# Contents

Preface xv Acknowledgements xvi

# Section 1 General principles

# 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 4

# 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 11 Partial agonists as antagonists 13 Other forms of drug antagonism 16

Desensitisation and tolerance 18 Change in receptors 18 Translocation of receptors 19 Exhaustion of mediators 19 Altered drug metabolism 19

Physiological adaptation 19 Quantitative aspects of drug-receptor interactions 19 The binding reaction 19 Binding when more than one drug is present 20 The nature of drug effects 21

# 3 How drugs act: molecular aspects 23

Overview 23 Protein targets for drug action 23 Receptors 23 Ion channels 23 Enzymes 24 Transporters 24 Receptor proteins 25

Ion selectivity 47

Gating 47

Cloning of receptors 25 Types of receptor 25 Molecular structure of receptors 26 Type 1: Ligand-gated ion channels 27 Type 2: G protein-coupled receptors 29 Type 3: Kinase-linked and related receptors 40 Type 4: Nuclear receptors 44 lon channels as drug targets 46

Molecular architecture of ion channels 48 Pharmacology of ion channels 49 Control of receptor expression 49 Receptors and disease 49

### 4 How drugs act: cellular aspects — excitation, contraction and secretion 52

Overview 52 Regulation of intracellular calcium 52 Calcium entry mechanisms 52 Calcium extrusion mechanisms 55 Calcium release mechanisms 55

Calmodulin 56

Excitation 56

The 'resting' cell 57 Electrical and ionic events underlying the action potential 57

Channel function 58

Muscle contraction 61

Skeletal muscle 62 Cardiac muscle 64 Smooth muscle 64

Release of chemical mediators 64

Exocytosis 65 Non-vesicular release mechanisms 66 Epithelial ion transport 67

# 5 How drugs act: biopharmaceuticals and gene therapy 69

Introduction 69 Protein and oligonucleotide biopharmaceuticals 69 Proteins and polypeptides 70

Monoclonal antibodies 71 Oligonucleotides 72

Overview 69

Overview 82

Pharmacology of protein and oligonucleotide pharmaceuticals 73

Gene therapy 74 Gene delivery 75 Controlling gene expression 77 Safety and societal issues 77 Therapeutic applications 77 Concluding remarks 79

# 6 Cell proliferation, apoptosis, repair and regeneration 82

Cell proliferation 82 The cell cycle 82 Interactions between cells, growth factors and the extracellular matrix 85 Angiogenesis 86

Apoptosis and cell removal 86 Morphological changes in apoptosis 87 The major players in apoptosis 87

Pathways to apoptosis 88

Repair and healing 89 Hyperplasia 89

Pathophysiological implications 89

The growth, invasion and metastasis of tumours 89

Stem cells and regeneration 90 Overview 133 Therapeutic prospects 90 Introduction 133 Apoptotic mechanisms 90 Drug metabolism 133 Angiogenesis and metalloproteinases 91 Phase 1 reactions 133 Cell cycle regulation 91 Phase 2 reactions 135 Stereoselectivity 135 Inhibition of P450 136 7 Cellular mechanisms: host defence 93 Induction of microsomal enzymes 136 Presystemic ('first-pass') metabolism 136 Overview 93 Pharmacologically active drug metabolites 137 Introduction 93 Drug interactions due to enzyme induction or The innate immune response 93 inhibition 137 Pattern recognition 93 Drug and metabolite excretion 139 The adaptive immune response 98 Biliary excretion and enterohepatic The induction phase 99 circulation 139 The effector phase 100 Renal excretion of drugs and metabolites 139 Systemic responses in inflammation 103 Drug interactions due to altered drug The role of the nervous system in excretion 140 inflammation 103 Unwanted inflammatory and immune responses 103 11 Pharmacokinetics 143 The outcome of the inflammatory response 104 Overview 143 Introduction: definition and uses of pharmacokinetics 143 8 Method and measurement in pharmacology 106 Uses of pharmacokinetics 144 Scope of this chapter 144 Overview 106 Drug elimination expressed as clearance 144 Bioassay 106 Single-compartment model 145 Biological test systems 106 Effect of repeated dosing 146 General principles of bioassay 107 Effect of variation in rate of absorption 146 Animal models of disease 110 More complicated kinetic models 147 Genetic and transgenic animal models 110 Two-compartment model 148 Pharmacological studies in humans 111 Saturation kinetics 149 Clinical trials 111 Population pharmacokinetics 149 Avoidance of bias 112 Limitations of pharmacokinetics 150 The size of the sample 113 Clinical outcome measures 114 Placebos 114 12 Individual variation, pharmacogenomics and Meta-analysis 114 Balancing benefit and risk 114 personalised medicine 152 Overview 152 Introduction 152 Absorption and distribution of drugs 117 Epidemiological factors and inter-individual variation of Overview 117 drug response 153 Introduction 117 Ethnicity 153 Age 153 Physical processes underlying drug disposition 117 Pregnancy 155 The movement of drug molecules across cell Disease 155 barriers 117 Drug interactions 155 Binding of drugs to plasma proteins 121 Genetic variation in drug responsiveness 156 Partition into body fat and other tissues 124 Single-gene pharmacokinetic disorders 157 Drug absorption and routes of administration 124 Therapeutic drugs and clinically available Oral administration 124 pharmacogenomic tests 159 Oromucosal (sublingual or buccal) HLA gene tests 159 administration 126 Drug metabolism-related gene tests 160 Rectal administration 127 Drug target-related gene tests ('companion Application to epithelial surfaces 127 diagnostics') 161 Distribution of drugs in the body 128 Combined (metabolism and target) gene tests 161

Conclusions 161

Volume of distribution 129

Special drug delivery systems 131

10 Drug metabolism and elimination 133

Body fluid compartments 128

### Section 2 Chemical mediators

# 13 Chemical mediators and the autonomic nervous system 163

Overview 163

Historical aspects 163

The autonomic nervous system 164

Basic anatomy and physiology 164

Transmitters in the autonomic nervous system 165

Some general principles of chemical

transmission 167

Presynaptic modulation 167

Postsynaptic modulation 169

Transmitters other than acetylcholine and

noradrenaline 170

Co-transmission 170

Termination of transmitter action 170

Denervation supersensitivity 171

Basic steps in neurochemical transmission: sites of drug action 173

## 14 Cholinergic transmission 175

Overview 175

Muscarinic and nicotinic actions of

acetylcholine 175

Acetylcholine receptors 175

Nicotinic receptors 175

Muscarinic receptors 177

Physiology of cholinergic transmission 178

Acetylcholine synthesis and release 178

Electrical events in transmission at fast cholinergic

synapses 180

Effects of drugs on cholinergic transmission 181

Drugs affecting muscarinic receptors 181

Drugs affecting autonomic ganglia 185

Drugs that act presynaptically 190

Drugs that enhance cholinergic transmission 192

Other drugs that enhance cholinergic

transmission 196

### 15 Noradrenergic transmission 197

Overview 197

Catecholamines 197

Classification of adrenoceptors 197

Physiology of noradrenergic transmission 198

The noradrenergic neuron 198

Uptake and degradation of catecholamines 201

Drugs acting on noradrenergic transmission 202

Drugs acting on adrenoceptors 202

Drugs that affect noradrenergic neurons 213

# 16 5-Hydroxytryptamine and the pharmacology of migraine 217

Overview 217

5-Hydroxytryptamine 217

Distribution, biosynthesis and degradation 217

Pharmacological effects 221

Drugs acting at 5-HT receptors 221

# Migraine and other clinical conditions in which 5-HT plays a role **223**

Migraine and antimigraine drugs 223

Antimigraine drugs 224

Carcinoid syndrome 224

Pulmonary hypertension 225

#### 17 Purines 228

Overview 228

Introduction 228

Purinergic receptors 228

Adenosine as a mediator 228

Adenosine and the cardiovascular system 230

Adenosine in asthma 231

Adenosine in inflammation 231

Adenosine in the CNS 231

ADP as a mediator 231

ADP and platelets 231

ATP as a mediator 231

ATP as a neurotransmitter 231

ATP in nociception 232

ATP in inflammation 232

Future prospects 232

# 18 Local hormones 1: histamine and the biologically active lipids 233

Overview 233

Introduction 233

What is a 'mediator'? 233

Histamine 233

Synthesis and storage of histamine 234

Histamine release 234

Histamine receptors 234

Actions 234

Eicosanoids 235

General remarks 235

Structure and biosynthesis 235

Prostanoids 235

Leukotrienes 240

Leukotriene receptors 240

Leukotriene actions 241

Other important fatty acid derivatives 241

Platelet-activating factor 242

Biosynthesis 242

Actions and role in inflammation 242

Concluding remarks 242

# 19 Local hormones 2: peptides and proteins 244

Overview 244

Introduction 244

General principles of protein and peptide

pharmacology 244

Structure 244

Types of protein and peptide mediator 244

Biosynthesis and regulation of peptides 245

Peptide precursors 246

Diversity within peptide families 246

Peptide trafficking and secretion 246

Bradykinin 247

Source and formation of bradykinin 247
Metabolism and inactivation of bradykinin 247

Bradykinin receptors 247 Actions and role in inflammation 247

Neuropeptides 248 Cytokines 248

Interleukins and related compounds 249

Chemokines 249 Interferons 249

The 'cytokine storm' 251

Proteins and peptides that down-regulate inflammation 251

Concluding remarks 251

#### 20 Cannabinoids 253

Overview 253

Plant-derived cannabinoids and their pharmacological effects 253

Pharmacological effects 253 Pharmacokinetic aspects 253 Adverse effects 253

Tolerance and dependence 254

Cannabinoid receptors 254 Endocannabinoids 255

Biosynthesis of endocannabinoids 255 Termination of the endocannabinoid signal 256 Physiological mechanisms 257 Pathological involvement 257

Synthetic cannabinoids 258 Clinical applications 258

#### Nitric oxide and related mediators 260

Overview 260 Introduction 260

Biosynthesis of nitric oxide and its control 260 Degradation and carriage of nitric oxide 262

Effects of nitric oxide 263

Biochemical and cellular aspects 263 Vascular effects 264 Neuronal effects 264

Host defence 264

Therapeutic aspects 265

Nitric oxide 265

Nitric oxide donors/precursors 265 Inhibition of nitric oxide synthesis 265 Nitric oxide replacement or potentiation 266

Clinical conditions in which nitric oxide may play a

part 266

Related mediators 267

# Section 3 Drugs affecting major organ systems

#### 22 The heart 271

Overview 271 Introduction 271

Physiology of cardiac function 271

Cardiac rate and rhythm 271 Cardiac contraction 274

Myocardial oxygen consumption and coronary blood

Autonomic control of the heart 276

Sympathetic system 276 Parasympathetic system 277 Cardiac natriuretic peptides 278

Ischaemic heart disease 278

Angina 278

Myocardial infarction 279

Drugs that affect cardiac function 279

Antidysrhythmic drugs 279

Drugs that increase myocardial contraction 283

Anti-anginal drugs 284

# 23 The vascular system 290

Overview 290

Introduction 290

Vascular structure and function 290

Control of vascular smooth muscle tone 291

The vascular endothelium 291 The renin-angiotensin system 295

Vasoactive drugs 296

Vasoconstrictor drugs 296 Vasodilator drugs 297

Clinical uses of vasoactive drugs 301

Systemic hypertension 301

Heart failure 304

Vasodilatory shock and hypotensive states 306

Peripheral vascular disease 307

Raynaud's disease 307 Pulmonary hypertension 307

24 Atherosclerosis and lipoprotein metabolism 310

Overview 310

Introduction 310

Atherogenesis 310

Lipoprotein transport 311

Dyslipidaemia 312

Prevention of atheromatous disease 313

Lipid-lowering drugs 314

Statins: HMG-CoA reductase inhibitors 314

Proprotein convertase subtilisin/kexin type-9 (PCSK9)

inhibitors 315

Fibrates 315

Drugs that inhibit cholesterol absorption 316

Nicotinic acid 316

Fish oil derivatives 316

Mipomersen 317

Lomitapide 317

#### 25 Haemostasis and thrombosis 319

Overview 319

Introduction 319

Blood coagulation 319

Coagulation cascade 319

Vascular endothelium in haemostasis and

thrombosis 321

Drugs that act on the coagulation cascade 322

Coagulation defects 322

Thrombosis 323

Platelet adhesion and activation 327

Antiplatelet drugs 329

Fibrinolysis (thrombolysis) 330

Fibrinolytic drugs 331

#### 26 Haematopoietic system and treatment of anaemia 334

Overview 334 Introduction 334

The haematopoietic system 334

Types of anaemia 334

Haematinic agents 335

Iron 335

Folic acid and vitamin B<sub>12</sub> 337

Haematopoietic growth factors 338

Haemolytic anaemia 341

Drugs used to treat haemolytic anaemias 341

#### 27 Anti-inflammatory and immunosuppressant drugs 343

Overview 343 Introduction 343

Cyclo-oxygenase inhibitors 343

Mechanism of action 344

Pharmacological actions 345

Therapeutic actions 346

Some important NSAIDs and coxibs 348

Antirheumatoid drugs 351

Anticytokine drugs and other biopharmaceuticals 355

Drugs used in gout 356

Antagonists of histamine 358

Possible future developments in antiinflammatory

therapy 359

#### 28 Skin 362

Overview 362

Introduction 362

Structure of skin 362

Common diseases of the skin 364

Acne 364

Rosacea 365

Sone structure and composition A. Baldness and hirsutism 365

Eczema 365

Pruritus 365

Urticaria 365

Psoriasis 366
Warts 366
Other infections 366

Drugs acting on skin 366

Formulation 366

Principal drugs used in skin disorders 366

Antimicrobial agents 366

Glucocorticoids and other anti-inflammatory agents 367

Drugs used to control hair growth 367

Retinoids 368

Vitamin D analogues 369

Agents acting by other mechanisms 369

Concluding remarks 369

### Respiratory system 371

Overview 371

The physiology of respiration 371

Control of breathing 371

Regulation of musculature, blood vessels and glands of the airways 371

#### Pulmonary disease and its treatment 372

Bronchial asthma 372

Drugs used to treat and prevent asthma 375

Severe acute asthma (status asthmaticus) 379

Allergic emergencies 379

Chronic obstructive pulmonary disease 379

Idiopathic pulmonary fibrosis 380

Surfactants 380

Cough 380

### 30 The kidney and urinary system 382

Overview 382

Introduction 382

Outline of renal function 382

The structure and function of the nephron 382

Tubular function 384

Acid-base balance 387

Potassium balance 388

Excretion of organic molecules 388

Natriuretic peptides 388

Prostaglandins and renal function 388

Drugs acting on the kidney 388

Diuretics 388

Drugs that alter the pH of the urine 392

Drugs that alter the excretion of organic

molecules 392

Drugs used in renal failure 393

Hyperphosphataemia 393

Hyperkalaemia 393

Drugs used in urinary tract disorders 393

# 31 The gastrointestinal tract 395

Overview 395

The innervation and hormones of the gastrointestinal tract 395

Neuronal control 395

Hormonal control 395

Gastric secretion 395

The regulation of acid seceretion by parietal

cells 395

The coordination of factors regulating acid

secretion 396

Drugs used to inhibit or neutralise gastric acid

secretion 397

Treatment of Helicobacter pylori infection 399

Drugs that protect the mucosa 400

Vomiting 400

The reflex mechanism of vomiting 400

Antiemetic drugs 401

The motility of the GI tract 403

Purgatives 404

Drugs that increase gastrointestinal motility 404

Antidiarrhoeal agents 405

Drugs for chronic bowel disease 406

Drugs affecting the biliary system 406

Future directions 407

#### 32 The control of blood glucose and drug treatment of diabetes mellitus 408

Overview 408

Introduction 408

Control of blood glucose 408

Pancreatic islet hormones 409

Insulin 410

Glucagon 412

Somatostatin 413

Amylin (islet amyloid polypeptide) 413

Incretins 413

Diabetes mellitus 413

Drugs used in the treatment of diabetes 414

Treatment of diabetes mellitus 419

### **33** Obesity **422**

Overview 422

Introduction 422

Definition of obesity 422

Obesity as a health problem 422

Homeostatic mechanisms controlling energy

balance 423

The role of gut and other hormones in body weight regulation 423

Neurological circuits that control body weight and eating behaviour 423

The pathophysiology of human obesity 426

Food intake and obesity 426

Physical exercise and obesity 427

Obesity as a disorder of the homeostatic control of energy balance 427

Genetic factors and obesity 427

Pharmacological approaches to the problem of obesity 428

Centrally acting appetite suppressants 429 Orlistat 429

New approaches to obesity therapy 430

### 34 The pituitary and the adrenal cortex 432

Overview 432

The pituitary gland 432

The anterior pituitary gland 432

Hypothalamic hormones 432

Anterior pituitary hormones 433

Posterior pituitary gland 437

The adrenal cortex 438

Glucocorticoids 440

Mineralocorticoids 444

New directions in glucocorticoid therapy 445

### 35 The thyroid 448

Overview 448

Synthesis, storage and secretion of thyroid

hormones 448

Uptake of plasma iodide by the follicle cells 448 Oxidation of iodide and iodination of tyrosine

residues 448

Secretion of thyroid hormone 448

Regulation of thyroid function 448

Actions of the thyroid hormones 450

Effects on metabolism 450

Effects on growth and development 451

Mechanism of action 451

Transport and metabolism of thyroid hormones 451 Abnormalities of thyroid function 451

Hyperthyroidism (thyrotoxicosis) 451

Simple, non-toxic goitre 452

Hypothyroidism 452

#### Drugs used in diseases of the thyroid 452

Hyperthyroidism 452 Hypothyroidism 453

# 36 The reproductive system 455

Overview 455

Introduction 455

Endocrine control of reproduction 455

Neurohormonal control of the female reproductive

system 455

Neurohormonal control of the male reproductive

system 457

Behavioural effects of sex hormones 458

#### Drugs affecting reproductive function 458

Oestrogens 458

Antioestrogens 459

Progestogens 459

Postmenopausal hormone replacement therapy

(HRT) 460

Androgens 461

Anabolic steroids 461

Anti-androgens 462

Gonadotrophin-releasing hormone: agonists and

antagonists 462

Gonadotrophins and analogues 463

#### Drugs used for contraception 463

Oral contraceptives 463

Other drug regimens used for contraception 464

The uterus 465

The motility of the uterus 465

Drugs that stimulate the uterus 465

Drugs that inhibit uterine contraction 466

Erectile dysfunction 467

# 37 Bone metabolism 470

Overview 470

Introduction 470

Bone structure and composition 470

Bone remodelling 470

The action of cells and cytokines 470

The turnover of bone minerals 472

Hormones involved in bone metabolism and

remodelling 473

Disorders of bone 474

Drugs used in bone disorders 475

Bisphosphonates 475

Oestrogens and related compounds 476

Parathyroid hormone and teriparatide 476

Vitamin D preparations 477

Biopharmaceuticals 477

Calcitonin 477

Calcium salts 477

Calcimimetic compounds 478

Potential new therapies 478

## Section 4 Nervous system

### 38 Chemical transmission and drug action in the central nervous system 480

Overview 480 Introduction 480 Chemical signalling in the nervous system 480 Targets for drug action 482
Drug action in the central nervous system 483
Blood-brain barrier 483

The classification of psychotropic drugs 484

#### 39 Amino acid transmitters 486

Overview 486

Excitatory amino acids 486

Excitatory amino acids as CNS transmitters 486
Metabolism and release of excitatory amino
acids 486

Glutamate 487

Glutamate receptor subtypes 487
Synaptic plasticity and long-term potentiation 491
Drugs acting on glutamate receptors 491

Prugs acting on glutamate receptors 491
 γ-Aminobutyric acid (GABA) 493
 Synthesis, storage and function 493
 GABA receptors: structure and pharmacology 494
 Drugs acting on GABA receptors 496

Glycine **497**Concluding remarks **497** 

#### 40 Other transmitters and modulators 499

Overview **499** Introduction **499** Noradrenaline **499** 

Noradrenergic pathways in the CNS 499 Functional aspects 500

Dopamine 500

Dopaminergic pathways in the CNS 501
Dopamine receptors 502
Functional aspects 502

5-Hydroxytryptamine **504** 

5-HT pathways in the CNS 504 5-HT receptors in the CNS 504 Functional aspects 505 Clinically used drugs 506

Acetylcholine **506**Cholinergic pathways in the CNS **507**Acetylcholine receptors **507** 

Functional aspects 507
Purines 508
Histamine 509

Other CNS mediators 509

Melatonin 509
Nitric oxide 509
Lipid mediators 510
A final message 512

# Neurodegenerative diseases 514

Overview 514

Protein misfolding and aggregation in chronic neurodegenerative diseases 514

Mechanisms of neuronal death 514

Excitotoxicity 516
Apoptosis 516
Oxidative stress 516

Ischaemic brain damage 518

Pathophysiology 518
Therapeutic approaches 519

Alzheimer's disease 519

Pathogenesis of Alzheimer's disease 519

Therapeutic approaches 521

Parkinson's disease 522

Features of Parkinson's disease 522
Pathogenesis of Parkinson's disease 523
Drug treatment of Parkinson's disease 524

Huntington's disease **527**Amyotrophic lateral sclerosis **528**Spinal muscular atrophy **528**Multiple sclerosis **528** 

### 42 General anaesthetic agents 531

Overview **531**Introduction **531** 

Mechanism of action of anaesthetic drugs 531

Lipid solubility 531
Effects on ion channels 532
Effects on the nervous system 533
Effects on the cardiovascular and respiratory systems 533

Intravenous anaesthetic agents 534

Propofol 534
Thiopental 534
Etomidate 535
Other intravenous agents 535
Inhalation anaesthetics 536

Pharmacokinetic aspects 536
Individual inhalation anaesthetics 539

lsoflurane, desflurane, sevoflurane, enflurane and halothane 539
Nitrous oxide 540

Balanced anaesthesia 540

#### 43 Analgesic drugs 542

Overview 542

Neural mechanisms of pain **542**Nociceptive afferent neurons **542** 

Modulation in the nociceptive pathway 543

Neuropathic pain 546

Chemical signalling in the nociceptive pathway 546

Analgesic drugs 548
Opioid drugs 548

Paracetamol 559

Treatment of chronic pain 559 Other pain-relieving drugs 560

New approaches 560

# 44 Local anaesthetics and other drugs affecting sodium channels 563

Overview 563

Local anaesthetics 563

Chemical aspects 563
Mechanism of action 563
Pharmacokinetic aspects 566
New approaches 566

Other drugs that affect sodium channels 567

Tetrodotoxin and saxitoxin 567
Agents that affect sodium-channel gating 568

# 45 Anxiolytic and hypnotic drugs 569

Overview 569

The nature of anxiety and its treatment 569

Measurement of anxiolytic activity 569

Animal models of anxiety 569

Tests on humans 570

Drugs used to treat anxiety 571

Delayed anxiolytic effect of SSRIs and buspirone 572

Benzodiazepines and related drugs 572 Other potential anxiolytic drugs 576

Drugs used to treat insomnia (hypnotic drugs) 577
Induction of sleep by benzodiazepines 578

#### 46 Antiepileptic drugs 580

Overview 580

Introduction 580

The nature of epilepsy 580

Types of epilepsy 580

Neural mechanisms and animal models of epilepsy 582

Antiepileptic drugs 582

Carbamazepine 586

Phenytoin 586

Valproate 587

Ethosuximide 588

Phenobarbital 588

Benzodiazepines 588

Newer antiepileptic drugs 589

New drugs 590

Other uses of antiepileptic drugs 590

Antiepileptic drugs and pregnancy 590

Muscle spasm and muscle relaxants 590

# 47 Antipsychotic drugs 592

Overview 592

Introduction 592

The nature of schizophrenia 592

Aetiology and pathogenesis of schizophrenia 593

Antipsychotic drugs 595

Classification of antipsychotic drugs 595

Clinical efficacy in treatment of schizophrenia 595

Other uses of antipsychotic drugs 598

Pharmacological properties 598

Unwanted effects 599

Pharmacokinetic aspects 601

Future developments 601

#### 48 Antidepressant drugs 603

Overview 603

The nature of depression 603

Theories of depression 603

The monoamine theory 603

Negative affective bias 604

Neuroendocrine mechanisms 604

Trophic effects and neuroplasticity 605

Antidepressant drugs 606

Types of antidepressant drug 606

Testing of antidepressant drugs 607

Mechanism of action of antidepressant drugs 611

Monoamine uptake inhibitors 611

Monoamine receptor antagonists 616

Monoamine oxidase inhibitors 616

Melatonin agonist 618

Ketamine 618

Other antidepressant approaches 618

Clinical effectiveness of antidepressant treatments 618

Future antidepressant drugs 619

Brain stimulation therapies 619

Drug treatment of bipolar disorder 620

Lithium 620

Antiepileptic drugs 621

Second-generation antipsychotic drugs 621

# 49 Psychoactive drugs 623

Overview 623

Introduction 623

Psychomotor stimulants 623

Amphetamines 623

Methylphenidate 625

Modafinil 626

Cocaine 626

MDMA 628

Cathinones 628

Methylxanthines 629

Nicotine 629

Pharmacological effects of nicotine 630

Pharmacokinetic aspects 631

Tolerance and dependence 631

Harmful effects of tobacco smoking 632

Cognition-enhancing drugs 633

Psychedelic drugs 634

LSD, psilocybin and mescaline 634

Other psychedelic drugs 635

Ketamine and related drugs 635

Depressants 635

Ethanol 636

Pharmacological effects of ethanol 636

Pharmacokinetic aspects 638

Tolerance and dependence 640

Synthetic cannabinoids 640

#### 50 Drug abuse and dependence 642

Overview 642

Drug use and abuse 642

Drug administration 642

Drug harm 643

Drug dependence 643

Withdrawal 644

Tolerance 646

Pharmacological approaches to treating drug

dependence 646

# Section 5 **Drugs used for the treatment** of infections and cancer

# 51 Basic principles of antimicrobial chemotherapy 649

Overview 649

Background 649

The molecular basis of chemotherapy 649

Bacteria 649

Biochemical reactions as potential targets 650

The formed structures of the cell as potential

targets 654

Resistance to antibacterial drugs 656

The spread of antibiotic resistance 656 Biochemical mechanisms of resistance to

antibiotics 657

Current status of antibiotic resistance in bacteria 659

# 52 Antibacterial drugs 661

Overview 661 Introduction 661

Antibacterial agents that interfere with folate synthesis or action 661

Sulfonamides 661 Trimethoprim 662

B-lactam antibiotics and other agents that interfere with bacterial wall or membrane synthesis 663

Penicillins 663

Cephalosporins and cephamycins 665

Other B-lactam antibiotics 665

Other antibiotics that inhibit bacterial cell wall peptidoglycan synthesis 665

Antimicrobial agents affecting bacterial protein synthesis 666

Tetracyclines 666 Chloramphenicol 667 Aminoglycosides 667 Macrolides 670 Oxazolidinones 670 Fusidic acid 671

Streptogramins 671 Clindamycin 671

Antimicrobial agents affecting topoisomerase 672 Quinolones 672

Miscellaneous antibacterial agents 672

Antimycobacterial agents 673

Drugs used to treat tuberculosis 673 Drugs used to treat leprosy 675 Possible new antibacterial drugs 675

### 53 Antiviral drugs 678

Overview 678

Background information about viruses 678

An outline of virus structure 678 Examples of pathogenic viruses 678 Virus function and life history 678

The host-virus interaction 679

Host defences against viruses 679 Viral plays to circumvent host defences 680

HIV and AIDS 680

Induction of the disease 681 Progress of infection 681

Antiviral drugs 681

Reverse transcriptase inhibitors 684

Non-nucleoside reverse transcriptase inhibitors 684

Protease inhibitors 685

DNA polymerase inhibitors 685

Neuraminidase inhibitors and inhibitors of viral coat disassembly 685

Drugs acting through other mechanisms 686 Biopharmaceutical antiviral drugs 686

Other agents 686 Combination therapy for HIV 687 Prospects for new antiviral drugs 687

# 54 Antifungal drugs 690

Overview 690 Fungi and fungal infections 690 Drugs used to treat fungal infections 691 Antifungal antibiotics 691

Synthetic antifungal drugs 693 Future developments 694

# 55 Antiprotozoal drugs 696

Overview 696 Background 696

Host-parasite interactions 696

Malaria and antimalarial drugs 696

The life cycle of the malaria parasite 698

Antimalarial drugs 699

Potential new antimalarial drugs 705

Amoebiasis and amoebicidal drugs 705 Trypanosomiasis and trypanocidal drugs 706

Other protozoal infections and drugs used to treat

them 707

Leishmaniasis 707 Trichomoniasis 707 Giardiasis 708 Toxoplasmosis 708 Pneumocystis 708

Future developments 708

# 56 Antihelminthic drugs 710

Overview 710 Helminth infections 710 Antihelminthic drugs 711 Resistance to antihelminthic drugs 713 Vaccines and other novel approaches 714

### 57 Anticancer drugs 716

Overview 716 Introduction 716

The pathogenesis of cancer 716

The genesis of a cancer cell 717 The special characteristics of cancer cells 717

General principles of cytotoxic anticancer drugs 719

Anticancer drugs 720

Alkylating agents and related compounds 722

Antimetabolites 723 Cytotoxic antibiotics 724

Plant derivatives 726

Hormones 726

Hormone antagonists 727 Monoclonal antibodies 727

Protein kinase inhibitors 728

Miscellaneous agents 729

Resistance to anticancer drugs 729

Combination therapies 730

Control of emesis and myelosuppression 730

Future developments 730

# Section 6 Special topics

# 58 Harmful effects of drugs 733

Overview 733 Introduction 733

Classification of adverse drug reactions 733

Adverse effects related to the known pharmacological action of the drug 733

Adverse effects unrelated to the known pharmacological action of the drug 734

Drug toxicity 734

Toxicity testing 734
General mechanisms of toxin-induced cell damage
and cell death 735

Mutagenesis and assessment of genotoxic potential 736

Immunological reactions to drugs **741**Immunological mechanisms **742** 

Clinical types of allergic response to drugs 742

# 59 Lifestyle and drugs in sport 744

Overview 744
What are lifestyle drugs? 744
Classification of lifestyle drugs 744
Drugs and sex 745
Drugs in sport 745
Anabolic steroids 746

Human growth hormone 748
Stimulant drugs 748
Conclusion 748

# 60 Drug discovery and development 750

Overview **750**The stages of a project **750**The drug discovery phase **750**Preclinical development **752** 

Preclinical development 752
Clinical development 753
Biopharmaceuticals 753

Commercial aspects **754**Future prospects **754**A final word **755** 

Index 756

Self-assessment questions compiled by Dr. Christine Edmead, University of Bath, are available through https://studentconsult.inkling.com