

1021889

25330

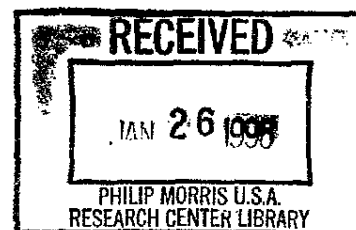
RM

101

B6.

# GOODMAN & GILMAN'S The PHARMACOLOGICAL BASIS OF THERAPEUTICS

Ninth Edition



McGraw-Hill  
HEALTH PROFESSIONS DIVISION

New York St. Louis San Francisco Auckland Bogotá Caracas Lisbon London Madrid  
Mexico City Milan Montreal New Delhi San Juan Singapore Sydney Tokyo Toronto

2063642305

EDITORS-IN-CHIEF

Joel G. Hardman, Ph.D.

Professor of Pharmacology  
Associate Vice-Chancellor for Health Affairs  
Vanderbilt University School of Medicine  
Nashville, Tennessee

Lee E. Limbird, Ph.D.

Professor and Chair  
Department of Pharmacology  
Vanderbilt University School of Medicine  
Nashville, Tennessee

EDITORS

Perry B. Molinoff, M.D.

A. N. Richards Professor and Chairman  
Department of Pharmacology  
University of Pennsylvania School of Medicine  
Philadelphia, Pennsylvania

Current Position:  
Vice-President, CNS Drug Discovery  
Bristol-Myers Squibb  
Wallingford, Connecticut

Raymond W. Ruddon, M.D., Ph.D.

Eppley Professor of Oncology  
Director, Eppley Cancer Center  
University of Nebraska Medical Center  
Omaha, Nebraska

CONSULTING EDITOR

Alfred Goodman Gilman, M.D., Ph.D., D.Sc. (Hon.)

Raymond and Ellen Willie Professor of Molecular Neuropharmacology  
Regental Professor and Chairman, Department of Pharmacology  
University of Texas Southwestern Medical Center  
Dallas, Texas

ILLUSTRATIONS BY EDNA KUNKEL.

2063642306

**McGraw-Hill**

A Division of The McGraw-Hill Companies



Goodman and Gilman's THE PHARMACOLOGICAL BASIS OF THERAPEUTICS. 9/e

Copyright © 1996, 1990, 1985, 1980, 1975, 1970, 1965, 1955, 1941 by *The McGraw-Hill Companies, Inc.* All rights reserved. Printed in the United States of America. Except as permitted under the United States Copyright Act of 1976, no part of this publication may be reproduced or distributed in any form or by any means, or stored in a data base or retrieval system, without the prior written permission of the publisher.

1234567890 DOWDOW 98765

ISBN 0-07-026266-7

This book was set in Times Roman by York Graphic Services, Inc. The editors were Martin J. Wonsiewicz and Peter McCurdy; the production supervisors were Robert Laffler and Clare Stanley, and the cover designer was Marsha Cohen/Parallelogram. The index was prepared by Irving Condé Tullar.

R.R. Donnelley and Sons Company was printer and binder.

This book is printed on acid-free paper.

**Library of Congress Cataloging-in-Publication Data**

Goodman & Gilman's *The Pharmacological Basis of Therapeutics*. —9th ed. / Joel G. Hardman, Alfred Goodman Gilman, Lee E. Limbird.

p. cm.

Includes bibliographical references and index.

ISBN 0-07-026266-7 (hardcover)

I. Pharmacology. 2. Chemotherapy. I. Goodman, Louis Sanford. II. Gilman, Alfred. III. Hardman, Joel G. IV. Gilman, Alfred Goodman. V. Limbird, Lee E.

[DNLM: 1. Pharmacology. 2. Drug Therapy. QV 4 G6532 1995]

RM300.G644 1995

615'.7—dc20

DNLM/DLC

for Library of Congress

95-36658

2063642307

# Contents

Contributors	xiii
Consultants to the Editors	xvii
Preface	xix
Preface to the First Edition	xxi

## SECTION I

### GENERAL PRINCIPLES

<b>Introduction</b>	1
<i>Leslie Z. Benet</i>	
<b>1. Pharmacokinetics: The Dynamics of Drug Absorption, Distribution, and Elimination</b>	3
<i>Leslie Z. Benet, Deanna L. Kroetz, and Lewis B. Sheiner</i>	
<b>2. Pharmacodynamics: Mechanisms of Drug Action and the Relationship Between Drug Concentration and Effect</b>	29
<i>Elliott M. Ross</i>	
<b>3. Principles of Therapeutics</b>	43
<i>Alan S. Nies and Stephen P. Spielberg</i>	
<b>4. Principles of Toxicology and Treatment of Poisoning</b>	63
<i>Curtis D. Klaassen</i>	
<b>5. Gene-Based Therapy</b>	77
<i>Stephen L. Eck and James M. Wilson</i>	

## SECTION II

### DRUGS ACTING AT SYNAPTIC AND NEUROEFFECTOR JUNCTIONAL SITES

<b>6. Neurotransmission: The Autonomic and Somatic Motor Nervous Systems</b>	103
<i>Brian B. Hoffman, Robert J. Lefkowitz, and Palmer Taylor</i>	105

2063642308

<b>7. Muscarinic Receptor Agonists and Antagonists</b>	141
<i>Joan Heller Brown and Palmer Taylor</i>	
<b>8. Anticholinesterase Agents</b>	161
<i>Palmer Taylor</i>	
<b>9. Agents Acting at the Neuromuscular Junction and Autonomic Ganglia</b>	177
<i>Palmer Taylor</i>	
<b>10. Catecholamines, Sympathomimetic Drugs, and Adrenergic Receptor Antagonists</b>	199
<i>Brian B. Hoffman and Robert J. Lefkowitz</i>	
<b>11. 5-Hydroxytryptamine (Serotonin) Receptor Agonists and Antagonists</b>	249
<i>Elaine Sanders-Bush and Steven E. Mayer</i>	

## SECTION III

**DRUGS ACTING ON THE CENTRAL NERVOUS SYSTEM** 265

<b>12. Neurotransmission and the Central Nervous System</b>	267
<i>Floyd E. Bloom</i>	
<b>13. History and Principles of Anesthesiology</b>	295
<i>Sean K. Kennedy and David E. Longnecker</i>	
<b>14. General Anesthetics</b>	307
<i>Bryan E. Marshall and David E. Longnecker</i>	
<b>15. Local Anesthetics</b>	331
<i>William A. Catterall and Kenneth Mackie</i>	
<b>16. Therapeutic Gases</b>	349
<i>Roderic G. Eckenhoff and David E. Longnecker</i>	
<b>17. Hypnotics and Sedatives; Ethanol</b>	361
<i>William R. Hobbs, Theodore W. Rall, and Todd A. Verdoorn</i>	
<b>18. Drugs and the Treatment of Psychiatric Disorders: Psychosis and Anxiety</b>	399
<i>Ross J. Baldessarini</i>	
<b>19. Drugs and the Treatment of Psychiatric Disorders: Depression and Mania</b>	431
<i>Ross J. Baldessarini</i>	
<b>20. Drugs Effective in the Therapy of the Epilepsies</b>	461
<i>James O. McNamara</i>	

- 21. Drugs Effective in the Therapy of Migraine** 487  
*Stephen J. Peroutka*
- 22. Treatment of Central Nervous System Degenerative Disorders** 503  
*David G. Standaert and Anne B. Young*
- 23. Opioid Analgesics and Antagonists** 521  
*Terry Reisine and Gavril Pasternak*
- 24. Drug Addiction and Drug Abuse** 557  
*Charles P. O'Brien*

## SECTION IV

**AUTACOIDS; DRUG THERAPY OF INFLAMMATION** 579

- Introduction** 579  
*William E. Serafin and Kenneth S. Babe, Jr.*
- 25. Histamine, Bradykinin and Their Antagonists** 581  
*Kenneth S. Babe, Jr., and William E. Serafin*
- 26. Lipid-Derived Autacoids: Eicosanoids and Platelet-Activating Factor** 601  
*William B. Campbell and Perry V. Halushka*
- 27. Analgesic-Antipyretic and Antiinflammatory Agents and Drugs Employed in the Treatment of Gout** 617  
*Paul A. Insel*
- 28. Drugs Used in the Treatment of Asthma** 659  
*William E. Serafin*

## SECTION V

**DRUGS AFFECTING RENAL AND CARDIOVASCULAR FUNCTION** 683

- 29. Diuretics** 685  
*Edwin K. Jackson*
- 30. Vasopressin and Other Agents Affecting the Renal Conservation of Water** 715  
*Edwin K. Jackson*
- 31. Renin and Angiotensin** 733  
*Edwin K. Jackson and James C. Garrison*

2063642310

<b>32. Drugs Used for the Treatment of Myocardial Ischemia</b>	759
<i>Rose Marie Robertson and David Robertson</i>	
<b>33. Antihypertensive Agents and the Drug Therapy of Hypertension</b>	781
<i>John A. Oates</i>	
<b>34. Pharmacological Treatment of Heart Failure</b>	809
<i>Ralph A. Kelly and Thomas W. Smith</i>	
<b>35. Antiarrhythmic Drugs</b>	839
<i>Dan M. Roden</i>	
<b>36. Drugs Used in the Treatment of Hyperlipoproteinemias</b>	875
<i>Joseph L. Witztum</i>	
 <b>S E C T I O N V I</b>  	
<b>DRUGS AFFECTING GASTROINTESTINAL FUNCTION</b>	899
<b>37. Agents for Control of Gastric Acidity and Treatment of Peptic Ulcers</b>	901
<i>Laurence L. Brunton</i>	
<b>38. Agents Affecting Gastrointestinal Water Flux and Motility; Emesis and Antiemetics; Bile Acids and Pancreatic Enzymes</b>	917
<i>Laurence L. Brunton</i>	
 <b>S E C T I O N V I I</b>  	
<b>DRUGS AFFECTING UTERINE MOTILITY</b>	937
<b>39. Agents That Cause Contraction or Relaxation of the Uterus</b>	939
<i>Cornelia R. Graves</i>	
 <b>S E C T I O N V I I I</b>  	
<b>CHEMOTHERAPY OF PARASITIC INFECTIONS</b>	955
<b>Introduction</b>	955
<i>James W. Tracy and Leslie T. Webster, Jr.</i>	
<b>40. Drugs Used in the Chemotherapy of Protozoal Infections: Malaria</b>	965
<i>James W. Tracy and Leslie T. Webster, Jr.</i>	

<b>41. Drugs Used in the Chemotherapy of Protozoal Infections: Trypanosomiasis, Leishmaniasis, Amebiasis, Giardiasis, Trichomoniasis, and Other Protozoal Infections</b>	987
<i>James W. Tracy and Leslie T. Webster, Jr.</i>	
<b>42. Drugs Used in the Chemotherapy of Helminthiasis</b>	1009
<i>James W. Tracy and Leslie T. Webster, Jr.</i>	
<b>S E C T I O N I X</b>	
<b>CHEMOTHERAPY OF MICROBIAL DISEASES</b>	1027
<b>43. Antimicrobial Agents: General Considerations</b>	1029
<i>Henry F. Chambers and Merle A. Sande</i>	
<b>44. Antimicrobial Agents: Sulfonamides, Trimethoprim-Sulfamethoxazole, Quinolones, and Agents for Urinary Tract Infections</b>	1057
<i>Gerald L. Mandell and William A. Petri, Jr.</i>	
<b>45. Antimicrobial Agents: Penicillins, Cephalosporins, and Other <math>\beta</math>-Lactam Antibiotics</b>	1073
<i>Gerald L. Mandell and William A. Petri, Jr.</i>	
<b>46. Antimicrobial Agents: The Aminoglycosides</b>	1103
<i>Henry F. Chambers and Merle A. Sande</i>	
<b>47. Antimicrobial Agents: Tetracyclines, Chloramphenicol, Erythromycin, and Miscellaneous Antibacterial Agents</b>	1123
<i>Joan E. Kapusnik-Uner, Merle A. Sande, and Henry F. Chambers</i>	
<b>48. Antimicrobial Agents: Drugs Used in the Chemotherapy of Tuberculosis and Leprosy</b>	1155
<i>Gerald L. Mandell and William A. Petri, Jr.</i>	
<b>49. Antimicrobial Agents: Antifungal Agents</b>	1175
<i>John E. Bennett</i>	
<b>50. Antimicrobial Agents: Antiviral Agents</b>	1191
<i>Frederick G. Hayden</i>	
<b>S E C T I O N X</b>	
<b>CHEMOTHERAPY OF NEOPLASTIC DISEASES</b>	1225
<b>Introduction</b>	1225
<i>Paul Calabresi and Bruce A. Chabner</i>	

2063642312

- 51. Antineoplastic Agents** 1233  
*Bruce A. Chabner, Carmen J. Allegra, Gregory A. Curt,  
and Paul Calabresi*

## S E C T I O N X I

**DRUGS USED FOR IMMUNOMODULATION** 1289

- 52. Immunomodulators: Immunosuppressive Agents and Immunostimulants** 1291  
*Robert B. Diasio and Albert F. LoBuglio*

## S E C T I O N X I I

**DRUGS ACTING ON THE BLOOD AND THE BLOOD-FORMING  
ORGANS** 1309

- 53. Hematopoietic Agents: Growth Factors, Minerals, and Vitamins** 1311  
*Robert S. Hillman*

- 54. Anticoagulant, Thrombolytic, and Antiplatelet Drugs** 1341  
*Philip W. Majerus, George J. Broze, Jr., Joseph P. Miletich, and Douglas M. Tollefsen*

## S E C T I O N X I I I

**HORMONES AND HORMONE ANTAGONISTS** 1361

- 55. Adenohypophyseal Hormones and Their Hypothalamic Releasing Factors** 1363  
*Mario Ascoli and Deborah L. Segaloff*

- 56. Thyroid and Antithyroid Drugs** 1383  
*Alan P. Farwell and Lewis E. Braverman*

- 57. Estrogens and Progestins** 1411  
*Cynthia L. Williams and George M. Stancel*

- 58. Androgens** 1441  
*Jean D. Wilson*

- 59. Adrenocorticotrophic Hormone; Adrenocortical Steroids and Their Synthetic  
Analogues; Inhibitors of the Synthesis and Actions of Adrenocortical Hormones** 1459  
*Bernard P. Schimmer and Keith L. Parker*

60. **Insulin, Oral Hypoglycemic Agents, and the Pharmacology of the Endocrine Pancreas** 1487  
*Stephen N. Davis and Daryl K. Granner*

61. **Agents Affecting Calcification and Bone Turnover: Calcium, Phosphate, Parathyroid Hormone, Vitamin D, Calcitonin, and Other Compounds** 1519  
*Robert Marcus*

S E C T I O N X I V

**THE VITAMINS** 1547

- Introduction** 1547  
*Robert Marcus and Ann M. Coulston*

62. **Water-Soluble Vitamins: The Vitamin B Complex and Ascorbic Acid** 1555  
*Robert Marcus and Ann M. Coulston*

63. **Fat-Soluble Vitamins: Vitamins A, K, and E** 1573  
*Robert Marcus and Ann M. Coulston*

S E C T I O N X V

**DERMATOLOGY** 1591

64. **Dermatological Pharmacology** 1593  
*Cynthia Guzzo, Gerald S. Lazarus, and Victoria P. Werth*

S E C T I O N X V I

**OPHTHALMOLOGY** 1617

65. **Ocular Pharmacology** 1619  
*Sayoko E. Moroi and Paul R. Lichter*

S E C T I O N X V I I

**TOXICOLOGY** 1647

66. **Heavy Metals and Heavy-Metal Antagonists** 1649  
*Curtis D. Klaassen*

2063642314

- 67. Nonmetallic Environmental Toxicants: Air Pollutants, Solvents, Vapors,  
and Pesticides** 1673  
*Curtis D. Klaassen*

## A P P E N D I C E S

- I. Principles of Prescription Order Writing and Patient Compliance  
Instructions** 1697  
*Leslie Z. Benet*
- II. Design and Optimization of Dosage Regimens; Pharmacokinetic Data** 1707  
*Leslie Z. Benet, Svein Øie, and Janice B. Schwartz*
- Index** 1793