

## Section 1: General principles

### 1. What is pharmacology? 1

#### Overview 1

#### What is a drug? 1

#### Origins and antecedents 1

#### Pharmacology in the 20th and 21st centuries 2

Alternative therapeutic principles 2

The emergence of biotechnology 3

Pharmacology today 3

### 2. How drugs act: general principles 6

#### Overview 6

#### Introduction 6

#### Protein targets for drug binding 6

Drug receptors 6

Drug specificity 7

Receptor classification 8

Drug-receptor interactions 8

Competitive antagonism 10

Partial agonists and the concept of efficacy 12

Other forms of drug antagonism 15

#### Desensitisation and tolerance 17

Change in receptors 17

Translocation of receptors 17

Exhaustion of mediators 17

Altered drug metabolism 18

Physiological adaptation 18

#### Quantitative aspects of drug-receptor interactions 18

The binding reaction 18

Binding when more than one drug is present 19

#### The nature of drug effects 20

### 3. How drugs act: molecular aspects 22

#### Overview 22

#### Targets for drug action 22

Receptors 22

Ion channels 22

Enzymes 23

Transporters 23

#### Receptor proteins 24

Cloning of receptors 24

Types of receptor 24

Molecular structure of receptors 25

Type 1: Ligand-gated ion channels 26

Type 2: G protein-coupled receptors 27

Type 3: Kinase-linked and related receptors 39

Type 4: Nuclear receptors 42

#### Ion channels as drug targets 45

Ion selectivity 45

Gating 45

Molecular architecture of ion channels 46

Pharmacology of ion channels 47

#### Control of receptor expression 47

#### Receptors and disease 48

### 4. How drugs act: cellular aspects – excitation, contraction and secretion 50

#### Overview 50

#### Regulation of intracellular calcium 50

Calcium entry mechanisms 50

Calcium extrusion mechanisms 53

Calcium release mechanisms 53

Calmodulin 53

#### Excitation 54

The 'resting' cell 55

Electrical and ionic events underlying the action potential 55

Channel function 56

#### Muscle contraction 60

Skeletal muscle 60

Cardiac muscle 60

Smooth muscle 61

#### Release of chemical mediators 63

Exocytosis 63

Non-vesicular release mechanisms 64

#### Epithelial ion transport 64

### 5. Cell proliferation, apoptosis, repair and regeneration 67

#### Overview 67

#### Cell proliferation 67

The cell cycle 67

Interactions between cells, growth factors and the extracellular matrix 69

#### Angiogenesis 70

#### Apoptosis and cell removal 71

Morphological changes in apoptosis 71

The major players in apoptosis 71

Pathways to apoptosis 72

#### Pathophysiological implications 73

Repair and healing 74

Hyperplasia 74

The growth, invasion and metastasis of tumours 74

Stem cells and regeneration 74

#### Therapeutic prospects 75

Apoptotic mechanisms 75

Angiogenesis and metalloproteinases 75

Cell cycle regulation 75

### 6. Cellular mechanisms: host defence 78

#### Overview 78

#### Introduction 78

#### The innate immune response 78

Pattern recognition 78

#### The adaptive immune response 83

The induction phase 84

The effector phase 85

#### Systemic responses in inflammation 88

The role of the nervous system in inflammation 88

Unwanted inflammatory and immune responses 88

The outcome of the inflammatory response 89

**7. Method and measurement in pharmacology 91****Overview 91****Bioassay 91**

- Biological test systems 91
- General principles of bioassay 92

**Animal models of disease 94**

- Genetic and transgenic animal models 95

**Pharmacological studies in humans 96****Clinical trials 96**

- Avoidance of bias 97
- The size of the sample 98
- Clinical outcome measures 98
- Placebos 99
- Meta-analysis 99
- Balancing benefit and risk 99

**8. Absorption and distribution of drugs 101****Overview 101****Introduction 101****Physical processes underlying drug disposition 101**

- The movement of drug molecules across cell barriers 101
- Binding of drugs to plasma proteins 106
- Partition into body fat and other tissues 107

**Drug absorption and routes of administration 108**

- Oral administration 109
- Sublingual administration 110
- Rectal administration 110
- Application to epithelial surfaces 110

**Distribution of drugs in the body 112**

- Body fluid compartments 112
- Volume of distribution 113

**Special drug delivery systems 114****9. Drug metabolism and elimination 116****Overview 116****Introduction 116****Drug metabolism 116**

- Phase 1 reactions 116
- Phase 2 reactions 118
- Stereoselectivity 118
- Inhibition of P450 118
- Induction of microsomal enzymes 119
- First-pass (presystemic ['first-pass'] metabolism) 119
- Pharmacologically active drug metabolites 119
- Drug interactions due to enzyme induction or inhibition 120

**Drug and metabolite excretion 122**

- Biliary excretion and enterohepatic circulation 122
- Renal excretion of drugs and metabolites 122
- Drug interactions due to altered drug excretion 123

**10. Pharmacokinetics 125****Overview 125****Introduction: definition and uses of pharmacokinetics 125**

- Uses of pharmacokinetics 125
- Scope of this chapter 126

**Drug elimination expressed as clearance 126****Single-compartment model 127**

- Effect of repeated dosing 127
- Effect of variation in rate of absorption 128

**More complicated kinetic models 128**

- Two-compartment model 129
- Saturation kinetics 130

**Population pharmacokinetics 131****Limitations of pharmacokinetics 131****11. Individual variation, pharmacogenomics and personalised medicine 133****Overview 133****Introduction 133****Epidemiological factors and inter-individual variation of drug response 134**

- Ethnicity 134
- Age 134
- Pregnancy 135
- Disease 136
- Drug interactions 136

**Genetic variation in drug responsiveness 137**

- Relevant elementary genetics 137
- Single-gene pharmacokinetic disorders 138

**Therapeutic drugs and clinically available pharmacogenomic tests 139**

- HLA gene tests 140
- Drug metabolism-related gene tests 140
- Drug target-related gene tests 141
- Combined (metabolism and target) gene tests 141

**Conclusions 141****Section 2: Chemical mediators****12. Chemical mediators and the autonomic nervous system 143****Overview 143****Historical aspects 143****The autonomic nervous system 144**

- Basic anatomy and physiology 144
- Transmitters in the autonomic nervous system 145

**Some general principles of chemical transmission 147**

- Dale's principle 147
- Denervation supersensitivity 147
- Presynaptic modulation 148
- Postsynaptic modulation 149
- Transmitters other than acetylcholine and noradrenaline 149
- Co-transmission 149
- Termination of transmitter action 151

**Basic steps in neurochemical transmission: sites of drug action 153****13. Cholinergic transmission 155****Overview 155****Muscarinic and nicotinic actions of acetylcholine 155****Acetylcholine receptors 155**

- Nicotinic receptors 155
- Muscarinic receptors 157

- Physiology of cholinergic transmission 158**  
 Acetylcholine synthesis and release 158  
 Electrical events in transmission at fast cholinergic synapses 160  
**Effects of drugs on cholinergic transmission 161**  
 Drugs affecting muscarinic receptors 161  
 Drugs affecting autonomic ganglia 165  
 Drugs that act presynaptically 170  
 Drugs that enhance cholinergic transmission 171  
 Other drugs that enhance cholinergic transmission 176

## 14. Noradrenergic transmission 177

- Overview 177**  
**Catecholamines 177**  
**Classification of adrenoceptors 177**  
**Physiology of noradrenergic transmission 178**  
 The noradrenergic neuron 178  
 Uptake and degradation of catecholamines 181  
**Drugs acting on noradrenergic transmission 182**  
 Drugs acting on adrenoceptors 182  
 Drugs that affect noradrenergic neurons 192

## 15. 5-Hydroxytryptamine and the pharmacology of migraine 197

- Overview 197**  
**5-Hydroxytryptamine 197**  
 Distribution, biosynthesis and degradation 197  
 Pharmacological effects 197  
 Drugs acting at 5-HT receptors 201  
**Migraine and other clinical conditions in which 5-HT plays a role 203**  
 Migraine and antimigraine drugs 203  
 Carcinoid syndrome 205  
 Pulmonary hypertension 206

## 16. Purines 207

- Overview 207**  
**Introduction 207**  
**Purinergic receptors 207**  
**Adenosine as a mediator 207**  
 Adenosine and the cardiovascular system 209  
 Adenosine and asthma 209  
 Adenosine in the CNS 210  
**ADP as a mediator 210**  
 ADP and platelets 210  
**ATP as a mediator 210**  
 ATP as a neurotransmitter 210  
 ATP in nociception 210  
 ATP in inflammation 210  
**Future prospects 211**

## 17. Local hormones 1: histamine and the biologically active lipids 212

- Overview 212**  
**Introduction 212**  
**What is a 'mediator'?** 212  
**Histamine 212**  
 Synthesis and storage of histamine 212  
 Histamine release 213

- Histamine receptors 213  
 Actions 213  
**Eicosanoids 214**  
 General remarks 214  
 Structure and biosynthesis 214  
 Prostanoids 214  
**Leukotrienes 218**  
 Leukotrienes receptors 219  
 Leukotrienes actions 219  
**Lipoxins and resolvins 220**  
**Platelet-activating factor 220**  
 Biosynthesis 220  
 Actions and role in inflammation 220  
 Concluding remarks 220

## 18. Local hormones 2: peptides and proteins 222

- Overview 222**  
**Introduction 222**  
**General principles of protein and peptide pharmacology 222**  
 Structure 222  
 Types of protein and peptide mediator 222  
**Biosynthesis and regulation of peptides 223**  
 Peptide precursors 223  
 Diversity within peptide families 224  
 Peptide trafficking and secretion 224  
**Bradykinin 224**  
 Source and formation of bradykinin 224  
 Metabolism and inactivation of bradykinin 225  
 Bradykinin receptors 225  
 Actions and role in inflammation 225  
**Neuropeptides 226**  
**Cytokines 226**  
 Interleukins and related compounds 228  
 Chemokines 228  
 Interferons 228  
 The 'cytokine storm' 228  
**Proteins and peptides that downregulate inflammation 229**  
 Concluding remarks 229

## 19. Cannabinoids 231

- Overview 231**  
**Plant-derived cannabinoids and their pharmacological effects 231**  
 Pharmacological effects 231  
 Pharmacokinetic and analytical aspects 231  
 Adverse effects 231  
 Tolerance and dependence 232  
**Cannabinoid receptors 232**  
**Endocannabinoids 233**  
 Biosynthesis of endocannabinoids 233  
 Termination of the endocannabinoid signal 234  
 Physiological mechanisms 235  
 Pathological involvement 235  
**Synthetic cannabinoids 235**  
 Clinical applications 235

## 20. Nitric oxide and related mediators 237

- Overview 237**  
**Introduction 237**  
**Biosynthesis of nitric oxide and its control 237**  
**Degradation and carriage of nitric oxide 239**

- Effects of nitric oxide **240**
  - Biochemical and cellular aspects 240
  - Vascular effects 241
  - Neuronal effects 241
  - Host defence 241
- Therapeutic aspects **242**
  - Nitric oxide 242
  - Nitric oxide donors/precursors 242
  - Inhibition of nitric oxide synthesis 242
  - Nitric oxide replacement or potentiation 243
- Clinical conditions in which nitric oxide may play a part **243**
- Related mediators **244**

### Section 3: Drugs affecting major organ systems

## 21. The heart 247

- Overview **247**
- Introduction **247**
- Physiology of cardiac function **247**
  - Cardiac rate and rhythm 247
  - Cardiac contraction 250
  - Myocardial oxygen consumption and coronary blood flow 251
- Autonomic control of the heart **252**
  - Sympathetic system 252
  - Parasympathetic system 253
- Cardiac natriuretic peptides **254**
- Ischaemic heart disease **254**
  - Angina 254
  - Myocardial infarction 255
- Drugs that affect cardiac function **255**
  - Antidysrhythmic drugs 255
  - Drugs that increase myocardial contraction 259
  - Antianginal drugs 260

## 22. The vascular system 265

- Overview **265**
- Introduction **265**
- Vascular structure and function **265**
- Control of vascular smooth muscle tone **266**
  - The vascular endothelium 266
  - The renin-angiotensin system 269
- Vasoactive drugs **271**
  - Vasoconstrictor drugs 271
  - Vasodilator drugs 272
- Clinical uses of vasoactive drugs **276**
  - Systemic hypertension 276
  - Heart failure 279
  - Shock and hypotensive states 280
  - Peripheral vascular disease 282
  - Raynaud's disease 282
  - Pulmonary hypertension 282

## 23. Atherosclerosis and lipoprotein metabolism 285

- Overview **285**
- Introduction **285**
- Atherogenesis **285**
- Lipoprotein transport **286**
  - Dyslipidaemia 286

- Prevention of atheromatous disease **288**
- Lipid-lowering drugs **289**
  - Statins: HMG-CoA reductase inhibitors 289
  - Fibrates 290
  - Drugs that inhibit cholesterol absorption 290
  - Nicotinic acid 291
  - Fish oil derivatives 291

## 24. Haemostasis and thrombosis 293

- Overview **293**
- Introduction **293**
- Blood coagulation **293**
  - Coagulation cascade 293
  - Vascular endothelium in haemostasis and thrombosis 295
- Drugs that act on the coagulation cascade **296**
  - Coagulation defects 296
  - Thrombosis 297
- Platelet adhesion and activation **301**
  - Antiplatelet drugs 302
- Fibrinolysis (thrombolysis) **304**
  - Fibrinolytic drugs 304
  - Antifibrinolytic and haemostatic drugs 307

## 25. Haemopoietic system and treatment of anaemia 308

- Overview **308**
- Introduction **308**
- The haemopoietic system **308**
- Types of anaemia **308**
- Haematinic agents **309**
  - Iron 309
  - Folic acid and vitamin B<sub>12</sub> 311
- Haemopoietic growth factors **312**
  - Erythropoietin 313
- Haemolytic anaemia **315**
  - Drugs used to treat haemolytic anaemias 315

## 26. Anti-inflammatory and immunosuppressant drugs 317

- Overview **317**
- Cyclo-oxygenase inhibitors **317**
  - Mechanism of action 318
  - Pharmacological actions 320
  - Therapeutic actions 320
  - Some important NSAIDs and coxibs 322
- Antirheumatoid drugs **325**
  - Disease-modifying anti-rheumatic drugs 326
  - Immunosuppressant drugs 327
- Anticytokine drugs and other biopharmaceuticals **329**
- Drugs used in gout **330**
- Antagonists of histamine **331**
- Possible future developments **333**

## 27. Skin 335

- Overview **335**
- Introduction **335**
- Structure of skin **335**
- Common diseases of the skin **337**
  - Acne 337
  - Rosacea 338

Baldness and hirsutism 338

Eczema 338

Pruritus 338

Urticaria 338

Psoriasis 338

Warts 339

Other infections 339

### Drugs acting on skin 339

Formulation 339

### Principal drugs used in skin disorders 339

Antimicrobial agents 339

Glucocorticoids and other anti-inflammatory agents 340

Drugs used to control hair growth 340

Retinoids 341

Vitamin D analogues 341

### Agents acting by other mechanisms 342

### Concluding remarks 342

## 28. Respiratory system 344

### Overview 344

#### The physiology of respiration 344

Control of breathing 344

Regulation of musculature, blood vessels and glands of the airways 344

#### Pulmonary disease and its treatment 345

Bronchial asthma 345

Drugs used to treat and prevent asthma 348

Severe acute asthma (status asthmaticus) 351

Allergic emergencies 352

Chronic obstructive pulmonary disease 352

Surfactants 353

Cough 353

## 29. The kidney and urinary system 355

### Overview 355

### Introduction 355

### Outline of renal function 355

#### The structure and function of the nephron 355

Tubular function 356

Acid–base balance 360

Potassium balance 360

Excretion of organic molecules 360

Natriuretic peptides 361

Prostaglandins and renal function 361

#### Drugs acting on the kidney 361

Diuretics 361

#### Drugs that alter the pH of the urine 365

#### Drugs that alter the excretion of organic molecules 365

#### Drugs used in renal failure 365

Hyperphosphataemia 365

Hyperkalaemia 366

#### Drugs used in urinary tract disorders 366

## 30. The gastrointestinal tract 367

### Overview 367

#### The innervation and hormones of the gastrointestinal tract 367

Neuronal control 367

Hormonal control 367

### Gastric secretion 367

The regulation of acid secretion by parietal cells 367

The coordination of factors regulating acid secretion 368

Drugs used to inhibit or neutralise gastric acid secretion 339

Treatment of *Helicobacter pylori* infection 371

Drugs that protect the mucosa 372

### Vomiting 372

The reflex mechanism of vomiting 372

Antiemetic drugs 373

### The motility of the gastrointestinal tract 375

Purgatives 376

Drugs that increase gastrointestinal motility 376

Antidiarrhoeal agents 376

### Drugs for chronic bowel disease 378

### Drugs affecting the biliary system 378

### Future directions 378

## 31. The control of blood glucose and drug treatment of diabetes mellitus 380

### Overview 380

### Introduction 380

### Control of blood glucose 380

### Pancreatic islet hormones 380

Insulin 380

Glucagon 384

Somatostatin 384

Amylin (islet amyloid polypeptide) 385

Incretins 385

### Diabetes mellitus 385

Treatment of diabetes mellitus 386

Potential new antidiabetic drugs 391

## 32. Obesity 393

### Overview 393

### Introduction 393

Definition of obesity 393

### Obesity as a health problem 393

### Homeostatic mechanisms controlling energy balance 394

The role of gut and other hormones in body weight regulation 394

Neurological circuits that control body weight and eating behaviour 394

### The pathophysiology of human obesity 397

Food intake and obesity 397

Physical exercise and obesity 398

Obesity as a disorder of the homeostatic control of energy balance 398

Genetic factors and obesity 398

### Pharmacological approaches to the problem of obesity 399

Centrally acting appetite suppressants 399

Orlistat 399

### New approaches to obesity therapy 400

## 33. The pituitary and the adrenal cortex 402

### Overview 402

### The pituitary gland 402

The anterior pituitary gland 402

Hypothalamic hormones 402

- Anterior pituitary hormones 403
- Posterior pituitary gland 407
- The adrenal cortex 408**
  - Glucocorticoids 409
  - Mineralocorticoids 414
- New directions in glucocorticoid therapy 415

## 34. The thyroid 418

- Overview 418**
- Synthesis, storage and secretion of thyroid hormones 418**
  - Uptake of plasma iodide by the follicle cells 418
  - Oxidation of iodide and iodination of tyrosine residues 418
  - Secretion of thyroid hormone 418
- Regulation of thyroid function 418**
- Actions of the thyroid hormones 420**
  - Effects on metabolism 420
  - Effects on growth and development 420
  - Mechanism of action 420
- Transport and metabolism of thyroid hormones 420**
- Abnormalities of thyroid function 421**
  - Hyperthyroidism (thyrotoxicosis) 421
  - Simple, non-toxic goitre 421
  - Hypothyroidism 421
- Drugs used in diseases of the thyroid 421**
  - Hyperthyroidism 421
  - Hypothyroidism 423

## 35. The reproductive system 425

- Overview 425**
- Introduction 425**
- Endocrine control of reproduction 425**
  - Neurohormonal control of the female reproductive system 425
  - Neurohormonal control of the male reproductive system 426
  - Behavioural effects of sex hormones 427
- Drugs affecting reproductive function 428**
  - Oestrogens 428
  - Antioestrogens 429
  - Progestogens 429
  - Postmenopausal hormone replacement therapy 430
  - Androgens 430
  - Anabolic steroids 431
  - Antiandrogens 431
  - Gonadotrophin-releasing hormone: agonists and antagonists 432
  - Gonadotrophins and analogues 432
- Drugs used for contraception 433**
  - Oral contraceptives 433
  - Other drug regimens used for contraception 434
- The uterus 435**
  - The motility of the uterus 435
  - Drugs that stimulate the uterus 435
  - Drugs that inhibit uterine contraction 436
- Erectile dysfunction 436**

## 36. Bone metabolism 439

- Overview 439**
- Introduction 439**
- Bone structure and composition 439**

- Bone remodelling 439**
  - The action of cells and cytokines 439
  - The turnover of bone minerals 441
  - Hormones involved in bone metabolism and remodelling 441
- Disorders of bone 444**
- Drugs used in bone disorders 444**
  - Bisphosphonates 444
  - Oestrogens and related compounds 445
  - Parathyroid hormone and teriparatide 446
  - Strontium 446
  - Vitamin D preparations 446
  - Biologicals 447
  - Calcitonin 447
  - Calcium salts 447
  - Calcimimetic compounds 447
- Potential new therapies 447**

## Section 4: Nervous system

### 37. Chemical transmission and drug action in the central nervous system 449

- Overview 449**
- Introduction 449**
- Chemical signalling in the nervous system 449**
- Targets for drug action 450**
- Drug action in the central nervous system 451**
  - Blood-brain barrier 452
- The classification of psychotropic drugs 452**

### 38. Amino acid transmitters 454

- Overview 454**
- Excitatory amino acids 454**
  - Excitatory amino acids as CNS transmitters 454
  - Metabolism and release of excitatory amino acids 454
- Glutamate 455**
  - Glutamate receptor subtypes 455
  - Synaptic plasticity and long-term potentiation 458
  - Drugs acting on glutamate receptors 459
- $\gamma$ -Aminobutyric acid (GABA) 462**
  - Synthesis, storage and function 462
  - GABA receptors: structure and pharmacology 462
  - Drugs acting on GABA receptors 463
- Glycine 465**
- Concluding remarks 465**

### 39. Other transmitters and modulators 467

- Overview 467**
- Introduction 467**
- Noradrenaline 467**
  - Noradrenergic pathways in the CNS 467
  - Functional aspects 467
- Dopamine 468**
  - Dopaminergic pathways in the CNS 469
  - Dopamine receptors 470
  - Functional aspects 471
- 5-Hydroxytryptamine 472**
  - 5-HT pathways in the CNS 473
  - 5-HT receptors in the CNS 473
  - Functional aspects 473
  - Clinically used drugs 474

**Acetylcholine 474**

- Cholinergic pathways in the CNS 474
- Acetylcholine receptors 475
- Functional aspects 476

**Purines 476****Histamine 477****Other CNS mediators 477**

- Melatonin 477
- Nitric oxide 478
- Lipid mediators 478

**A final message 479****40. Neurodegenerative diseases 482****Overview 482****Protein misfolding and aggregation in chronic neurodegenerative diseases 482****Mechanisms of neuronal death 482**

- Excitotoxicity 484
- Apoptosis 484
- Oxidative stress 485

**Ischaemic brain damage 486**

- Pathophysiology 486
- Therapeutic approaches 487

**Alzheimer's disease 487**

- Pathogenesis of Alzheimer's disease 487
- Therapeutic approaches 489

**Parkinson's disease 491**

- Features of Parkinson's disease 491
- Pathogenesis of Parkinson's disease 492
- Drug treatment of Parkinson's disease 493

**Huntington's disease 496****Neurodegenerative prion diseases 496****41. General anaesthetic agents 498****Overview 498****Introduction 498****Mechanism of action of anaesthetic drugs 498**

- Lipid solubility 498
- Effects on ion channels 499
- Effects on the nervous system 500
- Effects on the cardiovascular and respiratory systems 500

**Intravenous anaesthetic agents 501**

- Propofol 501
- Thiopental 501
- Etomidate 502
- Other intravenous agents 502

**Inhalation anaesthetics 503**

- Pharmacokinetic aspects 503

**Individual inhalation anaesthetics 506**

- Isoflurane, desflurane, sevoflurane, enflurane and halothane 506
- Nitrous oxide 507

**Balanced anaesthesia 507****42. Analgesic drugs 509****Overview 509****Neural mechanisms of pain 509**

- Nociceptive afferent neurons 509
- Modulation in the nociceptive pathway 510
- Neuropathic pain 511
- Chemical signalling in the nociceptive pathway 512

**Analgesic drugs 515**

- Opioid drugs 515
- Paracetamol 526
- Treatment of neuropathic pain 527
- Other pain-relieving drugs 528

**New approaches 529****43. Local anaesthetics and other drugs affecting sodium channels 530****Overview 530****Local anaesthetics 530**

- Chemical aspects 530
- Mechanism of action 530
- Pharmacokinetic aspects 533
- New approaches 533

**Other drugs that affect sodium channels 534**

- Tetrodotoxin and saxitoxin 534
- Agents that affect sodium channel gating 535

**44. Anxiolytic and hypnotic drugs 536****Overview 536****The nature of anxiety and its treatment 536****Measurement of anxiolytic activity 536**

- Animal models of anxiety 536
- Tests on humans 537

**Drugs used to treat anxiety 538**

- Benzodiazepines and related drugs 538
- Buspirone 543
- Other potential anxiolytic drugs 543

**Drugs used to treat insomnia (hypnotic drugs) 544****45. Antiepileptic drugs 546****Overview 546****Introduction 546****The nature of epilepsy 546**

- Types of epilepsy 546
- Neural mechanisms and animal models of epilepsy 548

**Antiepileptic drugs 549**

- Carbamazepine 552
- Phenytoin 553
- Valproate 554
- Ethosuximide 554
- Phenobarbital 554
- Benzodiazepines 555
- Newer antiepileptic drugs 555
- Development of new drugs 556
- Other uses of antiepileptic drugs 557
- Antiepileptic drugs and pregnancy 557
- Muscle spasm and muscle relaxants 557

**46. Antipsychotic drugs 559****Overview 559****Introduction 559****The nature of schizophrenia 559**

- Aetiology and pathogenesis of schizophrenia 560

**Antipsychotic drugs 562**

- Classification of antipsychotic drugs 562
- Clinical efficacy 562
- Pharmacological properties 565
- Unwanted effects 566
- Pharmacokinetic aspects 567

**Future developments 568**

**47. Antidepressant drugs 570****Overview 570**

The nature of depression 570

**Theories of depression 570**

The monoamine theory 570

Neuroendocrine mechanisms 571

Trophic effects and neuroplasticity 571

**Antidepressant drugs 572**

Types of antidepressant drug 572

Testing of antidepressant drugs 573

Mechanism of action of antidepressant drugs 577

Monoamine uptake inhibitors 577

Monoamine receptor antagonists 582

Monoamine oxidase inhibitors 582

Melatonin agonist 584

Miscellaneous agents 584

Future antidepressant drugs 584

**Brain stimulation therapies 585****Clinical effectiveness of antidepressant treatments 585****Other clinical uses of antidepressant drugs 586****Drug treatment of bipolar disorder 586**

Lithium 586

Antiepileptic drugs 587

Atypical antipsychotic drugs 587

**48. CNS stimulants and psychotomimetic drugs 589****Overview 589****Psychomotor stimulants 589**

Amphetamines 589

Methylphenidate 591

Modafinil 591

Cocaine 592

Methylxanthines 593

Cathinones 594

Other stimulants 594

Cognition-enhancing drugs 594

**Psychotomimetic drugs 595**

LSD, psilocybin and mescaline 595

MDMA (ecstasy) 596

Ketamine and phencyclidine 596

Other psychotomimetic drugs 597

**49. Drug addiction, dependence and abuse 598****Overview 598****Drug use and abuse 598**

Drug administration 598

Drug harm 600

Drug dependence 600

Tolerance 601

Pharmacological approaches to treating drug addiction 603

**Nicotine and tobacco 603**

Pharmacological effects of smoking 603

Pharmacokinetic aspects 605

Tolerance and dependence 605

Harmful effects of smoking 606

Pharmacological approaches to treating nicotine dependence 607

**Ethanol 608**

Pharmacological effects of ethanol 608

Pharmacokinetic aspects 611

Tolerance and dependence 612

Pharmacological approaches to treating alcohol dependence 613

**Section 5: Drugs used for the treatment of infections and cancer****50. Basic principles of antimicrobial chemotherapy 615****Overview 615**

Background 615

**The molecular basis of chemotherapy 615**

Biochemical reactions as potential targets 616

The formed structures of the cell as potential targets 620

**Resistance to antibacterial drugs 621**

Genetic determinants of antibiotic resistance 622

Biochemical mechanisms of resistance to antibiotics 623

Current status of antibiotic resistance in bacteria 624

**51. Antibacterial drugs 626****Overview 626****Introduction 626**

Antimicrobial agents that interfere with folate synthesis or action 626

Sulfonamides 626

Trimethoprim 629

 **$\beta$ -Lactam antibiotics 630**

Penicillins 630

Cephalosporins and cephamycins 631

Other  $\beta$ -lactam antibiotics 632

Glycopeptides 632

**Antimicrobial agents affecting bacterial protein synthesis 632**

Tetracyclines 632

Chloramphenicol 634

Aminoglycosides 634

Macrolides 635

**Antimicrobial agents affecting topoisomerase 635**

Quinolones 635

**Miscellaneous and less common antibacterial agents 637****Antimycobacterial agents 638**

Drugs used to treat tuberculosis 638

Drugs used to treat leprosy 639

**Possible new antibacterial drugs 640****52. Antiviral drugs 642****Overview 642****Background information about viruses 642**

An outline of virus structure 642

Examples of pathogenic viruses 642

Virus function and life history 642

**The host-virus interaction 643**

Host defences against viruses 643

Viral ploys to circumvent host defences 644

**HIV and AIDS 644****Antiviral drugs 645**

Reverse transcriptase inhibitors 645

Non-nucleoside reverse transcriptase inhibitors 647

Protease inhibitors 647



- DNA polymerase inhibitors 648
- Neuraminidase inhibitors and inhibitors of viral coat disassembly 649
- Drugs acting through other mechanisms 649
- Biopharmaceutical antiviral drugs 650
- Other agents 650
- Combination therapy for HIV 650
- Prospects for new antiviral drugs 651

## 53. Antifungal drugs 653

- Overview 653
- Fungi and fungal infections 653
- Drugs used to treat fungal infections 654
  - Antifungal antibiotics 654
  - Synthetic antifungal drugs 655
- Future developments 657

## 54. Antiprotozoal drugs 658

- Overview 658
- Host-parasite interactions 658
- Malaria and antimalarial drugs 658
  - The life cycle of the malaria parasite 659
  - Antimalarial drugs 661
  - Potential new antimalarial drugs 666
- Amoebiasis and amoebicidal drugs 666
- Trypanosomiasis and trypanocidal drugs 667
- Other protozoal infections and drugs used to treat them 668
  - Leishmaniasis 668
  - Trichomoniasis 668
  - Giardiasis 669
  - Toxoplasmosis 669
  - Pneumocystis 669
- Future developments 669

## 55. Anthelmintic drugs 671

- Overview 671
- Helminth infections 671
- Anthelmintic drugs 672
- Resistance to anthelmintic drugs 674
- Vaccines and other novel approaches 675

## 56. Anticancer drugs 676

- Overview 676
- Introduction 676
- The pathogenesis of cancer 676
  - The genesis of a cancer cell 676
  - The special characteristics of cancer cells 677
- General principles of cytotoxic anticancer drugs 679
- Anticancer drugs 679
  - Alkylating agents and related compounds 680
  - Antimetabolites 683
  - Cytotoxic antibiotics 685
  - Plant derivatives 685
  - Hormones 686
  - Hormone antagonists 686
  - Monoclonal antibodies 687
  - Protein kinase inhibitors 687
  - Miscellaneous agents 688
- Resistance to anticancer drugs 689
- Combination therapies 689
- Control of emesis and myelosuppression 689
- Future developments 690

## Section 6: Special topics

### 57. Harmful effects of drugs 692

- Overview 692
- Introduction 692
- Classification of adverse drug reactions 692
  - Adverse effects related to the known pharmacological action of the drug 692
  - Adverse effects unrelated to the known pharmacological action of the drug 693
- Drug toxicity 693
  - Toxicity testing 693
  - General mechanisms of toxin-induced cell damage and cell death 693
  - Mutagenesis and assessment of genotoxic potential 696
- Immunological reactions to drugs 700
  - Immunological mechanisms 700
  - Clinical types of allergic response to drugs 700

### 58. Lifestyle drugs and drugs in sport 703

- Overview 703
- What are lifestyle drugs? 703
- Classification of lifestyle drugs 703
- Drugs in sport 703
  - Anabolic steroids 705
  - Human growth hormone 706
  - Stimulant drugs 706
- Conclusion 706

### 59. Biopharmaceuticals and gene therapy 708

- Overview 708
- Introduction 708
- Biopharmaceuticals 708
  - Proteins and polypeptides 709
  - Monoclonal antibodies 710
- Gene therapy 711
  - Gene delivery 711
  - Controlling gene expression 713
- Safety and societal issues 714
- Therapeutic applications 714
  - Gene therapy for cancer 714
  - Single-gene defects 715
  - Gene therapy and infectious disease 716
  - Gene therapy and cardiovascular disease 716
  - Oligonucleotide approaches 716

### 60. Drug discovery and development 718

- Overview 718
- The stages of a project 718
  - The drug discovery phase 718
  - Preclinical development 720
  - Clinical development 720
- Biopharmaceuticals 721
- Commercial aspects 721
- Future prospects 721
- A final word 722