

CONTENTS

<i>Preface</i>	iv
<i>Contributors</i>	vi

CHAPTER 1

<i>Introduction</i>	1
----------------------------------	---

John M. Beale, Jr. and John H. Block

CHAPTER 2

<i>Drug Design Strategies</i>	3
--	---

John H. Block

Drug Distribution.....	3
Acid-Base Properties.....	12
Computer-Aided Drug Design: Early Methods... ..	17
Computer-Aided Drug Design: Newer Methods... ..	25
Selected Web Pages.....	40

CHAPTER 3

<i>Metabolic Changes of Drugs and Related Organic Compounds</i>	43
---	----

Stephen J. Cutler and John H. Block

General Pathways of Drug Metabolism.....	43
Sites of Drug Biotransformation.....	45
Role of Cytochrome P450 Monooxygenases in Oxidative Biotransformations.....	45
Oxidative Reactions.....	47
Reductive Reactions.....	78
Hydrolytic Reactions.....	86
Phase II or Conjugation Reactions.....	88
Factors Affecting Drug Metabolism.....	104

CHAPTER 4

<i>Biotechnology and Drug Discovery</i> ..	119
---	-----

John M. Beale, Jr.

Biotechnology and Pharmaceutical Care.....	119
Literature of Biotechnology.....	119
Biotechnology and New Drug Development.....	119
The Biotechnology of Recombinant DNA.....	121
Some Types of Cloning.....	126
Expression of Cloned DNA.....	127
Manipulation of DNA Sequence Information... ..	127
New Biological Targets for Drug Development... ..	128
Novel Drug-Screening Strategies.....	129
Processing of the Recombinant Protein.....	131
Pharmaceuticals of Recombinant DNA-Produced Agents.....	131
Delivery and Pharmacokinetics of Biotechnology Products.....	134
Recombinant Drug Products.....	134
The Interleukins.....	141
Enzymes.....	142
Vaccines.....	145
Preparation of Antibodies.....	146
Genomics.....	150

Antisense Technology.....	152
Gene Therapy.....	153
Afterword.....	153

CHAPTER 5

<i>Immunobiologicals</i>	156
---------------------------------------	-----

John M. Beale, Jr.

Cells of the Immune System.....	156
Immunity.....	159
Acquisition of Immunity.....	165
New Vaccine Technologies: Adjuvant Technology.....	174
New Vaccine Technologies: Nucleic Acid Vaccines.....	177

CHAPTER 6

<i>Anti-infective Agents</i>	179
---	-----

John M. Beale, Jr.

Evaluation of the Effectiveness of a Sterilant... ..	180
Alcohols and Related Compounds.....	181
Phenols and Their Derivatives.....	183
Oxidizing Agents.....	185
Halogen-Containing Compounds.....	185
Cationic Surfactants.....	186
Dyes.....	188
Mercury Compounds (Mercurials).....	189
Preservatives.....	190
Antifungal Agents.....	191
Synthetic Antibacterial Agents.....	206
Antiprotozoal Agents.....	220
Anthelmintics.....	224
Antiscabious and Antipedicular Agents.....	227
Antibacterial Sulfonamides.....	228
Dihydrofolate Reductase Inhibitors.....	239
Sulfones.....	239

CHAPTER 7

<i>Antimalarials</i>	242
-----------------------------------	-----

John H. Block

Stimulation of Antimalarial Research by War... ..	245
Cinchona Alkaloids.....	245

CHAPTER 8

<i>Antibacterial Antibiotics</i>	258
---	-----

John M. Beale, Jr.

Historical Background.....	258
Current Status.....	259
Commercial Production.....	259
Spectrum of Activity.....	259
Mechanisms of Action.....	259
Chemical Classification.....	260
Microbial Resistance.....	260
β -Lactam Antibiotics.....	260

The Penicillins	261	Antipsychotic Drugs	478
β -Lactamase Inhibitors	274	Future Directions	488
Cephalosporins	278		
Monobactams	293	CHAPTER 14	
Aminoglycosides	294	Anticonvulsants	491
Tetracyclines	301	<i>Matthias C. Lu</i>	
Macrolides	308	Disease States Requiring Anticonvulsant Therapy	491
Lincomycins	313	Mechanisms of Action of Anticonvulsants	492
Polypeptides	315	Clinically Important Anticonvulsants	494
Unclassified Antibiotics	320	Future Development of Antiepileptic Drugs	501
Newer Antibiotics	324		
New Directions in Antibiotic Discovery	326		
		CHAPTER 15	
CHAPTER 9		Central Nervous System Stimulants	504
Antiviral Agents	330	<i>John M. Beale, Jr.</i>	
<i>John M. Beale, Jr.</i>		Analeptics	504
The Classification and Biochemistry of Viruses	330	Methylxanthines	505
Classification of Viruses	330	Central Sympathomimetic Agents (Psychomotor Stimulants)	506
Targets for the Prevention of Viral Infections—Chemoprophylaxis	331	Antidepressants	509
The Infectious Process for a Virus	333	Miscellaneous CNS-Acting Drugs	515
Nucleoside Antimetabolites: Inhibiting Viral Replication	339		
Newer Agents for the Treatment of HIV Infection	346	CHAPTER 16	
		Adrenergic Agents	519
CHAPTER 10		<i>Shengquan Liu</i>	
Antineoplastic Agents	355	Adrenergic Neurotransmitters	519
<i>Forrest T. Smith and C. Randall Clark</i>		Adrenergic Receptors	524
Introduction	355	Drugs Affecting Adrenergic Neurotransmission	528
Drug Classes	358	Sympathomimetic Agents	531
Antimetabolites	372	Adrenergic Receptor Antagonists (Blockers)	545
Antibiotics and Natural Products	383	Acknowledgment	554
Protein Kinase Inhibitors	400		
Miscellaneous Compounds	406	CHAPTER 17	
		Cholinergic Drugs and Related Agents	558
CHAPTER 11		<i>Stephen J. Cutler</i>	
Agents for Diagnostic Imaging	413	Cholinergic Receptors	559
<i>Jeffrey J. Christoff</i>		Cholinergic Neurochemistry	563
Radiopharmaceuticals	413	Cholinergic Agonists	564
Contrast Agents	430	Cholinergic Receptor Antagonists	567
		Cholinergic Blocking Agents	581
CHAPTER 12		Parasympathetic Postganglionic Blocking Agents	583
Central Nervous System Depressants	443	Solanaceous Alkaloids and Analogs	584
<i>Shengquan Liu</i>		Synthetic Cholinergic Blocking Agents	588
Anxiolytic, Sedative, and Hypnotic Agents	443	Ganglionic Blocking Agents	596
Antipsychotics	457	Neuromuscular Blocking Agents	599
Acknowledgment	469		
		CHAPTER 18	
CHAPTER 13		Drugs Acting on the Renal System	607
Central Dopaminergic Signaling Agents	471	<i>Stephen J. Cutler</i>	
<i>A. Michael Crider, Marcelo J. Nieto, and Kenneth A. Witt</i>		Renin–Angiotensin System Inhibitors	609
Dopamine	471	ACE-Inhibitor Prodrugs	610
Parkinson Disease	473	Angiotensin Antagonists	612

Angiotensin II Blockers	613
Renin Inhibitors	614
Aldosterone Antagonists	615

CHAPTER 19

Cardiovascular Agents 617*Stephen J. Cutler*

Antianginal Agents and Vasodilators	617
Antiarrhythmic Drugs	629
Antihypertensive Agents	637
Antihyperlipidemic Agents	647
Anticoagulants	654
Synthetic Hypoglycemic Agents	658
Thyroid Hormones	663
Antithyroid Drugs	663

CHAPTER 20

**Hormone-Related Disorders:
Nonsteroidal Therapies 666***Ronald A. Hill*

Disorders of Glucose Metabolism: Diabetes and the Metabolic Syndrome	666
Gonadotropins, Gonadotropin-Releasing Hormone, and GnRH Receptor Agonists and Antagonists	695
Concluding Remarks	701

CHAPTER 21

Agents Treating Bone Disorders 705*John H. Block*

Diseases of Bone Tissue Utilizing Approved Drug Therapies	705
Drugs Used to Treat Diseases of the Bone	706
Hormone Therapy	708
Future Directions	710

CHAPTER 22

Anesthetics 711*Carolyn J. Friel*

The Inhaled General Anesthetics	711
The Injectable General Anesthetics	716
The Local Anesthetics	718
Local Anesthetic Monographs, Individual Products Including Adverse Reactions	725

CHAPTER 23

**Histamine and Antihistaminic
Agents 733***Jack DeRuiter*

Histamine Chemistry	733
Histamine as a Chemical Messenger	733
Antihistamines	737
Inhibition of Histamine Release: Mast Cell Stabilizers	757

Recent Antihistamine Developments: the "Dual-Acting" Antihistamines	759
Histamine H ₂ -Antagonists	760
Histamine H ₃ - and H ₄ -Receptor Ligands	773

CHAPTER 24

Analgesics 776*Carolyn J. Friel and Matthias C. Lu*

Pain and Pain Management	776
Opioids	777
Drug Monographs	782
Nonsteroidal Anti-inflammatory Drugs	792
Disease-Modifying Antirheumatic Drugs	806
Drugs Used in the Management of Gout and Hyperuricemia	809
Triptans	811

CHAPTER 25

**Steroid Hormones and
Therapeutically Related
Compounds 819***Philip J. Proteau*

Steroid Nomenclature, Stereochemistry, and Numbering	819
Steroid Biosynthesis	819
Chemical and Physical Properties of Steroids	822
Changes to Modify Pharmacokinetic Properties of Steroids	822
Steroid Hormone Receptors	823
Gonadotropin-Releasing Hormone and Gonadotropins	826
Sex Hormones	827
Chemical Contraceptive Agents	841
Androgens	847
Adrenal Cortex Hormones	853
Neurosteroids	864
Acknowledgment	864

CHAPTER 26

**Prostaglandins, Leukotrienes,
and Essential Fatty Acids 868***Thomas J. Holmes, Jr.*

Essential Fatty Acids	868
History of Eicosanoid Discovery	868
Eicosanoid Biosynthesis	869
Drug Action Mediated by Eicosanoids	872
COX-2 Inhibitors	872
Design of Eicosanoid Drugs	872
Eicosanoid Receptors	875
Commercially Available Essential Fatty Acid Supplements	875
Eicosanoids Approved for Human Clinical Use	876
Prostaglandins for Ophthalmic Use	878
Veterinary Uses of Prostanoids	878
Eicosanoids in Clinical Development for Human Treatment	879

CHAPTER 27

Proteins, Enzymes, and Peptide Hormones 880

Stephen J. Cutler and Horace G. Cutler

Protein Hydrolysates	880
Amino Acid Solutions	881
Proteins and Proteinlike Compounds.....	881
Enzymes	885
Hormones	890
Blood Proteins	906
Impact of Biotechnology on the Development and Commercial Production of Proteins and Peptides as Pharmaceutical Products	907
Biotechnology-Derived Pharmaceutical Products	909

CHAPTER 28

Vitamins 915

Michael J. Deimling, M. O. Faruk Khan, and Gustavo R. Ortega

Introduction	915
Fat-Soluble Vitamins	917
Water-Soluble Vitamins	935

CHAPTER 29

An Introduction to the Medicinal Chemistry of Herbs..... 961

John M. Beale, Jr.

Historical Aspects	961
What Is an Herb?	962
Herbal Purity and Standardization.....	962
An Herb Is a Drug	962
Types of Herbs	963

APPENDIX

Calculated Log P, Log D, and pK_a .. 976

Index 984