducing the secretion of fluid and aiding adequate ventilation. They also inhibit cell infiltration into the airways. They act on steroid receptors within the cells to produce a number of beneficial effects:

- They promote the synthesis of lipocortin-1 which inhibits phospholipase A_2, one of the key enzymes in the production of eicosanoids, such as prostaglandins and leukotrienes.
- They inhibit the synthesis of the cytokines, interleukin-5 and tumour necrosis factor, important mediators in the inflammatory process.

Corticosteroids are of no benefit in acute asthma and must be given repeatedly. They may be used prophylactically to reduce the inflammation associated with bronchial asthma and are effective when given by inhalation in small doses (50–250 μg), or larger doses (30–40 mg) given orally.

Adverse effects of inhaled steroids may be divided into local and systemic effects. Locally, they increase the likelihood of candidial infections of the nose and throat and hoarseness of the voice as a result of relaxation of the vocal cords.

Systemically, high doses of these drugs can cause depression of the adrenal gland and changes in bone metabolism.

Chronic bronchitis

Chronic bronchitis is usually caused by either a gradual, irreversible decrease in the diameter of the airways over a period of years or an increase in the mucous secretions of the glands lining the airways. Typically it is associated with cigarette smoking and does not involve an allergic response. It can, however, lead to the development of a severe debilitating state and a tendency towards regular respiratory infections.

Typically chronic bronchitis patients show a decrease in adequate oxygenation of the blood and a build-up in carbon dioxide levels, both resulting from inadequate aeration of the alveoli. Secondary pulmonary hypertension may also develop which can lead to failure of the right side of the heart. Chronic bronchitis is often accompanied by emphysema, particularly in heavy smokers, giving rise to chronic obstructive airways disease (COAD).

Drugs used in the treatment of chronic bronchitis

β_2-Adrenoceptor agonists:	salbutamol, salmeterol
Xanthines:	theophylline, aminophylline
Mucolytics:	methylcysteine, carbocisteine, dornase alfa
Antimuscarinic drugs:	ipratropium, oxitropium

β_2-Adrenoceptor agonists
Short-acting and long-acting β_2-adrenoceptor agonists, such as salbutamol and salmeterol, are of benefit in the treatment of chronic bronchitis, but are less effective than in bronchial asthma as there is little increase in the degree of bronchoconstriction in these patients. Benefit is derived from the extra bronchodilatation allowing for better ventilation of the alveoli. The adverse effects of these drugs are discussed above.

Xanthines
Xanthines, such as theophylline and aminophylline, again cause dilatation of the airways and produce a small degree of benefit to the patient. However these drugs also have a mild stimulant action on the CNS, which is perceived to be beneficial in some patients. The adverse effects of these drugs are discussed above.

Mucolytics
Mucolytic drugs, such as carbocisteine and methyl cysteine, act by breaking down the chemical bonds which hold the glycoproteins of the mucus together, thus decreasing the viscosity and enabling expectoration from the airways. The major adverse effect is gastrointestinal disturbances.

Dornase alfa is a genetically modified version of the naturally occurring enzyme that breaks down extracellular DNA. It may be administered by inhalation and produces a thinning of the bronchial mucus. Adverse effects include pharyngitis, laryngitis, chest pain and conjunctivitis.

Antimuscarinic drugs
Anticholinergic drugs, such as ipratropium and oxitropium, are the mainstays of the treatment of chronic bronchitis. They are given by inhalation directly into the airways and cause a direct bronchodilatation by inhibition of the action of ACh on airways smooth muscle. Adverse effects include dry mouth, blurred vision, urinary retention and constipation.

Cough

Coughing is a reflex triggered by either mechanical or chemical stimulation of the upper respiratory tract or by stimulation of cough centres in the CNS. It is an important defensive reflex, which promotes the removal of potentially dangerous objects, or secretions, from the respiratory tract, but it may require treatment if it becomes distressing or exhausting.

Coughing involves the activation of a reflex arc, which is normally initiated by stimulation of cough-sensitive receptors in the walls of the respiratory tract. Afferent nerve fibres lead into the cough centre in the CNS and efferent fibres

innervate the intercostal muscles. The treatment of recurrent cough, in the absence of obvious mechanical stimulation, is directed to breaking the cough reflex arc.

Drugs used in the treatment of cough

Opioids:	codeine, pholcodine, dextromethorphan
Sedating antihistamines:	diphenhydramine

Opioids
The most effective drugs used for the control of cough are the opioid analgesics, such as codeine, pholcodine and dextromethorphan. They act as agonists on opiate receptors in the cough centre in the CNS to inhibit transmission through the centre and so break the cough reflex. The adverse effects of opioids are discussed in Chapter 5.

Sedating antihistamines
Sedating antihistamines, such as diphenhydramine, are often used in cough preparations. They do not have any direct action on the cough centre, but act by virtue of their sedating properties. Adverse effects include drowsiness, which may be associated with their mechanism of action. The major adverse effect is sedation, which may be too severe to allow continuation of treatment.

Cystic fibrosis

Cystic fibrosis is an inherited disease that usually results from a specific protein mutation resulting in a decreased clearance of Cl^- ions from apical cells, especially the mucus-secreting cells in the alveoli. It starts in early childhood and affects the lungs, pancreas and sweat glands. The decreased Cl^- excretion leads to water retention and the secretion of over-thick mucous, which forms a mucous plug, primarily in the airways, but it can also occur in the pancreas and sweat glands. The poor circulation of inspired air in the airways of cystic fibrosis patients renders them prone to respiratory infections.

Drugs used in the treatment of cystic fibrosis

Mucolytics:	carbocisteine, methyl cysteine
Antimuscarinic drugs:	ipratropium, oxitropium
Others:	dornase alfa
Antibacterials:	gentamicin, tobramycin, ciprofloxacin

The treatment of cystic fibrosis is centred on attempts to physically remove the mucus plug by back-slapping techniques, drugs to thin the mucus, drugs to prevent secretion of mucus and antibacterial drugs to combat infection.

Mucolytics
Mucolytic drugs, such as carbocisteine and methyl cysteine, decrease the viscosity of the mucus and render it easier to remove.

Antimuscarinic drugs
Antimuscarinic drugs (ipratropium and oxitropium) may be of benefit in some patients to reduce the mucous secretions.

Antibacterial drugs
The most common bacteria found in the airways of cystic fibrosis patients are *Staphylococcus aureus* and *Pseudomonas aeruginosa*. Therefore pneumonia is an extremely common consequence in these patients. Antibacterial drugs such as gentamicin and tobramycin are of major benefit in the control of these infections.

Other drugs
Dornase alfa is a genetically engineered version of a naturally occurring enzyme that cleaves extracellular DNA. It is discussed above.

Rhinitis and rhinorrhoea

Rhinitis is an acute or chronic inflammation of the mucosal lining of the nasal cavity, whereas rhinorrhoea is a condition characterised by the production of a watery secretion from the nasal mucosa. Both conditions may arise either as the

result of a viral infection of the nasal lining (common cold) or an antigen–antibody interaction in the nasal mucosa (allergic rhinitis). There is usually an increase in the blood flow to the nasal mucosa, and in the permeability of the blood vessels, resulting in an increase in the volume of the nasal mucosa producing the familiar 'sniffles and blocked nose' of the common cold.

The most important control of nasal blood flow is a sympathetically mediated neural mechanism involving the release of norepinephrine. Therefore drugs that mimic the actions of norepinephrine act as decongestants. There are several other targets for the drug control of rhinitis and rhinorrhoea. The immune response typical of rhinorrhoea releases histamine and other autacoids. Thus drugs which inhibit the immune response, act as antagonists of histamine or inhibit the actions of other autacoids to give symptomatic relief.

Drugs used in the treatment of rhinitis and rhinorrhoea

The treatment of rhinitis and rhinorrhoea should, ideally, be aimed at identifying and eliminating the cause, for example the removal of any stimulant allergen. However, this may not always be possible and so symptomatic treatment is required.

H_1 receptor antagonists:	azelastine, levocabastine, mepyramine, chlorpheniramine, diphenhydramine
Anti-inflammatory drugs:	beclomethasone, betamethasone, budesonide, dexamethasone, flunisolide, fluticasone, triamcinolone, sodium cromoglycate
Sympathomimetics:	ephedrine, phenylephrine, xylometazoline

H_1 receptor antagonists

Histamine is stored in mast cells of the nasal mucosa and may be released by a number of different chemical and physical stimuli. It is the major autacoid that is released as a result of allergic reactions in the nasal mucosa. H_1 receptor antagonists (antihistamines), such as azelastine and levocabastine, are effective in relieving the actions of histamine without causing undue drowsiness in the patient. These drugs are administered as an aqueous nasal spray. Adverse effects include irritation of the nasal mucosa, headache, and disturbances in taste.

Older antihistamines, such as chlorpheniramine and diphenhydramine, are equally effective but may cause considerable drowsiness in some patients. They may be given orally. The major adverse effect is drowsiness.

Anti-inflammatory drugs

Anti-inflammatory corticosteroids, such as beclomethasone, budesonide and fluticasone, are extremely effective for the treatment of allergic rhinitis. They are usually administered as nasal sprays to minimise their adverse effects. They have a marked anti-inflammatory action and may be used in the prophylactic treatment of allergic rhinitis. Sodium cromoglycate is a membrane stabiliser that inhibits the release of histamine from mast cells. It is effective in reducing the itching and sneezing associated with allergic rhinitis.

Adverse effects are usually localised to the nasal passages, mouth and throat. They include dryness and irritation of the nose and throat, perforation of the nasal septum and hoarseness of voice. A rise in intraocular pressure may result from prolonged treatment, and so their use in patients who have glaucoma should be carefully monitored. Care should also be taken in the presence of nasal infection as this may be exacerbated.

Sympathomimetics

The inflammatory response, and subsequent runny nose, seen in most patients who suffer rhinitis is associated with vasodilatation. Consequently, active vasoconstriction will tend to reverse the symptoms and dry up the rhinorrhoea. Sympathomimetic drugs, such as ephedrine,

phenylephrine and xylometazoline, are agonists on the α_1-adrenoceptor and cause a marked constriction of the blood vessels of the nasal mucosa, so reducing the 'stuffed-up' sensation typical of rhinitis and so are of use as nasal decongestants.

The prolonged use of nasal decongestants should be avoided as most patients show a reduced responsiveness after 1–2 weeks' treatment. Patients also experience a rebound nasal congestion as the effect of a dose wears off, sometimes resulting in their taking subsequent larger doses.

Adverse effects of nasal decongestants include local irritation (if applied as drops or sprays) and rebound congestion. Oral administration may give rise to a marked increase in blood pressure. They are, therefore, contraindicated in patients who suffer from hypertension.

Respiratory tract infections

The warm, moist environment of the respiratory tract is an ideal site for the potential growth of pathogenic bacteria, viruses and fungi that are carried in with the inhaled air. The clinical importance of a respiratory tract infection depends upon its location, the clinical status of the patient and the susceptibility of the infecting microorganism to drug treatment. Pharyngitis and laryngitis are infections of the pharynx and larynx respectively, which are usually of viral origin, although streptococcal infections can also occur. A number of organisms may be responsible for infections of the sinuses, termed sinusitis, including streptococci, *Haemophilus influenzae* and certain viruses. Pneumonia is an infection of the bronchioles and alveoli, which may also involve the pleural membranes (pleurisy). It is a common complication in elderly patients who have become bed-bound and who have impaired ventilation of the lungs.

Tuberculosis

Tuberculosis is an extremely dangerous respiratory tract infection that arises from infection by the microorganism *Mycobacterium tuberculosis*. Mycobacterial infections have arisen throughout recorded history and they present particular problems that render them difficult to treat and eradicate. In particular, mycobacteria grow very slowly and so they are not susceptible to antibacterial drugs that act by inhibiting cell replication. Furthermore, the mycobacteria become localised in areas of the lung to which drugs cannot easily gain access and so it is difficult to attain a sufficiently high concentration of drug for it to implement its antimycobacterial effect.

M. tuberculosis infections are most common in conditions of poverty and overcrowding, when it may be transmitted easily by spray from coughing patients. Improvements in social conditions during the nineteenth century, and the development of effective antitubercular drugs, led to a decrease in the incidence of tuberculosis during the earlier parts of the twentieth century. However, mycobacterial resistance has developed to the drugs currently in use and we now have a situation in which tuberculosis is emerging again throughout the Western world in a more virulent form.

Drugs used in the treatment of respiratory tract infections

The drug treatment of respiratory infections depends upon the successful identification of the invading microorganism. Most respiratory tract infections are the result of viruses, rather than bacteria, and so treatment of these infections with antibacterial drugs is of no benefit to the patient. In fact, the inappropriate use of antibacterial drugs may make the situation worse by allowing for the development of resistant microorganisms.

Antibacterial drugs:	erythromycin, penicillin, cephalosporins
Antituberculosis drugs:	capreomycin, isoniazid, ethambutol, pyrazinamide, rifabutin, rifampicin, streptomycin

Antibacterial drugs

The pharmacology of the antibacterial drugs used for the treatment of infections of the respiratory tract is discussed in Chapter 9.

Antituberculosis drugs

The treatment of tuberculosis usually requires the use of a cocktail of drugs, in order to achieve a high enough bactericidal response without the development of resistant mycobacteria in the patient. The pharmacology of the drugs used to treat tuberculosis is discussed in Chapter 9.

SUMMARY

- The respiratory system comprises the nasopharynx, trachea, lungs, bronchi, bronchioles and alveoli of the lungs.
- It is responsible for the efficient oxygenation of blood and for the excretion of carbon dioxide.
- Respiration is the process of rhythmical inspiration and expiration that results in the efficient movement of air into and out from the lungs.
- The respiratory centre in the brain controls respiration.
- Inspiration is brought about by contraction of both the diaphragm and the intercostal muscles.
- Major diseases of the respiratory system are bronchial asthma, chronic bronchitis, cough, cystic fibrosis, rhinitis/rhinorrhoea and respiratory tract infections.
- Bronchial asthma is a chronic inflammatory disease in which the airways become constricted and inflamed, resulting in serious breathing difficulties.
- In most cases, bronchial asthma is triggered by exposure to an allergen.
- Bronchial asthma may be treated with β_2-adrenoceptor agonists, xanthines, antimuscarinic drugs, leukotriene receptor antagonists, membrane stabilisers or corticosteroids.
- Chronic bronchitis usually results from a gradual decrease in the diameter of the airways and an increase in mucous secretion.
- It is often accompanied by the development of emphysema, giving rise to chronic obstructive airways disease.
- Chronic bronchitis may be treated with β_2-adrenoceptor agonists, xanthines, antimuscarinic drugs and mucolytics.
- Cough is a very common ailment resulting from either mechanical or chemical stimulation of the upper respiratory tract or the cough centres in the CNS.
- Cough may be treated with opioids and sedating antihistamines.
- Cystic fibrosis is an inherited disease that results in the production of a viscous mucus in the respiratory tract, which can form mucous plugs to block the movement of air.
- Patients who suffer from cystic fibrosis are prone to respiratory tract infections.
- Cystic fibrosis may be treated with mucolytic drugs, antimuscarinic drugs and antibacterial drugs. Dornase alfa is a genetically engineered enzyme that aids destruction of the mucous.
- Rhinitis is an acute or chronic inflammation of the mucosal lining of the nasal cavity.
- Rhinorrhea is a watery discharge from the nasal cavity (runny nose).
- Both conditions may be treated with H_1 receptor antagonists, anti-inflammatory drugs or sympathomimetic drugs.
- Infections of the respiratory tract may be bacterial, viral or, rarely, fungal.
- Infections of the upper respiratory tract are easier to treat than those in the lower tract.
- Bacterial respiratory tract infections can be treated with the appropriate antibacterial drug.
- Viral infections, such as the common cold, are usually self-limiting and only require symptomatic treatment.
- Tuberculosis is an extremely dangerous mycobacterial infection of the respiratory tract.
- The treatment of tuberculosis requires specialist drugs, used in combination to avoid the development of resistance.

9

Chemotherapeutic Drugs

INTRODUCTION

Throughout our normal everyday life we are exposed to a wide range of potentially harmful microorganisms and parasites. These microorganisms include *bacteria*, *fungi*, *viruses*, and the parasites include *worms* and *protozoa*. The development of chemotherapeutic drugs to combat the effects of these invading organisms has been one of the major therapeutic developments of the twentieth century. Consequently, diseases that once were fatal may now be treated successfully. However, while the widespread use of chemotherapeutic drugs throughout the world has been of major benefit in the control of infectious diseases, we are now witnessing the development of strains of invading microorganisms that are resistant to the drugs currently available.

The successful action of chemotherapeutic drugs lies in their *selective toxicity*, which means that they are able to kill invading microorganisms without causing significant damage to the normal cells of the patient. This ability to kill invading microorganisms depends upon exploitation of the differences between the biochemical process in the microorganism and those in the cells of the patient. However, the selective toxicity of chemotherapeutic agents is rarely absolute and it is necessary to control the dose of drug carefully in order to get the maximum therapeutic effect, while minimising the adverse side-effects. Consequently, the use of these drugs in patients is often associated with a range of adverse effects that result from their direct actions on the patient's normal, healthy cells and metabolic processes.

Chemotherapeutic drugs may be divided into four major groups:

(1) antibacterial drugs (including antimycobacterial drugs for tuberculosis)
(2) antifungal drugs
(3) antiviral drugs
(4) anthelmintic drugs.

ANTIBACTERIAL DRUGS

Folate antagonists:	sulphamethoxazole, sulphadiazine, trimethoprim
Penicillins:	phenoxymethylpenicillin, ampicillin, amoxycillin, flucloxacillin
Cephalosporins:	cephalexin, cephradine, cefuroxime, cefixime
β-Lactamase inhibitors:	clavulanic acid
Protein synthesis inhibitors:	tetracycline, oxytetracycline, minocycline, erythromycin, gentamicin, streptomycin, neomycin, tobramycin, chloramphenicol, clindamycin
Antimycobacterial drugs:	capreomycin, cycloserine, ethambutol, isoniazid, rifabutin, rifampicin

One of the greatest ranges of potential dangers to health to which we are exposed derives from infections by bacteria. Such infections can give rise to a wide variety of diseases, ranging in severity from a sore throat to those that are potentially life-threatening, such as bacterial pneumonia. Thus the use of antibacterial drugs (antibiotics) now represents one of the largest therapeutic areas. The success of antibacterial drugs, in killing the invading microorganism, depends upon highlighting the differences between the biochemical characteristics of the invading bacterium and inhibiting the normal growth process of the organism. Selection of a suitable antibacterial drug depends upon a number of factors. These are:

- correct identification of the organism and its known sensitivity to antibacterial drugs
- the site of the infection
- the health status of the patient.

In theory, successful identification of the invading organism, and its sensitivity to antibacterial drugs, requires the collection of a sample from the patient and subsequent laboratory evaluation. Whilst this is the procedure of choice in the case of serious infections where the patient is hospitalised, clearly it cannot be followed in general medical practice. Consequently, the choice of a suitable antibacterial drug in a wide range of bacterial infections that do not require hospital treatment is based upon the knowledge and expertise of the medical practitioner.

The actual site of the infection may also play an important part in the choice of antibacterial therapy. In order for the antibacterial drug to produce its effect it must be distributed to the site of the infection in a suitable concentration to kill the invading microorganism. Clearly, any factors that reduce the penetration of the antibacterial drug to the site of infection will reduce the effectiveness of the treatment. One of the major barriers to the distribution of antibacterial drugs is the blood–brain barrier. Consequently, treatment of bacterial infections in the CNS is difficult and so suitable antibacterial drugs may have to be administered by intrathecal injection. Similarly, the location of an infection site in an area where the flow of blood is low, such as an infected ulcer, may require the administration of higher doses than normal to attain the desired therapeutic effect.

The clinical status of the patient is also important in the choice of a suitable antibacterial drug. Antibacterial drugs only kill, or inhibit the growth of, invading bacteria. It is the role of the patient's immune system to ultimately eliminate the bacteria from the body. Consequently, patients whose immune system is inhibited in any way may require larger doses of antibacterial drug than normal. Clinical situations that may cause this effect include alcoholism, diabetes, malnutrition and advancing age.

Many antibacterial drugs are eliminated by the kidney. Therefore decreased renal function can result in a rise in the plasma levels of the drug, possibly leading to the development of toxicity. Similarly, decreased hepatic function may result in increases in the plasma levels of antibacterial drugs metabolised in the liver. Obviously care must be taken in the treatment of elderly patients.

CLASSIFICATION OF BACTERIA

Bacteria may be classified according to their reaction to the Gram stain. This is a staining technique that highlights differences in the chemical composition of the bacterial cell wall. Gram-positive bacteria contain a mucopolysaccharide in their cell wall that retains the Gram stain, such that they appear red when viewed under the microscope. Gram-negative bacteria do not contain this mucopolysaccharide molecule in their cell walls; consequently they do not retain the Gram stain and appear to be colourless when viewed under the microscope. Whilst the classification of bacteria as either Gram positive or Gram negative is based on the presence, or absence, of a particular structural component of the bacterial cell wall, it may be used to predict the bacteria's sensitivity to antibacterial drugs.

Examples of some common disease-causing bacteria, and their Gram classification, are shown in Table 9.1.

Table 9.1 Gram classification of common disease-causing bacteria.

Bacterium	Gram reaction
Staphylococcus aureus	Positive
Streptococcus pyogenes	Positive
Cornybacterium diphtheriae	Positive
Bacillus subtilis	Positive
Haemophilus influenzae	Negative
Neisseria gonorrhoeae	Negative
Escherichia coli	Negative
Vibrio cholerae	Negative

BACTERIAL RESISTANCE

Many bacteria exhibit the phenomenon of *resistance*, whereby they cease to become susceptible to the antibacterial drug and develop resistant strains, which are not controlled by the usual range of antibacterial drugs. The reasons why such resistance develops are manyfold, but it may be ascribed to the widespread use of antibacterial drugs in inappropriate clinical situations, or at inadequate doses to ensure complete elimination of the bacteria from the patient. The consequence of this process is the emergence of the so-called 'superinfections' seen in some hospitals.

Bacterial resistance may arise from changes in the bacterial DNA, either as a result of spontaneous mutations, or following the transfer of DNA from one microorganism to another. Other causes include modifications to the site at which the drug works, decreased accumulation of the drug inside the bacterium and the development of enzymes that destroy the antibacterial drug.

The possible mechanisms of bacterial resistance are summarised in Fig. 9.1.

Classification of antibacterial drugs

Antibacterial drugs may be classified according to their effects on the invading bacteria. *Bacteriostatic* drugs inhibit the growth and replication of bacteria, thus limiting the spread of the infection while the body's immune system attacks and destroys the bacteria. *Bactericidal* drugs actually kill the invading bacteria and directly cause a decrease in the number of bacteria in the patient.

Spectrum of activity

Not every antibacterial drug is equally effective against all bacteria. The term *chemotherapeutic spectrum of activity* refers to the species of bacterium that are sensitive to a particular antibacterial drug. Narrow-spectrum antibiotics, such as isoniazid, are only effective against a single species of organism, whereas broad-spectrum antibacterial drugs, such as amoxycillin, are effective against a wide range of both Gram-positive and Gram-negative bacteria.

It should be noted that the use of broad-spectrum antibacterial drugs, such as amoxycillin and tetracycline, might have an adverse effect on the patient in that they may well destroy the natural bacterial flora in the gastrointestinal tract and cause digestive problems, such as diarrhoea.

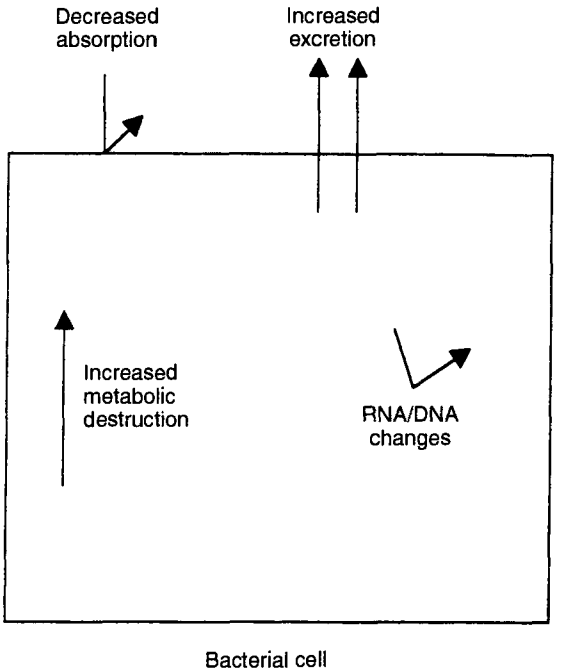

Fig. 9.1 Mechanisms of bacterial resistance. Bacterial resistance to antibacterial drugs can arise from decreased drug absorption, increased drug excretion, increased metabolic destruction of the drug or changes in the bacterial RNA/DNA which render the drug inactive.

Antibacterial drugs may be classified according to their mechanism of action as follows:

(1) folate antagonists
(2) inhibitors of cell wall synthesis
(3) inhibitors of protein synthesis.

FOLATE ANTAGONISTS

Folic acid is an essential vitamin that acts as a cofactor in the process of protein synthesis. Humans require folic acid in their diet and human cells are able to absorb it from the bloodstream. However, bacteria are unable to absorb folic acid and rely on its synthesis from p-aminobenzoic acid (PABA) inside the bacterial cell.

Sulphonamides, such as sulphamethoxazole, are structurally related to PABA, and are able to compete with PABA for the synthetic pathway to folic acid, thus reducing folic acid synthesis in the bacterial cell and inhibiting cell growth. Sulphonamides are bacteriostatic. Adverse effects include renal damage due to the deposition of crystals of the drug at acid pH, gastrointestinal disturbances, nausea and vomiting, and hypersensitivity reactions such as rashes.

The active form of folic acid is the tetrahydro-derivative formed by the reduction of folic acid by the enzyme dihydrofolate reductase. Trimethoprim is an inhibitor of this enzyme and so its administration prevents the production of tetrahydrofolate and therefore inhibits bacterial cell growth. Trimethoprim is about 50 times more active than the parent sulphonamides and is often used alone in the treatment of urinary tract infections. Adverse effects following the use of trimethoprim usually only appear on prolonged therapy. They are the result of decreased availability of folic acid in the patient's cells and include megaloblastic anaemia and granulocytopenia.

The mechanism of action of folate antagonists is summarised in Fig. 9.2.

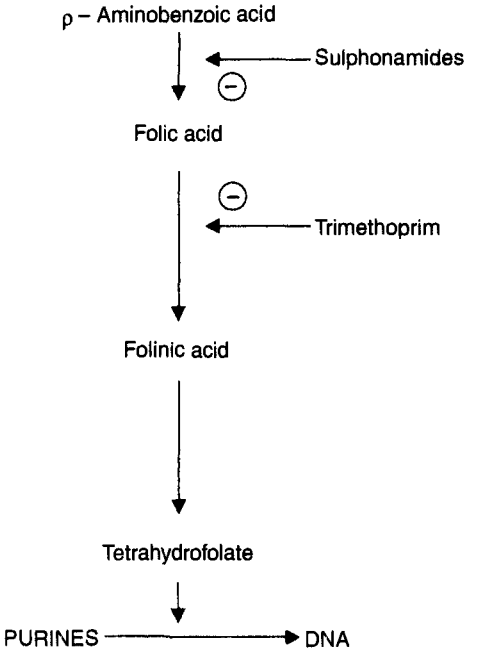

Fig. 9.2 The mechanism of action of folate antagonists. Sulphonamides inhibit the conversion of PABA to folic acid; trimethoprim inhibits the conversion of folic acid to folinic acid; both ultimately prevent bacterial DNA synthesis.

INHIBITORS OF CELL WALL SYNTHESIS

Bacterial cells have a well-defined cell wall. Interference with the production of the building blocks of the cell wall will, obviously, lead to inhibition of cell growth and subsequent elimination of the infecting microorganism.

Penicillins

Penicillins, such as phenoxymethylpenicillin, ampicillin and amoxycillin, are probably the most widely used antibacterial drugs currently available. They are members of the group of β-lactam antibacterial drugs that act primarily by inhibiting the synthesis of the bacterial cell wall. They are, therefore, bactericidal and more effective against bacteria that are multiplying rapidly. Penicillins bind to a number of penicillin-binding

proteins, found in the cell wall of susceptible bacteria, controlling the cross-linking between peptidoglycan chains that is essential for the stability of the cell wall.

Penicillins are active against both Gram-positive and Gram-negative bacteria, although their action against the latter is dependent upon their ability to penetrate the lipid membrane surrounding Gram-negative bacterial cells.

Phenoxymethylpenicillin (penicillin V) is used widely in the treatment of bacterial infections that do not produce the enzyme penicillinase, which destroys the drug molecule. Ampicillin, amoxycillin and flucloxacillin are examples of penicillins that are resistant to destruction by penicillinase, and so may be used to treat infections by penicillinase-producing bacteria.

Bacterial resistance to the penicillins arises from three major causes. The most common is the development of enzymes that can destroy the β-lactam ring in the penicillin molecule, which is essential for its action. Therefore the development of the ability to synthesise the enzyme β-lactamase renders the drug inactive due to destruction of the β-lactam ring. Structural alterations in the penicillin-binding proteins reduce the affinity of these proteins for the penicillin, thus reducing the effectiveness of the drug. Finally, a decrease in the penetration of the drug through the outer cell membrane of the bacterial cell prevents the drug from reaching the penicillin-binding proteins.

Adverse reactions to penicillins are rare. Diarrhoea is the most common adverse effect, resulting from an imbalance of the gastrointestinal flora. Neurotoxicity is a possible consequence of very high plasma levels, necessitating care in their administration to epileptic patients. Hypersensitivity reactions to penicillins are rare, but may be life-threatening in the small number of patients in which they occur. One of the major metabolites of penicillin is penicilloic acid, which reacts with proteins to cause an immune reaction. In most patients this reaction produces a mild rash which clears on cessation of treatment. However, in susceptible patients this reaction may result in swelling of the lips and tongue (causing breathing difficulties) and even death as a result of anaphylactic shock.

It should be noted that cross hypersensitivity might occur between penicillins and other β-lactam antibacterial drugs and, to a lesser extent, with other antibacterial drugs. Therefore it is essential to monitor carefully patients who have shown hypersensitivity reactions to penicillins, even if they are subsequently treated with drugs from another antibacterial group.

Cephalosporins

Cephalosporins, such as cephalexin, cefuroxime and cefixime, are β-lactam antibacterial drugs closely related to the penicillins. They have the same site and mechanism of action as the penicillins, but are more resistant to the β-lactamase enzymes. They may be classified into first, second and third generation cephalosporins. First generation drugs have a spectrum of activity similar to that of the penicillins. Second and third generation drugs have enhanced activity against Gram-negative bacteria.

Resistance to cephalosporin therapy arises from the same mechanisms as that for the penicillins, except that their resistance to β-lactamase reduces the incidence of resistance due to this mechanism. Adverse effects are similar to those derived from the penicillins and cross-sensitivity in hypersensitivity reactions occurs. In addition, some second and third generation cephalosporins inhibit alcohol metabolism, producing a disulphiram-like reaction on drinking alcohol. This is characterised by a throbbing headache and facial flushing and results from an accumulation of acetaldehyde.

β-Lactamase inhibitors

Hydrolysis of the β-lactam ring in penicillins and cephalosporins is the major mechanism by which the antibacterial activity of these drugs is reduced. Thus inhibitors of the enzyme β-lactamase, such as clavulanic acid, would be expected to inhibit the breakdown of the antibacterial drug and so prolong its activity in the patient. β-Lactamase inhibitors have no antibacterial activity of their own, but are usually given in combination with one of the penicillins to enhance their activity.

The basic structures of penicillins and cephalosporins are shown in Fig. 9.3.

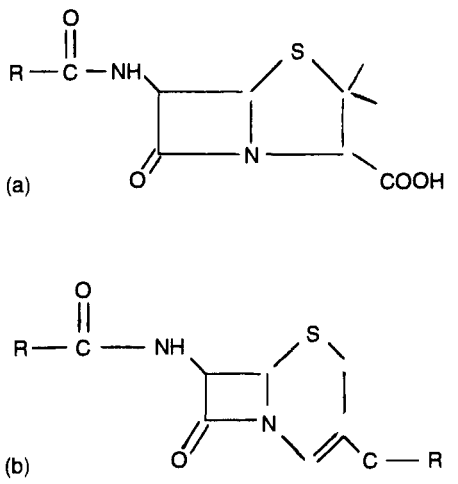

Fig. 9.3 The basic chemical structures of (a) penicillins and (b) cephalosporins.

PROTEIN SYNTHESIS INHIBITORS

A large number of antibacterial drugs produce their clinical effects by interfering with protein synthesis in the invading bacterium. They target the bacterial ribosomes, which differ in structure from those found in the cytoplasm of mammalian cells.

Tetracyclines

Tetracyclines, such as tetracycline, oxytetracycline and minocycline, produce their antibacterial effect by binding to the 30S subunit of the bacterial ribosome and therefore inhibiting bacterial protein synthesis and growth. They are broad-spectrum, bacteriostatic, antibacterial drugs effective against both Gram-positive and Gram-negative bacteria. Tetracyclines are incompletely absorbed from the gastrointestinal tract following oral administration. The presence of dairy products, Ca^{2+} ions and some indigestion remedies further decreases the absorption of tetracyclines and may render them ineffective in treating the infection. Tetracyclines are deposited in growing bone and dental enamel.

The development of resistance is common and limits their clinical usefulness. The most common mechanism of resistance is the development of a factor that prevents accumulation of the drug in the bacterial cell. Major adverse effects include nausea, vomiting, gastrointestinal upset, diarrhoea, discoloration of teeth in children and potentially fatal hepatic failure. Phototoxicity can also occur on prolonged treatment leading to severe sunburn in susceptible patients.

Aminoglycosides

Aminoglycoside antibacterial drugs, such as streptomycin, gentamicin and tobramycin, again act by binding to the 30S subunit of the bacterial ribosome, thus inhibiting protein synthesis and bacterial cell growth. Bacteria that are sensitive to these drugs have an oxygen-dependent accumulation system, which concentrates the drug inside the bacterial cell. Aminoglycosides are bactericidal drugs and are only effective against aerobic organisms since anaerobes do not have the oxygen-dependent accumulating system necessary to concentrate the drug inside the bacterial cell.

Resistance to aminoglycosides results from a decrease in the activity of the uptake system, alterations to the structure of the aminoglycoside-binding site on the 30S ribosome, or the development of destructive enzymes that render the drug inactive.

Aminoglycosides are highly polar molecules and so are not absorbed from the gastrointestinal tract. They are given by parenteral injection and become evenly distributed throughout the body fluids except the cerebrospinal fluid. Aminoglycosides are excreted unchanged by the kidney. Adverse effects include deafness, renal damage and some allergic reactions.

Macrolides

Erythromycin is a macrolide antibacterial drug that inhibits bacterial protein synthesis by binding irreversibly to the 50S subunit of the bacterial ribosome. It is bactericidal and is effective against a wide range of Gram-positive and Gram-negative microorganisms. It is often used as an alternative antibacterial drug in patients who are

allergic to the penicillins. However, great care must be exercised in these patients as a small degree of cross-sensitivity may occur.

Bacterial resistance to erythromycin is now becoming a major problem in many hospitals. It may occur either as a result of an alteration in the structure of the binding site on the 50S ribosomal subunit, or a decrease in the uptake of the drug into the bacterial cell.

Erythromycin is well absorbed from the gastrointestinal tract and widely distributed in all body fluids except the cerebrospinal fluid. It is extensively metabolised and is known to inhibit the cytochrome P-450 drug metabolising system. This gives rise to a series of potentially dangerous interactions, because erythromycin will inhibit the metabolism of any drug metabolised by this system. Major interactions occur between erythromycin and anti-arrhythmic drugs, other antibacterial drugs, anticoagulants, some antihistamines, antipsychotic drugs, anxiolytics and anti-epileptic drugs. Erythromycin is excreted via the bile and may be subjected to enterohepatic recirculation. Adverse effects of erythromycin include epigastric discomfort (bloatedness), nausea and vomiting, deafness and jaundice. It should not be used in patients with decreased liver function.

Other protein synthesis inhibitors

Chloramphenicol is a broad-spectrum antibacterial drug that acts by binding to the 50S ribosomal subunit. The toxicity of chloramphenicol means that it is only used systemically in life-threatening situations where no other antibacterial drug has been found to be effective. However, it is used in the form of eye drops and eye ointment for the treatment of conjunctivitis.

Clindamycin has the same mechanism of action as erythromycin and is used primarily in the treatment of infections by anaerobic bacteria.

The mechanisms of action of the major antibacterial drugs are summarised in Fig. 9.4.

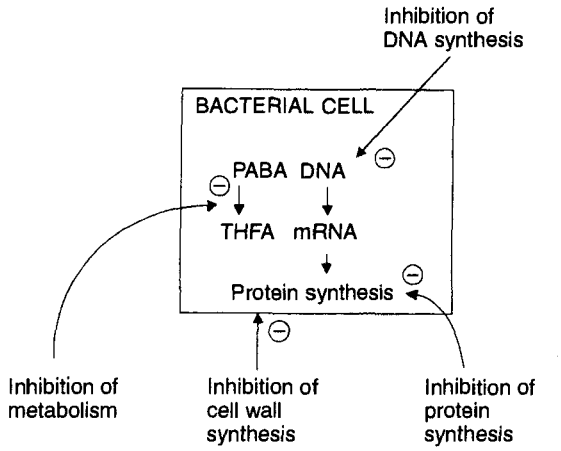

Fig. 9.4 The sites and mechanisms of action of antibacterial drugs. Antibacterial drugs act by either inhibition of bacterial DNA synthesis, inhibition of bacterial production of tetrahydrofolate (THFA), inhibition of bacterial cell wall synthesis or inhibition of bacterial protein synthesis.

ANTIMYCOBACTERIAL DRUGS

Drugs that are effective against mycobacteria, such as *M. tuberculosis*, are used in the treatment of tuberculosis. However, we have seen in Chapter 8 that mycobacteria are particularly resistant to antibacterial therapy and so complex treatment regimens must be used to ensure adequate eradication of the invading mycobacterium and to prevent the development of drug resistance.

Tuberculosis is a debilitating, eventually fatal, respiratory disease resulting from infection of the lungs by the microorganism *M. tuberculosis*. It may also affect the urinogenital tract, skeleton and meninges. Mycobacteria are characterised by being slow-growing and they are resistant to the common antibacterial agents discussed above. Structurally, they are unusual in that they have an outer coating containing mycolic acids, which are unique to these organisms.

In the early part of the twentieth century the introduction of drugs to combat tuberculosis led to a decrease in the incidence of the disease worldwide. However, the development of resistant strains of mycobacterium has led to a resurgence of the disease in many areas of the

world and it is now beginning to assume epidemic proportions in a number of areas.

One major problem associated with the treatment of tuberculosis is that, because of the slow rate of growth of the mycobacteria, it is quite possible for resistant strains to emerge in a patient during treatment with one antimycobacterial drug. To combat this tendency, treatment of tuberculosis usually consists of the administration of a number of different drugs at the same time.

Tuberculosis is usually treated in two stages, lasting a total of 6 months:

- Stage 1 (the initial phase) uses a combination of three different antimycobacterial drugs to reduce the population of mycobacteria as rapidly as possible and to prevent the development of resistance. This stage usually lasts for 2 months.
- Stage 2 (the continuation phase) uses a combination of two antimycobacterial drugs for another 4 months.

Typical drug combinations are:

- stage 1 – isoniazid, rifampicin, ethambutol: stage 2 – isoniazid, rifampicin
- stage 1 – isoniazid, rifampicin, ethambutol: stage 2 – isoniazid, pyrazinamide.

Isoniazid is bactericidal against *M. tuberculosis* and is the major drug used in all treatment schedules for tuberculosis. It acts by inhibiting the synthesis of mycolic acid, which is an essential component of the cell wall in mycobacteria. Adverse effects include nausea, vomiting, peripheral neuritis, optic neuritis, convulsions, hepatitis, hyperglycaemia and gynaecomastia. Its use is contraindicated in the presence of liver disease.

Ethambutol is bacteriostatic against *M. tuberculosis* and is thought to act by inhibiting RNA synthesis in the mycobacterium. It is widely distributed throughout the body and penetrates into the CNS. Therefore it is effective in the treatment of tuberculosis of the meninges. Adverse effects include optic neuritis, red/green colour blindness and peripheral neuritis. It is contraindicated in patients who have poor vision and in young children.

Rifampicin is bactericidal and acts by inhibiting protein synthesis in the mycobacterium. It is a major antitubercular drug used in most treatment regimens. Adverse effects include anorexia, nausea, vomiting, diarrhoea, flu-like symptoms, shortness of breath, muscular weakness and menstrual disturbances.

ANTIFUNGAL DRUGS

Polyenes:	amphotericin
Imidazoles:	ketoconazole, griseofulvin, nystatin, miconazole, clotrimazole, econazole

Fungi are different in structure to bacteria in that they have rigid cell walls that contain chitin. Fungal infections, called *mycoses*, tend to be chronic in nature and are resistant to the normal range of antibacterial drugs. Most fungal infections affect the skin and mucous membranes. However, systemic fungal infections, when they do occur, are extremely serious and difficult to treat.

Polyenes

Amphotericin is an extremely toxic drug but, despite this, it is the major drug of use in the treatment of systemic mycoses. The antifungal action of amphotericin depends upon the fact that fungal cell walls contain ergosterol, rather than the cholesterol which is found in the membranes of mammalian cells. When administered to a patient suffering from a systemic fungal infection, several amphotericin molecules bind to the ergosterol present in the fungal cell wall and form a pore through which Na^+ and K^+ ions can freely pass. This disrupts the normal function of the fungal cell and results in cell death.

Amphotericin is either fungicidal or fungistatic, depending upon the dose given and the susceptibility of the invading organism. It is particularly effective against *Candida* spp. Adverse effects include anorexia, nausea and vomiting, diarrhoea, epigastric pain, cardiac arrhythmias,

neurological disorders, renal impairment, hypotension and anaemia.

Imidazoles

Ketoconazole is a substituted imidazole used for the treatment of both systemic and superficial fungal infections. It inhibits the cytochrome P-450 system in fungal cells, inhibiting the synthesis of ergosterol, and disrupting the fungal cell membrane. This action of ketoconazole gives rise to some potentially serious interactions with other drugs, such as cyclosporin, terfenadine and astemizole. Adverse effects include nausea, vomiting, abdominal pain, dizziness, alopecia, gynaecomastia and hepatic failure. Its use is contraindicated in hepatic failure.

Fluconazole has a similar mechanism of action to that of ketoconazole, but it is devoid of the adverse effects on the endocrine system seen with ketoconazole.

Griseofulvin is taken up into fungal cells by an energy-dependent process and is thought to interfere with mitosis, thus inhibiting replication of the fungal cells. It is predominantly fungistatic and is used for the treatment of a range of fungal infections including tinea pedis (athlete's foot).

Nystatin, miconazole and clotrimazole are predominantly used for the treatment of topical fungal infections, such as *Candida albicans* (thrush). Their mechanism of action is similar to that of ketoconazole.

ANTIVIRAL DRUGS

Drugs for respiratory viruses:	amantadine, tribavirin, rimantadine
Drugs for herpes and cytomegolovirus:	aciclovir, famciclovir
Drugs for HIV infections:	zidovudine (AZT)
Drugs for viral hepatitis:	interferon

Viruses are devoid of both a cell wall and a cell membrane, but contain DNA or RNA peculiar to the virus. They are intracellular parasites, which do not carry out metabolic processes. Consequently, antimicrobial drugs that rely on inhibition of cell wall synthesis, or microbial metabolism, for their effects do not affect them. Most viruses reproduce themselves by using the host's cellular processes and, therefore, it is extremely difficult to interfere with viral reproduction without seriously affecting the host's cells and causing serious adverse effects. However, some drugs do show a degree of selectivity against viral processes sufficient for them to be used in antiviral therapy while producing an acceptable level of toxicity.

Viruses may be classified into the following groups:

- *adenoviruses* – polyhedral DNA viruses with a particular affinity for mucous membranes
- *arboviruses* – arthropod-borne RNA-containing viruses transmitted to humans by bites from mosquitoes, etc.
- *arenaviruses* – RNA-containing viruses typically transmitted by rodents
- *coronaviruses* – RNA-containing viruses that replicate in the cytoplasm of the cell
- *herpesviruses* – DNA-containing viruses that replicate in the nucleus and have a high affinity for skin and mucous membranes
- *myxoviruses* – helical RNA-containing viruses having an affinity for respiratory membranes
- *papovaviruses* – DNA-containing viruses that form papilloma
- *paramyxoviruses* – similar to myxoviruses, but which replicate in the cytoplasm
- *picornaviruses* – very small RNA-containing viruses, including poliomyelitis
- *poxviruses* – large DNA-containing viruses that cause pustules on the skin and leave 'pock marks' on healing
- *reoviruses* – RNA-containing viruses found in the respiratory tract
- *rhabdoviruses* – helically coiled RNA-containing viruses having a strong affinity for tissues in the CNS.

The treatment of respiratory viruses

The antiviral actions of amantadine and rimantadine depend on their ability to block ion

channels in the viral membrane, which prevents reproduction of the virus particles. They are only effective against the influenza A virus and must be given prophylactically as they are not effective in the treatment of an established infection. Consequently, their major therapeutic use is as an adjunct to vaccination to provide protection until the immune response becomes effective.

The adverse effects of amantadine are mainly confined to effects on the CNS. Common symptoms include insomnia, dizziness and ataxia; more serious effects include hallucinations and seizures in susceptible patients.

The treatment of herpes viruses

Herpes viruses give rise to a range of common diseases including cold sores, viral encephalitis and a number of genital herpes infections. The most common are herpes simplex virus, which gives rise to cold sores, and varicella zoster virus, which causes chickenpox and shingles.

Aciclovir is one of the most effective antiviral agents and is most effective against the viruses that produce cold sores and similar infections. Aciclovir is a prodrug that is converted ultimately to the triphosphate derivative. Aciclovir triphosphate becomes incorporated into the viral DNA and prevents replication. Specificity of action is conferred by the fact that the conversion of aciclovir into the monophosphate predominantly occurs in cells infected with virus particles rather than non-infected cells. The adverse effects of aciclovir depend on the route of administration. Topical application may produce mild irritation, whereas headache, nausea and diarrhoea may result from oral administration.

The treatment of HIV

Zidovudine (AZT) is one of the most effective drugs for the treatment of human immunodeficiency virus (HIV) infections. Like aciclovir, it is a prodrug that must be converted to the triphosphate derivative before it can act against the virus. Incorporation of zidovudine triphosphate into the viral DNA inhibits synthesis of the chain and prevents viral replication. The adverse effects of zidovudine result mainly from its toxic effects on the bone marrow. These include anaemia and leucopenia.

The treatment of viral hepatitis

Interferons are a group of naturally occurring glycoproteins that prevent virus particles from entering host cells. Unfortunately the interferons have not been found to be as effective in patients as laboratory tests have predicted.

The major mechanisms by which antiviral drugs exert their actions are summarised in Fig. 9.5.

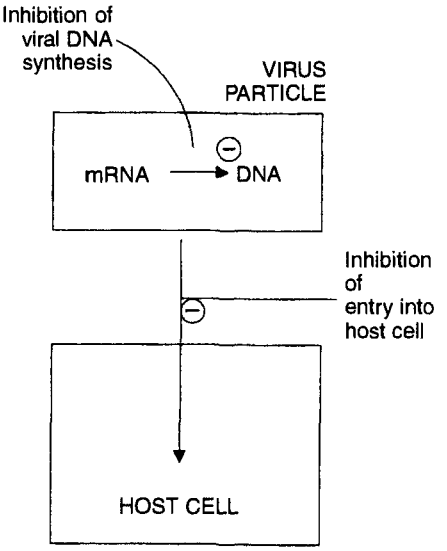

Fig. 9.5 The mechanisms of action of antiviral drugs. Antiviral drugs act either by inhibition of viral DNA synthesis or by preventing the entry of virus particles into host cells.

ANTHELMINTICS

Drugs for threadworms and roundworms:	mebendazole, piperazine, thiabendazole
Drugs for tapeworms:	niclosamide

Anthelmintic drugs are used to control worm infestations. There are three major groups of worms that commonly affect humans: *nematodes*, *trematodes* and *cestodes*. Nematodes are elongated roundworms that cause infestations in the

gastrointestinal tract, blood and tissues. Trematodes (flukes) are flatworms that typically infest the lungs, liver, gastrointestinal tract and blood. Cestodes are the true tapeworms and infest the gastrointestinal tract. Worm infestations are extremely common and are relatively easily passed from patient to patient if suitable standards of personal hygiene are not maintained. Nematode infestation is the most common problem in children.

The treatment of threadworms and roundworms

Mebendazole and piperazine are effective against a wide range of nematode infestations, especially those found in children. They are the drugs of choice for the treatment of roundworm and pinworm infestations. Mebendazole acts by inhibiting the formation of microtubules in the parasite and by decreasing the availability of glucose. Affected worms are excreted in the faeces. Piperazine acts by inhibiting muscle function in the invading worm, thus paralysing it and promoting its excretion from the host. Care should be taken during treatment with both mebendazole and piperazine that the patients do not accidentally reinfest themselves by inadequate washing, or pass the parasite onto others by the communal use of towels, etc.

Adverse effects following the use of mebendazole and piperazine are rare. These drugs are almost entirely retained within the gastrointestinal tract and very little is absorbed into the body. However, some adverse effects may be seen including abdominal pain, diarrhoea, rashes, nausea and vomiting. Animal studies have indicated that mebendazole is embryotoxic and its use in pregnant women is contraindicated.

Thiabendazole has a similar mechanism of action to that of mebendazole. However, it is more readily absorbed from the gastrointestinal tract. Adverse effects include dizziness, anorexia, nausea, vomiting and CNS abnormalities.

The treatment of tapeworms

Niclosamide is effective against the major tapeworm infestation, *Taenia solium*, found in humans. It is thought to act by inhibiting the production of ATP in the tapeworm. Adverse effects include lightheadedness and gastrointestinal disturbances.

ANTIPROTOZOAL DRUGS

Tissue schizonticide:	primaquine
Blood schizonticide:	quinine, chloroquine, mefloquine
Sporonticide:	pyrimethamine

Protozoal infections are often associated with underdeveloped countries, where they give rise to diseases such as malaria, amoebiasis, leishmaniasis, trichomoniasis and trypanosomiasis. However, the increase in world travel in recent years now means that these diseases are becoming more widespread and are no longer confined to specific geographical areas.

Protozoa are eukaryotic cells and, therefore, have metabolic processes much more similar to those in humans. Consequently the treatment of these diseases is less easily achieved without the development of serious adverse effects resulting from actions of the drugs used on tissues with high rates of metabolic activity, such as nerve cells, kidney cells and bone marrow stem cells.

The treatment of malaria

Malaria is an infectious disease caused by four species of *Plasmodium*, which are carried by the mosquito. When an infected mosquito bites it injects sporozoites of the *Plasmodium* spp. into the bloodstream. These sporozoites migrate to the liver where they form cyst-like structures containing thousands of merozoites. Release of these merozoites leads to an attack on the red blood cells which eventually rupture, releasing haem and more merozoites, which can infect other red blood cells. Gametocytes, derived from some of these merozoites, can then be transferred to another mosquito when it bites an infected patient. In this way, patients being bitten initially by infected mosquitoes and then subsequently being bitten again by a non-infected insect maintain the disease cycle.

The severity of the disease is dependent upon the species of *Plasmodium* carried by the mosquito. *P. falciparum* is the most dangerous, causing persistent high fever, hypotension and

massive red blood cell destruction. *P. vivax* causes similar symptoms, but is slightly less severe.

The cycle of *Plasmodium* infection and sites of therapeutic intervention are shown in Fig. 9.6.

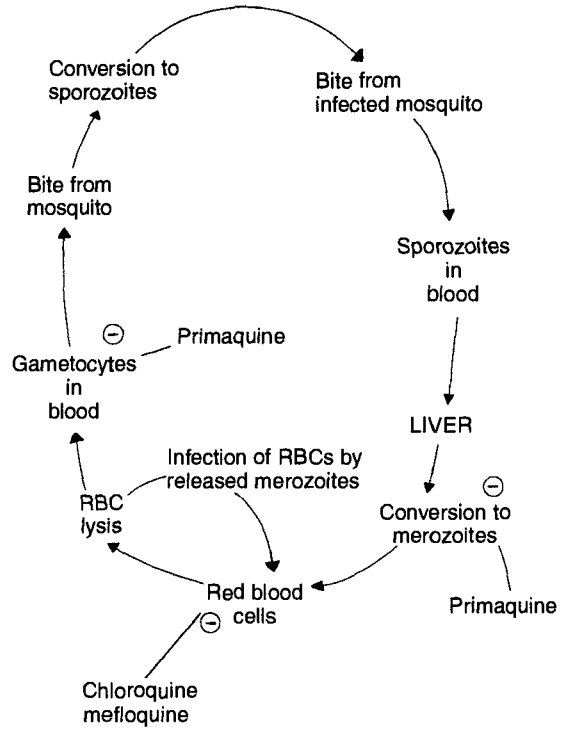

Fig. 9.6 The life cycle of *Plasmodium* spp. in malaria. A bite from an infected female mosquito injects sporozoites into the blood of the victim. These are converted to merozoites in the liver and, when released, cause lysis of red blood cells. Gametocytes are picked up by another mosquito, converted to sporozoites and reinfect another victim.

Tissue schizonticides

Primaquine is a tissue schizonticide. It is an 8-aminoquinoline, which eradicates the merozoites of *P. falciparum* and *P. vivax*, which occur outside the red blood cells. It also destroys the gametocyte forms of all four types of *Plasmodium* spp. The mechanism of action is not understood. It has a low incidence of adverse effects, causing mild gastrointestinal upset in some patients and, rarely, agranulocytosis and granulocytopenia.

Blood schizonticides

Chloroquine is a 4-aminoquinoline that kills the parasites by a number of different actions. Normally the haem released inside the red blood cell is toxic to the parasite. However, it protects itself by polymerising the haem to form haemozoin. Chloroquine inhibits the polymerase enzyme responsible for this change and so allows the build-up of haem to levels that destroy the parasite. Chloroquine also enters the parasite's food vacuole, renders it alkaline, and prevents the parasite digesting the haemoglobin it normally uses as a source of energy. Finally, chloroquine is able to disrupt the tertiary structure of the parasite's nucleic acid, thus inhibiting protein synthesis.

Chloroquine is the drug of choice in the treatment of falciparum malaria, except in the presence of resistant strains of *P. falciparum*. Resistance to chloroquine, resulting from extrusion of the drug from the parasite, is now a serious problem in many areas of the world including Asia and South America.

The adverse effects of chloroquine are normally minimal. Mild gastrointestinal disturbance, pruritis and headache occur in some patients, as does discoloration of the nail beds and visual disturbances. Higher doses of chloroquine may cause cardiac arrhythmias in susceptible patients as a result of a quinidine-like action. It should not be used in patients suffering from psoriasis.

Mefloquine is used for the prophylactic treatment of malaria in areas of the world where there is a high incidence of resistance to other antimalarial drugs. However, its use has been severely limited by the serious adverse effects that have occurred in some patients. These include nausea, vomiting, sleep disturbances, headache, loss of balance, anxiety, panic attacks, agitation, hallucinations, irreversible psychotic disorders, tachycardia, hypotension, cardiac arrhythmias and muscle weakness. The Committee for the Safety of Medicines (CSM) now recommends that patients who are given mefloquine should be made aware of the potential adverse effects of the drug and to seek immediate medical attention if they arise.

SUMMARY

- Chemotherapeutic drugs are used to treat infections by bacteria, funguses, viruses, worms and protozoa.
- The therapeutic usefulness of chemotherapeutic drugs is dependent upon their selective toxicity against the invading organisms.
- Bacteria may be classified as either Gram-positive or Gram-negative, according to their response to the Gram stain.
- Bacterial resistance to antibacterial drugs may be the consequence of the inappropriate exposure to these drugs, allowing bacteria to develop mechanisms for destroying the drugs.
- Antibacterial drugs may be classified as either bactericidal or bacteriostatic, depending upon whether they kill the bacteria or prevent their replication.
- Each antibacterial drug has a definite spectrum of activity, which defines the bacteria against which it is effective.
- Antibacterial drugs are either folate antagonists, inhibitors of bacterial cell wall synthesis or inhibitors of bacterial protein synthesis.
- Fungal infections are less common than bacterial infections.
- Most fungal infections are of the skin and mucous membranes; systemic fungal infections are extremely serious and difficult to eradicate.
- The major antifungal drugs are polyenes or imidazoles.
- Viruses are small invasive particles that do not have a cell membrane; they contain either DNA or RNA.
- Viruses are intracellular parasites, interfering with normal cell metabolism in order to ensure survival of the virus particle.
- Antiviral drugs act by inhibiting protein synthesis.
- Worm infestations include threadworms, roundworms and tapeworms, all of which invade the gastrointestinal tract.
- Worm infestations are common and are often transmitted from patient to patient as a result of poor personal hygiene.
- Protozoal infections are most common in developing countries and include malaria, amoebiasis, leishmaniasis and trichomoniasis.
- Malaria is the most common protozoal infection, which is now re-emerging as a major cause of death in many countries.
- Antimalarial drugs include tissue schizonticides, blood schizonticides and sporonticides.

10

Drugs Affecting the Endocrine System

INTRODUCTION

The endocrine system is the second major communication system in the body, transmitting messages around the body by way of chemical messengers called *hormones*. Hormones are secreted into the blood by *endocrine glands* and are carried throughout the body to target tissues, where they exert control over a large number of cellular functions at distant sites. Some hormones affect all cells in the body, whereas others affect more specific tissues. Hormones have a broad range of response times, ranging from hours to days, and may produce effects that last for several months. Many diseases, such as diabetes mellitus, occur as a result of malfunction of these endocrine control mechanisms.

The major locus of control of the endocrine system lies in the anterior pituitary–hypothalamus axis. This area of the brain controls a large number of essential body functions, some of which are summarised in Table 10.1.

The *hypothalamus* is part of the diencephalon of the brain. It is connected to the *pituitary gland*, which is situated immediately below, by the *pituitary stalk*. The pituitary stalk carries neurones from the hypothalamus to the *posterior lobe* of the pituitary and blood vessels to the *anterior lobe* of the pituitary. In this way, the secretion of hormones from the pituitary gland can be both initiated and regulated by the hypothalamus. The anatomical structure of the hypothalamus–pituitary axis is shown in Fig. 10.1.

The mechanism by which the hypothalamus–pituitary axis controls body functions may be understood by considering the control of *thyroid hormone*, which controls the rate of cellular metabolism. The level of thyroid hormone in plasma is monitored constantly by thyroid hormone receptors in the hypothalamus. If the level of thyroid hormone falls the hypothalamus responds by increasing the production of thyrotrophin releasing hormone (TRH), which then

Table 10.1 Major endocrine control systems of the body.

Function	Endocrine gland	Hormone(s)	Target tissues
Availability of glucose	Pancreas	Insulin	All cells
Control of metabolic rate	Thyroid	Thyroid hormone	All cells
Reproduction	Gonads	Oestrogen and testosterone	Reproductive organs
Calcium homeostasis	Parathyroid gland	Parathyroid hormone	Kidney cells, intestine and bone
Circulating plasma volume	Adrenal glands	Aldosterone	Kidney cells
Adaptation to stress	Adrenal glands	Epinephrine	Most cells
Growth	Pituitary gland	Growth hormone	All cells

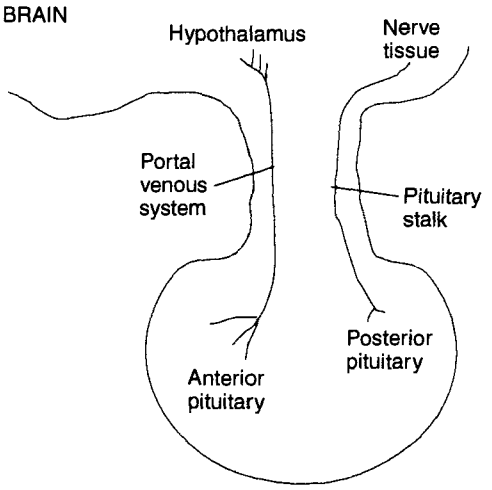

Fig. 10.1 The structure of the mammalian hypothalamus–pituitary gland axis. The pituitary gland is situated immediately below the hypothalamus; released hormones are carried to the anterior pituitary gland in the portal system; the posterior pituitary gland is controlled by neuronal mechanisms arising in the hypothalamus.

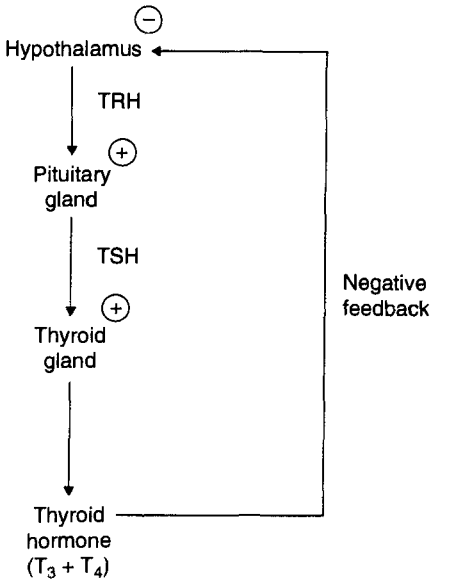

Fig. 10.2 The control of thyroid hormone secretion. Thyrotrophin-releasing hormone (TRH) is released from the hypothalamus and stimulates the pituitary gland to release TSH; this acts on the thyroid gland to release thyroid hormone. A negative feedback loop inhibits hypothalamic action if the plasma levels of thyroid hormone rise too high.

passes via the portal blood vessels to the anterior pituitary gland. TRH then acts on the anterior pituitary gland to promote the release of thyroid-stimulating hormone (TSH; thyrotrophin), which is secreted into the plasma and passes to the thyroid gland. The action of TSH is to stimulate the release of thyroid hormone. The thyroid hormone then exerts its effects on the tissues and also acts as a negative feedback to inhibit further production of TRH from the hypothalamus. This control mechanism is illustrated in Fig. 10.2.

We can see that the endocrine system exerts a wide-ranging control over the biochemical processes of the body. Clearly, therefore, any malfunction of these endocrine control systems will give rise to diseases that are potentially fatal to the individual. These endocrine disorders may be treated by the use of drugs that either mimic or inhibit the actions of the naturally occurring hormone(s). Some of the major endocrine disorders that may be successfully treated by drug therapy are:

- diabetes mellitus
- thyroid disorders
- sex hormones
- osteoporosis.

DIABETES MELLITUS

The endocrine portions of the pancreas produce two peptide hormones, called *insulin* and *glucagon*, which between them control the rates of glucose metabolism in the body. If the level of glucose in plasma is high then *insulin* release from the β-cells of the islets of Langerhans in the pancreas is increased. Insulin promotes the uptake of glucose into body cells. Conversely, a low level of glucose in plasma inhibits insulin release and stimulates the release of glucagon from the α-cells of the islets of Langerhans. Glucagon stimulates the conversion of glycogen to glucose, thus raising the plasma glucose levels to normal.

Diabetes mellitus is a group of diseases characterised by a raised level of glucose in the blood that results either from a decreased availability of insulin, or a decreased effectiveness of insulin at the cells. Patients who suffer from diabetes mellitus may be divided into two major groups, depending on their requirement for insulin.

Type I diabetes mellitus (insulin-dependent diabetes mellitus, IDDM) results from a decrease in the insulin-secreting capability of the β-cells. Sometimes the β-cells of the islets of Langerhans may become damaged by external factors such as viral infection or chemical toxins, but more commonly the damage is the result of attack by autoimmune antibodies targeted at the β-cells. The consequence of this damage to the β-cells is that they are unable to respond to elevated plasma glucose levels by the secretion of insulin. Patients who suffer from type I diabetes mellitus are completely dependent on insulin therapy to replace their insulin deficiency.

In normal patients, the β-cells maintain a basal level of insulin secretion. Following the ingestion of a meal, the rise in plasma glucose triggers an increased secretion of insulin. In the type I diabetic patient the basal level of insulin secretion is not present and there is no response to the rise in plasma glucose following a meal. The treatment of type I diabetes mellitus must aim to supply the patient with sufficient insulin, such that there is an adequate control of plasma glucose levels throughout the 24-hour period, without the wild swings that may contribute to complications of the disease. Type I diabetes mellitus affects some 10% of the diabetic population. The onset occurs most commonly in juveniles, but can develop in adults.

Type II diabetes mellitus (non-insulin-dependent diabetes mellitus, NIDDM) is a disease in which the β-cells maintain some insulin-secreting capability and, although the insulin levels may vary, they are consistently below those required to provide adequate control of plasma glucose levels. Type II diabetic patients are usually overweight and there is often some decrease in the responsiveness of the target cells to insulin. The development of the disease is almost entirely due to genetic disposition and there is little evidence of environmental or autoimmune factors contributing to the development of the disease.

Again, the goal of treatment of patients with type II diabetes mellitus is to maintain plasma glucose levels within the normal range and to avoid the long-term complications associated with the disease. Reduction in weight and dietary restrictions are often sufficient in patients who are in the early stages of the disease. Subsequently, it is necessary to use hypoglycaemic agents, and possibly insulin, to bring about an adequate control of plasma glucose levels.

Complications of diabetes

The complications of diabetes mellitus may be either acute metabolic disorders or chronic tissue damage, resulting from a failure to adequately control glucose levels in the blood. The most common acute complication of diabetes is a failure of the treatment to control glucose levels in the blood, giving rise to either hyperglycaemia/ketoacidosis or hypoglycaemia.

Hyperglycaemia occurs when the concentration of glucose in the blood rises above 15–20 mmol/l. As the glucose level in the blood rises, water is withdrawn from the cells, causing intracellular dehydration and a rise in intracranial pressure. The excess glucose is excreted through the kidney, causing an osmotic diuresis. Eventually this results in a decrease in the circulating plasma volume, hypotension and a reflex tachycardia. In the absence of glucose, most cells begin to metabolise fat and produce ketones as an alternative energy source. It is the excretion of some of these ketones via the lungs that gives rise to the smell of pear drops on the breath. The resulting metabolic acidosis stimulates the respiratory centre in the brain and decreases the ability of haemoglobin to carry oxygen, thus producing the characteristic 'gasping for air' syndrome seen in these patients.

Established ketoacidosis is a medical emergency requiring prompt hospital treatment and close monitoring of the patient's electrolyte balance.

The main symptoms of hyperglycaemia/ketoacidosis are:

- frequent passing of urine (polyuria)
- thirst and frequent drinking (polydipsia)
- hypotension
- rapid pulse and respiration

- dry mouth
- visual disturbances
- a smell of pear drops on the breath (keto-acidosis)
- drowsiness and eventual coma.

Hypoglycaemia is more common than hyperglycaemia and may result from either a failure of the patient to adequately control food intake, or mismanagement of the antidiabetic therapy, such as too large a dose of insulin. Hypoglycaemia gives rise to the following symptoms:

- hunger and salivation
- tremor, palpitations, sweating
- drowsiness and disorientation
- anxiety and aggression (subject appears to be drunk)
- convulsions and coma
- brain damage.

Clearly, it is very important that diabetic patients are taught not only to recognise the symptoms of both hyperglycaemia and hypoglycaemia, but also the steps to be taken to abort such attacks. It is also essential to treat both hyperglycaemia and hypoglycaemia rapidly, as a delay in treatment may well be fatal. It is sometimes difficult to distinguish some of the symptoms of hyperglycaemia from those of hypoglycaemia. However, the administration of sugar, chocolate or sweet tea to a conscious patient will rapidly reverse the effects of hypoglycaemia and not do any harm in hyperglycaemia. Whilst infrequent attacks of hyperglycaemia or hypoglycaemia may occur in any diabetic patient, their frequent occurrence requires reassessment of the treatment regimen.

In many patients the chronic effects of diabetes mellitus may well become established even before the disease has been diagnosed. The clinical consequences of diabetes mellitus appear to arise from a failure of current treatments to produce the extremely fine control of blood glucose levels seen in the non-diabetic patient. This can give rise to long-term adverse effects on a number of different body systems, including:

(1) *Eyes.* Diabetes is the most common cause of blindness in developed countries. Up to 10% of patients become blind after long-term diabetes and as many as 50% will show some signs of visual impairment as a result of retinal neuropathy.

(2) *Nervous system.* Diabetic neuropathy may affect any part of the peripheral nervous system, but the most commonly affected areas are the sensory nerves, giving rise to tingling and numbness of the extremities (paraesthesiae). Eventually there may be loss of balance and serious impairment of the autonomic control of the cardiovascular system.

(3) *Kidneys.* Diabetic nephropathy is the cause of death in about 25% of type I diabetic patients, the most common cause being glomerular sclerosis, which eventually progresses to renal failure.

(4) *Systemic.* Diabetic patients are at greater risk from infections, especially urinary tract infections, which may travel up the urinary tract to give rise to pyelonephritis.

(5) *Cardiovascular system.* Diabetic patients are at increased risk of stroke and heart attacks. Peripheral vascular disease is also extremely common in diabetic patients, leading to an increased risk of peripheral gangrene as a result of decreased perfusion of the extremities.

(6) *Locomotor system.* The 'diabetic foot' is a common problem in diabetic patients. Minor injuries, such as corns and blisters, which would normally heal in a healthy patient, often develop into ulcers that may cause irreversible damage before treatment is sought. This state of affairs usually results from a combination of the other effects of diabetes, such as paraesthesiae and poor peripheral circulation, so that the initial foot damage is not felt until it has progressed to a dangerous state. Consequently, all diabetics are encouraged to seek regular checks of their feet and to ensure that they have correctly fitting footwear. All foot problems in diabetic patients should be referred immediately to either a podiatrist or a medical practitioner.

Drugs used in the treatment of diabetes mellitus

Insulin preparations:	crystalline zinc insulin, isophane insulin, protamine zinc insulin
Sulphonylureas:	tolbutamide, chlorpropamide, glipizide, glibenclamide, tolazamide
Biguanides:	metformin
α-Glucosidase inhibitors:	acarbose

Treatment of type I diabetes mellitus

Type I diabetes mellitus results from a failure of the β-cells to secrete insulin in response to changes in the plasma levels of glucose. Consequently, the treatment of type I diabetes requires the administration of insulin in such a way that control of glucose levels in the plasma is maintained as closely as possible to the natural state. Insulin is a small protein consisting of two polypeptides connected by disulphide (S–S) bridges. The secretion of insulin from the β-cells of the islets of Langerhans is primarily dependent on glucose levels, but it is also partially under hormonal and neurotransmitter control.

Insulin can be obtained from a number of sources. For many years it was extracted from animal sources, such as cows and pigs. However, it may now be produced by recombinant DNA technology from pork insulin, in which the substitution of one amino acid converts it into human insulin. Most diabetic patients are now treated with this human insulin.

The fact that insulin is a protein means that it cannot be administered orally, as the enzymes of the gastrointestinal tract would destroy it. Currently, insulin has to be given by s.c. injection. However, much research is under way to develop alternative delivery systems for insulin that will eliminate the need for repeated injections. When insulin is administered by s.c. injection it gives a controlled rate of delivery of the insulin to the plasma, depending on the formulation of the insulin crystals in the injection solution. It must be borne in mind that the diabetic patient requires to gain adequate glucose control over a prolonged period of time with the minimum number of injections. Thus insulin preparations are formulated in such a way that some release their insulin quickly, to allow for rapid control of glucose levels, and some release their insulin more slowly to give a more prolonged control of plasma glucose levels. The major adverse reaction to insulin is hypoglycaemia.

Types of insulin preparation

Insulin preparations may be classified into three groups:

(1) rapidly acting preparations
(2) intermediately acting preparations
(3) long-acting preparations.

Rapidly acting preparations These preparations have a rapid onset of action following s.c. injection and yield insulin to the plasma over a short period of time. The most common preparation is crystalline zinc insulin. This preparation lowers plasma glucose levels within minutes of s.c. administration.

Intermediately acting preparations There are two intermediately acting preparations. Isophane insulin is a suspension of crystalline zinc insulin complexed with protamine at neutral pH. The insulin–protamine complex is less soluble than crystalline zinc insulin and so the rate at which insulin enters the plasma is slower, giving rise to a prolonged control of plasma glucose levels. Insulin–zinc suspension is a mixture of 30% rapidly acting insulin and 70% long-acting insulin. It is the most common method of treatment for previously untreated patients.

Long acting preparations These preparations give control of plasma glucose levels over many hours. However, the nature of their formulation means that insulin release from these preparations does not become significant for several hours after injection. Protamine zinc insulin is prepared by treating crystalline zinc insulin with protamine at neutral pH to give a fine precipitate.

It reaches a maximal effect about 24 hours after injection. Ultralente insulin is extremely poorly soluble crystalline zinc insulin, which has a prolonged duration of action.

The rates of onset and duration of action of the commonly available insulin preparations are summarised in Fig. 10.3.

Treatment of Type II diabetes mellitus

In its early stages, type II diabetes mellitus may be treated by careful attention to diet. It is commonly seen in obese patients and a controlled loss of weight is usually sufficient to control the symptoms of the diabetes. However, as the disease progresses, the necessity for pharmacological intervention becomes greater. The exact treatment regimen depends upon the severity of the disease and the patient's responsiveness to the drugs available. In many cases it is necessary to use a combination of antidiabetic drugs and, in severe cases, to resort to insulin therapy as well.

Biguanides

Biguanides, such as metformin, act primarily by decreasing the release of glucose from the liver by inhibiting gluconeogenesis. Metformin also causes a decrease in the plasma levels of lipoproteins and reverses hyperlipidaemia, with patients often losing weight on prolonged treatment. Adverse effects include anorexia, nausea, vomiting, diarrhoea, acidosis and a decrease in vitamin B_{12} absorption from the gastrointestinal tract. The use of metformin is contraindicated in patients who suffer from renal or hepatic failure.

Sulphonylureas

Sulphonylureas, such as tolbutamide and glipizide, stimulate the release of insulin from the β-cells of the islets of Langerhans. They also reduce the plasma levels of glucagon and promote the binding of insulin to its receptor. It should be noted that these drugs are only effective if there is a residual level of insulin secretion capability in the β-cells. Adverse effects include nausea, gastrointestinal disturbances, headache, pruritis and hypoglycaemia.

α-Glucosidase inhibitors

α-Glucosidase inhibitors, such as acarbose, inhibit the enzyme in the intestinal brush border and so decrease the absorption of starch and disaccharides from the gastrointestinal tract. Consequently the rise in plasma glucose levels, which occurs after a meal, is decreased. Acarbose does not alter either insulin secretion or insulin action; therefore there is a greatly reduced chance of hypoglycaemia with this drug. Adverse effects include flatulence, diarrhoea, abdominal pain and discomfort, jaundice and hepatitis. Its use is contraindicated in pregnancy, breastfeeding and inflammatory bowel disease.

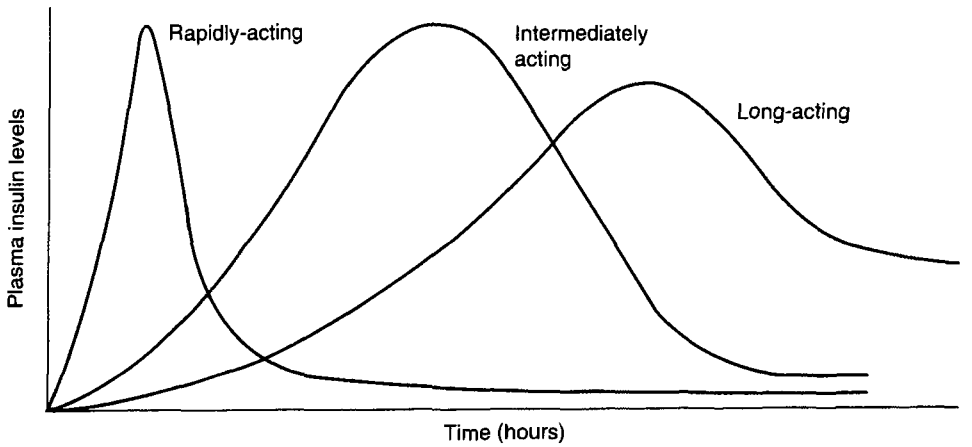

Fig. 10.3 The effects of various insulin preparations on plasma insulin levels following s.c. injection.

THYROID DISORDERS

The thyroid gland controls both the rates of body growth and maturation by controlling the levels of tissue metabolism. There are two major thyroid hormones, T_3 (triiodothyronine) and T_4 (thyroxine). Inadequate secretion of these thyroid hormones (*hypothyroidism*) results in a decrease in the rates of mental and physical development, which can result in mental retardation and dwarfism, an intolerance to cold and lethargy. A certain degree of decreased thyroid function occurs in many elderly patients. Conversely, oversecretion of these hormones (*hyperthyroidism, thyrotoxicosis*) is characterised by tachycardia and cardiac arrhythmias, body wasting, nervousness and tremor.

The synthesis of thyroid hormones by the thyroid gland is dependent on an adequate supply of iodide ions (I^-), which are used to iodinate tyrosine residues derived from thyroglobulin to produce T_3 and T_4. The synthesis of thyroid hormones is shown in Fig. 10.4.

Drugs used in the treatment of thyroid disorders

Hyperthyroidism:	carbimazole, iodide, propylthiouracil, propranolol
Hypothyroidism:	thyroxine, liothyronine

Hyperthyroidism is the syndrome in which there is an excessive production of thyroid hormone. It may be treated by the antithyroid drugs, carbimazole, propylthiouracil and iodide. Carbimazole and propylthiouracil both act by inhibiting the synthesis of thyroid hormone in the thyroid gland. Iodide ions (I^-) act by inhibiting the release of the hormone. The adverse effects of carbimazole and propylthiouracil are similar, including nausea, gastrointestinal disturbances, headache, alopecia and jaundice. Their use is contraindicated in hepatic failure, pregnancy and breastfeeding. Iodide ions cause headache, tear formation, laryngitis and bronchitis.

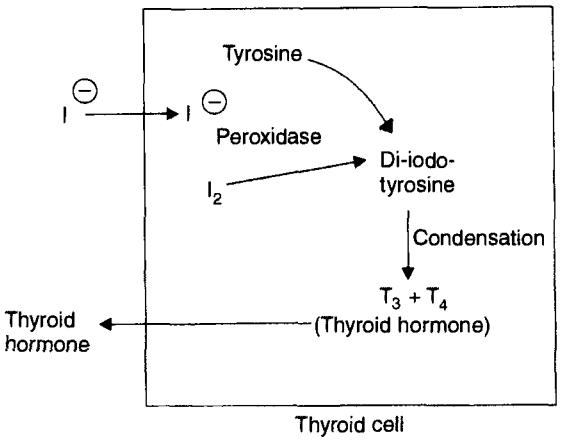

Fig. 10.4 The synthesis of the thyroid hormones (T_3 and T_4). Tyrosine and iodide (I^-) are combined to produce diiodotyrosine; this is then converted to T_3 and T_4 (thyroid hormone).

Hypothyroidism is the result of underproduction of thyroid hormone, and usually results from an autoimmune destruction of the thyroid gland. It may be treated by the administration of thyroid hormone substitutes, such as thyroxine and liothyronine. Adverse effects include anginal pain, cardiac arrhythmias, skeletal muscle cramps, tachycardia, insomnia, diarrhoea, headache, nervous excitability and tremor.

SEX HORMONES

Steroid hormones

Oestrogens:	oestradiol, oestrone, stilboestrol, mestranol, ethinyloestradiol
Antioestrogens:	clomiphene, tamoxifen
Progestogens:	medroxyprogesterone, hydroxyprogesterone, progesterone, dydrogesterone, norethisterone, levonorgestrel

Antiprogestogens:	mifepristone
Oral contraceptives:	see Chapter 12
Androgens:	testosterone, mesterolone
Anti-androgens:	cyproterone, finasteride
Corticosteroids:	hydrocortisone, fludrocortisone, prednisone, prednisolone, triamcinolone, betamethasone, dexamethasone, beclomethasone

The steroid sex hormones produced by the ovaries, testes and adrenal glands are extremely important not only for the development of the secondary sexual characteristics in males and females, but also for the control of conception and maturation of the embryo and fetus. The synthesis and release of the steroid sex hormones, oestrogen and progesterone, is under the overall control of the gonadotrophic hormones follicle-stimulating hormone (FSH) and luteinising hormone (LH) synthesised by the anterior pituitary gland which, in turn, are controlled by gonadotrophin-releasing hormone (GnRH) synthesised in the hypothalamus (see Fig. 10.5).

The cortex of the adrenal glands produces two major groups of steroid hormones, namely the adrenocorticosteroids (glucocorticoids and mineralocorticoids) and the androgens. Their synthesis and release is under the control of adrenocorticotrophic hormone (ACTH), which is synthesised in the anterior lobe of the pituitary gland (see Fig. 10.6).

Oestrogens and anti-oestrogens

The three major oestrogens produced by females are oestradiol, which is synthesised in the ovaries, oestrone and oestriol, which are synthesised from oestradiol by the liver. They produce their effects by interacting with intracellular steroid receptors located close to cell nuclei. The steroid–receptor complex then enters the nucleus of the cell and interacts specifically to produce hormone-specific

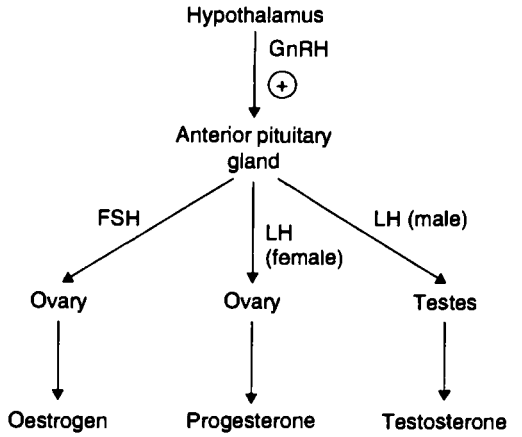

Fig. 10.5 The control of follicle-stimulating hormone (FSH) and luteinising hormone (LH) production. Gonadotrophin-releasing hormone (GnRH) is produced by the hypothalamus; this acts on the anterior pituitary to release FSH and LH. FSH controls oestrogen production in the ovaries, LH controls progesterone production in females and testosterone production in males.

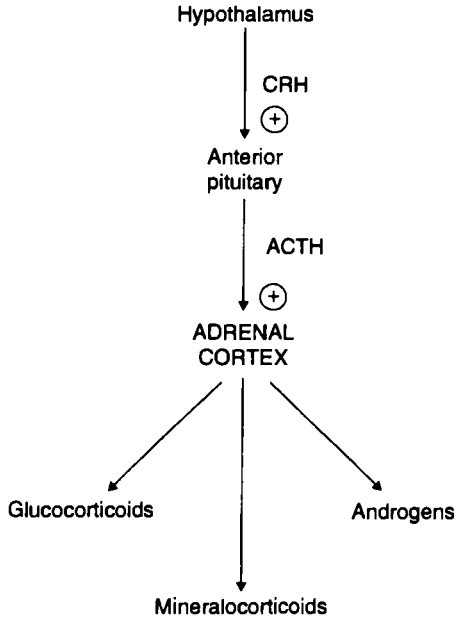

Fig. 10.6 The control of adrenal hormone production. The hypothalamus produces corticoptrophin-releasing hormone (CRH) which acts on the anterior pituitary gland to produce adrenocorticotrophic hormone (ACTH); this stimulates the production of steroids and androgens from the adrenal cortex.

changes in mRNA production and protein synthesis. The resultant proteins are responsible for the physiological actions of the steroid hormone.

Oestrogens are used as hormone replacement therapy (HRT) in patients in whom there is a decreased natural production of these compounds. Oestrogen therapy is used in postmenopausal women who experience the 'hot flushes' and atrophic vaginitis associated with the menopause. In women who have not undergone a hysterectomy, oestrogens are administered together with a progestogen, to reduce the incidence of endometrial carcinoma. Oestrogens can also be of benefit in the treatment of some types of breast cancer. Oestrogens are also used in contraceptive tablets (see later).

The most commonly used oestrogens for HRT are oestradiol and ethinyloestradiol; there is also a preparation available containing conjugated oestrogens. If a progestogen is required, it is usually norethisterone. The benefits of using HRT must be balanced against any possible adverse effects for the patient. Adverse effects of oestrogens include nausea and vomiting, weight gain, breast enlargement, fluid retention, depression, headache, sensitivity to contact lenses and increased risk of deep vein thrombosis. They are contraindicated in pregnancy and in patients who have oestrogen-dependent cancers or cardiovascular disease. These drugs are discussed more fully in Chapter 12.

Anti-oestrogens oppose the actions of oestrogens. The most common drugs in this group are tamoxifen and clomiphene. They are both competitive antagonists of oestrogen at its intracellular receptor sites. The major use of tamoxifen is in the treatment of breast cancer in postmenopausal women. Clompihene also inhibits the negative feedback effect that oestrogens have on the hypothalamus and pituitary gland. Consequently, there is an increase in the production of GnRH and of the gonadotrophins. The resultant stimulation in ovarian function may be beneficial in the treatment of female infertility. The adverse effects of anti-oestrogens may require cessation of treatment and include gastrointestinal disturbances, abdominal discomfort, fluid retention, visual disturbances, cataracts, insomnia, headache and breast tenderness.

Progestogens and antiprogestogens

There are two main groups of progestogens:

(1) progesterone and its analogues – progesterone, dydrogesterone, hydroxyprogesterone and medroxyprogesterone
(2) testosterone analogues – norethisterone and levonorgestrel.

The major use for progestogens in females is the treatment of endometriosis and severe dysmenorrhoea. They may also be used in HRT and some types of oral contraceptives. Adverse effects include acne, urticaria, fluid retention, gastrointestinal disturbances, changes in libido, breast discomfort, alopecia and hirsutism (testosterone analogues). The antiprogestogen mifepristone may be used to terminate intrauterine pregnancy up to 63 days after conception.

Oral contraceptives

The most common use of oestrogens is in oral contraceptive tablets, where they are used to suppress ovulation. Oral contraceptives can be divided into two main classes:

(1) progestogen-only tablets – containing only a progestogen
(2) combination tablets – containing an oestrogen to suppress ovulation and a progestogen. These are thought to be more reliable.

The pharmacology of oestrogens and progestogens in oral contraceptives is discussed in Chapter 12.

Androgens and anti-androgens

The administration of androgens, such as testosterone and mesterolone, cause marked masculinisation of the patient. However, they are of no value in the treatment of impotence. They are of use as replacement therapy in hypogonadism arising from either testicular disease or pituitary malfunction. In the normal male they inhibit the formation of sperm. Androgens also have a marked anabolic effect and this has led to the development of a series of anabolic steroids, such as nandrolone and stanozolol, which have been of

some benefit in the treatment of osteoporosis in women.

The adverse effects of androgens in males include prostate abnormalities, prostate cancer, headache, depression, nausea, gastrointestinal bleeding, sodium retention, hirsutism and the development of male-pattern baldness. The use of anabolic steroids gives rise to a wide range of adverse effects including acne, sodium retention, voice changes, amenorrhoea, hepatic failure and inhibition of sperm production. Their use is contraindicated in pregnancy, liver failure and prostate cancer.

Cyproterone is an anti-androgen used in the treatment of male hypersexuality and sexual deviation. It acts by inhibiting spermatogenesis and producing reversible male infertility. Its use is contraindicated in diabetes, depression and in patients with a history of thrombolytic disorders. Adverse effects include fatigue, breathlessness, gynaecomastia and hepatitis.

Finasteride is used in the treatment of benign prostatic hyperplasia. It is an inhibitor of the reductase enzyme responsible for the conversion of testosterone to dihydrotestosterone. This leads to a reduction in the size of the prostate gland and a relief of the clinical symptoms of the disease. Adverse effects include impotence, decreased sexual drive, gynaecomastia and hypersensitivity reactions.

Corticosteroids

Corticosteroids may be used either as replacement therapy in patients who suffer from a failure of the adrenal glands to secrete sufficient natural compounds for normal body function (Addison's disease), or as anti-inflammatory drugs in conditions associated with the development of an inflammatory response, such as rheumatoid arthritis.

Replacement therapy requires the administration of both a glucocorticoid, such as hydrocortisone, and a mineralocorticoid, such as fludrocortisone, to ensure the complete range of corticosteroid actions in the body. The use of corticosteroids as anti-inflammatory drugs requires the use of those drugs with a high glucocorticoid activity, such as betamethasone, dexamethasone and triamcinolone.

The long-term use of corticosteroids leads to inhibition of adrenal function and so presents a range of adverse effects, which may severely restrict their use:

- Corticosteroid therapy in patients who have normal adrenal function leads to inhibition of adrenal gland activity such that, on withdrawal of the drug, they are not able to synthesise these essential compounds.
- Mineralocorticoid activity leads to sodium and water retention, hypertension and excessive loss of K^+ ions.
- Glucocorticoids may produce the signs and symptoms of endocrine diseases, such as diabetes and osteoporosis, and the development of depression and paranoia. High doses may cause the typical hunched back and moon face of Cushing's syndrome. It should be noted that long-term use of inhaled glucocorticoids may give rise to a hoarseness in the voices as a result of changes in the vocal cords.
- In children, these drugs may cause inhibition of growth.

The severity of these adverse effects of corticosteroids requires that their use is closely monitored and that they *must not be withdrawn rapidly*. Patients are advised to carry a 'steroid card' with them at all times and to bring it to the attention of any health care professionals with whom they come into contact. Withdrawal of corticosteroid therapy must be carried out gradually over a period of several weeks under strict medical supervision.

It should be noted that the atrophy of the adrenal glands that occurs following long-term corticosteroid therapy may last for several years after the cessation of treatment. It is, therefore, *essential* that patients bring this to the attention of anaesthetists if they are to undergo surgery in order to avoid a potentially fatal hypotension, either during the period of anaesthesia or in the immediate postoperative period.

OSTEOPOROSIS

Osteoporosis is a disease of the skeleton in which there is a thinning of the normal bone with ageing. It is most common in women, where it results in fractures of the forearm, hip, pelvis and spine. The development of osteoporosis is accelerated by the postmenopausal loss of ovarian function, long-term therapy with corticosteroids and by smoking and alcohol. Osteoporosis is characterised by there being a decrease in the quantity of bone. In normal patients, the rate of bone destruction (resorption) by osteoclasts is balanced by the rate of bone formation by osteoblasts. However, in patients suffering from osteoporosis, the rate of bone destruction is increased so that it exceeds the rate of formation.

Drugs used in the treatment of osteoporosis

Oestrogen-replacement therapy:	oestrogens
Inhibitors of bone destruction:	calcitonin, bisphosphonates

Oestrogen-replacement therapy

The use of oestrogens in HRT for osteoporosis depends upon their ability to inhibit osteoclast activity and so prevent bone destruction. The pharmacology of oestrogens is discussed above.

Inhibitors of bone destruction

Calcitonin is a peptide that directly inhibits the actions of osteoclasts, thus preventing the resorption of bone in patients suffering from osteoporosis. It must be given by either i.m. or s.c. injection as the peptide is destroyed by enzymes in the stomach. Adverse effects include nausea, vomiting, flushing, tingling of the hands and hypersensitivity reactions.

Biphosphonates, such as alendronic acid and disodium etidronate, act by binding to the hydroxyapatite crystals of bone, so slowing their rate of dissolution. The onset of action of the bisphosphonates takes about 48 hours and treatment may be required for many years. Adverse effects include nausea, diarrhoea, constipation, headache, skin reactions and paraesthesiae.

SUMMARY

- The endocrine system is the second major communication system of the body.
- Hormones are secreted by the endocrine glands, circulate in the body and act upon target cells in other tissues and organs.
- The major locus of control of the endocrine system is the hypothalamus–pituitary gland axis.
- The hypothalamus secretes 'releasing hormones' in response to changes in hormone levels in the plasma. These act on the pituitary gland and promote the release of 'stimulating hormones', which subsequently act upon endocrine glands to stimulate hormone production.
- Many diseases arise as a result of malfunctions of the endocrine system.
- The most common endocrine disorders are diabetes mellitus, thyroid disorders, malfunctions of the reproductive system and osteoporosis.
- Diabetes mellitus arises from a malfunction in the endocrine system that controls the levels of glucose in the blood and is characterised by a raised level of glucose in the blood.
- The endocrine pancreas normally secretes two hormones, insulin and glucagon, which control glucose metabolism in all cells.
- Type I diabetes mellitus is also known as insulin-dependent diabetes mellitus and type II diabetes mellitus is known as non-insulin-dependent (maturity-onset) diabetes mellitus.
- Uncontrolled diabetes mellitus can give rise to peripheral neuropathy, circulation problems and blindness.
- Insulin-dependent diabetes mellitus can be treated with various insulin preparations.

- Non-insulin-dependent diabetes mellitus can be treated with sulphonylureas, biguanides and α-glucosidase inhibitors.
- Thyroid hormone controls the rate of growth and maturation of the body and the rate of tissue metabolism.
- Disorders of thyroid gland function can give rise to either hyperthyroidism or hypothyroidism.
- Hypothyroidism is very common in elderly patients.
- Hyperthyroidism is treated with drugs that inhibit thyroid hormone synthesis.
- Hypothyroidism is treated by the administration of thyroid hormone.
- The steroid sex hormones are produced by the ovaries and testes, and they control the development, maturation and functioning of the reproductive organs.
- The adrenal glands produce two groups of corticosteroid hormones, called glucocorticoids and mineralocorticoids.
- Oestrogens are used in hormone replacement therapy and anti-oestrogens are used to treat oestrogen-sensitive tumours.
- Progestogens are used in the treatment of endometriosis.
- Both oestrogens and progestogens can be used in oral contraceptives.
- Androgens are used to treat hypogonadism in males.
- Corticosteroids are used to treat adrenal gland failure (Addison's disease).
- Patients who are receiving treatment with corticosteroids *must* inform health care professionals in order to avoid dangerous interactions with other drugs and in some surgical procedures requiring general anaesthesia.
- Osteoporosis is a disease in which there is a decrease in the density of bone and may result in serious fractures of the hip joint and major bones of the skeleton.
- Osteoporosis may be treated by oestrogen replacement therapy or with drugs that inhibit bone destruction.

11

Drugs Affecting the Urinary Tract

INTRODUCTION

The mammalian urinary tract consists of the following structures:

(1) The *kidneys* are responsible for excretion of nitrogen-containing waste products, regulation of electrolyte and water balance in the body and regulation of the pH of body fluids.
(2) The *ureters*, *bladder* and *urethra* are responsible for the draining of the kidneys, storage of urine and its transport to the outside of the body, respectively.

THE KIDNEYS

The mammalian kidneys are bean-shaped organs, each about the size of a human fist. They are located in the abdominal cavity, one on either side of the midline. Each kidney consists of two distinct regions, a dark, outer *cortex* and an inner, paler region called the *medulla*. The medulla is further divided into a number of conical areas called the *renal pyramids*.

The basic functional unit of the kidney is the *nephron* and each kidney contains about a million nephrons. The nephron is a blind-ended tubule, the blind end of which forms *Bowman's capsule*, which surrounds a knot of blood capillaries called the *glomerulus*. The capillaries of the glomerulus are supplied with blood via the *afferent arterioles*, but they are drained via the *efferent arterioles*, rather than by way of a vein. In this way the glomerular capillaries are unique in the body and we have the ability to control the blood pressure in these capillaries within very fine limits. The remaining parts of the nephron are:

- the proximal convoluted tubule
- the loop of Henle
- the distal convoluted tubule
- the collecting duct.

Collecting ducts, arising from adjacent nephrons, join together and drain into the renal pelvis. There are two populations of nephrons in the kidney, which are characterised by the location of the glomerulus from which they arise, and the anatomical structure of the loop of Henle:

(1) *Cortical nephrons* arise from glomeruli which are located in the outer two-thirds of the cortex. They have relatively short loops of Henle that may only just penetrate into the medulla. The efferent arterioles form a network of blood vessels surrounding all sections of the nephron.
(2) *Juxtamedullary nephrons* arise from glomeruli lying deep within the cortex. They have long loops of Henle, which penetrate deep into the medulla and are responsible for generating the medullary osmotic pressure gradient. The efferent arterioles from these nephrons form a series of vascular loops called the *vasa recta*.

The structure of the urinary tract and a nephron are shown in Fig. 11.1.

Renal function

The first step in the process of renal function is the physical filtration of blood passing through the

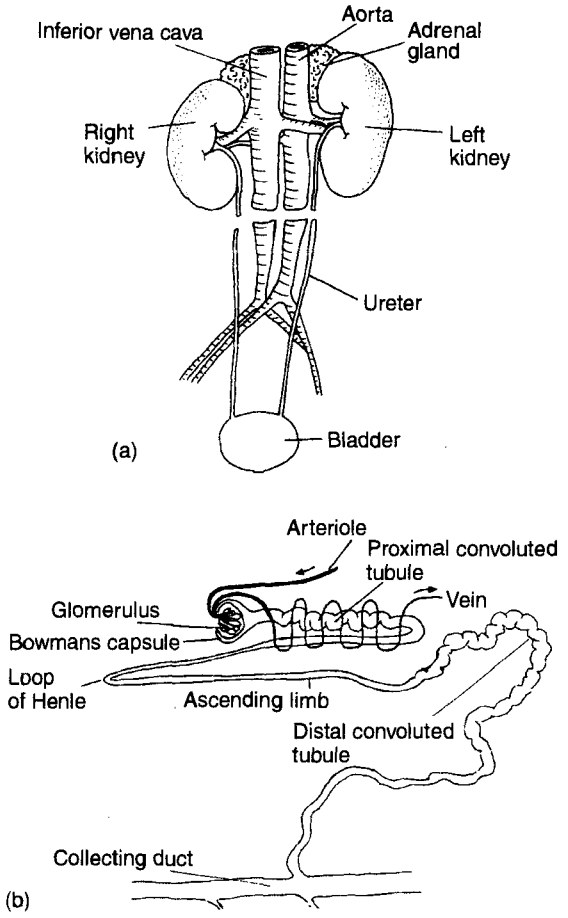

Fig. 11.1 The anatomical structure of the mammalian kidney and nephron. (a) Anatomical structure of the mammalian urinary tract. Note the positions of the two kidneys and the bladder. (b) Structure of a nephron. Note the position of the proximal convoluted tubule, loop of Henle, distal convoluted tubule and collecting duct.

glomerular capillaries. This takes place under the influence of the hydrostatic pressure of the blood in the capillaries, which sets up a pressure gradient from the capillary into Bowman's capsule. The process of filtration of the blood into Bowman's capsule takes place across the three layers of cells that constitute the wall of the capsule:

(1) The *endothelial cells* of the capillary contain many pores, which have a diameter of about 60 nm. These form a barrier to prevent the filtration of the cellular components of the blood.

(2) The *basement membrane* forms the major filtration barrier and allows the passage of molecules dependent upon their size and lipid solubility.

(3) The *podocytes* are specialised cells, having foot-like projections, and cover the basement membrane. They provide a further barrier to the filtration of large, negatively charged molecules.

The combined effects of these three barriers to filtration is to produce, inside Bowman's capsule, a cell-free ultrafiltrate of blood that does not contain any molecules having a relative molecular mass greater than 70 kDa. Molecules with a relative molecular mass of up to 7 kDa, such as glucose, Na^+ and K^+, are freely filtered and appear in the filtrate at the same concentration as they occur in the plasma. Molecules with a relative molecular mass in the range 7–70 kDa are filtered at rates inversely proportional to their size.

The ultrafiltrate produced in the lumen of Bowman's capsule then passes along the nephron towards the collecting duct and, during this passage, its composition is modified by the activity of the cells forming the walls of the various parts of the tubule. The major processes that occur along the length of the nephron are:

- proximal convoluted tubule – active transport of Na^+, K^+ and glucose; reabsorption of bicarbonate (HCO_3^-); the reabsorption of each of these substances results in the reabsorption of an osmotically equal amount of water (179 l/day)
- loop of Henle – reabsorption of Cl^- and Na^+ without the co-absorption of water; generation of the medullary osmotic pressure gradient
- distal convoluted tubule – reabsorption of Na^+ and Cl^- (without water) in the early segment (cortical diluting segment); Na^+/K^+ exchange and Na^+/H^+ exchange in the later segment with a net reabsorption of small amounts of water
- collecting duct – osmotic reabsorption of water, driven by the medullary osmotic

pressure gradient, and modified by the action of antidiuretic hormone (ADH).

It is important to note that the process of osmosis drives the reabsorption of water that takes place at sites both along the length of the nephron and in the collecting ducts. The reabsorption of electrolytes, such as Na^+, K^+ and glucose, establishes an osmotic pressure gradient along which the water moves by osmosis. These processes are discussed in more detail in the sections dealing with the drugs that affect them.

DISEASES OF THE KIDNEY

Whilst direct renal disease is of major consequence to the patient and, in fact, often leads to renal failure and the death of the patient, the major manifestations of renal disease in patients are associated with the development of clinical conditions consequent upon a reduced renal function. The major clinical conditions arising from impaired renal function are:

- oedema
- polyuria
- oliguria
- chronic renal failure
- nephrolithiasis.

Oedema

Oedema is an accumulation of water in the interstitial space between the cells and usually results from an imbalance between the rate of production of interstitial fluid and its rate of reabsorption. The formation of interstitial fluid is dependent upon the hydrostatic pressure of the blood in the capillaries and the osmotic pressure of the proteins in the interstitial fluid. Conversely, the reabsorption of interstitial fluid is dependent upon the hydrostatic pressure of the interstitial fluid and the osmotic pressure of the proteins in the blood.

Oedema can arise as the result of a number of underlying pathological causes, but the most common reasons for the development of oedema are congestive heart failure and liver disease.

The oedema in congestive heart failure results from a decrease in renal function, as a result of the decreased cardiac output. This leads to activation of the renin-angiotensin system and retention of Na^+ and water by the kidney. Ultimately this leads to a typical accumulation of fluid in the lower trunk, giving rise to the characteristic swollen ankles. This disease used to be called dropsy. The oedema associated with liver failure results from a decrease in the amount of protein circulating in the blood and an increased hydrostatic pressure in the portal vein.

Drugs used in the treatment of oedema

Diuretics:	thiazides, loop diuretics, potassium-sparing diuretics, osmotic diuretics

Diuretics are drugs that produce an increase in urine output by a direct action on the kidney. The primary effect of most diuretics is to decrease the reabsorption of Na^+ at various sites along the nephron and so reduce the osmotic pressure gradients that drive water reabsorption. The result is an increased loss of water in the urine.

Thiazides

Thiazides act primarily on the Na^+/Cl^- reabsorption process in the early part of the distal convoluted tubule. They produce a moderate diuretic effect and promote the excretion of about 5% of the filtered Na^+ entering the nephron. Examples of thiazide diuretics are hydrochlorothiazide, bendrofluazide, indapamide and metolazone. The clinical pharmacology of thiazides is discussed in the section dealing with their use in the treatment of cardiovascular diseases (Chapter 7).

Loop diuretics

Loop diuretics, such as frusemide and ethacrynic acid, act on the ascending limb of the loop of Henle to inhibit the reabsorption of Cl^- and Na^+. As a consequence, there is a reduction in the medullary osmotic pressure gradient and so a decrease in the rate of water reabsorption from the collecting ducts. These drugs are called 'high-ceiling'

diuretics in respect of their ability to produce a large diuretic effect resulting from excretion of 20–25% of the filtered sodium load. The clinical pharmacology of loop diuretics is discussed in the section dealing with their use in the treatment of cardiovascular diseases (Chapter 7).

Potassium-sparing diuretics
Potassium-sparing diuretics act on the late distal convoluted tubule to inhibit the ion-exchange mechanisms that control water reabsorption at that site. They produce a very small diuretic effect (equivalent to about 2% of the filtered sodium load), but may be used to increase the diuretic response in a patient while offsetting the hypokalaemia that can result from the use of thiazides and loop diuretics. Potassium-sparing diuretics may be divided into two groups:

(1) Na^+ channel-blocking drugs, such as amiloride and triamterene, inhibit the reabsorption of Na^+ through channels located on the principal cells of the distal convoluted tubule. This reduces the driving force for K^+ secretion and also decreases water reabsorption.
(2) Aldosterone antagonists, such as spironolactone and canrenoate, inhibit the production of the K^+-carrier protein in the principal cells. The mineralocorticoid hormone aldosterone, which is produced in the adrenal gland, controls production of this protein. These drugs act as competitive antagonists of aldosterone and so reduce the synthesis of the carrier protein.

The clinical pharmacology of potassium-sparing diuretics is discussed in the section dealing with their use in the treatment of cardiovascular diseases (Chapter 7).

Osmotic diuretics
Osmotic diuretics, such as mannitol given by i.v. injection, are freely filtered across the glomerular filter bed and enter the lumen of the nephron at the same concentration as that found in blood. However, they are not reabsorbed from sites within the nephron and so are passed out into the urine, taking with them an osmotically equivalent amount of water.

Polyuria

Polyuria is the excessive production of a dilute urine. It is often accompanied by a marked increase in fluid intake (polydipsia). The main causes of polyuria are diabetes mellitus and *diabetes insipidus*. Diabetes mellitus is discussed in Chapter 10. Diabetes insipidus results from either a failure to produce sufficient amounts of ADH to promote water reabsorption from the collecting ducts (central diabetes insipidus), or a failure of the cells of the collecting ducts to respond to normal amounts of ADH (nephrogenic diabetes insipidus).

Drugs used in the treatment of polyuria

ADH analogues:	desmopressin, lypressin
Combination therapy:	chlorothiazide/indomethacin

ADH analogues
The action of ADH on the V_2 receptors of the cells of the collecting ducts is to increase water permeability by promoting the coalescence of water channels. Synthetic analogues of ADH, such as desmopressin, mimic this action without causing any vasopressor action and are of benefit in the treatment of central diabetes insipidus. This drug may also be used in the treatment of nocturnal enuresis. Adverse effects include fluid retention, stomach pain, headache, nausea and vomiting.

Combination therapy
Combination therapy with the long-acting thiazide diuretic chlorothiazide and the NSAID indomethacin is of benefit in the treatment of nephrogenic diabetes insipidus. The thiazide reduces the effective circulating fluid volume and so increases the osmotic pressure of the plasma proteins, and hence reduces the hydrostatic pressure of the peritubular capillaries. This increases the retention of Na^+ and water in the nephron and decreases the amount of water entering the collecting ducts. Indomethacin is thought to decrease the rate of glomerular filtration and to promote fluid reabsorption from both

the proximal and distal convoluted tubules, and this further reduces the amount of fluid entering the collecting ducts.

Oliguria

Oliguria is a condition of reduced urine volume and, in the absence of other underlying pathology, is usually indicative of acute renal failure. The normal urine output in a healthy adult is about 1.5 l per 24 hours. However, in oliguria it can fall to less than 50 ml per 24 hours, at which point the patient is considered to be anuric. Normal renal function is dependent upon there being adequate perfusion of the glomeruli, normal tubular cell function and adequate drainage of urine via the ureters, bladder and urethra. Factors that tend to decrease these normal functions of the kidney are likely to precipitate oliguria.

Drugs used in the treatment of oliguria

Diuretics:	frusemide, mannitol

Diuretics
The scope for drug treatment of oliguria is extremely limited, as there are currently no drugs that are effective in either preventing or reversing renal failure. However, the use of diuretic agents, such as frusemide or mannitol, may be of benefit if the oliguria is due to partial blockage of the nephron, as they increase renal blood flow.

Chronic renal failure

Chronic renal failure is a gradual decrease in renal function resulting from a number of disease states, such as severe hypertension, diabetes mellitus, glomerulonephritis or severe obstruction of the urinary tract.

Drugs used in the treatment of chronic renal failure

The effective treatment of chronic renal failure requires either dialysis or transplant of a healthy organ. However, drug treatment can be used to aid management of the patient until suitable surgery can be made available.

Loop diuretics:	frusemide
ACE inhibitors:	captopril, enalapril
Vitamin D derivatives:	alfacalcidol, calcitriol

Loop diuretics
The increased excretion of Na^+ and water following the administration of frusemide is of benefit in chronic renal failure.

ACE inhibitors
Antihypertensive drugs are of use in preventing the hypertension that develops as a result of chronic renal failure, and ACE inhibitors, such as captopril and enalapril, have been shown to reduce the rate of decline of renal function in this disease.

Vitamin D derivatives
Another consequence of chronic renal failure is interference with vitamin D metabolism, resulting in a decrease in the absorption of dietary Ca^{2+} possibly leading to hypocalcaemia and secondary hypothyroidism. Alfacalcidol (1α-hydroxycholecalciferol) and calcitriol (1,25-dihydroxycholecalciferol) are both vitamin D derivatives, which can be used to reverse the decrease in Ca^{2+} absorption and so prevent the onset of thyroid disorder. Adverse effects include anorexia, lassitude, nausea, vomiting, weight loss and headache.

Nephrolithiasis (kidney stones)

Nephrolithiasis is an extremely painful condition that occurs when poorly soluble substances precipitate out of solution in the lumen of the nephron and the crystals coalesce together to form deposits large enough to physically block the nephron or urinary tract. This disease state is characterised by intense pain in the back and anuria.

Drugs used in the treatment of nephrolithiasis

Thiazides:	hydrochlorothiazide, chlorothiazide
Xanthine oxidase inhibitors:	allopurinol

Thiazides

Most renal stones are composed of Ca^{2+} salts, such as calcium phosphate or calcium oxalate. The ability of long-term thiazide therapy to decrease Ca^{2+} excretion decreases the likelihood of stone formation and can lead to the dissolution of small stones. The adverse effects of thiazides are discussed in Chapter 7.

Xanthine oxidase inhibitors

Some renal stones result from the deposition of uric acid. Therefore, the xanthine oxidase inhibitor allopurinol decreases the formation of uric acid and prevents its reaching sufficient concentration to precipitate out of solution. Adverse effects include malaise, headache, vertigo, drowsiness, hypertension and rashes.

THE BLADDER AND URETHRA

The urine produced by the kidneys is transferred, via the ureters, to the bladder, where it is stored until it can be voided at an appropriate time. The lower urinary tract comprises the *detrusor muscle* and *trigone*, which together make up the wall of the bladder, and the *urethra* through which urine is voided. These are smooth muscle structures, which are controlled by a complex central and peripheral nerve-mediated control mechanism that allows not only for the voiding of urine when the bladder is full, but also for this process to be controlled according to social demands.

The detrusor muscle receives a parasympathetic, cholinergic innervation which releases ACh and causes muscle contraction and bladder emptying by an action on M_1, M_2 and M_3 mAChRs. This muscle also receives a sparse sympathetic innervation that releases norepinephrine, causing muscle relaxation by an action on β_2-adrenoceptors. The trigone receives a predominantly sympathetic, adrenergic innervation that mediates muscle contraction by the action of norepinephrine on α_1-adrenoceptors to prevent loss of urine. It is this adrenergic activity that keeps the urethra closed during bladder filling. The outflow region of the bladder also receives a non-adrenergic-non-cholinergic (NANC)-mediated innervation. In males, the prostate gland surrounds the base of the urethra.

Distention of the detrusor muscle in the wall of the bladder initiates the micturition reflex. Afferent fibres from the wall of the bladder are stimulated by stretching of the detrusor muscle and pass impulses to the spinal cord and up to the micturition centre in the brain. Efferent fibres pass from the micturition centre back down the spinal cord to the sacral micturition centre, from which the parasympathetic nerves innervate the detrusor muscle to promote voiding of urine. At the same time, stimulation of the sympathetic innervation to the urethra causes muscle relaxation, so aiding the passage of urine.

The innervation of the lower urinary tract is shown in Fig. 11.2.

With the exception of diseases of the prostate gland, diseases of the urinary tract arise either from a failure of the nerve-mediated control

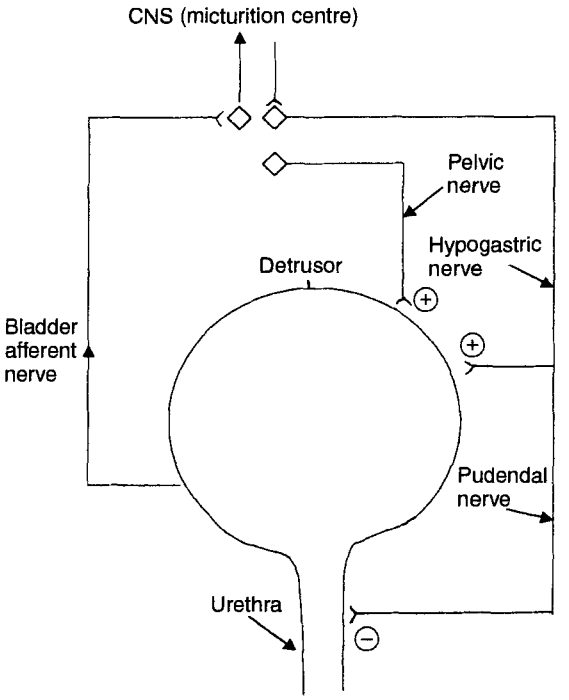

Fig. 11.2 The innervation of the lower urinary tract. Stretch receptors in the bladder wall activate the micturition centre in the CNS; the hypogastric and pelvic nerves stimulate the detrusor to contract, while the pudendal nerve causes the urethral sphincter to relax.

mechanisms that control bladder filling and emptying or from the introduction of infective agents into the urinary tract. They may be classified as follows:

(1) urinary incontinence
(2) urinary retention
(3) urinary tract infections.

Urinary incontinence

Urinary incontinence, to some degree, occurs in about 10% of the population. It is characterised by an uncontrolled, involuntary voiding of urine and may be a symptom of an underlying pathological disease. Urinary incontinence may be subdivided into three different types:

(1) *Stress incontinence* results from ineffective closing of the urethra as a result of partial failure of the closure mechanism. It usually occurs following defective transmission of the intra-abdominal pressure to the urethra, such that the pressure in the bladder is greater than that in the urethra. It may also result from a lack of oestrogen.
(2) *Urge incontinence* is usually associated with a strong desire (urge) to void urine.
(3) *Hyperreflexia* is the uncontrolled contractions of the detrusor, as a result of neurological damage.

Drugs used in the treatment of urinary incontinence

Antimuscarinic drugs:	oxybutynin, flavoxate, dicyclomine, propantheline
Tricyclic antidepressants:	imipramine, amitriptyline, nortriptyline
ADH analogue:	desmopressin

Antimuscarinic drugs
Inhibition of the parasympathetic drive to the detrusor has a major effect as the mAChR probably has the major contribution to muscle contraction in the overactive detrusor. However, the effectiveness of antimuscarinic drugs in the overactive detrusor is limited because of the contribution to muscle contraction made by NANC-mediated mechanisms, which are not affected by these drugs. Antimuscarinic drugs, such as oxybutynin and propanthelin, may control hyperreflexia, but the adverse effects limit their usefulness. Adverse effects include dry mouth, blurred vision, tachycardia, constipation, nausea, drowsiness and headache.

Tricyclic antidepressants
Imipramine is the most effective tricyclic antidepressant for the treatment of detrusor overactivity, especially in the elderly patient. The mechanism by which this drug produces its beneficial effects in urinary incontinence is probably as a consequence of its antimuscarinic activity.

ADH analogue
Desmopressin is effective in the treatment of both stress incontinence and nocturnal enuresis in children. Adverse effects include fluid retention, stomach pain, headache, nausea, vomiting and possible convulsions. Its use is contraindicated in patients who have impaired cardiac function.

Urinary retention

Urinary retention may occur from either a decreased contractility of the detrusor, or an elevated pressure in the urethra that cannot be overcome by contraction of the detrusor. Acute urinary retention is extremely painful and, while chronic urinary retention is less painful, it may lead to infection problems in the bladder if left untreated. The treatment of urinary retention aims either to increase the activity of the detrusor or to decrease the pressure in the urethra.

Drugs used in the treatment of urinary retention

α_1-Adrenoceptor antagonists:	alfuzosin, doxazosin, indoramin, prazosin, tamsulosin, terazosin
Parasympathomimetic drugs:	bethanechol, carbachol, distigmine

α_1-Adrenoceptor antagonists

α_1-Adrenoceptor antagonists, such as indoramin and prazosin, act to decrease the tone of urethral smooth muscle. They are more effective in causing bladder emptying as they bring about a direct decrease in the intraurethral pressure. Adverse effects include severe hypotension, dizziness and drowsiness.

Parasympathomimetic drugs

Contraction of the detrusor is mediated primarily through mAChRs and so parasympathomimetic drugs, such as bethanechol and distigmine, act by increasing the parasympathetic drive to the detrusor and so produce an increase in bladder tone. However, their effectiveness depends on the pressure in the urethra and, in some cases, administration of these drugs alone is insufficient to bring about bladder emptying. Adverse effects include nausea, vomiting, blurred vision, sweating, bradycardia and intestinal colic.

Urinary tract infections

Infections of the urinary tract are very common, especially in females. The most common pathogen, responsible for over 75% of urinary tract infections, is *Escherichia coli*. Other pathogens include *Staphylococcus saprophyticus*, *Pseudomonas aeruginosa* and various microorganisms of the *Proteus* spp. Urinary tract infections may be subdivided into those affecting the lower urinary tract (cystitis) and those affecting the upper urinary tract (pyelonephritis):

- Lower urinary tract infections in women give rise to the symptoms of cystitis, which are urinary frequency and a burning sensation and pain on passing urine. In men, infections of the lower urinary tract are uncommon and, when they do occur, usually involve the prostate gland. There is a variable incidence in children.
- Upper urinary tract infections are potentially life-threatening and are characterised by fever, malaise, back pain and vomiting. Such infections require immediate treatment.

Drugs used in the treatment of urinary tract infections

Antibacterial drugs:	trimethoprim, gentamicin, cephalosporins, norfloxacin, pivampicillin, nitrofurantoin

The treatment of urinary tract infections is aimed at eliminating the infecting microorganism by the use of antibacterial drugs. The choice of the correct drug is dependent upon the positive identification of the microorganism concerned. However, a number of broad-spectrum antibacterial drugs may be used to treat urinary tract infections without prior identification of the microorganism.

Cystitis, in both male and non-pregnant female patients, may be adequately treated by trimethoprim or pivampicillin, although norfloxacin is sometimes more effective in males. In pregnant females, the use of nitrofurantoin is to be preferred. Acute pyelonephritis may be treated with norfloxacin in both males and non-pregnant females. Pregnant females require hospitalisation and treatment with cephalosporins.

SUMMARY

- The urinary tract consists of the kidneys, ureters, bladder and urethra.
- The kidneys are bean-shaped organs consisting of an outer cortex and an inner medulla.
- The basic functional unit of the kidney is the nephron, which consists of a glomerulus, proximal convoluted tubule, loop of Henle, distal convoluted tubule and collecting duct.
- Cortical nephrons have short loops of Henle and juxtamedullary nephrons have long loops that penetrate deep into the renal medulla.
- Renal function consists of glomerular filtration to produce an ultrafiltrate of blood, followed by selective reabsorption of electrolytes and other solutes accompanied by the osmotic reabsorption of water.

- Major diseases involving the kidney are oedema, polyuria, oliguria, chronic renal failure and nephrolithiasis.
- Oedema is an accumulation of water in the interstitial spaces between cells and can arise from either heart failure, kidney failure or liver disease.
- Oedema may best be treated by treating the underlying cause and by the use of diuretic drugs that increase water output.
- Polyuria is the excessive production of urine, most commonly occurring as a result of either diabetes mellitus or diabetes insipidus.
- Polyuria may be treated with ADH analogues, or by combination treatment with a diuretic and a non-steroidal anti-inflammatory drug.
- Oliguria is a condition in which there is a reduced urine output and, in the absence of an obvious pathological cause, is indicative of renal failure.
- Oliguria may be treated with diuretic drugs.
- Chronic renal failure is a gradual decrease in the functional status of the kidneys, which may be the result of hypertension, diabetes, glomerulonephritis or physical obstruction of the urinary tract.
- Chronic renal failure may be treated, in the absence of physical obstruction, by the use of diuretics, ACE inhibitors or vitamin D derivatives.
- Nephrolithiasis is the deposition of stones in the kidney and may be treated with either thiazide diuretics or xanthine oxidase inhibitors.
- The bladder stores urine delivered from the kidneys and it is voided via the urethra at micturition.
- Bladder continence is controlled by adjusting the contraction of the wall of the bladder and of the urethra.
- Distention of the bladder stimulates the micturition reflex and leads to the voiding of urine.
- The major diseases of this part of the urinary tract are urinary incontinence, urinary retention and urinary tract infections.
- Urinary incontinence is characterised by the uncontrolled voiding of urine and may result from either stress or damage to the neuronal mechanisms controlling the bladder and urethra.
- Urinary incontinence may be treated with either antimuscarinic drugs, tricyclic antidepressants or ADH analogues.
- Urinary retention is an inability to void urine; it is extremely painful and may lead to an increased incidence of urinary tract infections. Urinary retention is a common adverse effect of antimuscarinic drugs.
- Urinary retention may be treated with α_1-adrenoceptor antagonists or with parasympathomimetic drugs.
- Infections of the lower urinary tract are more common in females than in males and, in most cases, *E. coli* is the causative microorganism.
- Infections of the upper urinary tract are potentially life-threatening.
- Urinary tract infections are treated with the appropriate antibacterial drugs.

12

Drugs Affecting the Reproductive System

THE FEMALE REPRODUCTIVE SYSTEM

The female reproductive system consists of two *ovaries*, each of which is surrounded by the open end of a *fallopian tube* that leads into a muscular *uterus*. The lower end of the uterus narrows down to form a muscular structure called the *cervix*. The cervix contains a large number of *secretory glands* and, at its lower end, protrudes into the *vagina*. The secretory glands of the cervix produce mucus that acts as a barrier to the transmission of infections between the vagina and the uterus.

Each ovary consists of a large number of *spherical follicles* that are embedded in the stroma and which are surrounded by a membrane called the *tunica albuginea*. Each follicle contains one egg cell (*oocyte*). Initially about 7 million oocytes are laid down in early fetal life, but the majority of these do not mature. In most women about 400 of these will mature by the age of 40. The ovaries are also responsible for the production of the important sex hormones *oestradiol* and *progesterone*, the production of which are controlled by the hypothalamic–pituitary axis via the actions of follicle-stimulating hormone (FSH) and luteinising hormone (LH).

The anatomical structure of the female reproductive system is shown in Fig. 12.1.

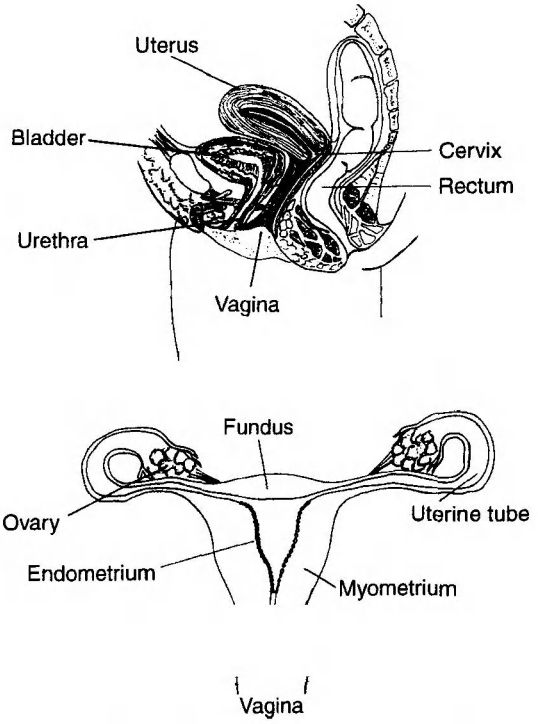

Fig. 12.1 The anatomical structure of the female reproductive tract.

The menstrual cycle

The female menstrual cycle may be defined as the period between two successive ovulations and usually lasts for between 24 and 32 days. Day 1 is considered to be the point at which the endometrium of the uterus starts to shed and bleeding begins. This process takes about 3–6 days and is followed by the follicular phase, which lasts until day 14, at which point ovulation occurs. During the follicular phase of the cycle the ovarian follicles produce large quantities of oestradiol, which acts on the endometrium of the uterus, causing it to become thicker and to develop a network of blood capillaries.

After ovulation, the ruptured ovarian follicle, from which the ovum has arisen, develops into the *corpus luteum* and begins to secrete progesterone.

The progesterone stimulates the secretory glands of the endometrium and prepares the endometrium to receive a fertilised ovum. If the ovum is fertilised then the corpus luteum is maintained. It continues to secrete progesterone and provides a suitable environment for implantation of the fertilised ovum into the endometrium. If the ovum is not fertilised then the corpus luteum begins to decay at the mid-luteal phase, at day 21 of the cycle. Eventually, the fall in progesterone levels and a concomitant rise in prostaglandin levels in the endometrium lead to cell death and the shedding of the lining at day 1 of the next cycle.

It can be seen from the discussion above that correct functioning of the female reproductive system is dependent upon the regular production of both oestrogen and progesterone. This is necessary in order to maintain the correct timing of endometrial development and ovulation such that, on fertilisation, the ovum has the greatest chance of survival and development. Consequently, the majority of disorders of the female reproductive system which are susceptible to drug therapy involve disorders of the control mechanisms for the production of oestrogen and/or progesterone. However, there is also the possibility that this system can be altered by drug therapy either to produce a contraceptive effect or to replace these hormones when their production is inhibited during the menopause. The pharmacology of oral contraceptive drugs, and of hormone replacement therapy, is discussed separately at the end of this chapter.

The most common diseases of the female reproductive system are:

- disorders of the hypothalamic–pituitary axis
- disorders of the ovary
- disorders of the uterus
- infections.

Disorders of the hypothalamic–pituitary axis

The major chemical control of the female reproductive system arises in the hypothalamus, which secretes gonadotrophin-releasing hormone (GnRH). This acts on the pituitary gland to promote the synthesis and release of both LH and FSH. In turn, these hormones act on the ovaries to control the production of oestrogen and progesterone. The control of GnRH secretion from the hypothalamus is partially under the influence of these steroids, acting in a feedback loop, and partially under the influence of dietary and other factors. Thus, disorders of the hypothalamic–pituitary axis may arise from a direct malfunction of either the hypothalamus or the pituitary gland (primary disorders) or as a result of a failure of the systems controlling the function of the hypothalamus (secondary disorders).

Primary disorders include hypogonadotrophic hypogonadism, which is a congenital failure in the release of GnRH from the hypothalamus. It is characterised by incomplete development of the secondary sexual characteristics and the absence of menstrual periods. Secondary disorders can arise from an imbalance of the fat : lean ratio in the body at puberty, possibly as a consequence of dietary insufficiency, leading to the delayed onset of sexual maturity and infertility. It is not uncommon for these secondary disorders to arise from an inadequate diet in young females, either as a result of a lack of animal-based protein in the food or excessive dieting.

Drugs used in the treatment of disorders of the hypothalamic–pituitary axis

Hypothalamic hormones:	gonadorelin
Anterior pituitary hormones:	chorionic gonadotrophin, follitropin

Hypothalamic hormones

Gonadorelin (GnRH), when given by i.v. injection, causes a rapid rise in plasma levels of both LH and FSH. It is of benefit in the treatment of certain types of female infertility and some analogues of gonadorelin are used in the treatment of endometriosis and breast cancer. Adverse effects include nausea, headache, abdominal pain and increased menstrual bleeding.

Anterior pituitary hormones

Anterior pituitary hormones are of clinical benefit in the treatment of disorders of the pituitary

gland. Chorionic gonadotrophin and follitropin may be used in the treatment of female infertility and their use mimics the effects of LH and FSH. Adverse effects include oedema, headache, tiredness, mood changes and possible over-stimulation of the ovaries leading to multiple pregnancies.

Disorders of the ovary

Disorders of ovarian function are the most common cause of female infertility arising from a decreased availability of ova suitable for fertilisation. Polycystic ovarian syndrome (PCOS) is a common ovarian disorder associated with obesity and is characterised by the production of many cyst-like follicles on the ovaries, an elevated level of oestrogen, a decreased level of progesterone and a low FSH : LH ratio. The high level of oestrogen in this disease increases the risk of the development of endometrial cancer.

Drugs used in the treatment of disorders of the ovary

Anti-oestrogens:	clomiphene, tamoxifen
Anti-androgens:	cyproterone

Anti-oestrogens
The anti-oestrogen drugs, clomiphene and tamoxifen, are effective in the treatment of female infertility arising from PCOS. They act by antagonising the actions of oestrogen in the hypothalamus and so promote the release of GnRH, which acts on the pituitary gland to release FSH and LH. Adverse effects include visual disturbances, over-stimulation of the ovaries, hot flushes, abdominal discomfort, depression, nausea and vomiting.

Anti-androgens
Drugs which block the actions of progesterone, such as cyproterone, are also of benefit in combating the hirsutism (increased hair growth) which is a characteristic of PCOS. This drug acts by preventing the progesterone-induced stimulation of hair growth in the hair follicle. Adverse effects include fatigue, breathlessness, and osteoporosis.

Disorders of the uterus

The uterus is a muscular organ consisting of the endometrium and the myometrium. The cyclical changes associated with the menstrual cycle are mediated via changes in the endometrium of the uterus and so disorders of this organ are associated with disorders of the menstrual cycle.

- *Dysmenorrhoea* (painful menstruation) is associated with cramps of the lower abdomen and legs, gastrointestinal upset and neurological disorders. It is characterised by increased contractions of uterine smooth muscle and an increased degree of resting tone of the organ. The probable cause of these effects is an increase in the levels of prostaglandins, especially $PGF_{2\alpha}$ and PGE_1.
- *Amenorrhoea* is an absence of menstrual flow.
- *Menorrhagia* is a frequent, heavy and unpredictable menstrual flow, the cause of which is not known. In this condition, the levels of oestrogen and progesterone are normal. Prostaglandin levels are elevated.
- *Endometriosis* is characterised by the presence of functional endometrial cells outside the uterus. The symptoms are severe cyclical pain, backache and infertility.
- *Uterine fibroids* are benign tumours of the myometrium, which consist of a mass of smooth muscle surrounded by connective tissue. Drug therapy may be of benefit in the early stages of this disease, but eventually surgical intervention is required to remove the tumour.

Drugs used in the treatment of disorders of the uterus

Oral contraceptives:	progesterone-only preparations, combination preparations
Steroid analogues:	danazol
NSAIDs:	mefenamic acid, diclofenac
Thrombus promoters:	ethamsylate, tranexamic acid

Oral contraceptives
Oral contraceptive preparations are of benefit in the treatment of uterine disorders, including dysmenorrhoea and amenorrhoea. Their pharmacology is discussed below.

Steroid analogues
Danazol is a weak steroid analogue that reduces the release of FSH and LH and so reduces oestrogen levels in the patient. This inhibits menstruation and so relieves the symptoms of dysmenorrhoea and of endometriosis. Its wide range of adverse effects, which include nausea, dizziness, rashes, photosensitivity, menopausal symptoms, anxiety, epigastric pain and vaginal dryness, restricts the use of danazol.

NSAIDs
The anti-inflammatory actions of NSAIDs, such as mefenamic acid and diclofenac, derive from their ability to inhibit prostaglandin production by inhibition of the COX enzyme system. This reduces the contraction of uterine smooth muscle and any inflammation associated with the breakdown of the endometrium. Adverse effects include gastrointestinal upset, aggravation of peptic ulcer disease, headache and water retention.

Thrombus promoters
Ethamsylate increases platelet aggregation and capillary resistance, both effects leading to a decrease in capillary bleeding and a reduction in blood loss. Tranexamic acid inhibits the breakdown of fibrin clots. Both drugs reduce blood loss in menorrhagia, but the major adverse effect is an increased tendency to thrombus formation.

Infections

Infections of the female reproductive system can be divided into two major groups:

(1) *Vulvovaginal infections*, including candidiasis, bacterial vaginosis and endocervicitis, are associated with infections of the lower reproductive system.
(2) *Pelvic inflammatory disease* is associated with bacterial infections in the upper reproductive system. The presence of microorganisms in the vagina is common and is not necessarily associated with disease. However, any conditions that upset the balance of the natural flora, or infection by a non-resident microorganism, can give rise to clinical symptoms.

The most common vulvovaginal infection is candidiasis (thrush) which is caused by the fungus *Candida albicans*. Thrush is characterised by an inflammation of the vaginal walls, itching, irritation, painful and frequent micturition and, in severe cases, a white discharge from the vagina. Whilst *C. albicans* is a not uncommon infection present in the vagina it normally lies dormant unless some predisposing factor arises that allows it to proliferate when the clinical symptoms are produced. Predisposing factors include stress, diabetes mellitus, tight clothing (tights) and antibacterial therapy.

Bacterial vaginosis usually occurs as a result of an upset in the natural balance of the Gram-positive bacteria normally present in the vagina. It is a non-irritative disease that is characterised by a grey discharge from the vagina. The typical 'fishy' odour associated with this bacterial vaginosis arises from the products of anaerobic metabolism in the bacteria, including putrescine and cadaverine. *Trichomonas vaginalis* is a flagellated protozoan which causes an anaerobic infection of the vagina. It produces considerable inflammation of the vaginal wall and a malodorous frothy discharge.

Endocervicitis usually results from infection by either the bacteria *Neisseria gonorrhoeae* and/or *Chlamydia trachomatis*. Both of these microorganisms are sexually transmitted and give rise to severe cervical inflammation and a pus-like vaginal discharge. However, in about half of infected patients, there are no overt symptoms and so the disease is spread rapidly by sexual contact. If untreated it can lead to pelvic inflammatory disease and severe infections at extrapelvic sites giving rise to diseases such as endocarditis, septic arthritis and hepatitis.

Drugs used in the treatment of infections

Antifungal drugs:	clotrimazole, ketoconazole, fluconazole, itraconazole, nystatin
Antibacterial drugs:	amoxycillin, ciprofloxacin, erythromycin, clindamycin, metronidazole, cephalexin, cefoxitin

Antifungal drugs
Candidial infections are best treated with antifungal drugs, such as clotrimazole and fluconazole. Infections of the lower vagina and vulva may be treated by the topical application of creams, but infections inside the vagina are best treated either with clotrimazole pessaries, or by the oral administration of a single dose of fluconazole. Adverse effects of topical application include mild stinging on application. Orally administered drugs can cause nausea, abdominal discomfort, diarrhoea and flatulence.

Antibacterial drugs
Correct identification of the infecting microorganism is again important in the treatment of infections of the female reproductive system. Bacterial vaginosis may be treated successfully with a 7-day course of metronidazole given orally, whereas trichomonas vaginalis may be eradicated with a single dose of either metronidazole or tinidazole. Macrolides, such as erythromycin, and the penicillin derivative amoxycillin, are both equally effective in the treatment of endocervicitis, although more resistant cases may require the use of ciprofloxacin or cefoxitin. Adverse effects of antibacterial treatment include diarrhoea, gastrointestinal disturbances and hypersensitivity reactions. Care must be taken with metronidazole as the patient must be advised not to drink alcohol during the course of treatment as it will produce a severe 'hangover' effect similar to that produced by the drug disulfiram used in the control of alcoholism.

Oral contraceptives

Oral contraceptive preparations prevent fertility by acting at a number of sites in the female reproductive system to inhibit release of ova and/or to render the endometrium inhospitable to a fertilised ovum, such that it does not become embedded. The rationale of treatment is to deliver oestrogen and/or progesterone at sufficient concentrations to effect a negative feedback on the hypothalamic–pituitary axis and so prevent the release of FSH and LH, both of which are essential for fertility.

Drugs used as oral contraceptives

Combined therapy preparations:	ethinyloestradiol plus norethisterone, ethinyloestradiol plus levonorgestrel
Progesterone only preparations:	norethisterone
Emergency preparations:	levonorgestrel plus ethinyloestradiol

Combined therapy preparations
Oral contraceptives that contain both an oestrogen and a progestogen are the most effective agents for preventing female fertility. They are available in three different 'strengths', thus allowing the tailoring of the dose to the individual requirements of the patient. They are not recommended for women over 50 years of age.

- 'Low-dose' preparations, typically containing 20 μg of ethinyloestradiol, are appropriate for older women.
- 'Standard-dose' preparations contain 30–35 μg of ethinyloestradiol and are suitable for most women of childbearing age.
- 'High-dose' preparations contain 50 μg of ethinyloestradiol and provide a greater level of contraceptive security, but show an increased incidence of adverse effects. All combined preparations contain either 1 mg of norethisterone or 150 μg desogestrel as the progestogen component.

The adverse effects of combined preparation oral contraceptives must be balanced against the need for adequate contraceptive cover. Adverse effects include nausea, vomiting, breast tenderness, fluid retention, mood changes, depression, hypersensitivity reactions, hypertension and impaired liver function. In addition to these adverse effects, which may be experienced to a greater or lesser extent, these drugs increase the tendency for blood clotting and this can severely restrict their use in susceptible patients. The increased incidence of deep vein thrombosis in some women is more marked in preparations containing desogestrel as the progestogen. However, it must be borne in mind that, while this is an important consideration in the choice of oral contraceptive, the incidence of deep vein thrombosis is little higher than that experienced in pregnancy.

Progesterone-only preparations
Progesterone-only preparations offer an alternative oral contraceptive effect for use in patients who are recognised as being at high risk of developing deep vein thrombosis. However, they have a higher failure rate than combined preparations, but are suitable for older women, heavy smokers and patients with hypertension. Adverse effects include menstrual irregularities, nausea, vomiting, headache, breast discomfort, depression, loss of appetite and skin disorders.

Emergency contraception
High-dose combination therapy has been shown to be effective in providing emergency (morning after) contraception. The treatment consists of taking two tablets, each containing 50 μg ethinyloestradiol and 250 μg levonorgestrel within 72 hours of unprotected intercourse, followed by another two tablets 12 hours later. Whilst this treatment has a high success rate, it is not successful in all cases and patients must be counselled that pregnancy may still result and that barrier contraception must be used until the next menstrual period. The adverse effects of this treatment include nausea, vomiting, headache, dizziness and breast discomfort. If vomiting occurs within 2 hours of taking the first tablets, the treatment may be recommenced with the addition of an antiemetic drug, such as domperidone.

Hormone replacement therapy

The menopause in females is the point at which there is a cessation of cyclical menstruation resulting from a decrease in function of the ovarian follicles and, typically, occurs between 40 and 50 years of age. The secretion of oestrogen and progesterone by the ovaries begins to fail and this is accompanied by a well-documented set of clinical symptoms. Early symptoms include vaginal dryness, painful intercourse, hot flushes and sweats. Later symptoms include recurrent urinary tract infections, urinary incontinence and atrophy of the urethral mucosa.

Whilst these symptoms of the menopause are serious and, in some cases, debilitating, a more serious consequence of the decrease in oestrogen production is a progressive loss of bone mass, leading to the development of osteoporosis and an increased susceptibility to bone fractures. This is due to a decrease in the inhibitory effect of oestrogen on the processes of bone resorption. Further cardiovascular consequences of the menopause include an increased tendency to myocardial infarction and hypertension, due to an increased deposition of atheromatous plaques in the coronary arteries and other major arteries of the systemic circulation.

Drugs used in hormone replacement therapy

Oestrogen only:	oestradiol, mestranol, conjugated oestrogens
Oestrogen/ progesterone combinations:	oestradiol plus norethisterone, oestradiol plus levonorgestrel

Oestrogen-only preparations
Oestrogen-only preparations should only be used in women who have had their uterus removed. Early treatment with oestrogen reduces the onset of osteoporosis and myocardial infarction. Conventionally, oestrogen therapy for menopausal symptoms is treated with natural oestrogens, rather than the synthetic compounds used in many contraceptive tablets. They may be given

either orally or as a transdermal patch. The most common oestrogen used is oestradiol, although conjugated oestrogens prepared from the urine of pregnant mares is also used. Adverse effects include nausea, vomiting, weight gain, breast enlargement, fluid retention, hypersensitivity reactions, headache and depression.

Oestrogen/progesterone combinations
In women who have an intact uterus, it is necessary to give a progestogen as well as an oestrogen. This is necessary in order to inhibit the increase in endometrial growth and possible fibroid production that follows oestrogen-only treatment. The most common progestogen used is norethisterone. Adverse effects of the combination therapy are the same as those for oestrogen-only therapy.

THE MALE REPRODUCTIVE SYSTEM

Introduction

The male reproductive system includes both internal and external genitalia. The internal genitalia include the *testes*, *epididymis*, *vas deferens*, *prostate gland* and *posterior urethra*. The external genitalia comprise the *anterior urethra* and the *penis*. The testes produce spermatozoa, which are stored in the epididymis, from where they pass to the vas deferens, prostate gland and posterior urethra ready for ejaculation. The anatomical structure of the male reproductive system is shown in Fig. 12.2.

The testes are the sites of sperm production (*spermatogenesis*). Each testicle contains many primitive germ cells (*spermatogonia*), each of which has an associated Sertoli cell that provides structural stability to the testicle. The process of spermatogenesis takes place in a cyclical fashion, under the control of *testosterone*.

Spermatogenesis is the process of sperm production and is under the control of the hypothalamic–pituitary axis. GnRH is released from the hypothalamus, in response to feedback from the periphery, and this stimulates the pituitary gland

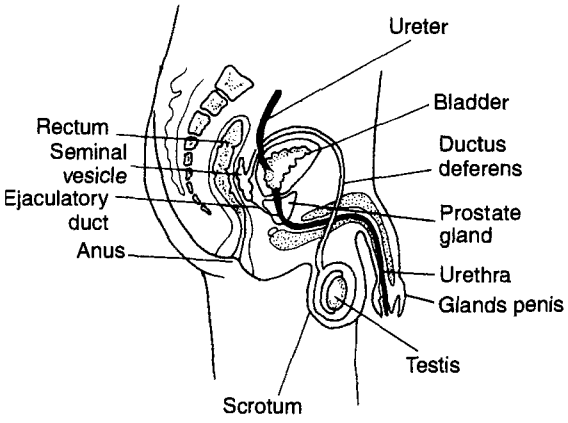

Fig. 12.2 The anatomical structure of the male reproductive tract.

to release FSH and LH. FSH acts on the testicular tubules to increase production of testosterone receptors and LH acts on the Leydig cells of the testicle to induce synthesis of testosterone. Testosterone acts on the testicular tissue to promote sperm production and elsewhere in the body to produce the secondary sexual characteristics of the male.

Sperm accumulate in the seminiferous tubules and the epididymal tract where they undergo a process of maturation. The wall of the vas deferens contains smooth muscle, innervated by sympathetic nerves that release norepinephrine. This acts on α_1-adrenoceptors to produce rhythmical contractions that move the sperm towards the prostate gland.

Delivery of the sperm into the vagina of the female, at intercourse, requires the development of an erect penis, movement of the sperm into the posterior urethra (emission) and ejaculation, which is the ejection of sperm and seminal fluid. The pressure for ejaculation is derived from coordinated contractions of the smooth muscle surrounding the urethra, retrograde ejaculation into the bladder being prevented by increased tone in the trigone.

The development of an erect penis is dependent upon the coordination of both neuronal and vascular events. The stimuli for an erection are both psychological and tactile. Sensory nerves from the penis enter the CNS, and both sympathetic and parasympathetic efferent nerves

innervate the smooth muscle of the penis. Stimulation of the sympathetic nerves to the penis inhibits the development of an erection, whereas stimulation of the parasympathetic nerves promotes an erection. There is also a NANC innervation to the penis, mediated via NO, which is erectile.

Erection of the penis is brought about by relaxation of the smooth muscle of the *corpora cavernosa*. This causes dilatation of the cavernosal artery and filling of the corpora cavernosa and the *corpus spongiosum* with arterial blood. Over-swelling of the penis is prevented by the *tunica albuginea*. As the pressure in the corpora cavernosa rises, venous drainage is impaired by compression of the veins draining the penis. This further enhances the erection and limits the demand on the cardiac output by the erect penis.

Disorders of the male reproductive system may arise from either malfunction of the physical components of the system, or of the chemical control of function. The main disorders of the male reproductive system are:

- benign prostatic hyperplasia
- testicular tumours
- prostate cancer
- male infertility
- infections.

Benign prostatic hyperplasia

Benign prostatic hyperplasia (BPH) arises from an increase in the size of the prostate gland and is a common disease in males over 70 years of age. It results from an increase in the number of stromal and epithelial cells in the prostate gland and causes an increase in the size of the prostate gland, such that micturition becomes both difficult and painful. There is also a sense of urinary urgency and frequency.

As micturition is normally controlled by stimulation of the cholinergic, and NANC, innervation to the bladder, drugs that have an antimuscarinic action, such as atropine and class IA anti-arrhythmic drugs, may make the situation worse. A similar situation may develop following the used of Ca^{2+} channel-blocking drugs, such as nifedipine,verapamil and diltiazem.

Drugs used in the treatment of benign prostatic hyperplasia

Anti-androgens:	finasteride
α_1-Adrenoceptor antagonists:	alfuzosin, terazosin, doxazosin, prazosin, indoramin

Anti-androgens

Finasteride is a potent inhibitor of the enzyme 5α-reductase, which normally metabolises testosterone into its more active metabolite. Inhibition of this enzyme produces a gradual decrease in testosterone levels in the body with a consequent decrease in the size of the prostate gland. This effect may take up to 6 months to become apparent and, although the size of the effect is modest, it produces relief of the symptoms of BPH and increased ease of micturition. Adverse effects result from a decrease in testosterone levels and include impotence, decreased libido, breast tenderness and enlargement and hypersensitivity reactions, especially swelling of the lips.

α_1-Adrenoceptor antagonists

Activation of the sympathetic innervation to the trigone increases the resistance to urine flow. Therefore reversible antagonists of norepinephrine at the α_1-adrenoceptor, such as terazosin and doxazosin, inhibit this action and so reduce the resistance to the passage of urine. Adverse effects include hypotension, nausea, sedation, dizziness, depression, headache, dry mouth and urinary frequency.

Testicular tumours

Testicular tumours are relatively uncommon, affecting less than 0.1% of males under the age of 50 years. There is an increased risk of developing testicular cancer in males who have undescended testicles, or who have had mumps-induced orchitis as an adult. The incidence of testicular tumours increases in men over 50 years of age, but still affects less than 1% of the population. The cure rate in testicular cancers is greater than 80%, using a combination of drug therapy, radiation therapy and surgery.

Drugs used in the treatment of testicular tumours

cisplatin, bleomycin, cyclophosphamide, doxorubicin, vinblastine

The rationale for the drug treatment of testicular cancer is similar to that for other forms of cancer. Drugs are usually used in combination in order to attain the maximum kill rate of the tumour cells, and the doses are tailored to suit the individual patient's responsiveness to the drugs. The adverse effects of anticancer drugs are discussed in Chapter 17.

Prostate cancer

Cancer of the prostate gland accounts for about 25% of all male cancers. Most prostate cancers occur late in life and are of limited malignancy. However, the prognosis depends upon the degree of invasion of other tissues. The majority of prostate cancers are testosterone-dependent and so lend themselves to successful treatment with hormones, usually following surgery and/or radiation therapy.

Drugs used in the treatment of prostate cancer

Gonadorelin analogues:	buserelin, goserelin, triptorelin
Anti-androgens:	bicalutamide, flutamide, cyproterone, finasteride
Inhibitors of testosterone release:	aminoglutethimide, ketoconazole

Gonadorelin analogues
Gonadorelin analogues, such as buserelin and goserelin, act by inhibiting the production of LH by the pituitary gland and so inhibit the production of testosterone by the testes. In the early stages of treatment, there is an increase in LH production and this causes a characteristic 'tumour flare' which makes the symptoms worse for a short period. However, continuation of the treatment results in regression of the cancer and relief of the symptoms. The adverse effects of gonadorelin analogues in males are similar to the symptoms of the menopause in females, including hot flushes, sweating, sexual dysfunction and gynaecomastia.

Anti-androgens
The anti-androgen drugs, cyproterone and flutamide, act as antagonists at the dihydrotestosterone receptor and so reduce the effect of the steroid on the tumour cells. Finasteride inhibits the 5α-reductase enzyme essential for the metabolism of testosterone to its active metabolite. Adverse effects include hot flushes, pruritis, gynaecomastia and hepatic jaundice.

Inhibitors of testosterone release
Testosterone is released primarily from the testes, but a significant amount is also produced by the adrenal glands. Aminoglutethimide or ketoconazole can inhibit this release, to produce regression in tumour size.

Male infertility

Male infertility can arise from a number of causes, including failure of spermatogenesis, failure of the vasa deferentia to move sperm to the urethra or erectile dysfunction. Decreased sperm production may also result from drug treatment with antineoplastic drugs. Failure to produce an erection may also result from drug therapy with antihypertensives, antidepressants and some psychotropic drugs.

Treatments to reverse a decreased sperm count, or inactivity in the vasa deferentia, are of dubious value. However, the treatment of problems of erectile dysfunction is more successful. In some cases, erectile dysfunction may be psychosomatic in origin but the majority of cases result from malfunction of the nervous control systems that control the development of the erect penis.

Drugs used in the treatment of male infertility

Prostaglandin analogues:	alprostadil
Phosphodiesterase inhibitors:	sildenafil
Miscellaneous drugs:	papaverine, thymoxamine

Prostaglandin analogues
Alprostadil is a synthetic analogue of prostaglandin E_1; it must be given by injection directly into the corpus cavernosum. Adverse effects include penile pain, priapism (uncontrolled erection), inflammation and swelling.

Phosphodiesterase inhibitors
A major contributory factor to the generation of an erection is the production and release of NO within the cells of the corpus cavernosum. This NO activates the enzyme guanylyl cyclase leading to a rise in the intracellular concentration of cGMP and vasodilatation. The cGMP is normally destroyed by the enzyme phosphodiesterase. Specific inhibitors of the phosphodiesterase isoenzyme found at this site, such as sildenafil (Viagra), cause a prolonged elevation in cGMP levels and so aid the attainment, and maintenance, of an erection. It should be noted that, as the phosphodiesterase enzyme that is inhibited by sildenafil is specific to the corpus cavernosum, the drug only produces a successful erection in the presence of normal sexual arousal.

Adverse effects of sildenafil include dyspepsia, headache, flushing, dizziness, visual disturbances and nasal congestion. Its use is contraindicated in patients who are receiving nitrate therapy, or patients who have recently suffered a heart attack.

Miscellaneous drugs
Papaverine, if given by direct injection into the corpus cavernosum, produces an erection in patients suffering from psychosomatic disorders; phentolamine may be added if the response to papaverine alone is inadequate. Adverse effects include penile pain, priapism, inflammation and swelling.

Infections of the male reproductive system may arise from bacteria, viruses or parasites and can frequently occur as a result of sexual activity. The main sites at risk of infection are the urethra, prostate gland and epididymis. Viral infections include herpes and mumps-induced orchitis. Bacterial infections include syphilis, gonorrhoea and *Chlamydia*.

Drugs used in the treatment of infections of the male reproductive system
Successful treatment of infections of the male reproductive system again depends upon identification of the infecting microorganism. Viral infections can be treated by aciclovir; bacterial infections are treated by the appropriate antibacterial drug(s).

SUMMARY

- The female reproductive system consists of two ovaries, two fallopian tubes and the uterus. At its lower end, the uterus forms the cervix, which opens into the vagina.
- Each ovary contains many oocytes that mature under the influence of oestrogen and progestogen. One oocyte passes from an ovary to the uterus at the ovulation stage of the menstrual cycle.
- The menstrual cycle usually lasts for 24–32 days, day 1 being the point at which menstrual bleeding begins. Ovulation occurs at day 14 and, if it is not fertilised, the corpus luteum begins to decay at day 21, eventually leading to the next menstrual bleed.
- If the ovum is fertilised then the corpus luteum is maintained and the ovum becomes implanted in the wall of the uterus.
- Diseases of the female reproductive system usually result from disorders of the hypothalamic–pituitary control mechanism, disorders of the ovary, disorders of the uterus or infections.
- Disorders of the hypothalamic–pituitary control axis usually result in failure to release the hormones that control normal ovarian and uterine function.
- These disorders may be treated by replacement therapy with either hypothalamic hormones or anterior pituitary hormones.
- Disorders of the ovary are the most common cause of female infertility; they may be treated with either anti-oestrogen or antiprogestogen drugs.

- Uterine disorders include dysmenorrhoea, menorrhagia, endometriosis and uterine fibroids.
- These disorders may be treated with oral contraceptives, steroid analogues, NSAIDs and thrombus promoters.
- Infections of the female reproductive tract can be divided into infections of the lower tract and infections of the upper tract.
- Infections of the lower female reproductive tract include candidiasis (thrush), bacterial vaginosis and endocervicitis.
- Infections of the upper female reproductive tract include pelvic inflammatory disease.
- Infections of the female reproductive tract may be treated with the appropriate antibacterial or antifungal drugs.
- Oral contraceptives are drug(s) used to prevent fertilisation or implantation of an ovum as a result of sexual intercourse.
- Preparations include either progestogen-only preparations or, more reliably, oestrogen–progestogen combined preparations.
- High-dose combination therapy may be used as emergency postcoital contraception.
- Hormone replacement therapy may be used to alleviate the symptoms of the female menopause, which are due to a decrease in oestrogen and progesterone production.
- Oestrogen-only preparations are used in women who have had their uterus removed and oestrogen/progesterone combination treatment is used in women who have not had a hysterectomy.
- The male reproductive system consists of both internal and external genitalia.
- Internal male genitalia include the testes, epididymis, vas deferens, prostate gland and the posterior urethra; external genitalia comprise the anterior urethra and penis.
- Sperm are produced in the testes and mature in the epididymal tract; they are transferred to the female by ejaculation during sexual intercourse.
- Development of an erect penis is dependent upon changes in blood flow within the organ and is, in part, controlled by nitric oxide.
- Disorders of the male reproductive tract arise from malfunction either of the physical organs or of their chemical control.
- The most common disorders are benign prostatic hyperplasia, testicular tumours, prostate cancer, male infertility and infections.
- Benign prostatic hyperplasia is an enlargement of the prostate gland that gives rise to difficulty in micturition. It may be treated with anti-androgen drugs and α_1-adrenoceptor antagonists.
- Testicular tumours affect less than 0.1% of the male population, but the incidence increases in individuals over 50 years of age. They are treated with the anticancer drugs described in Chapter 17.
- Cancer of the prostate gland accounts for 25% of male cancers. Most prostate cancers are testosterone-dependent and may be treated with gonadorelin analogues, anti-androgens and drugs that inhibit the release of testosterone.
- Male infertility can arise from a number of different causes, including impaired spermatogenesis, failure of sperm maturation and erectile dysfunction.
- Prostaglandin analogues and phosphodiesterase inhibitors are of use in erectile dysfunction.
- Infections of the male reproductive tract are usually bacterial although viral infections, such as herpes infections, do occur.

13

Drugs Affecting the Musculoskeletal System

INTRODUCTION

Diseases of the musculoskeletal system include the rheumatic diseases, gout, neuromuscular disorders and inflammation. In the early stages, most rheumatic diseases require analgesic and anti-inflammatory treatment (NSAIDs) to relieve the pain. As the disease becomes more advanced, and tissue/joint degeneration becomes significant, more aggressive therapy may be required (disease-modifying antirheumatic drugs; DMARDs). Gout may be treated prophylactically to decrease the frequency of gout attacks and more aggressively to abort an attack. Neuromuscular disorders, such as muscle spasticity, may be treated by muscle relaxants and inflammatory diseases may be treated with a range of drugs that inhibit the processes of initiation and maintenance of the inflammatory response.

TREATMENT OF RHEUMATOID ARTHRITIS

NSAIDs:	aspirin, indomethacin, ibuprofen, naproxen, fenbufen, ketoprofen, tiaprofenic acid, azapropazone, mefenamic acid, diclofenac, meloxicam, piroxicam, sulindac, tenoxicam, nabumetone, rofecoxib
DMARDs:	methotrexate, gold salts, penicillamine, chloroquine, hydroxychloroquine
Non-opioid analgesics:	paracetamol

What is rheumatoid arthritis?

Rheumatoid arthritis is an inflammatory disease principally affecting the joints, especially the joints of the hands and feet. It varies in severity from mild swelling and stiffness of the joints to severe degeneration of the joints and complete immobility. Rheumatoid arthritis can result from physical injury to a joint leading to the release of mediators of inflammation and subsequent joint swelling. However, in the majority of cases, rheumatoid arthritis is thought to be an autoimmune disease in which an antigen–antibody reaction triggers off the release of mediators of inflammation.

In both cases the release of these inflammatory mediators, such as histamine, 5-HT, bradykinin, prostaglandins and tumour necrosis factor (TNF), sets up a positive feedback system in which localised tissue damage promotes the release of more inflammatory factors and hence more tissue damage. Eventually, invasion of the damaged joint by macrophages results in the destruction and finally the immobility of the joint.

What is inflammation?

Inflammation is a normal response to tissue injury and represents the body's attempt to protect itself from attack by irritants, invading microorganisms and physical damage and to initiate the processes of tissue repair. Under

normal circumstances the inflammatory response is self-limiting and subsides when the irritant has been removed. However, in some cases such as rheumatoid arthritis, the inflammatory response becomes self-sustaining and results in the ultimate destruction of the tissue. Whilst all the mediators of inflammation are important in maintenance of the inflammatory response, the major role is played by prostaglandins.

Prostaglandins and related compounds (thromboxanes and leukotrienes) are derived from the 20-carbon fatty acid arachidonic acid. Arachidonic acid is a component of the phospholipids that are structural components of all cell membranes. It is released from cell membranes by the enzyme phospholipase A_2, and is metabolised to a number of different eicosanoid products by either cyclo-oxygenase (COX) or lipoxygenase.

Two isoenzymes of COX have been identified. COX I is present in most cells, both in the periphery and the CNS, and is responsible for the synthesis of the small amounts of prostaglandins necessary for normal cellular control. COX II is an inducible form of the enzyme which is expressed in damaged cells and is responsible for the increased synthesis of prostaglandins in damaged tissues. Inhibition of peripheral COX isoenzymes produces an anti-inflammatory response, whereas inhibition of COX in the CNS produces both an antipyretic and analgesic effect. The metabolism of arachidonic acid and the production of eicosanoids are summarised in Fig. 13.1.

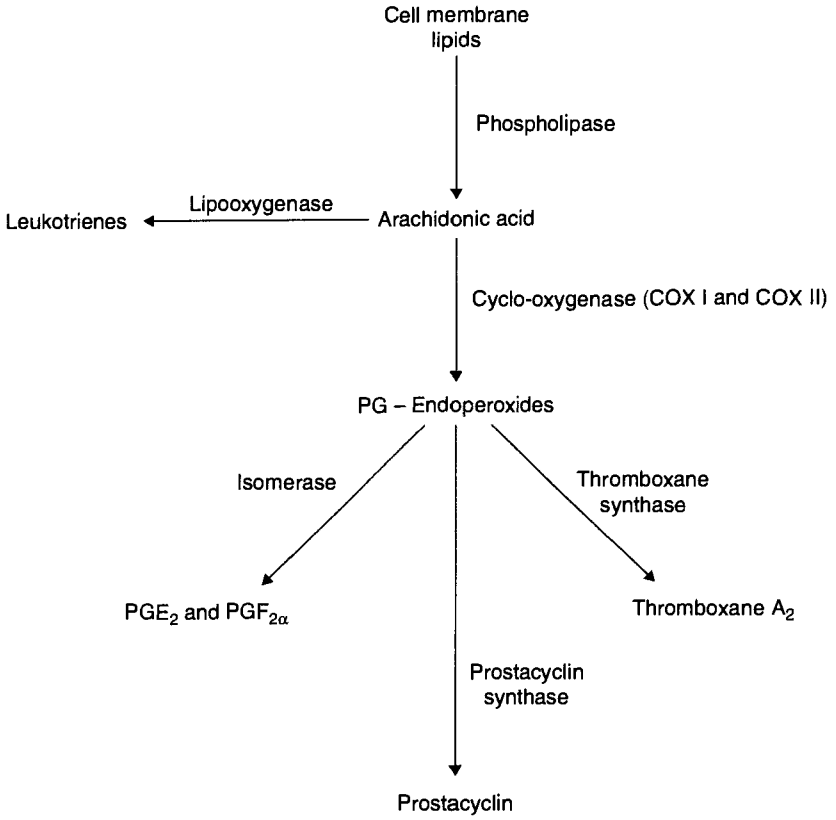

Fig. 13.1 The production of prostaglandins from arachidonic acid. Arachidonic acid is synthesised from cell membrane lipids by the action of the enzyme phospholipase; this is then converted to either leukotrienes (lipoxygenase) or PG–endoperoxides (cyclo-oxygenase). These endoperoxides are then converted to either prostaglandins (isomerase), prostacyclin (prostacyclin synthase) or thromboxanes (thromboxane synthase).

Under normal circumstances, prostaglandins are produced in small quantities in most tissues and they exert a controlling effect on a number of cell responses. The effects of prostaglandins are mediated by way of their action on a number of prostaglandin receptors, some of which are G-protein-coupled receptors, modifying cAMP levels in the cell, and some of which directly increase intracellular levels of Ca^{2+}. The normal actions of the common prostaglandins, thromboxane A_2 and prostacyclin are summarised in Table 13.1.

Non-steroidal anti-inflammatory drugs

NSAIDs are a group of non-structurally related compounds, all of which have the ability to inhibit the production of prostaglandins by inhibiting the actions of COX. The prototype NSAID is aspirin, which irreversibly inhibits the enzyme by direct acetylation of the active site. The adverse effects of aspirin, which include gastric ulceration, nausea, vomiting and hypersensitivity reactions, preclude its use in many patients. It should be noted, however, that the irreversible inhibition of COX in blood platelets leads to a decrease in thromboxane A_2 production and so inhibits platelet aggregation. This is the basis of the use of low-dose aspirin in patients who have suffered a heart attack, where excessive blood clotting is potentially fatal.

There are a large number of NSAIDs now available for the treatment of the pain and inflammation associated with rheumatoid arthritis and similar inflammatory conditions. They all act in the same manner, a reversible inhibition of the COX enzyme system, and so reduce the production of the prostaglandin mediators of inflammation. First-generation NSAIDs are equi-effective against both COX I and COX II, however the second-generation NSAIDs, such as nabumetone and rofecoxib, are selective COX II inhibitors. However, while all NSAIDs are powerful anti-inflammatory drugs, they vary considerably in their analgesic effects, as some do not penetrate into the CNS in sufficient quantities to inhibit central COX isoenzymes. The choice of which drug to use rests on an assessment of the patient's physical condition, responsiveness to a particular drug and ability to tolerate adverse effects.

It is important to note that many rheumatoid arthritis patients experience residual pain even if they are taking NSAIDs and, consequently, they often seek further pain relief. Several NSAIDs, such as ibuprofen and ketoprofen, are available over the counter from pharmacies and, while pharmacists are trained to check a patient's medication before selling these drugs, the possibility exists that these patients may obtain NSAID-containing drugs from other sources. It is important to counsel these patients not to take extra NSAIDs as analgesics in case adverse effects become more serious. In such patients who seek extra pain relief, the use of paracetamol is recommended, providing their *total dose* of paracetamol does not exceed eight tablets per day.

The adverse effects of NSAIDs arise primarily from their inhibition of prostaglandin synthesis at sites other than the rheumatoid joint. Prostaglandins control a large number of effects within the body and so inhibition of the synthesis of these molecules will have widespread consequences for the patient. The most common adverse effects following the ingestion of NSAIDs

Table 13.1 Summary of the effects of prostaglandins, thromboxane A_2 and prostacyclin on various organs of the body.

Organ	PGE_2	$PGF_{2\alpha}$	Thromboxane A_2	Prostacyclin
Blood vessels	Dilate	Constrict	Constrict	Dilate
Capillary permeability	Increase	No effect	No effect	No effect
Gastric acid secretion	Decrease	No effect	No effect	Decease
Bronchiolar smooth muscle	Relax	Contract	Contract	Relax
Uterine smooth muscle	Contract	Contract	Little effect	No effect
Platelet aggregation	No effect	No effect	Increase	Decrease

are gastrointestinal disturbances, including nausea, vomiting and abdominal pain. The recently introduced COX II inhibitors, such as nabumetone and rofecoxib, are thought to produce fewer adverse effects when compared with the less specific NSAIDs.

In some patients, ulceration of the upper gastrointestinal tract can occur, resulting in severe, possibly life-threatening bleeding. This develops as a consequence of the inhibition of prostaglandin synthesis in the stomach by the NSAID, and both an increase in the release of gastric acid into the stomach and a decrease in the production of the protective mucus normally secreted from the stomach wall. Great care must be exercised if NSAIDs are used to treat patients with known gastric ulceration. In some patients, co-administration of an inhibitor of gastric acid synthesis, such as cimetidine or omeprazole, can offset the development of this problem. Similarly, the administration of a stable prostaglandin analogue, such as misoprostol, can relieve the problem.

A small number of asthmatic patients are extremely sensitive to aspirin and other NSAIDs, and ingestion of one of these drugs can trigger off a severe asthma attack. This effect is a result of the drug's interference in arachidonic acid metabolism in the lung leading to an overproduction of leukotrienes, which cause severe bronchoconstriction. Clearly the use of NSAIDs in asthmatic patients requires careful monitoring of the patient. Other adverse effects of NSAIDs include rashes and fluid retention.

Disease-modifying antirheumatic drugs

Whilst the NSAIDs discussed above are extremely effective in controlling the symptoms of rheumatoid arthritis, they do not impede the progress of the disease. Consequently the patient's condition will continue to deteriorate unless more aggressive therapy is used to attempt to slow down the progression of the disease. DMARDs are a group of drugs that do not inhibit COX, but which are able to slow down the rate of degeneration of the affected joints and, in some cases, actually produce a remission of the disease symptoms. They do not have any anti-inflammatory or analgesic actions. These drugs are characterised by having a slow onset of action; patients often do not report benefit from their use for 8–12 weeks.

Gold salts have been used for many years for the treatment of rheumatoid arthritis. They are thought to be taken up by macrophages, to inhibit phagocytosis and to decrease lysosomal enzyme activity. All of these actions serve to decrease the rate of tissue degeneration in the affected joint. Sodium aurothiomalate and aurothioglucose are usually given by i.m. injection, whereas auranofin is orally active. Adverse effects are common with gold salts and include skin reactions such as dermatitis, agranulocytosis and aplastic anaemia.

Chloroquine and hydroxychloroquine are drugs normally used in the control of malaria. The mechanism by which they produce benefit in the rheumatoid patient is not known.

Penicillamine is a cysteine analogue, which slows the rate of progression of bone destruction in the advanced stages of rheumatoid arthritis. Penicillamine is not well tolerated by most patients and gives rise to a range of serious adverse effects, including nausea, anorexia, fever, haematuria, aplastic anaemia, mouth ulcers, alopecia and bronchitis.

Methotrexate is a cytotoxic drug normally used in cancer chemotherapy. At lower doses it is effective in the treatment of patients who have not responded to other forms of treatment. Adverse effects are fewer than when this drug is used in cancer chemotherapy, but include nausea and vomiting, rash and diarrhoea.

Non-opioid analgesics

We have seen in the discussion above that both NSAIDs and DMARDs provide effective treatment in the control of both the symptoms and progression of rheumatoid arthritis. However, these drugs are not effective analgesic agents and so in many cases patients report that they experience residual pain from their arthritis. Non-narcotic analgesics have very little anti-inflammatory activity but, unlike the narcotic analgesics, they do not cause dependence.

Paracetamol is the non-narcotic analgesic of choice in the majority of patients, including children, suffering rheumatoid arthritis and many

other painful conditions. It is a common ingredient in most headache products. Paracetamol may be administered alone, or in combination with other analgesics for the relief of mild to moderate pain. However, it is now thought questionable whether combination analgesics are any better than paracetamol alone. Paracetamol is an inhibitor of the COX enzyme system, but it is more effective in the CNS than in the periphery, thus explaining its analgesic and antipyretic actions.

Paracetamol is normally well tolerated in most patients, with adverse effects such as skin rashes and hypersensitivity reactions occurring in a very small number of patients. Paracetamol is metabolised in the liver, some by a hydroxylation reaction to form a highly reactive, and potentially dangerous, metabolite which can interact with other molecules containing sulphydryl (-SH) groups. At normal doses of paracetamol, this metabolite reacts with the -SH group in glutathione to form a non-toxic metabolite.

However, if the liver is depleted of glutathione, or if the dose of paracetamol is large, then the reactive metabolite will react with other -SH-containing compounds such as liver proteins. The result is necrosis of the liver and death. The amount of paracetamol that will produce this fatal reaction varies from patient to patient and is dependent on the amount of glutathione available at the time of the overdose. Death has occurred following the ingestion of as little as 10 g (20 tablets) of paracetamol.

The maximum recommended daily dose of paracetamol is 4 g (eight tablets) and care must be taken that patients do not accidentally exceed this dose by the consumption of other analgesic preparations containing the drug.

THE TREATMENT OF GOUT

Acute gout:	colchicine
Chronic gout:	allopurinol, probenecid, sulphinpyrazone

What is gout?

Gout is an extremely painful disease that is actually the result of a metabolic disorder. It is characterised by there being high levels of uric acid (hyperuricaemia) in the blood. This hyperuricaemia results in the deposition of crystals of uric acid in the kidney and joints of the skeleton. The deposited crystals of uric acid initiate an inflammatory response that results in the painful, swollen joints typical of this disease.

The actual cause of the hyperuricaemia, which results in gout, is usually an imbalance between the rate of production of uric acid, as a result of increased purine metabolism, and its excretion via the kidneys. Uric acid is usually excreted via the acid-secreting pathway in the proximal convoluted tubule of the renal nephron, and in hyperuricaemia exceeds the maximal transport capacity of this system leading to crystal deposition.

The treatment of acute gout is centred on an inhibition of the inflammatory process that is triggered by the deposition of crystals. Colchicine is the most effective drug for the relief of pain associated with an acute attack of gout. It is a plant alkaloid that binds to the microtubules inside cells and so inhibits the mobility of granulocytes and prevents their migration into the affected area of tissue. Colchicine also inhibits the formation of leukotrienes, which normally serve to mediate the inflammatory process. Adverse effects of colchicine include nausea and vomiting, abdominal pain and diarrhoea. Long-term use may produce agranulocytosis, anaemia and alopecia.

Chronic gout may be relieved by the administration of allopurinol, a purine analogue. It reduces the production of uric acid by inhibiting the enzyme xanthine oxidase. It is of major use as a prophylactic to reduce the incidence of gout attacks. Allopurinol is well tolerated by most patients. Adverse effects include hypersensitivity reactions (rashes) which can occur even after several years of therapy.

Both probenecid and sulphinpyrazone are uriscuric agents, drugs that promote the excretion of uric acid. They both inhibit tubular reabsorption of uric acid and so increase its renal excretion. Adverse effects of probenecid and

sulphinpyrazone include gastrointestinal disturbances, urinary frequency, headache, flushing, dizziness, alopecia, anaemia, sore gums, hypersensitivity reactions, fever and hepatic failure.

- Non-opioid analgesics, such as paracetamol, may be used to alleviate the residual pain experienced by patients taking NSAIDs.
- Several combination analgesic preparations are available, but are not thought to be of any greater benefit than paracetamol used alone.
- The daily dose of paracetamol must not exceed eight tablets.
- Paracetamol is metabolised in the liver and the metabolite reacts with glutathione; if glutathione availability is decreased then paracetamol becomes very toxic.
- In some circumstances, 20 tablets of paracetamol may be fatal.
- Gout is a painful disease that results from a deposition of crystals of uric acid in the joints.
- Acute gout may be treated with colchicine and chronic gout may be treated either with drugs that decrease uric acid production or drugs that increase its excretion.

14

Drugs Affecting the Eye and Ear

THE EYE

Introduction

The role of the eye is to focus the light arising from images of the outside world onto the *retina*, which then converts these images into electrical impulses that are perceived and interpreted by the brain. Vision is a major sense and so a large portion of the brain is dedicated to processing the information coming from the eyes. Each eye is an approximately spherical organ, about 25 mm in diameter, which lies in a bony, protective socket on each side of the midline of the face. Each eye contains a *lens* and *iris*, which separate two fluid-filled chambers. The chamber in front of the iris is called the *anterior chamber* and is filled with the *aqueous humour*. The larger *posterior chamber* lies behind the iris, contains the lens, and is filled with the *vitreous humour*.

The wall of the eye consists of four layers of highly specialised tissue:

(1) the cornea and sclera
(2) the uveal tract (consisting of the iris, ciliary body and choroid)
(3) the pigmented epithelium
(4) the retina.

The *cornea* of the eye is the transparent layer at the front of the organ which allows light to enter. The *sclera* is a continuation of the cornea and is the tough, white protective layer of the eye. The *uveal tract* is the layer of tissue immediately inside the sclera. At the front of the eye it forms the iris (containing both circular and radial pigmented smooth muscle), the *ciliary body* and the *choroid*, which acts as a vascular bed supplying the retina. The hole in the iris at the front of the eye is called the *pupil*.

The *retina* is the sensitive layer of neural tissue that converts the light entering the eye into the electrical impulses, which pass to the brain via the *optic nerves*. This layer contains the photoreceptors (called rods and cones) which actually convert light into electrical signals. The rods are the most numerous of the photoreceptors and are concerned with vision in conditions of low light intensity. The cones are sensitive to red, green or blue light and are responsible for our ability to see in colour. They require higher levels of light intensity to respond. The anatomical structure of the eye is shown in Fig. 14.1. Each eye may be moved in its socket by six *extraocular muscles*. These are striated muscles which receive inner-

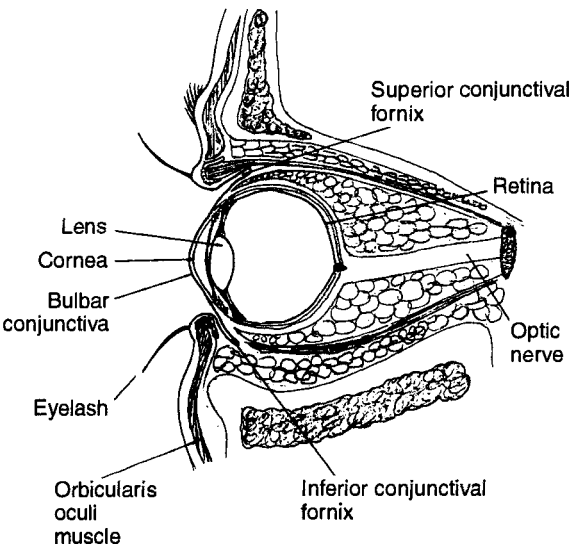

Fig. 14.1 The anatomical structure of the eye.

vation via the third, fourth and sixth cranial nerves.

The amount of light entering the eye is controlled by the diameter of the pupil. In conditions of bright light, the pupil is constricted to prevent damage to the retina. In conditions of poor light the pupil is dilated to allow the maximum entry of light to ensure adequate vision. These changes in the diameter of the pupil are known as the consensual pupil response and are dependent on the ability of the brain to process the information arriving via the optic nerves. It is a useful diagnostic tool for assessing brain function in unconscious or comatose patients.

The circular smooth muscle of the iris is innervated by neurones of the parasympathetic nervous system. Therefore stimulation of this system causes constriction of the pupil (miosis). The radial smooth muscle of the iris is innervated by neurones from the sympathetic nervous system and stimulation of this system causes dilation of the pupil (mydriasis).

Accommodation

Accommodation is the ability of the eye to change its refractive power on the incoming light and so focus the image on the retina. The majority of the refractive power of the eye occurs at the air/cornea interface and this is fixed. Variations in the refractive power of the eye are brought about by changes in the radius of curvature of the lens.

The lens is suspended in the eye from the ciliary body by the suspensory ligaments and the smooth muscle in the ciliary body receives innervation from the parasympathetic nervous system. When the ciliary muscle is relaxed, the suspensory ligaments are taut, the lens is elliptical, and the eye is focused on distant objects. Conversely, when the ciliary muscles are stimulated, the suspensory ligaments are loosened and the lens assumes a greater radius of curvature and the eye is focused on near objects. This explains why our eyes get tired if we read for prolonged periods.

We have seen that accommodation of the eye for near vision requires stimulation of the parasympathetic nerves to the smooth muscle of the ciliary body. At the same time, stimulation of the parasympathetic nerves to the smooth muscle of the iris constricts the pupil and helps to ensure that the light passes through the centre of the lens and so improves the quality of the image.

Production of aqueous humour

The anterior chamber of the eye is filled with a watery fluid called the aqueous humour. This fluid is produced continuously by the blood vessels of the ciliary body at a rate of about 3 ml/day. The aqueous humour flows first into the posterior chamber, then through the gap between the lens and the iris into the anterior chamber. It drains from the anterior chamber via the trabecular meshwork and the canal of Schlemm.

The production of the aqueous humour by the ciliary body is dependent on the systemic blood pressure and the rate of blood flow through the ciliary body. Both of these physiological parameters are affected by the degree of activity of the sympathetic nervous system and by circulating epinephrine. The enzyme carbonic anhydrase plays an important role in the production of aqueous humour.

Under normal circumstances, the rate at which aqueous humour is produced is balanced by the rate at which it is drained from the anterior chamber and the intraocular pressure is maintained in the range 16–21 mm Hg. However, if the balance between production and drainage is upset, then a rise in intraocular pressure can occur due to an accumulation of aqueous humour within the eye. This rise in intraocular pressure may be transmitted throughout the eye and, in particular, cause severe damage to the retina resulting in blindness. This rise in intraocular pressure is termed *glaucoma* and this is one of the most common, and serious, diseases of the eye.

DISEASES OF THE EYE

Introduction

The correct functioning of the eye is dependent on a number of factors. Anything that decreases the optical clarity of the cornea, lens, aqueous

humour and vitreous humour will decrease the amount of light getting to the retina. For example, a decrease in the optical clarity of the lens gives rise to the condition known as *cataracts*. Similarly, detachment of the retina from its underlying choroid layer leads to destruction of the rods and cones and eventual blindness. Both of these conditions require surgical intervention for their treatment.

Drugs can, however, treat a number of conditions affecting the eye and these include:

- glaucoma
- inflammation and allergic conditions
- tear deficiency
- infections.

Glaucoma

Glaucoma is the disease that results from a decrease in the rate of drainage of the aqueous humour from the anterior chamber of the eye. The resultant rise in intraocular pressure causes damage to the retina and the optic nerve and results in blindness. Glaucoma is characterised by an intraocular pressure greater than 21 mm Hg, 'cupping' of the optic disk and changes in the field of vision, especially a loss of peripheral vision.

Glaucoma may be subdivided into two forms:

(1) Open-angle glaucoma is a chronic disease that may be successfully treated with drugs. The primary defect in open-angle glaucoma is a decrease in the drainage rate of the aqueous humour into the canal of Schlemm. There is considerable evidence that this is a genetically linked disease.
(2) Closed-angle glaucoma results from a forward movement of the iris so that it touches the back surface of the cornea. This is called *iris bombe*. Closed-angle glaucoma can also occur if the anterior chamber of the eye is too shallow.

Drugs used in the treatment of glaucoma

β-Adrenoceptor antagonists:	betaxolol, carteolol, levobunolol, metipranolol, timolol
α-Adrenoceptor agonists:	epinephrine, dipivefrine, brimonidine, apraclonidine
Carbonic anhydrase inhibitors:	acetazolamide, dorzolamide
Prostaglandin analogues:	latanoprost
Miotics:	carbachol, pilocarpine

β-Adrenoceptor antagonists

β-Adrenoceptor antagonists, such as carteolol and timolol, are probably the drugs of choice in the treatment of open-angle glaucoma. Most of the drugs in this group are non-selective in that they block both β_1- and β_2-adrenoceptors and they act by blocking these receptors in the ciliary body. Betaxolol is more selective for the β_1-adrenoceptor, but is just as effective as the other drugs. They are usually given as eye drops as this reduces the incidence of adverse effects. However, it must be borne in mind that, even when given as eye drops, sufficient quantities of the drug may be absorbed into the systemic circulation to produce unwanted effects. Adverse effects include bradycardia, peripheral vasoconstriction and bronchoconstriction in sensitive patients. Their use in asthmatics is contraindicated.

α-Adrenoceptor agonists

α-Adrenoceptor agonists, such as dipivefrine and brimonidine, act on α_2-adrenoceptors to decrease the production of aqueous humour. Dipivefrine is a prodrug that is subsequently metabolised to epinephrine, whereas brimonidine is a specific α_2-adrenoceptor agonist. Apraclonidine is used postoperatively. Again, they are administered as eye drops to reduce the incidence of adverse effects, which include blurring of vision, headache, dry mouth, taste alteration and fatigue.

Carbonic anhydrase inhibitors
Inhibitors of carbonic anhydrase, such as acetazolamide and dorzolamide, act by inhibiting the production of aqueous humour as a result of decreased bicarbonate formation in the ciliary body. Acetazolamide is orally active and dorzolamide is given in the form of eye drops. Adverse effects depend on the route of administration. Acetazolamide causes nausea and vomiting, diarrhoea, loss of appetite and paraesthesiae. Dorzolamide causes a burning sensation and blurring of vision and conjunctivitis, but sufficient may also be absorbed to produce systemic adverse effects including headache, dizziness and paraesthesiae.

Prostaglandin analogues
Latanoprost is a synthetic prostaglandin analogue that increases the outflow of aqueous humour and so reduces the intraocular pressure. Its use is restricted to those patients who do not respond well to other forms of treatment for open-angle glaucoma. Adverse effects include brown pigmentation of the iris and ocular irritation.

Miotics
Miotic drugs, such as carbachol and pilocarpine, are agonists at the mAChRs found in the ciliary smooth muscle of the eye. They produce an increase in the outflow of the aqueous humour, by opening the trabecular meshwork and the canal of Schlemm, and so produce a fall in intraocular pressure. These drugs may be of benefit in the treatment of closed-angle glaucoma prior to surgery. Adverse effects include blurred vision and headache.

Inflammation and allergic reactions

Inflammation of the eye can arise from a number of causes, the most common being post-operative inflammation, uveitis and scleritis. The correct choice of drug used to treat inflammation of the eye requires accurate identification of the cause. Allergic reactions arise from exposure to a number of allergens, the most common being the various substances associated with hay fever.

Drugs used in the treatment of inflammation and allergic reactions

Corticosteroids:	betamethasone, clobetasone, dexamethasone, fluoromethalone, hydrocortisone, prednisolone
Antihistamines:	antazoline, levocabastine
Membrane stabilisers:	nedocromil, cromoglycate

Corticosteroids
Corticosteroids, such as betamethasone and prednisolone, may be administered topically, as drops, or systemically to treat inflammation in the eye and may also be used in cases of severe inflammation resulting from antigen–antibody reactions. They must only be used for short periods under medical supervision and should not be used for undiagnosed 'red eye' conditions. Great care should be taken in the use of these drugs for the treatment of inflammatory conditions of the eye, as their use may produce the phenomenon of 'steroid glaucoma' in susceptible patients even after their use for only a few weeks. Other adverse effects include delayed hypersensitivity reactions and thinning of the cornea and sclera.

Antihistamines
The use of antihistamine drugs, such as antazoline and levocabastine, is common in the treatment of the red eyes resulting from hay fever.

Membrane stabilisers
The membrane stabilisers, cromoglycate and nedocromil, are of benefit in the treatment of allergic reactions in the eye. Adverse effects include stinging on application and taste alteration (nedocromil).

Tear deficiency

Tears are produced continually to lubricate the outer surface of the cornea and facilitate movement of the eyes behind the eyelids. Tears are

produced by the *lachrymal glands* situated above the eyes and flow across the surface of the cornea, exiting into the nasal passages. In addition to their lubricant action, tears also have a mild antibacterial action and serve to control the minor infections associated with the intrusion of foreign objects into the eye. Tear deficiency is a common effect seen in patients suffering from chronic rheumatoid arthritis and is known as Sjogren's syndrome.

Drugs used in the treatment of tear deficiency

Artificial tears:	hypromellose, polyvinyl alcohol, hydroxyethylcellulose

A number of substances may be used to replace the tears in Sjorgen's syndrome. They are well tolerated and have virtually no adverse effects. The most common are hypromellose and polyvinyl alcohol.

Infections of the eye

Most eye infections are bacterial or viral in origin, although a small number of fungal infections have been reported on rare occasions. Most superficial eye infections can be treated by the topical application of antibacterial or antiviral drops or ointments.

Bacterial infections, such as *conjunctivitis* and *blepharitis*, are usually treated with antibacterial drops or ointments applied to the surface of the eye. Similarly, viral infections, such as those produced by herpes simplex virus, may be treated with antiviral drugs. The treatment of fungal infections requires specialist treatment.

Drugs used in the treatment of infections of the eye

Antibacterial drugs:	chloramphenicol, chlortetracycline, framycetin, gentamicin, neomycin, fusidic acid
Antiviral drugs:	aciclovir

Antibacterial drugs

A wide range of antibacterial drugs is available for use in the eye and their use depends on identification of the susceptibility of the invading organism. However, chloramphenicol is the drug of choice for superficial infections of the eye, as it has a broad spectrum of activity. Other broad-spectrum antibacterial drugs include framycetin, gentamicin and neomycin. Adverse effects associated with the use of these drugs in the eye are minimal, usually consisting of transient stinging on application and itching. Long-term use of chloramphenicol has been associated with the development of aplastic anaemia.

Antiviral drugs

The most commonly used antibacterial drug for the treatment of the corneal ulcers produced by herpes simplex infections of the eye is aciclovir. Localised inflammation and mild stinging are the only adverse effects reported.

THE EAR

Introduction

The ear is the organ that detects sound and also senses the head's position and movement. The outer ear collects sound waves and directs them onto the *tympanic membrane*, or eardrum. Vibrations of the tympanic membrane are transmitted across the middle ear via the three bones called the *malleus*, *incus* and *stapes*. The sound waves are amplified during this process and then passed to the fluid-filled inner ear.

The *organ of Corti*, which is located in the *cochlea* of the inner ear, contains a large number of sensory receptor hair cells which react to the incoming sound waves by vibrating in parallel with the waveform of the sound. Movement of the hair cells in the organ of Corti displaces the stereocilia located on the apical border of the hair cell and causes depolarisation of the cell membrane. When this displacement occurs the hair cell releases a neurotransmitter from the basal end of the cell and stimulation of the auditory nerve

results. Movement of the stereocilia in the opposite direction hyperpolarises the cell membrane and inhibits the release of the neurotransmitter. In this way the train of impulses in the auditory nerve mimics the waveform of the initial sound.

Balance is dependent upon the vestibular system of the ear as well as input from the eyes. However, the major contribution to the maintenance of balance and posture is derived from the structures that comprise the vestibular system of the inner ear. The vestibular system consists of:

- the otolithic organs, the utricle and the saccule, which detect linear acceleration
- three semicircular canals, which are located at right angles to each other and which detect rotation.

The three-dimensional location of these structures results in the generation of nerve action potentials in the sensory nerves feeding into the brain. In the brain, the inputs from these structures are computed to determine the position of the body. The structure of the ear is shown in Fig. 14.2.

DISEASES OF THE EAR

Diseases of the ear can be divided into those that are associated with the processes of hearing and those that are associated with the perception of balance. The loss of hearing is a major problem for many patients and may result from a number of causes, including disorders of the transmission mechanism of the middle ear or drug-induced damage to the auditory nerves. It should be noted that ototoxicity, and an associated impairment of hearing, is a major adverse effect with drugs such as salicylate analgesics, aminoglycoside antibacterial drugs, some antineoplastic drugs and loop diuretics.

The major diseases of the ear that may be treated with drugs are:

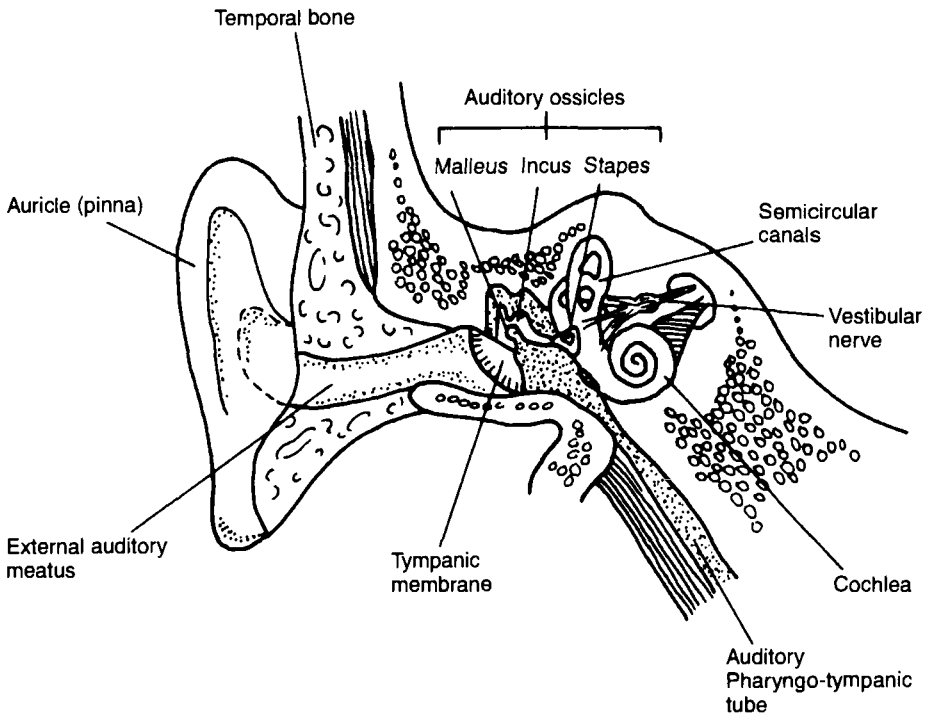

Fig. 14.2 The anatomical structure of the ear.

- tinnitus
- vertigo and Ménière's disease
- ear infections
- ear wax and its removal.

Tinnitus

Tinnitus is a disease in which the patient 'hears' sounds that are not present. It is characterised by a ringing in the ears in the absence of any obvious external source. It is often accompanied by a loss of hearing in the high-frequency range. Tinnitus may arise from a number of causes, including the enhanced perception of noises from within the body such as the heartbeat (objective tinnitus) and the perception of noises that do not exist (subjective tinnitus). The treatment of tinnitus requires the identification of the cause and, in the case of underlying disease, its eradication. However, in many cases there is no identifiable underlying disease and so the tinnitus must be treated symptomatically.

Drugs used in the treatment of tinnitus

Local anaesthetics:	procaine, lignocaine, tocainide
Benzodiazepines:	diazepam, clonazepam, alprazolam
Tricyclic antidepressants:	amitriptyline

Local anaesthetics
Local anaesthetic drugs, such as lignocaine and tocainide, have been shown to be effective in the relief of subjective tinnitus. Their mechanism of action is probably blockade of the Na^+ channels on the auditory nerve and so inhibition of impulse transmission into the brain via the cochlear nerve. Lignocaine has been shown to be most effective when given by i.v. injection, however tocainide is orally active. Adverse effects include cardiac arrhythmias, CNS confusion and hypersensitivity reactions.

Benzodiazepines
Benzodiazepines, such as diazepam and clonazepam, not only improve the patient's emotional response to the tinnitus, but also act on the $GABA_A$ receptor to enhance the effects of the inhibitory neurotransmitter GABA. Adverse effects include drowsiness, CNS depression and the development of dependence.

Tricyclic antidepressants
The use of tricyclic antidepressant drugs, such as amitriptyline, has been shown to be effective in a number of patients. However, the adverse effects resulting from the use of these drugs limits their usefulness in this disease.

Vertigo and Ménière's disease

Vertigo is a disease in which the patient perceives that there is movement when none exists. It can result from disorders of the peripheral and central vestibular systems. It may result from the presence of infections in the middle ear or may be indicative of more serious underlying disease, such as Ménière's disease.

Ménière's disease arises from the accumulation of endolymphatic fluid in the inner ear. It causes bouts of vertigo, loss of hearing, tinnitus and a sense of pressure in the ear. Initially these bouts occur as attacks of dizziness, but eventually the patient is left with seriously impaired hearing. The drug treatment of vertigo and Ménière's disease is aimed at stabilising the fluctuations in neuronal activity in the vestibular system.

Drugs used in the treatment of vertigo and Ménière's disease

Diuretics:	hydrochlorothiazide, frusemide
Antihistamines:	cinnarizine, cyclizine, promethazine, dimenhydrinate
Anticholinergic drugs:	hyoscine
Phenothiazines:	prochlorperazine
Other drugs:	betahistine

Diuretics
Diuretics, such as hydrochlorothiazide and frusemide, act by reducing the production of endolymph and so prevent the build-up that is

characteristic of these disease states. They are well tolerated, the major adverse effect being hypokalaemia.

Antihistamines
Cinnarizine and cyclizine are antihistamines that produce a decrease in the incidence in the symptoms of vertigo and Ménière's disease without undue sedation of the patient. A more sedating effect can be obtained with promethazine and dimenhydrinate. These drugs are well tolerated.

Anticholinergic drugs
Hysocine is a potent drug for controlling the symptoms of vertigo and Ménière's disease. However the adverse effects, which include drowsiness, blurred vision, dry mouth and urinary retention, limit its usefulness.

Phenothiazines
These drugs are dopamine receptor antagonists. Prochlorperazine is the most effective drug of this group for the treatment of vertigo, however the adverse effects of extrapyramidal symptoms, drowsiness and tardive dyskinesia limit its use in susceptible patients.

Ear infections

Ear infections may affect the outer ear (otitis externa) or the middle ear (otitis media). Otitis externa is an inflammatory condition usually caused by either a bacterial or a fungal infection of the external ear canal leading to the eardrum. The most common species of bacteria causing otitis externa are staphylococci and streptococci; *Candida* spp. and *Aspergillus* spp. are the most common species of fungi. Otitis media is usually caused by species such as streptococci, *Haemophilus* spp. and *Moraxella*. It is the most common cause of ear pain in young children.

The treatment of otitis externa requires a thorough cleaning of the external ear canal before commencing drug treatment of the infecting organism, usually by the topical application of ear drops. The treatment of otitis media requires the systemic administration of suitable antibacterial drugs.

Drugs used in the treatment of ear infections

Astringents:	aluminium acetate
Anti-inflammatory drugs:	betamethasone, dexamethasone, flumethasone
Antibacterial drugs:	chloramphenicol, clioquinol, framycetin, gentamicin
Antifungal drugs:	clotrimazole

Astringents
Many cases of otitis externa recover after thorough cleaning of the external ear canal and the use of an astringent, such as aluminium acetate, is often the only treatment needed.

Anti-inflammatory drugs
Anti-inflammatory drugs, such as betamethasone and dexamethasone, are of benefit in the treatment of otitis externa that is accompanied by inflammation of the eardrum and the wall of the external ear canal. They are well tolerated, the major adverse effect being hypersensitivity.

Antibacterial drugs
The choice of antibacterial drug depends on the correct identification of the infecting organism. However, the use of broad-spectrum antibacterial drugs, such as chloramphenicol, is widespread. Other antibacterial drugs are used in specific instances. Adverse effects are limited to hypersensitivity reactions.

The use of antibacterial drugs for the treatment of otitis media is dependent on the use of the appropriate drug for the infecting organism. The adverse effects of systemically administered antibacterial drugs are discussed in Chapter 9.

Antifungal drugs
Clotrimazole is the most commonly used drug for the treatment of otitis externa resulting from fungal infections. Adverse effects are limited to local irritation and sensitivity reactions.

The secretion of wax into the external ear canal is a normal bodily function that provides a protective layer over the lining of the canal and the eardrum. Its removal is only necessary if it interferes with hearing or if it harbours infecting microorganisms. Ear wax may be removed by gentle syringing with warm water, but sometimes ear drops are necessary.

Other chemicals

Sodium bicarbonate, used as ear drops, produces a gentle removal of the ear wax whereas hydrogen peroxide is more aggressive and can cause local irritation.

SUMMARY

- The human eye is spherical, about 25 mm in diameter, and consists of an anterior chamber, posterior chamber, lens system and retina.
- The retina is the part of the eye that detects incoming light and converts it into electrical signals using the rods and cones.
- Accommodation is the ability of the eye to react to incoming light and to ensure that the image is accurately focused onto the retina.
- The anterior chamber of the eye is filled with aqueous humour, which is produced by the ciliary body at a rate of 3 ml/day; it drains from the eye via the canal of Schlemm.
- The major diseases of the eye that are treatable with drugs are glaucoma, inflammation, tear deficiency and infections.
- Glaucoma is the disease in which the intraocular pressure rises due to an imbalance between the rate of production of the aqueous humour and the rate of its drainage from the eye.
- If not satisfactorily controlled, the rise in intraocular pressure can result in damage to the retina and eventual blindness.
- Glaucoma may be treated with β-adrenoceptor antagonists, α-adrenoceptor agonists, carbonic anhydrase inhibitors, prostaglandin analogues and cholinomimetic drugs.
- Inflammation of the eye may arise from either infections or allergic reactions.
- It may be treated with corticosteroids, antihistamines or membrane stabilisers.
- A deficiency in the amount of tears produced by the lachrymal glands can render the eyes more susceptible to infections. This deficiency may be counteracted by the use of artificial tear preparations.
- Infections of the eye are usually either bacterial or viral.
- The ear is the major organ of hearing and of the control of balance. It consists of the outer ear for the collection of sounds and the inner ear for the conversion of these sounds into electrical activity in the auditory nerves.
- Control of balance is brought about by the structures of the inner ear.
- Major diseases of the ear include tinnitus, vertigo, Ménière's disease, infections and the accumulation of ear wax.
- Tinnitus is a disease in which the patient 'hears' sounds that are not present, the most common is a ringing sound in the ears. It is often accompanied by a loss of hearing at high frequencies.
- Tinnitus may be treated with local anaesthetics, benzodiazepines and tricyclic antidepressant drugs.
- Vertigo is a disease in which the patient thinks that they are moving when they are not.

- Ménière's disease results from a build-up of fluid in the inner ear; it is characterised by bouts of vertigo and loss of hearing.

- Vertigo and Ménière's disease may be treated with diuretics, antihistamines, anticholinergic drugs or phenothiazines.

15

Drugs Acting on the Skin

INTRODUCTION

The skin is one of the largest organs of the body, having a surface area of approximately 1.75 m^2 and accounting for about 15% of the total body weight. The major functions of the skin include:

- protection against the environment
- prevention of the loss of protein
- prevention of the loss of water and electrolytes
- an aid to the control of body temperature by regulating heat loss.

The skin is composed of three layers. The outermost layer is the *epidermis*, which varies in thickness at different places on the body. The second layer is the *dermis*, consisting of collagen and elastic tissue. The innermost layer is the *subcutis*, containing mainly adipose tissue and being intercepted by fibrous septa. Sweat glands and hair follicles (with their associated sebaceous glands) are located in the subcutis. The structure of the skin is shown in Fig. 15.1.

Skin diseases are one of the most common reasons for seeking medical advice, amounting to 1–2% of all general practice consultations. The most common diseases of the skin are:

- eczema and dermatitis
- psoriasis
- acne
- skin infections.

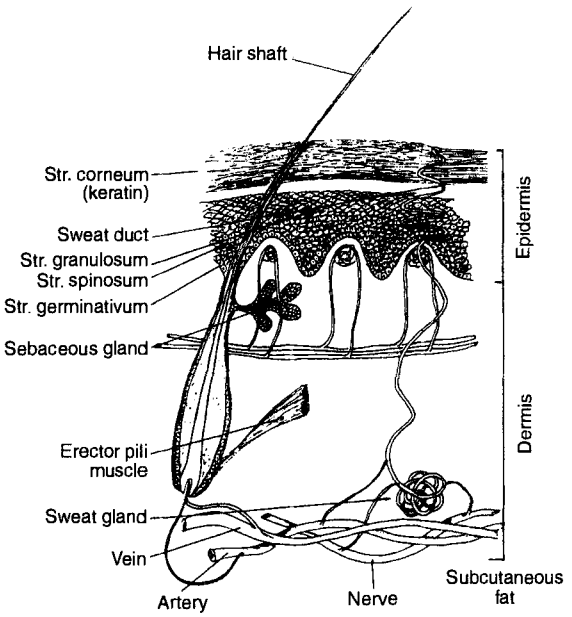

Fig. 15.1 The structure of the skin.

Eczema and dermatitis

Eczema and dermatitis are two names for what is, essentially, the same skin disease. They are characterised by inflammation of the skin and this may result from a number of different causes including irritants, allergic reactions, infections, the adverse effects of drugs and environmental factors such as low humidity and ultraviolet (UV) light. The most common form of eczema is atopic eczema and this is characterised by an intercellular oedema in the dermis and a dry, scaly epidermis and marked inflammation of the whole thickness of the skin. Weeping eczema is much less common and is often infected as well, requiring antibacterial therapy. Dermatitis most commonly arises from contact with irritants.

Drugs used in the treatment of eczema and dermatitis

Emollients:	liquid paraffin, aqueous cream, calamine, urea
Corticosteroids:	hydrocortisone, betamethasone, clobetasone, fluocortolone

Emollients
The use of emollients, such as aqueous cream and liquid paraffin, soothes and hydrates the skin and they are found to be of considerable benefit in all types of eczema where there is dry and scaly skin. They act by reducing the transdermal loss of water that is typical of inflamed, eczematous tissues. They may be formulated as creams, ointments, bath oils or sprays to aid their application. Some are greasy to use and can be too occlusive, causing damage to underlying tissues, but the creams are usually formulated to be light and non-greasy. Adverse effects are very few, mainly a stinging sensation on application to new areas of treatment.

Corticosteroids
In more established cases of eczema and dermatitis, the use of emollients may not be sufficient to relieve the symptoms of the disease. In these cases the use of topically applied corticosteroids is required to reduce the inflammation, provided that there is no indication of an accompanying infection.

Hydrocortisone is the mainstay of corticosteroid therapy in eczema. It may be applied formulated as an ointment or cream and is effective in reducing the inflammation associated with most cases of eczema. More powerful corticosteroids, such as betamethasone and clobetasol, should only be used if hydrocortisone is found to be ineffective. Adverse effects include thinning of the skin, exacerbation of any infection, depigmentation of the skin and adrenal disorders resulting from absorption of the corticosteroid through the skin.

Psoriasis

Psoriasis is usually a genetically determined disorder that may be triggered by a number of different stimuli including infection, stress, drugs, UV light and hypocalcaemia. It is characterised by a speeding up of the turnover rate of the skin. Psoriatic skin turns over in 7–10 days, rather than the 56-day turnover of normal skin. This results in a thickening of the epidermis, scaling, itching, capillary dilatation in the dermis and neutrophil infiltration of the dermis. The result, in the worst cases, is an inflamed, erythematous area of scaly skin with thick plaques of exfoliating skin. Psoriasis may occur anywhere on the body, but is predominant on extensor surfaces and on the scalp.

Drugs used in the treatment of psoriasis

In its early stages psoriasis may be successfully treated with emollients, such as those described above. However, in more serious cases drug therapy may be required.

Keratolytics:	coal tar, dithranol, salicylic acid
Vitamin D derivatives:	calcipotriol, tacalcitol
Retinoids:	acitretin
Immunosuppresants:	cyclosporin, methotrexate

Keratolytics
Coal tar, dithranol and salicylic acid are examples of keratolytic drugs that increase the rate at which scaly skin is removed. They may be applied directly to the affected areas, as ointments or creams, but are likely to produce unacceptable staining of clothes and skin. Adverse effects include local irritation and, in the case of salicylic acid, sufficient may be absorbed through the skin to produce salicylism and even death in susceptible patients.

Vitamin D derivatives
Derivatives of vitamin D, such as calcipotriol, are now used widely as ointments and creams for the treatment of psoriasis. They act by inhibiting the proliferation of epidermal cells that occurs in

psoriasis and they also have a mild anti-inflammatory action. Thus they are of benefit in reducing both the scaling and the inflammation that occurs in this disease. In psoriasis there is thought to be an increase in the number of vitamin D receptors in the basal layers of the epidermis and these analogues are thought to act on these receptors to reduce the accumulation of neutrophils at the psoriatic site. Adverse effects include local irritation, dermatitis, pruritis, erythema and photosensitivity.

Retinoids
Retinoids, such as acitretin, are orally active compounds used in the treatment of severe, resistant psoriasis. They may only be used in severe cases and then only under strict medical supervision. Adverse effects include dryness of mucous membranes, erythema of the face, hair thinning, conjunctivitis and skin erosion. Acitretin must not be used in pregnant women.

Immunosuppressants
Immunosuppressant drugs, such as cyclosporin and methotrexate, are again reserved for severe, resistant cases of psoriasis. They act by inhibiting the synthesis of DNA, and so reduce the rate of formation of keratin in the skin.

Acne

Acne is a disease of the sebaceous system and is characterised by the production of comedones (keratin plugs in the sebaceous ducts), rash, inflammatory papules and pustules. In severe cases there may be permanent scar formation. The rash occurs more often in areas where there is a high concentration of sebaceous glands, such as the face, back and chest. Acne is a common disease in males undergoing puberty and is due to the androgen stimulation of sebaceous gland activity. In many cases the sebaceous duct is colonised by the microorganism *Propriobacterium acnes* and this may give rise to increased severity of the clinical symptoms, requiring treatment with antibacterial drugs.

Drugs used in the treatment of acne

Topical applications:	benzoyl peroxide, azelaic acid, Benzamycin, tetracycline, isotretinoin
Oral drugs:	oxytetracycline, erythromycin, clindamycin, doxycycline, minocycline

Topical applications
Mild to moderate acne can usually be treated successfully by the topical application of drugs such as benzoyl peroxide or azelaic acid. The choice of drug depends on the presence or absence of inflammation and whether comedones are present. Benzoyl peroxide is effective against comedones and has a marked anti-inflammatory action. Azelaic acid has antimicrobial properties and is less likely to cause irritation to the surrounding tissues.

Both Benzamycin and tetracycline are useful adjuncts to treatment in the presence of signs of bacterial infection which may not be controlled with azelaic acid. They are best reserved for treatment of patients who choose not to take oral antibacterial drugs.

Oral drugs
The oral administration of antibacterial drugs, such as oxytetracycline or erythromycin, is effective for the treatment of infected acne that does not respond to topical application. Adverse effects include skin irritation, hypersensitivity reactions and diarrhoea. Topical application and systemic administration of different antibacterial drugs is undesirable as bacterial resistance may develop.

Skin infections

Infections of the skin may arise as a result of many different invading microorganisms including bacteria, fungi, viruses or parasites. The correct treatment requires accurate identification of the invading organism.

Drugs used in the treatment of skin infections

Antibacterial drugs:	fusidic acid, mupirocin, flucloxacillin, erythromycin, metronidazole, neomycin, polymyxin, framycetin
Antifungal drugs:	clotrimazole, econazole, miconazole, ketoconazole, terbinafine, tioconazole
Antiviral drugs:	aciclovir, penciclovir, idoxuridine
Antiparasitic drugs:	benzoyl benzoate, carbaryl, malathion

Antibacterial drugs

Whilst some skin infections, such as impetigo, may be treated by the topical application of a suitable antibacterial drug, others such as erysipelas require systemic administration of the drug. There is a wide range of antibacterial formulations for topical application. Framycetin and neomycin are potent antibacterial agents which have a wide spectrum of activity and are, therefore, effective against a wide range of infecting microorganisms. Mupirocin is unrelated to other antibacterial drugs and is particularly effective against Gram-positive microorganisms. Adverse effects of the topical application of antibacterial drugs are usually confined to local skin irritation and hypersensitivity reactions.

Orally administered antibacterial drugs include metronidazole, tetracycline and fusidic acid. They may be used to treat deep-seated infections at skin sites not easily accessible to topical application. Adverse effects include diarrhoea and hypersensitivity reactions.

Antifungal drugs

Fungal infections of the skin include ringworm (tinea pedis) and the candidal infections (thrush). In most cases they may be treated by topical application of a suitable antifungal drug. Ringworm may be treated with econazole, miconazole, terbinafine or clotrimazole. Adverse effects are usually restricted to localised skin irritation and hypersensitivity reactions.

Antiviral drugs

Viral infections give rise to clinical symptoms such as cold sores (herpes simplex) and shingles (herpes zoster). Topical application of aciclovir or penciclovir is effective in the treatment of herpes simplex infections of the skin, but successful treatment depends upon application of the drug as early as possible. Adverse effects include a burning sensation on application and drying of the skin around the infected area. The systemic administration of aciclovir is effective in the treatment of shingles. Adverse effects include rashes and gastrointestinal upset.

Antiparasitic drugs

Parasitic infestations of the skin include head lice (*Pediculus humanus capitis*), scabies (*Sarcoptes scabiei*) and crab lice (*Pthirus pubis*).

Head lice are a common skin infestation in many schools. Contrary to popular opinion, head lice do not prefer to inhabit dirty hair, nor can they jump from head to head. Transmission from one host to another requires prolonged head contact. They may be treated by the topical application of either malathion or carbaryl as a cream or a shampoo. A contact time of 12 hours is required for effective eradication of the parasite and its eggs. A second application is required after 7 days to kill lice hatching from eggs that have survived the first application. Carbaryl is not recommended for use in asthmatics. Adverse effects include localised skin irritation.

Malathion is effective against scabies infestations and aqueous preparations are preferred to alcoholic preparations as they cause less skin irritation. Treatment must be applied to the whole body and the application must be left on the skin for 12 hours. Care must be taken to treat all members of the patient's family. It should be noted that the itching associated with scabies infestations often lasts for several days after the parasite has been eradicated. This residual itching can be treated successfully by the application of crotamiton.

Crab lice may also be treated with either

malathion or carbaryl. Again, aqueous solutions must be applied to the whole body and left on for 12 hours. Repeat treatment is necessary after 7 days.

SUMMARY

- The surface area of the skin is about 1.75 m^2 and it accounts for nearly 15% of the total body weight.
- Skin is composed of three layers, the outer epidermis, the dermis and the subcutis.
- The most common diseases of the skin are eczema, dermatitis, psoriasis, acne and infections.
- Eczema and dermatitis are essentially similar and are characterised by an inflammation of the skin that may result in the production of dry scales and intercellular oedema. They may result from exposure of the skin to irritant agents and some drugs.
- Eczema and dermatitis may be treated by removal of identifiable causative agents and the use of emollients and corticosteroids.
- Psoriasis may be triggered by a number of stimuli, such as stress and UV light. It is characterised by thickening of the epidermis, and a dry itchy skin.
- Psoriasis may be treated by the use of keratolytics, vitamin D derivatives, retinoids and immunosuppressant drugs.
- Acne is a very common disease characterised by the formation of keratin plugs in the ducts of the sebaceous glands, rash, inflammation and the formation of infected pustules.
- Acne may be treated with topical applications of drugs to decrease the formation of keratin plugs and by systemic antibacterial drugs.
- Skin infections may result from bacteria, viruses, fungi and parasites.
- They may be treated by the use of an appropriate chemotherapeutic drug.
- The most common parasitic infestation is head lice, which may be treated with malathion.

16

Local Anaesthetics

INTRODUCTION

Local anaesthetics are drugs which, when administered either topically or by injection, produce a localised analgesia that allows either for the performance of minor surgical procedures or provides relief from localised painful stimuli. All local anaesthetics act by producing a reversible blockade of conduction in sensory nerves; however, they vary widely in their potency, toxicity, duration of action and their ability to penetrate mucous membranes. These variations determine the usefulness of individual drugs and the routes by which they may be administered.

Mechanism of action

Local anaesthetics are weak bases that are combined with a strong acid to provide a water-soluble salt. They consist of a hydrophilic group (usually an amino group), coupled to a lipophilic aromatic group by a carbon chain. At the normal pH of the body (pH 7.4) local anaesthetics exist as a mixture of ionised and un-ionised forms, the proportion of each being dependent on the pKa of the drug (see Chapter 1). Only the un-ionised form of the drug is able to penetrate the membrane barriers, reach the site of action inside the neuronal cell and produce a clinical effect. However, it is the cationic form of the drug which is the active form and so the drug must be re-ionised at its site of action before producing its effect.

Local anaesthetics work by blocking the influx of Na^+ ions through voltage-sensitive Na^+ channels in the membrane of the neurone and so prevent the passage of a nerve action potential towards the CNS. Under normal circumstances, the generation and propagation of an impulse along a neurone is dependent upon the movement of ions through Na^+, K^+ and Ca^{2+} ion channels in the neuronal cell membrane. The carefully controlled opening (gating) of these channels is dependent upon the transmembrane potential difference across the neuronal membrane. Therefore the condition of their gating is dependent upon the size of the membrane potential and the time for which it lasts.

The Na^+ and Ca^{2+} channels each consist of a single protein that comprises four almost identical domains (domains I to IV), each having six transmembrane domains that span the neuronal membrane. It is thought that the P loops which connect the domains I to IV form the lining of the ion channel. The K^+ channel consists of four individual proteins, each having six membrane-spanning domains; the four proteins are clustered together to form the ion channel.

The ion channels in the neuronal membrane exist in three different configurations, open, closed and inactivated. In the *open* state, the channel forms an aqueous pore (channel), through which ions can pass from the extracellular side of the membrane to the intracellular side. There is a 'selectivity filter' that determines which ion can pass through the channel. In the *closed* state, there is no channel and so ion movement across the neuronal membrane cannot take place. The gating between these two states is controlled by a voltage-sensitive focus located in the S4 regions of the channel protein.

At the normal resting membrane potential of a neurone, the ion channels are gated closed. However, the changes in transmembrane potential brought about by the arrival of an action potential cause an alteration in the protein configuration in the S4 region, thus causing the

channel to open and allowing ion movement across the neuronal membrane. In this way, the action potential is propagated along the neurone. Following the opening of the ion channel, and the passage of ions, the channel rapidly enters its inactivated state, probably due to a physical blockade of the channel by the intracellular loop between domains III and IV. The channel does not return to its closed state until the membrane potential has returned to its resting level for several milliseconds. The time taken for the Na^+ channels to recover from inactivation and return to the closed state is the *refractory period.*

Unusually, the Na^+ channels contain two 'gates' called the m-gate and the h-gate. When the channel is at rest, the m-gate is closed and the h-gate is open. Activation of the ion channel opens the m-gate and allows for the rapid influx of Na^+ ions into the cell and depolarisation of the cell membrane. The depolarisation of the cell membrane causes the h-gate to close slowly, thus preventing further influx of Na^+ ions. Subsequently, the m-gate closes, the h-gate reopens and the ion channel is ready to be re-activated. The sequence of activation of the Na^+ channel is shown in Fig. 16.1.

Repolarisation of the neuronal cell membrane is assisted by the outward movement of K^+ ions through voltage-gated K^+ channels that open during the upstroke of the action potential.

The cationic forms of the local anaesthetics produce their effect by binding to an intracellular receptor site located inside the Na^+ ion channel. Many local anaesthetic drugs exhibit the phenomenon of 'state dependence', which means that their effectiveness (degree of anaesthesia) increases with the frequency at which action potentials are passing along the neurone. In neurones where there is a high frequency of action potentials, there is a greater percentage of Na^+ channels in the open state. Consequently more drug can enter these open channels and produce the blockade necessary for local anaesthesia.

It must be borne in mind that local anaesthetics are relatively non-specific and that they will have a similar action on voltage-gated Na^+ channels elsewhere in the body. In fact, we have seen in Chapter 7 that some drugs used for the treatment of cardiac arrhythmias are, in fact, local anaesthetic drugs. However, while the actions of these drugs in the heart is clinically beneficial, similar actions elsewhere may contribute to unwanted adverse drug effects.

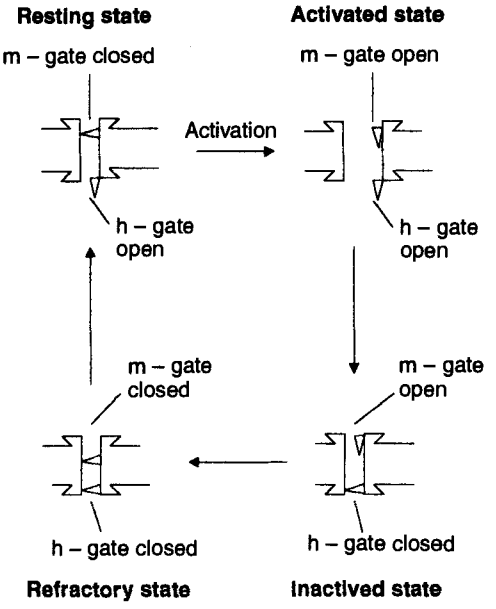

Fig. 16.1 The structure and function of the neuronal Na^+ channel. In the resting state the m-gate is closed and the h-gate is open; on activation, the m-gate opens allowing the influx of Na^+ ions; the channel is closed by the closing of the h-gate; the m-gate then closes and the channel enters its resting state before reopening of the h-gate primes the channel for action.

Differential blockade

A number of factors can determine the effectiveness of a local anaesthetic drug on a neurone. In particular, the diameter of the neurone is of great importance and small-diameter neurones are more susceptible to local anaesthetics than those having a larger diameter. In myelinated neurones, the Na^+ channels are concentrated at the nodes of Ranvier and the distance between these nodes varies with the diameter of the neurone. We have seen above that local anaesthetic drugs often exhibit 'state dependence' and so rapidly firing neurones are more susceptible to these drugs than neurones firing at a slower rate.

As a consequence of these differential effects, application of a local anaesthetic to a nerve containing a mixture of different neurones usually

results in the loss of pain sensation before the sensations of touch and warmth. Motor neurones, which have a low firing rate, are affected last of all.

Recovery

Recovery from the application of a local anaesthetic drug is dependent upon the removal of the drug from its site of action inside the Na^+ channel of the neurone. This takes place by diffusion of the drug down a concentration gradient into the interstitial fluid and its subsequent removal by the bulk flow of this fluid into the venous end of the capillaries draining the site. Most, but not all, local anaesthetics promote dilatation of blood vessels, as a consequence of their effect on the sympathetic neurones that normally mediate vasoconstriction. Therefore these drugs promote their own removal and self-limit their duration of action. The concomitant administration of a vasoconstrictor drug, such as epinephrine, would prevent the rapid removal of the local anaesthetic and so prolong its duration of action. However, in podiatry, this practice has now been discontinued because of the potential for ischaemic damage to the digit as a result of prolonged vasoconstriction.

Drugs used for local anaesthesia

Lignocaine, bupivacaine, prilocaine, procaine, amethocaine, ropivacaine, benzocaine

The use of drugs to produce local anaesthesia allows for the performance of a wide range of minor surgical procedures, and their use in the practice of dentistry, nursing and podiatry is widespread. The choice of drug, and its method of administration, depends upon the site and duration of the required analgesic effect.

In estimating the safe dosage of local anaesthetic to be used for a given procedure, it is essential to take account of the drug's rate of absorption and excretion, the age, sex and weight of the patient and the degree of vascularity in the area to be anaesthetised. In addition, the ability of some local anaesthetic drugs to cross the blood–brain barrier, enter the CNS and produce CNS depression must be taken into account.

Lignocaine (lidocaine) is one of the most commonly used local anaesthetic drugs in current use. It is rapidly and completely absorbed from mucous membranes and is useful both in an injected form and as a surface anaesthetic. The duration of local anaesthesia is about 45 minutes, extended to 90 minutes on co-administration with epinephrine. Bupivacaine has a slow onset, and long duration, of action. Typically it takes up to 30 minutes to produce a full blockade of neuronal activity. It is used primarily for lumbar epidural anaesthesia and is used as an infusion for epidural anaesthesia in labour. Prilocaine has the lowest toxicity of the local anaesthetics in general use. Amethocaine is effective as a topical local anaesthetic allowing for the insertion of venous catheters.

Local anaesthetics are generally well tolerated, the major adverse effect being hypersensitivity reactions, which may limit their use.

SUMMARY

- Local anaesthetic drugs are used to produce anaesthesia for small surgical procedures and for the extraction of teeth.
- Local anaesthetic drugs act by blocking the movement of Na^+ ions through voltage-gated ion channels in the neurone and so prevent the passage of impulses along the nerve fibre towards the CNS.
- Ion channels in the neuronal membrane may be either open, closed or inactivated.
- The gating of the Na^+ channel is brought about by the m-gate and the h-gate.
- The effectiveness of a local anaesthetic depends not only upon the physical properties of the drug, but also upon the diameter of the neurone.
- This differential effect results in a loss of pain sensation before the loss of touch and warmth.

17

Cytotoxic Drugs

INTRODUCTION

Cytotoxic drugs are used in the treatment of cancer. Whilst, in the first instance, many forms of cancer are treated by surgery or radiation therapy, most patients also receive a course of chemotherapy with cytotoxic drugs at some stage during their treatment. The main aim of cancer chemotherapy is to completely eradicate the disease from the patient. However, this would require the destruction of every neoplastic cell. In the majority of cases, chemotherapy leads to remission of the disease, in which the neoplastic cells are removed to such an extent that the patient becomes symptom-free. However, in this situation, the cancer may return.

Cancer cells and the patient's normal cells both undergo similar cycles of growth and reproduction, but the number of cells that are in the various stages of the growth cycle may vary considerably. The major difference between the two lies in the fact that cancer cells undergo an uncontrolled number of regenerative cycles, resulting in the production of a tumour and associated clinical symptoms. Cytotoxic drugs, in order to treat the cancer, must be able to inhibit the growth and reproductive cycles of the neoplastic cells. Unfortunately, it is extremely difficult to distinguish between cancer cells and healthy cells and so the use of these drugs is associated with a wide range of adverse effects.

STRATEGIES FOR CHEMOTHERAPY OF CANCER

The destruction of cancer cells by cytotoxic drugs follows essentially first-order kinetics. This means that the fraction of cancer cells killed by a given dose of drug is approximately the same, irrespective of the number of cells present. This phenomenon is called *log kill*. For example, if a dose of 10 mg of a cytotoxic drug is given to a patient with 10^{10} cancer cells and 99.9% are killed, then 0.1% (10^7) cells remain. A similar dose given to a patient harbouring 10^5 cancer cells would result in 10^2 cells remaining. Both of these scenarios are an example of a 3-log kill.

Unfortunately, unlike invading micro-organisms, the remaining cancer cells are not easily eliminated by the patient's immune system and they may become localised in tissue, such as the CNS, where the cytotoxic drug cannot penetrate. In this situation the patient may be deemed to be in remission (no symptoms), but the disease has not been cured.

In order to circumvent this problem of residual cancer cells, treatment schedules have been devised which use a cocktail of cytotoxic drugs, each of which has a different mechanism of action. In this way, it is hoped that a greater log kill effect may be achieved without using doses of each individual drug large enough to cause serious adverse effects for the patient. This use of combinations of cytotoxic drugs, each at an appropriate dosage, offsets the tendency for the cancer cells to develop resistance to their use. It should be noted that, as most of the cytotoxic drugs currently in use are mutagenic themselves, the possibility of the development of new tumours

resulting from the chemotherapy must always be borne in mind.

Drugs used in the treatment of cancer

Antimetabolites:	methotrexate, 5-fluorouracil, 6-mercaptopurine, cytarabine
Alkylating agents:	cyclophosphamide
Cytotoxic antibiotics:	dactinomycin, doxorubicin, bleomycin
Taxanes:	paclitaxel
Topoisomerase inhibitors:	irinotecan, topotecan
Other cytotoxic drugs:	vincristine, vinblastine, cisplatin, interferons

Antimetabolites

Antimetabolites, such as methotrexate, 6-mercaptopurine and 5-fluorouracil, act either by inhibiting the production of the purines and pyrimidines, which are the natural precursors of nucleotides, or by preventing their interaction with DNA and RNA.

Methotrexate is an analogue of folic acid and acts by inhibiting the actions of folic acid in the cell, by competing for its binding site on the enzyme dihydrofolate reductase. The result is a reduction in the availability of tetrahydrofolate and hence reduced protein synthesis in the cell. Resistance to methotrexate usually results from either an increase in the levels of dihydrofolate reductase in the cancer cells or changes in the binding site for methotrexate on the enzyme. Adverse effects of methotrexate include nausea and vomiting, stomatitis, alopecia, rash, diarrhoea and decreased immune system activity.

6-Mercaptopurine is an analogue of hypoxanthine. Following its entry into cells, 6-mercaptopurine is metabolised to the nucleotide 6-mercaptopurine ribose phosphate (6-MPRP) which inhibits the synthesis of proteins by generating unnatural forms of RNA and DNA. Resistance to 6-mercaptopurine results from a decreased metabolism of the drug to the nucleotide form or increased destruction of the parent drug by the cancer cells. Adverse effects include nausea and vomiting, diarrhoea and depression of bone marrow activity.

5-Fluorouracil is a pyrimidine analogue. When metabolised to the corresponding nucleotide (5-fluorodeoxyuridine monophosphate) it acts to prevent the synthesis of thymidilic acid, an important precursor for the synthesis of DNA. Resistance to the effects of 5-fluorouracil occurs in cells that develop a decrease in the ability to convert the parent drug to the active metabolite. Adverse effects include nausea and vomiting, diarrhoea, alopecia, bone marrow depression and ulceration of the gastrointestinal tract. Prolonged administration of 5-fluorouracil can result in a shedding of skin from the palms of the hands and the soles of the feet.

Cytarabine acts as a pyrimidine antagonist, preventing the incorporation of these important molecules into the synthetic pathway for proteins in cancer cells. Following phosphorylation to the corresponding nucleotide (cytarabine arabinoside phosphate), it is incorporated into DNA and terminates chain elongation. Resistance to the actions of cytarabine results from either a decreased phosphorylation of the parent drug or increased metabolism to inactive metabolites. Adverse effects include nausea and vomiting, diarrhoea, granulocytopenia and decreased liver function.

Alkylating agents

Alkylating agents, such as cyclophosphamide, exert their effects by forming stable, covalent bonds with susceptible chemical groups on cell proteins. This process of alkylation, especially to compounds such as DNA, is lethal to the cell. Alkylating agents do not discriminate between resting cells and those that are dividing rapidly. However, they are more effective against rapidly dividing cells.

Cyclophosphamide is a derivative of the mustard gases used in World War I. It is a prodrug that must be activated by hydroxylation, an action carried out by the cytochrome P-450 system in the liver. The resultant hydroxyl derivative then breaks down into phospharamide mustard

and acrolein, which are the two active drugs. Resistance to the actions of cyclophosphamide arises as a result of decreased penetration of the drug into cells or increased inactivation of the drug by reaction with the sulphydryl groups in glutathione. Adverse effects include nausea and vomiting, diarrhoea, alopecia and bone marrow depression. Haemorrhagic cystitis is thought to be an effect of acrolein.

Cytotoxic antibiotics

Cytotoxic antibiotic drugs, such as dactinomycin, doxorubicin and bleomycin, produce their effects by interactions with DNA which result in an inhibition of protein synthesis. Dactinomycin (actinomycin D) acts by inserting itself into a small groove on the DNA double helix to form a dactinomycin–DNA complex. This results in a decrease in the ability of DNA to control protein synthesis. Resistance to dactinomycin results from an increase in the rate of elimination from the cancer cells. Adverse effects include nausea and vomiting, diarrhoea, alopecia, stomatitis and bone marrow depression.

Taxanes

Taxanes, such as paclitaxel, are a new group of drugs that act by inhibiting the process of mitosis, which is essential for cell proliferation. Adverse effects include hypersensitivity reactions, neuronal damage and defects in impulse conduction in the heart.

Topoisomerase inhibitors

Topoisomerase I and II are enzymes found in cell nuclei. They are responsible for the breakdown in the structure of the DNA double helix that allows it to unwind during cell reproduction. Inhibition of these enzymes will inhibit cell growth. Irinotecan and topotecan are topoisomerase inhibitors that are effective in the treatment of colorectal cancer. Adverse effects include nausea, vomiting, diarrhoea and neuronal damage.

Other cytotoxic drugs

Vincristine and vinblastine are alkaloids derived from the periwinkle. They act by preventing the assembly of intracellular microtubules that is essential for cell reproduction. This inhibition of

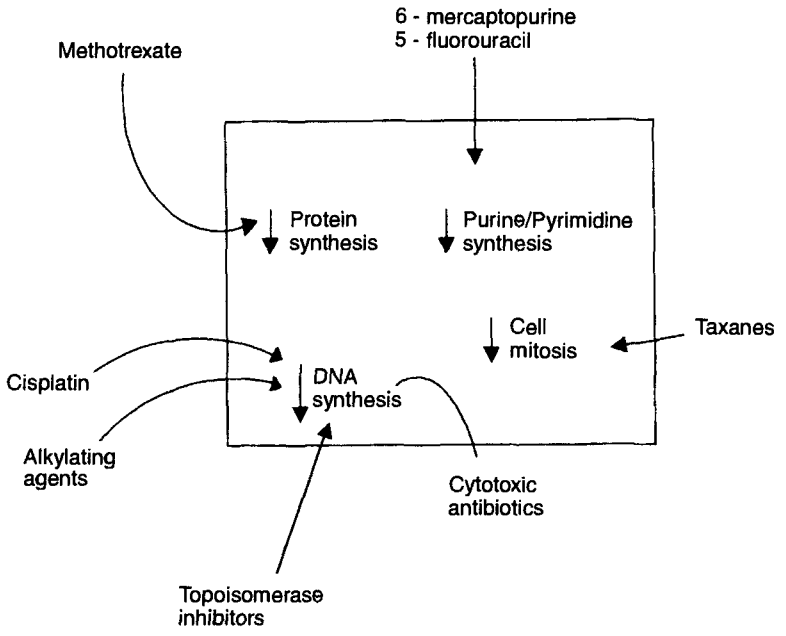

Fig. 17.1 The sites and mechanisms of action of the major cytotoxic (anticancer) drugs. Anticancer drugs act by either decreasing protein synthesis, inhibiting DNA synthesis, inhibiting purine/pyrimidine synthesis or inhibiting cell mitosis in the cancer cells.

microtubule formation is brought about by their binding to tubulin, an important protein necessary for the formation of the microtubules. Resistance to these drugs usually occurs as a result of changes in the structure of the tubulin binding site. Adverse effects include degeneration of sensory nerves, nausea, vomiting, alopecia and bone marrow suppression.

Cisplatin is a platinum-containing compound that acts by binding to guanosine residues in DNA and RNA, thus preventing unwinding of the DNA double helix. Adverse effects include renal toxicity and damage to peripheral nerves.

The mechanisms of action of the common cytotoxic drugs are summarised in Fig. 17.1.

SUMMARY

- Cytotoxic drugs are used for the chemotherapy of cancer.
- The major problem of chemotherapy is in the differentiation between cancer cells and the patient's normal cells.
- Destruction of cancer cells follows first order kinetics, which means that the proportion of cells killed is essentially the same irrespective of the number of cancer cells present. This is called the logkill.
- The chemotherapy of cancer usually involves the use of a cocktail of cytotoxic drugs in order to produce a greater log kill effect and to increase the chances of killing all cancer cells.
- Cancer may be treated with antimetabolites, alkylating agents, cytotoxic antibiotics, taxanes, topisomerase inhibitors and other cytotoxic drugs.

Appendix I

Drug Interactions

Many drug interactions are harmless and of little consequence to the patient. However, some are potentially life-threatening and, although they do not occur in every patient, it is important that all health care professionals are aware of these major interactions.

The table below lists some of the major drug interactions. A more complete list may be found in the *British National Formulary*.

Drug or drug group	Interacting drug or drug group	Major consequence
ACE inhibitors	Alcohol	Enhanced hypotensive effect
	Anaesthetics	Enhanced hypotensive effect
	Analgesics	Antagonism of hypotensive effect
	Diuretics	Enhanced hypotensive effect
	Lithium	Potential lithium toxicity
Adrenergic neurone blocking drugs	Anaesthetics	Enhanced hypotensive effect
	Cisapride	Increased risk of cardiac arrhythmias
	Sympathomimetics	Antagonism of hypotensive effect
Alcohol	Analgesics	Increased sedative effect of opioids
	Antibacterial drugs	Disulfiram-like effect with metronidazole
	Anticoagulants	Increased anticoagulant effect
	Antidepressants	Increased sedation and CNS depression
	Antidiabetic drugs	Enhanced hypoglycaemic effect
	Antihistamines	Increased sedation
	Antihypertensives	Enhanced hypotensive effect
	Antipsychotics	Increased sedation
α-Adrenoceptor antagonists	Anaesthetics	Enhanced hypotensive effect
	Antidepressants	Enhanced hypotensive effect
	Antihypertensives	Enhanced hypotensive effect
Aminoglycoside antibacterial drugs	Anticoagulants	Enhanced anticoagulant effect
	Cytotoxic drugs	Increased risk of kidney damage
	Diuretics	Increased risk of hearing loss
	Muscle relaxants	Enhanced effect of non-depolarising drugs
	Other antibacterials	Increased risk of kidney and hearing damage
	Parasympathomimetic drugs	Antagonism of effects

Amiodarone (Note that the very long half-life of amiodarone means that these interactions may occur several weeks after stopping the drug)	Antibacterials	Increased risk of ventricular arrhythmias
	Anticoagulants	Enhanced anticoagulant effect
	Antidepressants	Increased risk of ventricular arrhythmias
	Antiepileptic drugs	Increased phenytoin levels in plasma
	Antihistamines	Increased risk of ventricular arrhythmias
	Antimalarial drugs	Increased risk of ventricular arrhythmias
	Antipsychotics	Increased risk of ventricular arrhythmias
	Antiviral drugs	Increased risk of ventricular arrhythmias
	β-blockers	Increased risk of bradycardia
	Ca^{2+} channel blockers	Increased risk of bradycardia
	Cardiac glycosides	Increased plasma levels of digoxin
	Cisapride	Increased risk of ventricular arrhythmias
	Other anti-arrhythmic drugs	Additive effects
Antidepressants-SSRIs	Alcohol	Enhanced effects
	Anticoagulants	Enhanced anticoagulant effects
	Antiepileptics	Antagonism of antiepileptic effects
	Antihistamines	Increased risk of cardiac arrhythmias
	Antipsychotics	Increased plasma levels of antipsychotic
	β-Blockers	Increased plasma levels of β-blocker
	Dopaminergic drugs	Hypertension and CNS stimulation
	5-HT_1 agonists	Risk of CNS toxicity
	Lithium	Risk of CNS toxicity and lithium toxicity
	Theophylline	Plasma levels of theophylline increased
	Other antidepressants	Serious interactions with MAOIs, enhanced effects of other antidepressants
Antidepressants–tricyclic	Alcohol	Enhanced sedative effect
	α-Adrenoceptor agonists	Severe hypotension
	Anti-arrhythmic drugs	Increased risk of ventricular arrhythmias
	Antiepileptics	Antagonism of antiepileptic effects
	Antihistamines	Increased sedative effects
	Antihypertensives	Enhanced hypotensive effects
	Antipsychotics	Increased risk of ventricular arrhythmias
	β-Blockers	Increased risk of ventricular arrhythmias
	Dopaminergic drugs	Risk of CNS toxicity
	Sympathomimetics	Hypertension and arrhythmias
Antidiabetic drugs	ACE inhibitors	Enhanced hypoglycaemic effect
	Alcohol	Enhanced hypoglycaemic effect
	Analgesics	Enhanced hypoglycaemic effect
	Antibacterial drugs	Enhanced hypoglycaemic effect
	Anticoagulants	Enhanced hypoglycaemic effect
	Antidepressants	Enhanced hypoglycaemic effect
	Antiepileptics	Increased plasma levels of phenytoin. Enhanced hypoglycaemic effect
	Antipsychotics	Inhibition of hypoglycaemic effects
	Diuretics	Inhibition of hypoglycaemic effects
	Oral contraceptives	Inhibition of hypoglycaemic effects
	Sulphinpyrazone	Enhanced hypoglycaemic effect

Antihistamines (Note that some antihistamines are more sedative than others)	Alcohol	Enhanced sedative effects
	Anti-arrhythmics	Increased risk of ventricular arrhythmias with astemizole and terfenadine
	Antibacterial drugs	Increased risk of cardiac arrhythmias with macrolides
	Antidepressants	Increased sedative effects and arrhythmias
	Antifungal drugs	Increased risk of cardiac arrhythmias
	Antimuscarinic drugs	Enhanced antimuscarinic effects
	Antipsychotics	Increased risk of ventricular arrhythmias with astemizole and terfenadine
	Antivirals	Increased risk of ventricular arrhythmias with astemizole and terfenadine
	Anxiolytics	Enhanced sedative effects
	Cisapride	Increased risk of ventricular arrhythmias with astemizole and terfenadine
	Diuretics	Hypokalaemia
Antihypertensives	Alcohol	Enhanced hypotensive effects
	Antidepressants	Enhanced hypotensive effects
	Antipsychotics	Enhanced hypotensive effects
	Corticosteroids	Antagonism of hypotensive effects
	Lithium	Enhanced hypotensive effects
	MAOIs	Antagonism of hypotensive effects
	Muscle relaxants	Enhanced hypotensive effects
	NSAIDs	Antagonism of hypotensive effects
	Oral contraceptives	Antagonism of hypotensive effects
Antimuscarinic drugs (Note that many drugs have antimuscarinic properties and so their concomitant use will increase the incidence of dry mouth, urinary retention etc.)	Alcohol	Enhanced antimuscarinic effects
	Cisapride	Inhibition of action on GI tract
	Domperidone	Inhibition of action on GI tract
	Metoclopramide	Inhibition of action on GI tract
	Nitrates	Reduced effects of sublingual nitrates
	Parasympathomimetics	Antagonism of effects
Antipsychotics	Alcohol	Enhanced sedative effects
	Anaesthetics	Enhanced hypotensive effects
	Anti-arrhythmics	Increased risk of ventricular arrhythmias
	Antibacterial drugs	Increased risk of ventricular arrhythmias
	Antidepressants	Increased risk of ventricular arrhythmias
	Antiepileptics	Antagonism of antiepileptic effects
	Antihistamines	Increased risk of ventricular arrhythmias
	Antihypertensives	Enhanced hypotensive effects
	Diuretics	Increased risk of ventricular arrhythmias
	Dopaminergic drugs	Antagonism of effects
	Domperidone	Increased risk of extrapyramidal effects
	Metoclopramide	Increased risk of extrapyramidal effects
	Sympathomimetics	Antagonism of pressor action

Anxiolytics and hypnotics	Alcohol	Enhanced sedative effects
	Analgesics	Increased sedative effects of opioids
	Antibacterials	Some drugs inhibit metabolism
	Antidepressants	Enhanced sedative effects
	Antiepileptics	Changes in antiepileptic effects (especially phenytoin)
	Antipsychotics	Enhanced sedative effects
	Ca^{2+} channel blockers	Enhanced effects due to inhibition of metabolism
	Cisapride	Increased sedative effects
	Dopaminergic drugs	Antagonism of effects
	Muscle relaxants	Enhanced sedative effects
	Ulcer-healing drugs	Benzodiazepine metabolism inhibited
β-Blockers	ACE inhibitors	Enhanced hypotensive effects
	Alcohol	Enhanced hypotensive effects
	Anaesthetics	Enhanced hypotensive effects
	Antiarrhythmics	Increased risk of myocardial depression
	Antibacterials	Increased risk of cardiac arrhythmias
	Antidepressants (tricyclic)	Increased risk of cardiac arrhythmias
	Antihistamines	Increased risk of cardiac arrhythmias
	Antipsychotics	Increased risk of cardiac arrhythmias
	Ca^{2+} channel blockers	Increased risk of bradycardia and heart block
	Cisapride	Increased risk of cardiac arrhythmias
	5-HT agonists	Antagonism of effects
	Muscle relaxants	Enhanced effects
	Sympathomimetics	Severe hypertension with epinephrine, norepinephrine and dobutamine
	Ulcer-healing drugs	Cimetidine inhibits metabolism
Ca^{2+} channel blockers (Note that grapefruit juice increases the plasma levels of the dihydropyridines, except amlodipine)	ACE inhibitors	Enhanced hypotensive effects
	Alcohol	Enhanced hypotensive effects
	Anaesthetics	Enhanced hypotensive effects, risk of AV block
	Anti-arrhythmics	Increased myocardial depression
	Antibacterials	Variations in rates of drug metabolism
	Antidepressants	Enhanced antidepressant action
	Antiepileptics	Loss of antiepileptic control
	β-Blockers	Increased risk of bradycardia
	Cardiac glycosides	Increased risk of digoxin toxicity
	Diuretics	Enhanced hypotensive effects
	Lithium	Increased risk of lithium toxicity
	Muscle relaxants	Enhanced effects of non-depolarising drugs
Cardiac glycosides	ACE inhibitors	Increased risk of digoxin toxicity
	Anti-arrhythmics	Increased risk of digoxin toxicity
	Antibacterials	Increased risk of digoxin toxicity
	Antiepileptics	Decreased plasma levels of digoxin
	Antimalarials	Increased risk of digoxin toxicity
	β-Blockers	Increased AV block and bradycardia
	Ca^{2+} channel blockers	Increased risk of digoxin toxicity
	Corticosteroids	Increased risk of hypokalaemia
	Diuretics	Increased risk of digoxin toxicity
	Lipid-lowering drugs	Increased risk of digoxin toxicity with statins
	Muscle relaxants	Increased risk of cardiac arrhythmias
	NSAIDs	Increased risk of heart failure
	Ulcer-healing drugs	Increased risk of digoxin toxicity

Corticosteroids	Analgesics	Increased risk of gastrointestinal bleeding
	Antibacterials	Macrolides inhibit metabolism
	Anticoagulants	Changes in anticoagulant effects
	Antidiabetics	Antagonism of hypoglycaemic effects
	Antiepileptics	Increased metabolism of steroid
	Antihypertensives	Antagonism of hypotensive effects
	Diuretics	Antagonism of diuretic effects
Diuretics	Antihypertensives	Enhanced hypotensive effects
	Analgesics	Increased risk of kidney damage with NSAIDs
	Anti-arrhythmics	Increased risk of toxicity
	Antibacterials	Increased risk of hearing loss
	Antidepressants	Increased risk of postural hypotension
	Antidiabetics	Antagonism of antihypoglycaemic effects
	Antipsychotics	Increased risk of ventricular arrhythmias
	Cardiac glycosides	Increased risk of digoxin toxicity
	Corticosteroids	Antagonism of diuretic effects
	Lithium	Increased risk of lithium toxicity
	Muscle relaxants	Increased risk of hypotension
	Ulcer-healing drugs	Some antagonism of ulcer-healing effects
5-HT_1 Agonists	Antibacterials	Some inhibit metabolism of drug
	Antidepressants	Increased risk of CNS toxicity with MAOIs
	β-Blockers	Enhanced effects
	Cimetidine	Enhanced effects
	Ergotamine	Increased risk of vasospasm
	Lithium	Increased risk of CNS toxicity
Lithium	ACE inhibitors	Increased risk of lithium toxicity
	Analgesics	Increased risk of lithium toxicity
	Antacids	Reduced lithium absorption
	Anti-arrhythmics	Increased risk of hypothyroidism
	Antibacterials	Increased risk of lithium toxicity
	Antidepressants	Increased risk of lithium toxicity with SSRIs
	Antidiabetics	Impaired glucose tolerance
	Antiepileptics	Increased risk of neurotoxicity
	Antihypertensives	Neurotoxicity with methyldopa
	Antipsychotics	Increased risk of extrapyramidal effects
	Ca^{2+} channel blockers	Neurotoxicity with diltiazem and verapamil
	Cisapride	Increased risk of ventricular arrhythmias
	Diuretics	Increased risk of lithium toxicity
	Metoclopramide and domperidone	Increased risk of extrapyramidal effects
	Muscle relaxants	Enhanced muscle relaxant effects
	Parasympathomimetics	Inhibition of effects

Monoamine oxidase inhibitors	Alcohol	Hypotension, *but* if tyramine is present hypertensive crisis
	α_2-Adrenoceptor agonist	Severe hypertension
	Analgesics	CNS excitation or depression with opioids
	Antidepressants	Enhanced effects, avoid concomitant therapy
	Antidiabetics	Enhanced hypoglycaemic effects
	Antiepileptics	Loss of epileptic control
	Antihypertensives	Enhanced hypotensive effects
	Antihistamines	Increased sedation
	Antimuscarinics	Increased adverse effects
	Antipsychotics	CNS excitation and hypertension
	Dopaminergics	Hypertensive crisis with L-dopa
	5-HT agonists	Increased risk of CNS toxicity
	Sympathomimetics	Hypertensive crisis, avoid concomitant use
Muscle relaxants	ACE inhibitors	Enhanced hypotensive effect
	Alcohol	Enhanced sedative effect
	Analgesics	Increased risk of toxicity with NSAIDs
	Anti-arrhythmics	Enhanced relaxant effects
	Antidepressants	Enhanced relaxant effects with tricyclics
	Antiepileptics	Inhibition of relaxant effects
	Antihypertensives	Enhanced hypotensive effects
	Anxiolytics	Enhanced sedative effects
	β-Blockers	Enhanced relaxant effects
	Cardiac glycosides	Increased risk of cardiac arrhythmias
	Diuretics	Enhanced hypotensive effects
	Lithium	Enhanced relaxant effects
	Parasympathomimetics	Enhanced effects of depolarising relaxants, antagonism of non-depolarising drugs
Non-steroidal anti-inflammatory drugs	ACE inhibitors	Antagonism of hypotensive effect
	Analgesics	Increased adverse effects
	Antibacterials	Increased risk of convulsions with quinolones
	Anticoagulants	Enhanced anticoagulant effects
	Antidiabetics	Effects of sulphonylureas enhanced
	Antiepileptics	Enhanced effects of phenytoin
	Antihypertensives	Antagonism of hypotensive
	Cardiac glycosides	Increased risk of digoxin toxicity
	Diuretics	Increased risk of kidney damage
	Lithium	Enhanced effects of lithium
	Ulcer-healing drugs	NSAIDs produce ulcers
Opioid analgesics	Alcohol	Enhanced effects
	Anticoagulants	Increased anticoagulant effects
	Antidepressants	Enhanced CNS depression
	Antiepileptics	Possible loss of epileptic control
	Antipsychotics	Enhanced sedative effects
	Anxiolytics	Enhanced sedative effects
	Dopaminergics	Elevated temperature and CNS toxicity
	Metaclopramide and domperidone	Inhibition of gastrointestinal effects

Oral contraceptives	ACE inhibitors	Decreased hypotensive effect
	Antibacterial drugs	Inhibition of contraceptive effect
	Anticoagulants	Inhibition of anticoagulant effect
	Antidiabetic drugs	Inhibition of hypoglycaemic effect
	Antiepileptics	Loss of epileptic control
	Antihypertensives	Decreased hypotensive effects
	Antivirals	Inhibition of contraceptive effect
	β-Blockers	Inhibition of hypotensive effects
Parasympathomimetics	Anti-arrhythmics	Antagonism of drug effects
	Antibacterials	Antagonism of effects
	Antimuscarinics	Antagonism of effects
	β-Blockers	Increased risk of cardiac arrhythmias
	Lithium	Antagonism of drug effects
	Muscle relaxants	Antagonism of non-depolarising drugs, enhancement of depolarising drugs
Sympathomimetics	α_2-Adrenoceptor agonists	Possible hypertension with epinephrine
	Anaesthetics	Increased risk of cardiac arrhythmias
	Antidepressants	Increased risk of hypertension and cardiac arrhythmias
	Antiepileptics	Enhanced effects
	Antihypertensives	Hypertension
	β-Blockers	Severe hypertension with epinephrine
	Dopaminergics	Increased risk of toxicity
β_2-Sympathomimetics	Corticosteroids	Increased risk of hypokalaemia
	Diuretics	Increased risk of hypokalaemia
	Muscle relaxants	Enhanced effects of suxamethonium
Warfarin	Alcohol	Enhanced anticoagulant effects
	Analgesics	Increased risk of bleeding, enhanced anticoagulant effects
	Anion exchange resins	Loss of anticoagulant control
	Anti-arrhythmics	Enhanced anticoagulant effects
	Antibacterials	Loss of anticoagulant control
	Antidepressants	Enhanced anticoagulant effects
	Antiepileptics	Loss of anticoagulant control
	Antiplatelet drugs	Increased risk of bleeding
	Cisapride	Enhanced anticoagulant effects
	Corticosteroids	Loss of anticoagulant control
	Leukotriene antagonists	Enhanced anticoagulant effects
	Lipid-lowering drugs	Enhanced anticoagulant effects
	Oral contraceptives	Reduced anticoagulant effects

Further Reading

Whilst the various chapters in this book cover the areas of pharmacology and the mechanisms of action of drugs, you may wish to further develop your understanding of these topics. The following list of suggested further reading would allow you to gain further insight into not only the physiological control of body systems, but also details of drug dosage.

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