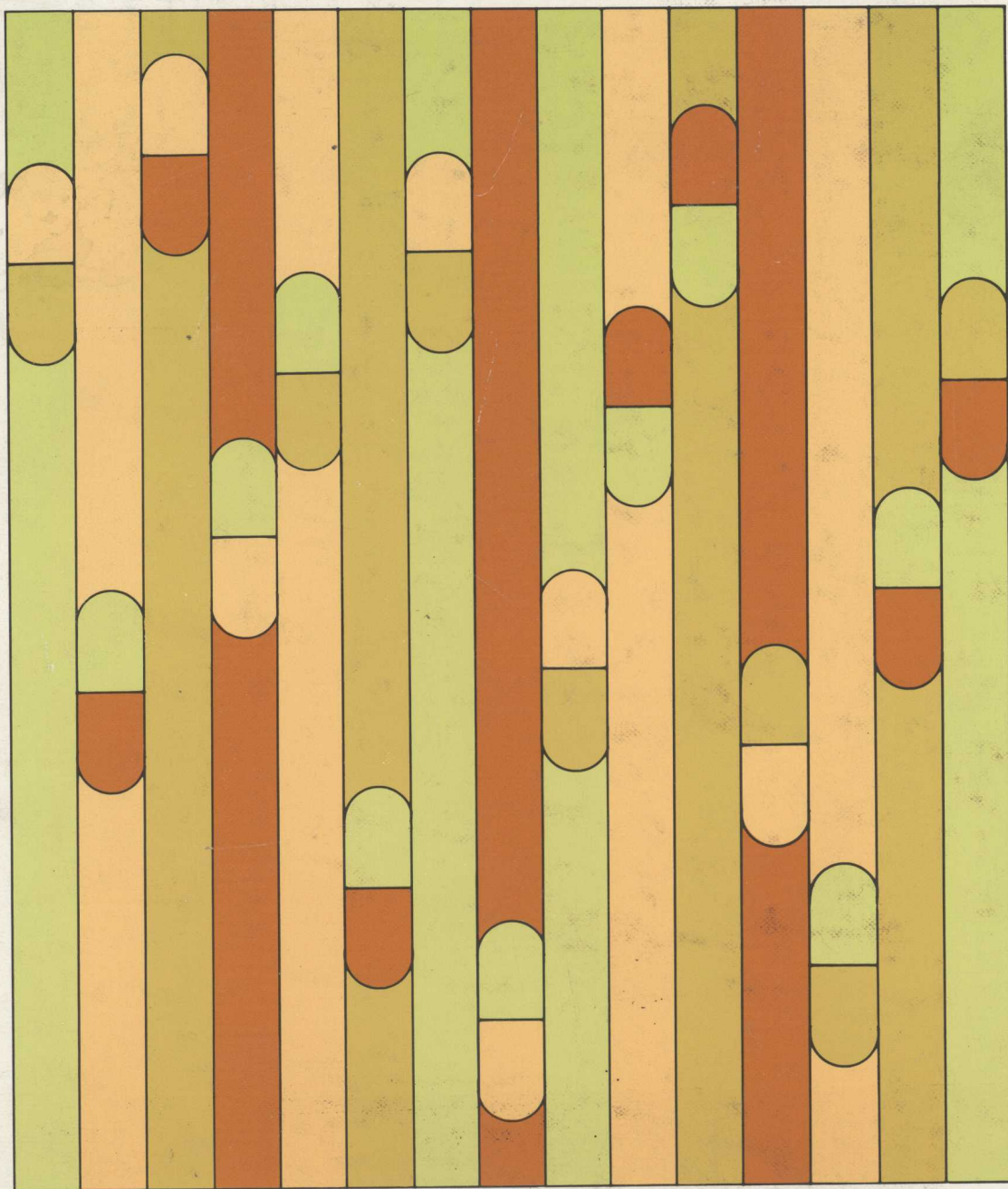


Modern Pharmacology

Charles R. Craig, Ph.D.

Robert E. Stitzel, Ph.D.



MODERN PHARMACOLOGY

EDITED BY

CHARLES R. CRAIG, Ph.D.

Professor of Pharmacology and Toxicology,
West Virginia University School of Medicine,
Morgantown, West Virginia

ROBERT E. STITZEL, Ph.D.

Professor and Associate Chairman, Department of
Pharmacology and Toxicology, West Virginia University
School of Medicine, Morgantown, West Virginia



Little, Brown and Company Boston

Copyright © 1982 by Charles R. Craig
and Robert E. Stitzel

First Edition

Fourth Printing

All rights reserved. No part of this book may be reproduced in any form or by any electronic or mechanical means, including information storage and retrieval systems, without permission in writing from the publisher, except by a reviewer who may quote brief passages in a review.

Library of Congress Catalog Card No. 81-82381

ISBN 0-316-15924-7

Printed in the United States of America

HAL

PREFACE

Modern Pharmacology was conceived as a teaching text, that is, a text written, organized, and edited specifically to fill needs identified by faculty and students in the health sciences. In determining the extent of detail and depth of analysis with which any topic would be treated, the editors have been guided by their conviction that, unlike a reference work or a supplementary manual, a teaching text should simultaneously fulfill two obligations:

1. To focus attention on the underlying principles of the discipline in order to facilitate and encourage a student's subsequent understanding of more specialized topics; and
2. To make easily and clearly accessible the most current and authoritative information on major issues in the field.

In *Modern Pharmacology*, readers will find the discussion of therapeutic agents sufficiently detailed to ensure accuracy and clarity without a counterproductive proliferation of detail. The extensive introductory section on general principles is intended to guarantee that the student's understanding of specific drugs will be grounded in the fundamentals of receptor theory, pharmacokinetics, and toxicology. In addition to the emphasis on general principles in the introductory section and throughout individual chapters, we felt that certain other topics needed to be covered in more detail than is usually the case in textbooks of pharmacology. For example, we have found that the role played by α and β adrenoceptors, both in normal autonomic regulation and following modulation by sympathetic agonists and antagonists, often involves concepts that initially are difficult for stu-

dents to grasp. We have, therefore, discussed these receptors from a number of viewpoints in different chapters within Parts II (Drugs Affecting the Autonomic Nervous System) and III (Cardiovascular Drugs). The functioning of receptors in normal sympathetic nervous system control is covered in Chapter 9 (Introduction to the Autonomic Nervous System); their activation by drugs is discussed in Chapter 11 (Sympathomimetic Drugs); their blockade is examined in Chapter 12 (Adrenoceptor Antagonists); and, finally, their modification by antihypertensive agents is thoroughly analyzed and summarized in Chapter 23 (Pharmacological Treatment of Hypertension). We feel that such reemphasis, especially when placed in the conceptual framework of physiological and pharmacological control and intervention will allow the student to fully comprehend the importance of these receptors in the clinical management of disease. Furthermore, the underlying mechanisms responsible for the appearance of certain side effects (e.g., orthostatic hypotension, gastrointestinal hypermotility and hypomotility, augmented salivary and pulmonary secretion, etc.) will be appreciated more easily.

Other areas that we believe have not received sufficient discussion in other texts include antiarrhythmic agents, antihypertensive drugs, contemporary drug abuse, antiasthmatic drugs, topical drug use, antirheumatic and antiinflammatory compounds, the principles underlying cancer chemotherapy, and new methods of drug delivery. These areas have been singled out for comprehensive discussion either in expanded chapters (Chapter 18, Pharmacology of Antiarrhythmic Drugs; Chapter 23, Pharmacological Treatment of Hypertension; Chapter 42, Contemporary Drug Abuse; Chapter 56, The Rational Basis for Cancer Chemotherapy) or in separate chapters that have unified material that other texts have discussed only briefly in disparate chapters (Chapter 6, Bioavailability, Dosage Regimens, and New Delivery Systems; Chapter 69, Pharmacological Control of Asthma; Chapter 70, Antiinflammatory and Antirheumatic Agents; Chapter 71, Drugs Used in

Dermatological Disorders). The latter approach is especially well illustrated in Chapter 71, which begins with a description of normal skin anatomy and physiology, progresses to the general principles of percutaneous drug transport, analyzes the utility of local versus systemic therapy, and then discusses the specific topical applications of previously mentioned classes of therapeutic agents. Chapters developed in this way provide an emphasis and focus not often evident in more general discussions of pharmacological activity.

In writing this textbook we have been guided by our view, which is consistent with that of other faculty in the United States as well as in other countries (most recently expressed at The Teaching and Learning in Pharmacology Symposium at the 1981 Eighth International Congress of Pharmacology in Tokyo), that there was still a need for a textbook of pharmacology, in addition to those currently available. Many teachers of pharmacology felt that such a book must avoid two pitfalls. It must not be so detailed that students are overwhelmed by the volume of material to be mastered, and it must not be so brief and simplistic that students are deprived of the fundamental background material (e.g., general principles and reviews of appropriate basic physiology) necessary for a broad understanding of drug therapy.

The contributors to *Modern Pharmacology* were chosen for their ability to balance the need for brevity, clarity, and accuracy without sacrificing essential depth. In general, each chapter has been written by individuals who teach and do research in the areas they have written about. In addition, each chapter has been reviewed and evaluated for completeness and relevance by other prominent authorities on that particular topic.

We hope that both faculty and students find that we have achieved our goals and that this book is an aid in learning about drugs currently available and in providing the background for the evaluation of compounds yet to be discovered.

C. R. C.
R. E. S.

ACKNOWLEDGMENTS

Acknowledgment is due to a variety of professional colleagues—pharmacologists and clinicians—for the review of various sections of this manuscript. We are especially indebted to the thoughtful and thorough reviews of Drs. Thomas Bithell, Howard Colby, Alan Goldberg, Scott Goodnight, Desmond Gourley, Edward Keenan, Eva Killam, Keith Killam, Ronica Kluge, Ruth Levine, Robert Mueller, Arthur Raines, Mark Reasor, Charles Rutledge, Radhey Singhal, Carol Smith, Lester Soyka, Frank Standaert, A. E. Takemori, Ralph Tanz, Irma Ullrich, and Ben Zimmerman. Their comments were timely and helpful. It should be borne in mind, however, that if inaccuracies remain, they are due to editorial oversight and not to reviewer error.

In addition to the above individuals we would like to thank our resident grammarian, Dr. Judith Stitzel; our medical illustration department, including Virginia S. Swecker, Marianne Peterson, and Barbara Gould; our library assistant, David L. Stitzel; and past and present members of our efficient and hardworking office staff, Louise Shepherd, Debra Dorinzi, Cheryl Zambito, Ellen Teicheira, Virginia Dwire, Pamela Giuliani, Hazel Fedro, and Thomas McBee. Lastly, we acknowledge the contributions of our wives, Margaret Craig and Judith Stitzel, who supported our efforts throughout the three years of this project.

CONTRIBUTING AUTHORS

JOHN U. BELL, Ph.D.
Associate Professor of Preventive Medicine, College of
Veterinary Medicine, University of Florida, Gainesville, Florida

ROBERT J. BORGMAN, Ph.D.
Research Scientist, Solutions Technology, Hospital Products
Division, Abbott Laboratories, North Chicago, Illinois

RICHARD J. CENEDELLA, Ph.D.
Professor and Chairman, Department of Biochemistry,
Kirksville College of Osteopathic Medicine, Kirksville, Missouri

BRENDA K. COLASANTI, Ph.D.
Professor of Ophthalmology and Pharmacology and Toxicology,
West Virginia University School of Medicine, Morgantown,
West Virginia

JOHN M. CONNORS, Ph.D.
Research Assistant Professor of Physiology, West Virginia
University School of Medicine, Morgantown, West Virginia

CHARLES R. CRAIG, Ph.D.
Professor of Pharmacology and Toxicology, West Virginia
University School of Medicine, Morgantown, West Virginia

BARBARA FARRELL, M.D.
Physician, Department of Neurology, Geissinger Medical
Center, Danville, Pennsylvania

JEFFREY S. FEDAN, Ph.D.
Adjunct Assistant Professor of Pharmacology and Toxicology,
West Virginia University School of Medicine; Research
Pharmacologist, Appalachian Laboratory for Occupational
Safety and Health, Morgantown, West Virginia

ROGER G. FINCH, M.B., Ch.B., M.R.C.P. (U.K.), M.R.C. Path.
Senior Lecturer in Microbial Diseases, Nottingham University
Medical School; Consultant in Microbial Diseases, the City
Hospital, Nottingham, England

NANCY A. FISHER, M.D., Ph.D.
Resident, Department of Anesthesiology, University of Virginia
School of Medicine, Charlottesville, Virginia

WILLIAM W. FLEMING, Ph.D.
Professor and Chairman, Department of Pharmacology and
Toxicology, West Virginia University School of Medicine,
Morgantown, West Virginia

JOHN K. GIBSON, Ph.D.
Research Scientist, Cardiovascular Disease Research, The
Upjohn Company, Kalamazoo, Michigan

THEODORE E. GRAM, Ph.D.
Head, Drug Interaction Section, Laboratory of Medicinal
Chemistry and Biology, National Institutes of Health, Bethesda,
Maryland

GARRETT J. GROSS, Ph.D.
Professor of Pharmacology and Toxicology, The Medical
College of Wisconsin, Milwaukee, Wisconsin

ANTHONY M. GUARINO, Ph.D.
Review Scientist, Bureau of Drugs, Food and Drug
Administration, Rockville, Maryland

DONALD B. HOOVER, Ph.D.
Assistant Professor of Pharmacology, East Tennessee State
University College of Medicine, Johnson City, Tennessee

MICHAEL B. HOWIE, M.D.
Associate Professor of Anesthesiology and Director of
Cardiovascular Anesthesia, The Ohio State University College
of Medicine and University Hospitals, Columbus, Ohio

JAMES M. IRISH III, Ph.D.
Assistant Professor of Physiology, West Virginia University
School of Medicine, Morgantown, West Virginia

EDWARD J. KEENAN, Ph.D.
Assistant Professor of Surgery and Pharmacology, University of
Oregon School of Medicine, Portland, Oregon

ROLAND L. KENNEDY, M.D.
Professor and Director of Obstetrical Anesthesia, West Virginia
University School of Medicine, Morgantown, West Virginia

RICHARD B. KNAPP, M.D.
Professor and Chairman, Department of Anesthesiology, West
Virginia University School of Medicine, Morgantown, West
Virginia

DONALD C. KVAM, Ph.D.
Manager of Clinical Pharmacology, Riker Laboratories, 3M
Company, Inc., St. Paul, Minnesota

BENEDICT R. LUCCHESI, Ph.D., M.D.
Professor of Pharmacology and Director, The Upjohn Center for
Clinical Pharmacology, The University of Michigan Medical
School, Ann Arbor, Michigan

MICHAEL G. MAWHINNEY, Ph.D.
Professor of Pharmacology and Toxicology and Urology, West
Virginia University School of Medicine, Morgantown, West
Virginia

JOSEPH J. McPHILLIPS, Ph.D.
Associate Director, Division of Scientific Affairs, G. D. Searle
and Company, Chicago, Illinois

EUGENE S. PATTERSON, Ph.D.
Postdoctoral Fellow, The University of Michigan Medical
School, Ann Arbor, Michigan

MICHAEL J. PEACH, Ph.D.
Professor of Pharmacology, University of Virginia School of
Medicine, Charlottesville, Virginia

ROBERT L. ROBINSON, Ph.D.
Professor of Pharmacology and Toxicology, West Virginia
University School of Medicine, Morgantown, West Virginia

RONALD P. RUBIN, Ph.D.
Professor of Pharmacology and Chief,
Autonomic-Cardiovascular Division, Medical College of
Virginia, Richmond, Virginia

FRANK L. SCHWARTZ, M.D.
Instructor, Department of Surgery, West Virginia University
School of Medicine; Staff Physician, Department of Surgery,
West Virginia University Hospital, Morgantown, West Virginia

ZAHID H. SIDDIK, Ph.D.
Research Associate, Department of Biochemical Pharmacology,
Institute for Cancer Research, Sutton, Surrey, England

BRANIMIR I. SIKIC, M.D.
Assistant Professor of Medicine, Divisions of Oncology and
Clinical Pharmacology, Stanford University School of Medicine,
Stanford, California

DAVID J. SMITH, Ph.D.
Professor of Anesthesiology and Pharmacology and Toxicology,
West Virginia University School of Medicine, Morgantown,
West Virginia

IRVIN S. SNYDER, Ph.D.
Professor and Chairman, Department of Microbiology, West
Virginia University School of Medicine, Morgantown, West
Virginia

ROBERT E. STITZEL, Ph.D.
Professor and Associate Chairman, Department of
Pharmacology and Toxicology, West Virginia University School
of Medicine, Morgantown, West Virginia

MARGARET SUMNER, Ph.D.
Lecturer, Department of Anatomy and Embryology, University
College London, London, England

KARL F. SWINGLE, Ph.D.
Senior Research Specialist (Pharmacology), Riker Laboratories,
3M Company, Inc., St. Paul, Minnesota

RALPH D. TANZ, Ph.D.
Professor of Pharmacology, School of Medicine,
University of Oregon School of Medicine, Portland, Oregon

JOHN A. THOMAS, Ph.D.
Professor of Pharmacology and Toxicology, West Virginia
University School of Medicine, Morgantown, West Virginia

RONALD J. TRANCIK, Ph.D.
Clinical Projects Manager (Skin Care), Riker Laboratories, 3M
Company, Inc., St. Paul, Minnesota

MICHAEL A. TRUSH, Ph.D.
Pharmacologist, Drug Interaction Section, Laboratory of
Medicinal Chemistry and Biology, National Institutes of Health,
Bethesda, Maryland

PEDRO R. URQUILLA, M.D.
Associate Director, Department of Clinical Research, Pfizer
Central Research, Pfizer, Inc., Groton, Connecticut

KNOX VAN DYKE, Ph.D.
Professor of Pharmacology and Toxicology, West Virginia
University School of Medicine, Morgantown, West Virginia

WILLIAM M. WARDELL, M.D., Ph.D.
Associate Professor of Pharmacology and Toxicology, Assistant
Professor of Medicine, The University of Rochester School of

Medicine and Dentistry; Associate Physician, Strong Memorial
Hospital, Rochester, New York

DAVID P. WESTFALL, Ph.D.
Professor of Pharmacology and Toxicology, West Virginia
University School of Medicine, Morgantown, West Virginia

THOMAS C. WESTFALL, Ph.D.
Professor and Chairman, Department of Pharmacology, Saint
Louis University School of Medicine, Saint Louis, Missouri

FRANK G. ZAVISCA, M.D., Ph.D.
Assistant Professor of Anesthesiology, West Virginia University
School of Medicine, Morgantown, West Virginia

MODERN PHARMACOLOGY

NOTICE

The indications and dosages of all drugs in this book have been recommended in the medical literature and conform to the practices of the general medical community. The medications described do not necessarily have specific approval by the Food and Drug Administration for use in the diseases and dosages for which they are recommended. The package insert for each drug should be consulted for use and dosage as approved by the FDA. Because standards for usage change, it is advisable to keep abreast of revised recommendations, particularly those concerning new drugs.

CONTENTS

PREFACE ix

ACKNOWLEDGMENTS xi

CONTRIBUTING AUTHORS xiii

I. GENERAL PRINCIPLES OF PHARMACOLOGY

1. DEVELOPMENT OF PHARMACOLOGICAL THOUGHT 3
Robert E. Stitzel
2. MECHANISMS OF DRUG ACTION 9
William W. Fleming
3. DRUG ABSORPTION AND DISTRIBUTION 20
Zahid H. Siddik, Michael A. Trush,
and Theodore E. Gram
4. METABOLISM OF DRUGS 37
Theodore E. Gram
5. EXCRETION OF DRUGS 55
Robert E. Stitzel
6. BIOAVAILABILITY, DOSAGE REGIMENS, AND NEW
DELIVERY SYSTEMS 63
Robert J. Borgman
7. DRUG TESTING IN HUMANS 75
William M. Wardell
8. BASIC PRINCIPLES OF TOXICOLOGY 81
Anthony M. Guarino

II. DRUGS AFFECTING THE AUTONOMIC NERVOUS SYSTEM

9. INTRODUCTION TO THE AUTONOMIC NERVOUS
SYSTEM 99
Robert L. Robinson
10. ADRENERGIC AND CHOLINERGIC
NEUROTRANSMISSION 113
William W. Fleming
11. SYMPATHOMIMETIC DRUGS 123
Robert L. Robinson

12. ADRENOCEPTOR ANTAGONISTS 141
David P. Westfall

13. PARASYMPATHOMIMETIC DRUGS 157
Brenda K. Colasanti

14. CHOLINESTERASES AND CHOLINESTERASE
INHIBITORS 165
Donald B. Hoover

15. MUSCARINIC BLOCKING DRUGS 179
Donald B. Hoover

16. GANGLIONIC NICOTINIC BLOCKING AGENTS 193
Thomas C. Westfall

17. NEUROMUSCULAR BLOCKING AGENTS AND
ANTISPASTICITY DRUGS 203
Nancy A. Fisher and Thomas C. Westfall

III. CARDIOVASCULAR DRUGS

18. PHARMACOLOGY OF ANTIARRHYTHMIC DRUGS 217
Benedict R. Lucchesi, John K. Gibson,
and Eugene Patterson

19. CARDIAC GLYCOSIDES 269
Ralph D. Tanz and Pedro R. Urquilla

20. ANTIANGINAL DRUGS 283
Garrett J. Gross and Pedro R. Urquilla

21. CHOLESTEROL AND HYPOCHOLESTEROLEMIC
DRUGS 295
Richard J. Cenedella

22. WATER, ELECTROLYTE METABOLISM, AND DIURETIC
AGENTS 309
Robert E. Stitzel and James M. Irish III

23. PHARMACOLOGICAL TREATMENT OF
HYPERTENSION 337
David P. Westfall

24. VASOACTIVE SUBSTANCES, I: RENIN, ANGIOTENSIN,
AND KININS 369
Michael J. Peach

25. VASOACTIVE SUBSTANCES, II: METABOLITES OF
ARACHIDONIC ACID, SEROTONIN,
AND SUBSTANCE P 383
Robert E. Stitzel and Brenda K. Colasanti

26. ANTICOAGULANT, ANTIPLATELET, AND FIBRINOLYTIC
(THROMBOLYTIC) DRUGS 395
Jeffrey S. Fedan

IV. CENTRAL NERVOUS SYSTEM DRUGS

27. INTRODUCTION TO NEUROPHARMACOLOGY 413
Charles R. Craig

28. UPTAKE, DISTRIBUTION, AND ELIMINATION OF
INHALATIONAL ANESTHETIC AGENTS 419
David J. Smith and Richard B. Knapp

29. GENERAL ANESTHETICS: GASES AND VOLATILE
LIQUIDS 429
Frank G. Zavisca

30. GENERAL ANESTHETICS: INTRAVENOUS AGENTS 441
Michael B. Howie and David J. Smith

31. LOCAL ANESTHETICS 453
Roland L. Kennedy and Richard B. Knapp

32. CENTRAL NERVOUS SYSTEM STIMULANTS 463
Charles R. Craig

33. CENTRAL NERVOUS SYSTEM DEPRESSANTS 473
Charles R. Craig

34. ETHANOL AND OTHER ALIPHATIC ALCOHOLS 485
Charles R. Craig

35. ANTIANXIETY DRUGS 493
Brenda K. Colasanti

36. ANTIPSYCHOTIC DRUGS 503
Brenda K. Colasanti

37. ANTIDEPRESSANT THERAPY 517
Brenda K. Colasanti

38. PHARMACOLOGICAL TREATMENT OF CONVULSIVE
DISORDERS 529
Charles R. Craig

39. DRUG THERAPY IN PARKINSONISM AND OTHER BASAL
GANGLIA DISORDERS 543
Charles R. Craig and Barbara Farrell

40. NONNARCOTIC ANALGESICS AND ANTIPYRETICS 553
Brenda K. Colasanti

41. NARCOTIC ANALGESICS AND ANTAGONISTS 563
Brenda K. Colasanti

42. CONTEMPORARY DRUG ABUSE 581
Brenda K. Colasanti

V. CHEMOTHERAPY

43. BASIC CONCEPTS OF CHEMOTHERAPY 603
Irvin S. Snyder and Roger G. Finch

- 44. SYNTHETIC ORGANIC ANTIMICROBIALS 613
Roger G. Finch and Irvin S. Snyder
- 45. PENICILLINS AND CEPHALOSPORINS 625
Irvin S. Snyder and Roger G. Finch
- 46. THE AMINOCYCLITOL ANTIBIOTICS 645
Roger G. Finch and Irvin S. Snyder
- 47. TETRACYCLINES, CHLORAMPHENICOL,
ERYTHROMYCIN, AND CLINDAMYCIN 653
Irvin S. Snyder and Roger G. Finch
- 48. BACITRACIN, VANCOMYCIN, AND THE
POLYMYXINS 663
Roger G. Finch and Irvin S. Snyder
- 49. DRUGS USED IN THE TREATMENT OF
MYCOBACTERIAL INFECTIONS 669
Irvin S. Snyder and Roger G. Finch
- 50. ANTIVIRAL DRUGS 683
Knox Van Dyke
- 51. ANTIPROTOZOAL DRUGS 691
Roger G. Finch and Irvin S. Snyder
- 52. ANTIMALARIAL DRUGS 703
Knox Van Dyke
- 53. ANTHELMINTIC DRUGS 715
Irvin S. Snyder and Roger G. Finch
- 54. ANTIFUNGAL DRUGS 727
Roger G. Finch and Irvin S. Snyder
- 55. ANTISEPTICS, DISINFECTANTS, AND
STERILIZATION 737
Irvin S. Snyder and Roger G. Finch
- 56. THE RATIONAL BASIS FOR CANCER
CHEMOTHERAPY 745
Branimir I. Sikic
- 57. ANTINEOPLASTIC AGENTS 757
Branimir I. Sikic

VI. DRUGS AFFECTING THE ENDOCRINE SYSTEM

- 58. INTRODUCTION TO ENDOCRINE PHARMACOLOGY 793
John A. Thomas

- 59. HORMONES OF THE HYPOTHALAMUS AND PITUITARY
GLAND 799
Edward J. Keenan
- 60. ADRENOCORTICAL HORMONES AND DRUGS
AFFECTING THE ADRENAL CORTEX 809
Ronald P. Rubin
- 61. ESTROGENS, PROGESTAGENS, ORAL CONTRACEPTIVES,
AND OVULATORY AGENTS 825
John A. Thomas
- 62. ANDROGENS AND ANABOLIC STEROIDS 841
Frank L. Schwartz and Michael G. Mawhinney
- 63. THYROID AND ANTITHYROID DRUGS 859
John M. Connors and John A. Thomas
- 64. PARATHYROID HORMONE, CALCITONIN, AND
VITAMIN D 873
Frank L. Schwartz
- 65. INSULIN AND ORALLY EFFECTIVE HYPOGLYCEMIC
DRUGS 887
John A. Thomas

VII. ADDITIONAL IMPORTANT DRUGS

- 66. DRUGS THAT ACT ON THE GASTROINTESTINAL
TRACT 903
Margaret Sumner
 - 67. HISTAMINE AND ANTIHISTAMINES 917
Knox Van Dyke
 - 68. DRUGS USED IN THE TREATMENT OF GOUT 929
Knox Van Dyke
 - 69. PHARMACOLOGICAL CONTROL OF ASTHMA 937
Joseph J. McPhillips
 - 70. ANTIINFLAMMATORY AND ANTIRHEUMATIC
AGENTS 951
Karl F. Swingle and Donald C. Kvam
 - 71. DRUGS USED IN DERMATOLOGICAL DISORDERS 969
Karl F. Swingle and Ronald J. Trancik
 - 72. VITAMINS 985
Margaret Sumner
- INDEX 995

PART I

**GENERAL PRINCIPLES
OF PHARMACOLOGY**

1. 1000 1000 1000
2. 1000 1000 1000

DEVELOPMENT OF PHARMACOLOGICAL THOUGHT

ROBERT E. STITZEL

To understand a science, one has to know its history and development. It should be useful, then, and we hope entertaining, for students to understand the background and underlying assumptions of *pharmacology*, a discipline which defines itself in simple yet all-encompassing terms: the study of the interaction of chemicals with biological systems.

One of the earliest concerns of mankind was a desire for protection against the evils of disease and suffering. Since the conquering of these afflictions often determined survival and since the current state of knowledge did not permit the rational use of *drugs* (chemical entities, both endogenous and foreign, that are capable of reacting with biological systems), it should not be surprising that additional help was sought from supernatural powers. This was especially true of the ancient Greeks who believed that it was by whim that the gods dispensed prosperity or pestilence. Thus, early in human history a natural bond was formed between religion and the use of drugs. Those who became most proficient in the use of drugs to treat disease were the “mediators” between this world and the spirit world, namely, the priests, shamans, holy persons, witches, and soothsayers. Much of their power within the community was derived from the cures that they could effect with drugs. Clearly then, these individuals were simultaneously the first physicians and the first pharmacologists.

Originally, religion dominated its partnership with *therapeutics* (the application of chemical sub-