

Contents

Preface xv
Acknowledgements xvi
Abbreviations and Acronyms xvii

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 11
Drug antagonism and synergism 15
Chemical antagonism 15
Pharmacokinetic antagonism 15
Block of receptor-effector linkage 15
Physiological antagonism 15
Desensitisation and tachyphylaxis 15
Quantitative aspects of drug-receptor interactions 16
The nature of drug effects 18

3. How drugs act: molecular aspects 20

Overview 20
Targets for drug action 20
Receptors 20
Ion channels 20
Enzymes 21
Transport proteins 21
Receptor proteins 23
Isolation and cloning of receptors 23
Types of receptor 23
Molecular structure of receptors 25
Type 1: ligand-gated ion channels 26
Type 2: G-protein-coupled receptors 28
Type 3: kinase-linked and related receptors 37
Type 4: Nuclear receptors 40
Ion channels as drug targets 43
Ion selectivity 43
Gating 43
Molecular architecture of ion channels 44
Pharmacology of ion channels 44
Control of receptor expression 44
Receptors and disease 45

4. How drugs act: cellular aspects—excitation, contraction and secretion 49

Overview 49
Regulation of intracellular calcium 49

Calcium entry mechanisms 49
Calcium extrusion mechanisms 51
Calcium release mechanisms 52
Calmodulin 52

Excitation 53

The 'resting' cell 53
Electrical and ionic events underlying the action potential 54
Channel function 55
Muscle contraction 59
Skeletal muscle 59
Cardiac muscle 59
Smooth muscle 60

Release of chemical mediators 61

Exocytosis 62
Non-vesicular release mechanisms 63
Epithelial ion transport 63

5. Cell proliferation, apoptosis, repair and regeneration 66

Overview 66
Cell proliferation 66
The cell cycle 66
Interactions between cells, growth factors and the extracellular matrix 69
Angiogenesis 70
Apoptosis and cell removal 70
Morphological changes in apoptosis 71
The major players in apoptosis 71
Pathways to apoptosis 72
Pathophysiological implications 73
Repair and healing 73
Hyperplasia 73
The growth, invasion and metastasis of tumours 73
Stem cells and regeneration 73
Therapeutic prospects 74
Apoptotic mechanisms 74
Angiogenesis and metalloproteinases 75
Cell cycle regulation 75

6. Cellular mechanisms: host defence 77

Overview 77
Introduction 77
The innate immune response 77
Pathogen recognition 77
The adaptive immune response 82
The induction phase 83
The effector phase 84
Systemic responses in inflammation 86
The role of the nervous system in inflammation 86
Unwanted inflammatory and immune responses 87
The outcome of the inflammatory response 87

7. Method and measurement in pharmacology 89

Overview 89
Bioassay 89
Biological test systems 89
General principles of bioassay 90
Animal models of disease 92
Genetic and transgenic animal models 93
Pharmacological studies in humans 93
Clinical trials 94
Avoidance of bias 95

- The size of the sample 95
- Clinical outcome measures 96
- Frequentist and Bayesian approaches 96
- Placebos 96
- Meta-analysis 97
- Balancing benefit and risk 97

8. Drug absorption and distribution 99

- Overview 99
- Introduction 99
- Physical processes underlying drug disposition 99
 - The movement of drug molecules across cell barriers 99
 - Binding of drugs to plasma proteins 103
 - Partition into body fat and other tissues 105
- Drug absorption and routes of administration 106
 - Oral administration 106
 - Sublingual administration 108
 - Rectal administration 108
 - Application to epithelial surfaces 108
 - Administration by inhalation 109
 - Administration by injection 109
- Distribution of drugs in the body 110
 - Body fluid compartments 110
 - Volume of distribution 111
- Special drug delivery systems 111
 - Biologically erodible nanoparticles 112
 - Prodrugs 112
 - Antibody–drug conjugates 113
 - Packaging in liposomes 113
 - Coated implantable devices 113

9. Drug metabolism and elimination 115

- Overview 115
- Introduction 115
- Drug metabolism 115
 - Phase 1 reactions 115
 - Phase 2 reactions 117
 - Stereoselectivity 117
 - Inhibition of P450 117
 - Induction of microsomal enzymes 118
 - First-pass (presystemic) metabolism 118
 - Pharmacologically active drug metabolites 118
- Drug and metabolite excretion 119
 - Biliary excretion and enterohepatic circulation 119
 - Renal excretion of drugs and metabolites 119

10. Pharmacokinetics 123

- Overview 123
- Introduction: definition and uses of pharmacokinetics 123
 - Uses of pharmacokinetics 123
 - Scope of this chapter 124
- Drug elimination expressed as clearance 124
- Single compartment model 124
 - Effect of repeated dosing 126
 - Effect of variation in rate of absorption 126
- More complicated kinetic models 126
 - Two-compartment model 127
 - Saturation kinetics 128
- Population pharmacokinetics 129
- Limitations of pharmacokinetics 129

11. Pharmacogenetics, pharmacogenomics and 'personalised medicine' 132

- Overview 132
- Introduction 132
- Relevant elementary genetics 132
- Single-gene pharmacogenetic disorders 133
 - Plasma cholinesterase deficiency 133
 - Acute intermittent porphyria 134
 - Drug acetylation deficiency 134
 - Aminoglycoside ototoxicity 135
- Therapeutic drugs and clinically available pharmacogenomic tests 135
 - HLA gene tests 135
 - Drug metabolism-related gene tests 136
 - Drug target-related gene tests 137
 - Combined (metabolism and target) gene tests 137
- Conclusions 137

Section 2: Chemical mediators

12. Chemical mediators and the autonomic nervous system 139

- Overview 139
- Historical aspects 139
- The autonomic nervous system 140
 - Basic anatomy and physiology 140
 - Transmitters in the autonomic nervous system 141
- Some general principles of chemical transmission 143
 - Dale's principle 143
 - Denervation supersensitivity 143
 - Presynaptic modulation 144
 - Postsynaptic modulation 145
 - Transmitters other than acetylcholine and noradrenaline 145
 - Co-transmission 147
 - Termination of transmitter action 147
- Basic steps in neurochemical transmission: sites of drug action 149

13. Cholinergic transmission 151

- Overview 151
- Muscarinic and nicotinic actions of acetylcholine 151
- Acetylcholine receptors 151
 - Nicotinic receptors 151
 - Muscarinic receptors 153
- Physiology of cholinergic transmission 154
 - Acetylcholine synthesis and release 154
 - Electrical events in transmission at fast cholinergic synapses 156
- Effects of drugs on cholinergic transmission 157
 - Drugs affecting muscarinic receptors 157
 - Drugs affecting autonomic ganglia 161
 - Neuromuscular-blocking drugs 163
 - Drugs that act presynaptically 167
 - Drugs that enhance cholinergic transmission 168
 - Other drugs that enhance cholinergic transmission 172

14. Noradrenergic transmission 174

- Overview **174**
- Catecholamines **174**
- Classification of adrenoceptors **174**
- Physiology of noradrenergic transmission **175**
 - The noradrenergic neuron 175
 - Uptake and degradation of catecholamines 178
- Drugs acting on noradrenergic transmission **181**
 - Drugs acting on adrenoceptors 181
 - Drugs that affect noradrenergic neurons 190

15. 5-Hydroxytryptamine and the pharmacology of migraine 194

- Overview **194**
- 5-Hydroxytryptamine **194**
 - Distribution, biosynthesis and degradation 194
 - Pharmacological effects 195
 - Classification of 5-HT receptors 195
 - Drugs acting on 5-HT receptors 196
- Migraine and other clinical conditions in which 5-HT plays a role **199**
 - Migraine and antimigraine drugs 199
 - Carcinoid syndrome 202
 - Pulmonary hypertension 203

16. Purines 204

- Overview **204**
- Introduction **204**
- Purinergic receptors **204**
- Adenosine as a mediator **204**
 - Adenosine and the cardiovascular system 205
 - Adenosine and asthma 206
 - Adenosine in the CNS 206
- ADP as a mediator **206**
 - ADP and platelets 206
- ATP as a mediator **207**
 - ATP as a neurotransmitter 207
 - ATP in nociception 207
 - ATP in inflammation 207
- Future prospects **207**

17. Local hormones: cytokines, biologically active lipids, amines and peptides 208

- Overview **208**
- Introduction **208**
- Cytokines **208**
 - Interleukins 208
 - Chemokines 210
 - Interferons 210
- Histamine **210**
 - Synthesis and storage of histamine 211
 - Histamine release 211
 - Histamine receptors 211
 - Actions 211
- Eicosanoids **212**
 - General remarks 212
 - Structure and biosynthesis 212
 - Prostanoids 213
 - Leukotrienes 215
 - Lipoxins and resolvins 217

- Platelet-activating factor **217**
 - Actions and role in inflammation 217
- Bradykinin **217**
 - Source and formation of bradykinin 218
 - Metabolism and inactivation of bradykinin 218
 - Bradykinin receptors 218
 - Actions and role in inflammation 219
- Nitric oxide **219**
- Neuropeptides **219**
- Concluding remarks **219**

18. Cannabinoids 221

- Overview **221**
- Plant-derived cannabinoids and their pharmacological effects **221**
 - Pharmacological effects 221
 - Pharmacokinetic and analytical aspects 222
 - Adverse effects 222
 - Tolerance and dependence 222
- Cannabinoid receptors **222**
- Endocannabinoids **223**
 - Biosynthesis of endocannabinoids 223
 - Termination of the endocannabinoid signal 224
 - Physiological mechanisms 225
 - Pathological involvement 225
- Synthetic cannabinoids **225**
- Clinical applications **226**

19. Peptides and proteins as mediators 228

- Overview **228**
- Introduction **228**
- Historical aspects **228**
- General principles of peptide pharmacology **228**
 - Structure of peptides 228
 - Types of peptide mediator 228
 - Peptides in the nervous system: comparison with conventional transmitters 229
- Biosynthesis and regulation of peptides **231**
 - Peptide precursors 231
 - Diversity within peptide families 232
 - Peptide trafficking and secretion 233
- Peptide antagonists **234**
- Proteins and peptides as drugs **234**
- Concluding remarks **235**

20. Nitric oxide 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**
- Therapeutic approaches **242**
 - Nitric oxide 242
 - Nitric oxide donors/precursors 242
 - Inhibition of nitric oxide synthesis 242
 - Potential of nitric oxide 243
- Clinical conditions in which nitric oxide may play a part **243**

Section 3: Drugs affecting major organ systems

21. The heart 246

- Overview 246
- Introduction 246
- Physiology of cardiac function 246
 - Cardiac rate and rhythm 246
 - Cardiac contraction 249
 - Myocardial oxygen consumption and coronary blood flow 250
- Autonomic control of the heart 251
 - Sympathetic system 251
 - Parasympathetic system 252
- Cardiac natriuretic peptides 252
- Ischaemic heart disease 253
 - Angina 253
 - Myocardial infarction 253
- Drugs that affect cardiac function 254
 - Antidysrhythmic drugs 254
 - Drugs that increase myocardial contraction 258
 - Antianginal drugs 259

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 270
- Vasoactive drugs 271
 - Vasoconstrictor drugs 271
 - Vasodilator drugs 271
- Clinical uses of vasoactive drugs 277
 - Systemic hypertension 277
 - Heart failure 278
 - Shock and hypotensive states 280
 - Peripheral vascular disease 281
 - Raynaud's disease 281
 - 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 288
 - 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 294

- Overview 294
- Introduction 294
- Blood coagulation 294
 - Coagulation cascade 294

- Vascular endothelium in haemostasis and thrombosis 296
- Drugs that act on the coagulation cascade 297
 - Coagulation defects 297
 - Thrombosis 298
- Platelet adhesion and activation 302
 - Antiplatelet drugs 302
- Fibrinolysis (thrombolysis) 306
 - Fibrinolytic drugs 306
 - Antifibrinolytic and haemostatic drugs 307

25. Haemopoietic system and treatment of anaemia 309

- Overview 309
- Introduction 309
- The haemopoietic system 309
- Types of anaemia 309
- Haematonic agents 309
 - Iron 310
 - Folic acid and vitamin B₁₂ 311
- Haemopoietic growth factors 314
 - Erythropoietin 314
 - Colony-stimulating factors 315
- Haemolytic anaemia 316
 - Hydroxycarbamide 316

26. Anti-inflammatory and immunosuppressant drugs 318

- Overview 318
- Cyclo-oxygenase inhibitors 318
 - Mechanism of action 319
 - Pharmacological actions 321
 - Therapeutic actions 321
 - Some important NSAIDs and coxibs 323
- Antirheumatoid drugs 326
 - Disease-modifying antirheumatic drugs 327
 - Immunosuppressant drugs 328
- Anticytokine drugs and other biopharmaceuticals 330
- Drugs used in gout 331
- Antagonists of histamine 332
- Possible future developments 334

27. Respiratory system 336

- Overview 336
- The physiology of respiration 336
 - Control of breathing 336
 - Regulation of musculature, blood vessels and glands of the airways 336
- Pulmonary disease and its treatment 337
 - Bronchial asthma 337
 - Drugs used to treat and prevent asthma 340
 - Severe acute asthma (status asthmaticus) 343
 - Allergic emergencies 344
 - Chronic obstructive pulmonary disease 344
 - Surfactants 345
 - Cough 345

28. The kidney 347

- Overview 347
- Introduction 347
- Outline of renal function 347
- The structure and function of the nephron 347
 - Tubular function 349

- Acid–base balance 352
- Potassium balance 352
- Excretion of organic molecules 352
- Natriuretic peptides 353
- Prostaglandins and renal function 353
- Drugs acting on the kidney 353**
 - Diuretics 353
- Drugs that alter the pH of the urine 356**
- Drugs that alter the excretion of organic molecules 357**
- Drugs used in renal failure 357**
 - Hyperphosphataemia 358
 - Hyperkalaemia 358
- Drugs used in urinary tract disorders 358**

29. The gastrointestinal tract 360

- Overview 360**
- The innervation and hormones of the gastrointestinal tract 360**
 - Neuronal control 360
 - Hormonal control 360
- Gastric secretion 360**
 - The regulation of acid secretion by parietal cells 360
 - The coordination of factors regulating acid secretion 362
 - Drugs used to inhibit or neutralise gastric acid secretion 362
 - Treatment of *Helicobacter pylori* infection 364
 - Drugs that protect the mucosa 365
- Vomiting 365**
 - The reflex mechanism of vomiting 365
 - Antiemetic drugs 366
- The motility of the gastrointestinal tract 367**
 - Purgatives 368
 - Drugs that increase gastrointestinal motility 368
 - Antidiarrhoeal agents 369
 - Antimotility and spasmolytic agents 369
- Drugs for chronic bowel disease 370**
- Drugs affecting the biliary system 370**
- Future directions 370**

30. The control of blood glucose and drug treatment of diabetes mellitus 372

- Overview 372**
- Introduction 372**
- Control of blood glucose 372**
- Pancreatic islet hormones 372**
 - Insulin 372
 - Glucagon 376
 - Somatostatin 377
 - Amylin (islet amyloid polypeptide) 377
 - Incretins 377
- Diabetes mellitus 377**
 - Treatment of diabetes mellitus 378
 - Potential new antidiabetic drugs 383

31. Obesity 385

- Overview 385**
- Introduction 385**
 - Definition of obesity 385
- The homeostatic mechanisms controlling energy balance 385**

- The role of gut and other hormones in body weight regulation 385
- Neurological circuits that control body weight and eating behaviour 388
- Obesity as a health problem 389**
 - The pathophysiology of human obesity 389
 - Obesity as a disorder of the homeostatic control of energy balance 390
 - Genetic factors and obesity 390
- Pharmacological approaches to the problem of obesity 391**
 - Sibutramine 391
 - Orlistat 392
- New approaches to obesity therapy 392**

32. The pituitary and the adrenal cortex 394

- Overview 394**
- The pituitary gland 394**
 - The anterior pituitary gland (adenohypophysis) 394
 - Hypothalamic hormones 394
 - Anterior pituitary hormones 396
 - Posterior pituitary gland (neurohypophysis) 399
- The adrenal cortex 400**
 - Glucocorticoids 402
 - Mineralocorticoids 406
- New directions in glucocorticoid therapy 407**

33. The thyroid 410

- Overview 410**
- Synthesis, storage and secretion of thyroid hormones 410**
 - Uptake of plasma iodide by the follicle cells 410
 - Oxidation of iodide and iodination of tyrosine residues 410
 - Secretion of thyroid hormone 410
- Regulation of thyroid function 410**
- Actions of the thyroid hormones 412**
 - Effects on metabolism 412
 - Effects on growth and development 412
 - Mechanism of action 412
- Transport and metabolism of thyroid hormones 412**
- Abnormalities of thyroid function 413**
 - Hyperthyroidism (thyrotoxicosis) 413
 - Simple, non-toxic goitre 413
 - Hypothyroidism 413
- Drugs used in diseases of the thyroid 414**
 - Hyperthyroidism 414
 - Hypothyroidism 415

34. The reproductive system 417

- Overview 417**
- Introduction 417**
- Endocrine control of reproduction 417**
 - Neurohormonal control of the female reproductive system 417
 - Neurohormonal control of the male reproductive system 418
 - Behavioural effects of sex hormones 419
- Drugs affecting reproductive function 420**
 - Oestrogens 420
 - Antioestrogens 421
 - Progestogens 421
 - Antiprogestogens 422

- Postmenopausal hormone replacement therapy 422
- Androgens 422
- Anabolic steroids 423
- Antiandrogens 424
- Gonadotrophin-releasing hormone: agonists and antagonists 424
- Gonadotrophins and analogues 425
- Drugs used for contraception 425**
 - Oral contraceptives 425
 - Other drug regimens used for contraception 427
- The uterus 427**
 - Drugs that stimulate the uterus 427
 - Drugs that inhibit uterine contraction 428
- Erectile dysfunction 429**

35. Bone metabolism 432

- Overview 432**
- Introduction 432**
- Bone structure and composition 432**
- Bone remodelling 432**
 - The action of cells and cytokines 432
 - The turnover of bone minerals 434
 - Hormones involved in bone metabolism and remodelling 435
- Disorders of bone 437**
- Drugs used in bone disorders 437**
 - Bisphosphonates 437
 - Oestrogens and related compounds 438
 - Parathyroid hormone and teriparatide 439
 - Strontium ranelate 439
 - Vitamin D preparations 439
 - Calcitonin 439
 - Calcium salts 439
 - Calcimimetic compounds 440
- Potential new therapies 440**

Section 4: The nervous system

36. Chemical transmission and drug action in the central nervous system 442

- Overview 442**
- Introduction 442**
- Chemical signalling in the nervous system 442**
- Targets for drug action 444**
- Drug action in the central nervous system 444**
 - Blood–brain barrier 445
- The classification of psychotropic drugs 446**

37. Amino acid transmitters 448

- Overview 448**
- Excitatory amino acids 448**
 - Excitatory amino acids as CNS transmitters 448
 - Metabolism and release of amino acids 448
- Glutamate 449**
 - Glutamate receptor subtypes 449
 - Synaptic plasticity and long-term potentiation 451
 - Drugs acting on glutamate receptors 453
- γ -Aminobutyric acid 456**
 - Synthesis, storage and function 456
 - GABA receptors: structure and pharmacology 456
 - Drugs acting on GABA receptors 457

- Glycine 458
- Concluding remarks 459

38. Other transmitters and modulators 461

- Overview 461**
- Introduction 461**
- Noradrenaline 461**
 - Noradrenergic pathways in the CNS 461
 - Functional aspects 461
- Dopamine 463**
 - Dopaminergic pathways in the CNS 463
 - Dopamine receptors 464
 - Functional aspects 464
- 5-Hydroxytryptamine 466**
 - 5-HT pathways in the CNS 467
 - Functional aspects 467
 - Clinically used drugs 468
- Acetylcholine 468**
 - Cholinergic pathways in the CNS 468
 - Acetylcholine receptors 469
 - Functional aspects 470
- Purines 470**
- Histamine 471**
- Other CNS mediators 471**
 - Melatonin 471
 - Nitric oxide 471
 - Lipid mediators 472
- A final message 473**

39. Neurodegenerative diseases 476

- Overview 476**
- Protein misfolding and aggregation in chronic neurodegenerative diseases 476**
- Mechanisms of neuronal death 476**
 - Excitotoxicity 477
 - Apoptosis 478
 - Oxidative stress 480
- Ischaemic brain damage 480**
 - Pathophysiology 480
 - Therapeutic approaches 481
- Alzheimer's disease 481**
 - Pathogenesis of Alzheimer's disease 481
 - Therapeutic approaches 483
- Parkinson's disease 485**
 - Features of Parkinson's disease 485
 - Pathogenesis of Parkinson's disease 486
 - Drug treatment of Parkinson's disease 486
- Huntington's disease 489**
- Neurodegenerative prion diseases 489**

40. General anaesthetic agents 492

- Overview 492**
- Introduction 492**
- Mechanism of action of anaesthetic drugs 492**
 - Lipid solubility 492
 - Effects on ion channels 493
 - Effects on the nervous system 494
 - Effects on the cardiovascular and respiratory systems 494
- Intravenous anaesthetic agents 495**
 - Propofol 495
 - Thiopental 495
 - Etomidate 496
 - Other intravenous agents 496

- Inhalation anaesthetics **497**
 - Pharmacokinetic aspects 497
- Individual inhalation anaesthetics **500**
 - Isoflurane, desflurane, sevoflurane, enflurane and halothane 500
 - Nitrous oxide 500
- Use of anaesthetics in combination with other drugs **502**

41. Analgesic drugs **503**

- Overview **503**
- Neural mechanisms of pain **503**
 - Nociceptive afferent neurons 503
 - Modulation in the nociceptive pathway 503
 - Neuropathic pain 506
 - Pain and nociception 507
 - Chemical signalling in the nociceptive pathway 507
 - Transmitters and modulators in the nociceptive pathway 509
- Analgesic drugs **510**
 - Opioid drugs 510
 - Paracetamol 521
 - Treatment of neuropathic pain 521
 - Other pain-relieving drugs 522
- New approaches **522**

42. Local anaesthetics and other drugs affecting sodium channels **525**

- Overview **525**
- Local anaesthetics **525**
- Other drugs that affect sodium channels **530**
 - Tetrodotoxin and saxitoxin 530
 - Agents that affect sodium channel gating 530

43. Anxiolytic and hypnotic drugs **531**

- Overview **531**
- The nature of anxiety and its treatment **531**
- Measurement of anxiolytic activity **531**
 - Animal models of anxiety 531
 - Tests on humans 532
- Drugs used to treat anxiety **532**
- Drugs used to treat insomnia (hypnotic drugs) **532**
- Benzodiazepines and related drugs **533**
 - Mechanism of action 533
 - Pharmacological effects and uses 534
 - Pharmacokinetic aspects 536
 - Unwanted effects 536
 - Benzodiazepine antagonists and inverse agonists 537
- Buspirone **538**
- Other potential anxiolytic drugs **539**

44. Antiepileptic drugs **540**

- Overview **540**
- Introduction **540**
- The nature of epilepsy **540**
 - Types of epilepsy 540
 - Neural mechanisms and animal models of epilepsy 542
- Antiepileptic drugs **543**
 - Carbamazepine 546
 - Phenytoin 546
 - Valproate 547
 - Ethosuximide 548

- Phenobarbital 548
- Benzodiazepines 548
- Newer antiepileptic drugs 549
- Development of new drugs 550
- Other uses of antiepileptic drugs 550
- Antiepileptic drugs and pregnancy 551
- Muscle spasm and muscle relaxants **551**

45. Antipsychotic drugs **553**

- Overview **553**
- Introduction **553**
- The nature of schizophrenia **553**
 - Aetiology and pathogenesis of schizophrenia 554
- Antipsychotic drugs **555**
 - Classification of antipsychotic drugs 555
 - Pharmacological properties 558
 - Behavioural effects 559
 - Unwanted effects 560
 - Pharmacokinetic aspects 562
 - Clinical use and clinical efficacy 562
- Future developments **563**

46. Antidepressant drugs **564**

- Overview **564**
- The nature of depression **564**
- Theories of depression **564**
 - The monoamine theory 564
- Antidepressant drugs **567**
 - Types of antidepressant drug 567
 - Testing of antidepressant drugs 571
 - Mechanism of action of antidepressant drugs 571
 - Monoamine uptake inhibitors 573
 - Monoamine receptor antagonists 577
 - Monoamine oxidase inhibitors 577
 - Miscellaneous agents 579
 - Future antidepressant drugs 579
- Brain stimulation therapies **579**
- Clinical effectiveness of antidepressant treatments **580**
- Other clinical uses of antidepressant drugs **581**
- Drug treatment of bipolar depression **581**
 - Lithium 581
 - Antiepileptic drugs 582
 - Atypical antipsychotic drugs 582

47. CNS stimulants and psychotomimetic drugs **584**

- Overview **584**
- Psychomotor stimulants **584**
 - Amphetamines and related drugs 584
 - Cocaine 587
 - Methylxanthines 588
 - Other stimulants 589
- Psychotomimetic drugs **589**
 - LSD, psilocybin and mescaline 589
 - MDMA (ecstasy) 590
 - Ketamine and phencyclidine 590
 - Other psychotomimetic drugs 590

48. Drug addiction, dependence and abuse **592**

- Overview **592**
- Drug use and abuse **592**
 - Drug administration 592
 - Drug harm 592
 - Drug dependence 594
 - Tolerance 595

Pharmacological approaches to treating drug addiction 597

Nicotine and tobacco 597

Pharmacological effects of smoking 598

Pharmacokinetic aspects 599

Tolerance and dependence 599

Harmful effects of smoking 600

Pharmacological approaches to treating nicotine dependence 601

Ethanol 602

Pharmacological effects of ethanol 602

Pharmacokinetic aspects 605

Tolerance and dependence 607

Pharmacological approaches to treating alcohol dependence 607

Section 5: Drugs used for the treatment of infections, cancer and immunological disorders

49. Basic principles of antimicrobial chemotherapy 609

Overview 609

Background 609

The molecular basis of chemotherapy 609

Biochemical reactions as potential targets 610

The formed structures of the cell as potential targets 615

Resistance to antibacterial drugs 617

Genetic determinants of antibiotic resistance 617

Biochemical mechanisms of resistance to antibiotics 618

Current status of antibiotic resistance in bacteria 619

50. Antibacterial drugs 622

Overview 622

Introduction 622

Antimicrobial agents that interfere with folate synthesis or action 622

Sulfonamides 622

Trimethoprim 625

β -Lactam antibiotics 625

Penicillins 625

Cephalosporins and cephamycins 627

Other β -lactam antibiotics 628

Antimicrobial agents affecting bacterial protein synthesis 629

Tetracyclines 629

Amphenicols 630

Aminoglycosides 630

Macrolides 631

Antimicrobial agents affecting topoisomerase 632

Quinolones 632

Miscellaneous and less common antibacterial agents 633

Antimycobacterial agents 634

Drugs used to treat tuberculosis 634

Drugs used to treat leprosy 635

Possible new antibacterial drugs 636

51. Antiviral drugs 638

Overview 638

Background information about viruses 638

An outline of virus structure 638

Examples of pathogenic viruses 638

Virus function and life history 638

The host-virus interaction 639

Host defences against viruses 639

Viral ploys to circumvent host defences 640

HIV and AIDS 640

Antiviral drugs 641

Combination therapy for HIV 646

Prospects for new antiviral drugs 647

52. Antifungal drugs 649

Overview 649

Fungi and fungal infections 649

Drugs used to treat fungal infections 649

Antifungal antibiotics 650

Synthetic antifungal drugs 652

Other antifungal drugs 653

Future developments 653

53. Antiprotozoal drugs 655

Overview 655

Host-parasite interactions 655

Malaria and antimalarial drugs 655

The life cycle of the malaria parasite 656

Antimalarial drugs 658

Potential new antimalarial drugs 663

Amoebiasis and amoebicidal drugs 664

Trypanosomiasis and trypanocidal drugs 664

Other protozoal infections and drugs used to treat them 665

Leishmaniasis 665

Trichomoniasis 666

Giardiasis 666

Toxoplasmosis 666

Pneumocystis 666

Future developments 666

54. Anthelmintic drugs 668

Overview 668

Helminth infections 668

Anthelmintic drugs 669

Resistance to anthelmintic drugs 671

Vaccines and other novel approaches 672

55. Anticancer drugs 673

Overview 673

Introduction 673

The pathogenesis of cancer 673

The genesis of a cancer cell 673

The special characteristics of cancer cells 674

General principles of cytotoxic anticancer drugs 676

Anticancer drugs 677

Alkylating agents and related compounds 678

Antimetabolites 680

Cytotoxic antibiotics 681

Plant derivatives 682

Hormones 682

Hormone antagonists 683

- Monoclonal antibodies 683
- Protein kinase inhibitors 684
- Miscellaneous agents 685
- Resistance to anticancer drugs **686**
- Treatment schedules **686**
- Control of emesis and myelosuppression **686**
- Future developments **687**

Section 6: Special topics

56. Individual variation and drug interaction 689

- Overview **689**
- Introduction **689**
- Factors responsible for quantitative individual variation **689**
 - Ethnicity 689
 - Age 690
 - Pregnancy 691
 - Disease 691
- Idiosyncratic reactions **692**
- Drug interactions **692**
 - Pharmacodynamic interaction 693
 - Pharmacokinetic interaction 693

57. Harmful effects of drugs 698

- Overview **698**
- Introduction **698**
- Classification of adverse drug reactions **698**
 - Adverse effects related to the main pharmacological action of the drug 698
 - Adverse effects unrelated to the main pharmacological action of the drug 699
- Drug toxicity **699**
 - Toxicity testing 699
 - General mechanisms of toxin-induced cell damage and cell death 700
 - Mutagenesis and carcinogenicity 702
 - Teratogenesis and drug-induced fetal damage 704
- Allergic reactions to drugs **707**
 - Immunological mechanisms 707
 - Clinical types of allergic response to drugs 707

58. Lifestyle drugs and drugs in sport 710

- Overview **710**
- What is a lifestyle drug? **710**
- Classification of lifestyle drugs **710**
- Drugs in sport **710**
 - Anabolic steroids 711
 - Human growth hormone 713
 - Stimulant drugs 713
- Conclusion **713**

59. Biopharmaceuticals and gene therapy 715

- Overview **715**
- Introduction **715**
- Biopharmaceuticals **715**
 - Proteins and polypeptides 716
 - Monoclonal antibodies 717
- Gene therapy **718**
 - Gene delivery 718
 - Controlling gene expression 721
- Safety issues **721**
- Therapeutic applications **722**
 - Single-gene defects 722
 - Gene therapy for cancer 722
 - Gene therapy and infectious disease 723
 - Gene therapy and cardiovascular disease 723
 - Other gene-based approaches 723

60. Drug discovery and development 726

- Overview **726**
- The stages of a project **726**
 - The drug discovery phase 726
 - Preclinical development 728
 - Clinical development 728
- Biopharmaceuticals **729**
- Commercial aspects **729**
- Future prospects **729**
- A final word **730**
 - Appendix 731
 - Index 742