

THE  
PHARMACOLOGICAL  
BASIS  
OF  
THERAPEUTICS

3 Edition

**THE  
PHARMACOLOGICAL  
BASIS  
OF  
THERAPEUTICS**

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In this textbook, reference to proprietary names of drugs is ordinarily made only in chapter sections dealing with preparations. Such names are given in italicized, lower-case type, usually immediately following the official or nonproprietary titles. Proprietary names of drugs also appear in the Index. This convention is similar to that employed in previous editions.

## PREFACE TO THE THIRD EDITION

The quarter century between the first and the third editions of *The Pharmacological Basis of Therapeutics* has witnessed the burgeoning of the biomedical sciences on a scale unprecedented in history. Parallel with important advances in the basic medical disciplines, there has been an ever-increasing number of new drugs available to the physician and a thickening of what has come to be called the "therapeutic jungle." In this setting, the three main objectives that directed the writing of the first two editions have provided excellent guideposts for this third edition. They bear repetition, as follows: the correlation of pharmacology with related medical sciences, the reinterpretation of the actions and uses of drugs from the viewpoint of important advances in medicine, and the placing of emphasis on the application of pharmacodynamics to therapeutics.

In the preface to the second edition, reference was made to the accelerated pace at which new drugs were being marketed, and a fourth objective of the book was emphasized—to provide the reader with a "way of thinking about drugs" to help him evaluate critically the promotional claims as well as the published literature on new therapeutic agents. This fourth guidepost is particularly stressed in the current edition because the flood of new drugs became a torrent by the mid-1950s, and both the birth and the mortality rates of drugs have accelerated. It is for this reason that, in areas where the number of therapeutic agents available is confusingly large, the reader will often find that a well-established, safe, and effective prototypal drug receives major attention and that the numerous congeneric and second-order compounds are described only briefly, in comparison with the prototype. It is also for this reason that the physician is advised not to be the first to adopt the new remedy nor the last to discard the old.

It is with mixed feelings that we have turned from authorship to editorship of this book. The writing of the first edition was completed in less than 3 years. That the interval between the first and second editions was 14 years was due not to the indolence of the authors but to the rapid growth of the field of pharmacology between 1941 and 1955. During the last decade there has been an accelerated tempo, with respect not only to the development of new drugs but also to the understanding of the mechanism of action of drugs at the most basic level. Thus, it became apparent, as the time for another edition came and passed, that the intervals between periodic revisions could no longer depend solely on the time available to us for such a difficult task in a rapidly changing field.

The fact that the book now has multiple authors does not mean that we have abrogated our responsibilities. Indeed, these responsibilities necessarily became even more important if the book was to maintain its readability, cohesiveness, organization, and, most essential, its philosophy and objectives. All these matters were made clear to the invited authors at the very outset, and we were most fortunate in the cooperation received. Also, our task was made pleasurable and nontraumatic by a number of favorable conditions. All authors were very patient, understanding, and cooperative, and for this they have our deep gratitude. Most of them had received their original pharmacological instruction from prior editions of the book or had used the text in their own teaching. Of the 42 contributors, 23 are either former students or former or current associates of ours, and several of the remainder are "second-generation relatives." All followed the same ground rules, and all uncomplainingly accepted our agreed-upon prerogatives as editors. Finally, all understood that they were writing segments of a unified text directed to medical students, interns, residents, and practitioners.

As the contributions of the various authors were received, it became increasingly apparent that a wise decision had been made in our selection of colleagues. Our "favorite" chapters were returned to us updated and invigorated, some in their original format, others completely

and expertly changed. Several of our authors accepted the unglamorous task of cutting to the bone certain chapters dealing with the less dynamic aspects of pharmacology, in order to make room for more exciting and important material. Others covered new fields and new developments with a perception that could only be achieved from intimate knowledge gained by research or from an overwhelming interest in a particular area.

The present edition has been rigorously *edited*, not only by us but also by our collaborators, in order to achieve a multiauthored volume that is much more than a series of individual contributions. How well this goal has been achieved is left to the judgment of the readers and the reviewers.

As a generation of medical students will attest, *The Pharmacological Basis of Therapeutics* has never been a "cram" book. As such it would be a travesty of basic medical science. It is designed to answer the probing questions of the physician who wishes to prescribe drugs on a rational rather than on an empirical basis. More important, the text is meant to provide the medical student with a bridge between basic medical science and clinical medicine by presenting the scientific approach to medical practice without neglecting the applied aspects of a basic science discipline. A textbook of pharmacology that does not satisfy fully both of these needs—that of the second-year medical student, as well as that of the intern, resident, and practicing physician—has failed in its purpose.

The achievement of these objectives in a text that could be bound as a single volume has again necessitated the liberal use of extract (fine) type as a space-saving device. Frankly, it is difficult to justify this use of large and fine print; however, with certain exceptions, extract type has been used for those portions of the text that are of somewhat lesser importance but still of such interest that fine print does not discourage the curious reader. For example, the fascinating history of drugs, which in essence is an exciting part of the history of medicine, is presented in this way. Likewise, details of structure-activity relationships appear in fine print. Nevertheless, in one instance, an entire important chapter, "Drug Addiction and Drug Abuse," is set in extract type; in a sense, this contribution is unique in a pharmacology textbook and is given as an extra dividend; it crosses the boundaries of sociology, law, clinical medicine, and pharmacology, and presents a subject that is one of the most challenging problems of modern society. But this cursory and partial explanation of the fine-print material offers no solace to the second-year medical student. In the last analysis, he must rely on his own judgment and on the advice of his teachers to determine the text material that is pertinent to his immediate interests and needs.

The organization of the material in the text is similar to that in previous editions; hence, old friends of the book will find themselves on familiar ground. Every chapter has been thoroughly revised, and nearly every page reflects important changes. It is unnecessary to recite the substantive changes between the second and the third editions. Suffice it to say that a decade of progress has been presented, as much in the old chapters as in the new. Our old friends will recognize the changes; our new readers need not.

In addition to paying tribute to our collaborators, we gratefully acknowledge the advice and help received from scores of individuals, too numerous to mention by name. These include many colleagues, reference librarians, secretaries, and proofreaders. But special thanks are due to Lou Ann Robinson and Mrs. Ethol Koelle for their editorial assistance, and once again we are delighted to express deep gratitude to Miss Joan Carolyn Zulch, Editor, Medical Department of The Macmillan Company, whose inexhaustible patience, fine sense of humor, and expert labors have facilitated the transformation of raw manuscript into a handsome textbook. Just as Miss Zulch survived her work with us, so did the editors survive each other, and we again wish to pay tribute to our mutual friendship, which has grown ever firmer in the years of preparation of this third edition.

LOUIS S. GOODMAN  
ALFRED GILMAN

June, 1965

## PREFACE TO THE SECOND EDITION

The three main objectives which guided the writing of the first edition of this book have also served in the preparation of the second edition. These objectives are the correlation of pharmacology with related medical sciences, the reinterpretation of the actions and the uses of drugs from the viewpoint of important advances in medicine, and the placing of emphasis on the applications of pharmacodynamics to therapeutics. Because of the accelerated pace at which new drugs are being marketed for clinical use, a fourth objective has been given prominent attention, namely, to provide the reader with a "way of thinking about drugs" so that he will be better prepared to withstand the flood of unsubstantiated claims that are often made for new drugs and to evaluate critically the published literature on the properties and the uses of the many new therapeutic agents in comparison with the older well-established compounds of the same class. In this connection, our British colleague, Dr. Gordon Millichap has supplied us with an appropriate paraphrase of Shakespeare's advice, given by Polonius to his son Laertes, in *Hamlet*, as follows:

Those drugs thou hast, and their adoption tried,  
Grapple them to thy soul with hoops of steel;  
But do not dull thy palm with entertainment  
Of each new-hatch'd, unfledged remedy.

In a real sense, this second edition constitutes a complete revision of the first edition. The 14 years which separate the two books have witnessed pharmacological and therapeutic advances which are probably unparalleled in the history of medicine. Nearly every page of the text reflects these advances. Nevertheless, the organization of the material in the first edition proved so sound that the numerous changes and new inclusions could readily and smoothly be incorporated. Hence the reader who is acquainted with the first edition will be on familiar ground.

The authors are indebted to so many score individuals for advice, help, and encouragement in the preparation of the book that it is not feasible to name all of them in this Preface. However, the contributions of a few persons require special comment. Our warm thanks are expressed to Professor Walter S. Loewe, who read much of the early drafts and made many sentences mean what the authors had intended them to mean. Dr. Mark Nickerson helped prepare the chapter on adrenergic blocking drugs, a field which his own able research has done so much to develop. Dr. Stewart C. Harvey assisted with some difficult sections on structure-activity relationship. Dr. Harry B. van Dyke was most generous with his sage advice and helpful criticism throughout the entire period of the preparation of the revision. Dr. Harry M. Rose patiently reviewed each succeeding draft of the chapters on antibiotics. To Dr. Edward Fingl, a special debt of gratitude is gladly acknowledged. In a real sense, he has been a junior partner in the preparation of several chapters and in the reading and correcting of original manuscript and galley proof. We are also grateful to the many secretaries, reference librarians, and proofreaders who have given us such able assistance. The fine cooperation of The Macmillan Company and the expert work of their copy editor, Miss Joan Carolyn Zulch, have greatly facilitated the transformation of the raw manuscript into a printed book. Thanks are also due to the many thousand readers whose

enthusiastic reception of the first edition has sustained us in the arduous task of preparing the new book. Finally, the authors wish to pay tribute to their mutual friendship which has vigorously survived the dual authorship of two editions of this text.

LOUIS S. GOODMAN  
ALFRED GILMAN

*November, 1954*

## PREFACE TO THE FIRST EDITION

Three objectives have guided the writing of this book—the correlation of pharmacology with related medical sciences, the reinterpretation of the actions and uses of drugs from the viewpoint of important advances in medicine, and the placing of emphasis on the applications of pharmacodynamics to therapeutics.

Although pharmacology is a basic medical science in its own right, it borrows freely from and contributes generously to the subject matter and technics of many medical disciplines, clinical as well as preclinical. Therefore, the correlation of strictly pharmacological information with medicine as a whole is essential for a proper presentation of pharmacology to students and physicians. Furthermore, the reinterpretation of the actions and uses of well-established therapeutic agents in the light of recent advances in the medical sciences is as important a function of a modern textbook of pharmacology as is the description of new drugs. In many instances these new interpretations necessitate radical departures from accepted but outworn concepts of the actions of drugs. Lastly, the emphasis throughout the book, as indicated in its title, has been clinical. This is mandatory because medical students must be taught pharmacology from the standpoint of the actions and uses of drugs in the prevention and treatment of disease. To the student, pharmacological data per se are valueless unless he is able to apply his information in the practice of medicine. This book has also been written for the practicing physician, to whom it offers an opportunity to keep abreast of recent advances in therapeutics and to acquire the basic principles necessary for the rational use of drugs in his daily practice.

The criteria for the selection of bibliographic references require comment. It is obviously unwise, if not impossible, to document every fact included in the text. Preference has therefore been given to articles of a review nature, to the literature on new drugs, and to original contributions in controversial fields. In most instances, only the more recent investigations have been cited. In order to encourage free use of the bibliography, references are chiefly to the available literature in the English language.

The authors are greatly indebted to their many colleagues at the Yale University School of Medicine for their generous help and criticism. In particular they are deeply grateful to Professor Henry Gray Barbour, whose constant encouragement and advice have been invaluable.

LOUIS S. GOODMAN  
ALFRED GILMAN

*New Haven, Connecticut*  
*November 20, 1940*



## CONTRIBUTORS

- Abildskov, J. A., M.D.** Professor of Medicine, State University of New York, Upstate Medical Center, School of Medicine, Syracuse, New York
- Astwood, E. B., M.D., Ph.D.** Professor of Medicine, Tufts University School of Medicine; Senior Physician, New England Medical Center Hospitals, Boston, Massachusetts
- Blythe, William B., M.D.** Assistant Professor of Medicine, University of North Carolina School of Medicine, Chapel Hill, North Carolina
- Brazeau, Paul, Ph.D.** Associate Professor of Pharmacology, Albert Einstein College of Medicine of Yeshiva University, Bronx, New York
- Burns, J. J., Ph.D.** Director of Research, Pharmacodynamics Division, The Wellcome Research Laboratories, Tuckahoe, New York; Visiting Professor of Pharmacology, Albert Einstein College of Medicine of Yeshiva University, Bronx, New York
- Calabresi, Paul, M.D.** Associate Professor of Medicine; Associate Professor of Pharmacology; Head, Section of Clinical Pharmacology, Yale University School of Medicine, New Haven, Connecticut
- Cohen, Peter J., M.D.** Associate in Anesthesia, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania
- Cohn, Victor H., Ph.D.** Associate Professor of Pharmacology, George Washington University School of Medicine, Washington, D.C.
- Douglas, William W., Ch.B., M.D.** Professor of Pharmacology, Albert Einstein College of Medicine of Yeshiva University, Bronx, New York
- Dripps, Robert D., M.D.** Professor and Chairman, Department of Anesthesia, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania
- Eder, Howard A., M.D.** Professor of Medicine, Albert Einstein College of Medicine of Yeshiva University; Attending Physician, Bronx Municipal Hospital Center, Bronx, New York
- Esplin, Don W., Ph.D.** Associate Professor of Pharmacology, University of Utah College of Medicine, Salt Lake City, Utah
- Farah, Alfred E., M.D.** Professor and Chairman, Department of Pharmacology, State University of New York, Upstate Medical Center, College of Medicine, Syracuse, New York
- Fingl, Edward, Ph.D.** Associate Professor of Pharmacology, University of Utah College of Medicine, Salt Lake City, Utah
- Greengard, Paul, Ph.D.** Director, Department of Biochemistry, Geigy Research Laboratories, Ardsley, New York; Visiting Associate Professor of Pharmacology, Albert Einstein College of Medicine of Yeshiva University, Bronx, New York
- Harvey, Stewart C., Ph.D.** Associate Professor of Pharmacology, University of Utah College of Medicine, Salt Lake City, Utah
- Herbert, Victor, M.D.** Associate Director of Hematology, The Mount Sinai Hospital; Associate Clinical Professor of Medicine, Columbia University College of Physicians and Surgeons, New York, New York
- Innes, Ian R., M.B., Ch.B., M.D.** Professor of Pharmacology and Therapeutics, University of Manitoba Faculty of Medicine, Winnipeg, Manitoba, Canada
- Jaffe, Jerome H., M.D.** Assistant Professor of Pharmacology, Instructor in Psychiatry, Albert Einstein College of Medicine of Yeshiva University, Bronx, New York
- Jarvik, Murray E., M.D., Ph.D.** Associate Professor of Pharmacology, Albert Einstein College of Medicine of Yeshiva University, Bronx, New York

- Koelle, George B.,** Ph.D., M.D. / Elmer Holmes Bobst Professor and Chairman, Department of Pharmacology, University of Pennsylvania Schools of Medicine, Philadelphia, Pennsylvania
- Levine, Walter G.,** Ph.D. Assistant Professor of Pharmacology, Albert Einstein College of Medicine of Yeshiva University, Bronx, New York
- Mandel, H. George,** Ph.D. Professor and Chairman, Department of Pharmacology, George Washington University School of Medicine, Washington, D.C.
- Moe, Gordon K.,** Ph.D., M.D. Director of Research, Masonic Medical Research Laboratory, Utica, New York; Research Professor of Physiology, State University of New York, Upstate Medical Center, School of Medicine, Syracuse, New York
- Mudge, Gilbert H.,** M.D. Professor of Experimental Therapeutics, Dartmouth Medical School, Hanover, New Hampshire
- Nickerson, Mark,** Ph.D., M.D. Professor and Chairman, Department of Pharmacology and Therapeutics, University of Manitoba Faculty of Medicine, Winnipeg, Manitoba, Canada
- Price, Henry L.,** M.D. Professor of Anesthesia, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania
- Ritchie, J. Murdoch,** Ph.D., D.Sc. Professor of Pharmacology, Albert Einstein College of Medicine of Yeshiva University, Bronx, New York
- Rollo, Ian M.,** B.Sc. Associate Professor of Pharmacology and Therapeutics, University of Manitoba Faculty of Medicine, Winnipeg, Manitoba, Canada
- Sayers, George,** Ph.D. Professor and Chairman, Department of Physiology, Western Reserve University School of Medicine, Cleveland, Ohio
- Sharpless, Seth K.,** Ph.D. Associate Professor of Pharmacology, Albert Einstein College of Medicine of Yeshiva University, Bronx, New York
- Swinyard, Ewart A.,** M.S., Ph.D. Professor of Pharmacology, College of Pharmacy; Lecturer in Pharmacology, University of Utah College of Medicine, Salt Lake City, Utah
- Toman, James E. P.,** Ph.D. Professor and Chairman, Department of Pharmacology, Chicago Medical School, Chicago, Illinois
- Travis, Randall H.,** M.D. Assistant Professor of Medicine, Assistant Professor of Physiology, Western Reserve University School of Medicine, Cleveland, Ohio
- Volle, Robert L.,** Ph.D. Associate Professor of Pharmacology, University of Pennsylvania Schools of Medicine, Philadelphia, Pennsylvania
- Weinstein, Louis,** Ph.D., M.D. Professor of Medicine, Tufts University School of Medicine; Lecturer on Infectious Disease, Harvard Medical School; Lecturer in Medicine, Boston University School of Medicine, Boston, Massachusetts
- Weiss, William P.,** M.D. Assistant Professor of Pharmacology, George Washington University School of Medicine, Washington, D.C.
- Welch, Arnold D.,** Ph.D., M.D. Eugene Higgins Professor and Chairman, Department of Pharmacology, Yale University School of Medicine, New Haven, Connecticut
- Welt, Louis G.,** M.D. Professor of Medicine, University of North Carolina School of Medicine, Chapel Hill, North Carolina
- Wollman, Harry,** M.D. Assistant Professor of Anesthesia, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania
- Woodbury, Dixon M.,** Ph.D. Professor of Pharmacology, University of Utah College of Medicine, Salt Lake City, Utah
- Zablocka, Barbara,** M.D. Assistant Research Professor of Pharmacology, University of Utah College of Medicine, Salt Lake City, Utah

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## S E C T I O N

# I

## INTRODUCTION

## C H A P T E R

# I

## General Principles

*Edward Fingl and Dixon M. Woodbury*

The basic pharmacological concepts summarized in this chapter apply to the characterization, evaluation, and comparison of all drugs. A clear understanding of these principles will facilitate subsequent study of the individual drugs. These preliminary considerations are discussed under the following headings: (1) absorption, distribution, biotransformation, and excretion; (2) mechanisms of drug action; (3) characterization of drug effects; (4) factors modifying drug effects; and (5) drug toxicity. The chapter starts with a consideration of the scope of pharmacology for the medical student and practitioner, and it concludes with a brief summary of the development of new drugs and a guide to the so-called "therapeutic jungle."

### SCOPE OF PHARMACOLOGY

In its entirety, *pharmacology* embraces the knowledge of the history, source, physical and chemical properties, compounding, biochemical and physiological effects, mechanisms of action, absorption, distribution, biotransformation and excretion, and therapeutic and other uses of drugs. Since a *drug* is broadly defined as any chemical agent that affects living protoplasm, the subject of pharmacology is obviously quite extensive.

For the physician and the medical student,

however, the scope of pharmacology is less expansive than indicated by the above definitions. The interests of the physician in pharmacology are clearly different than those of the chemist who synthesizes new medicinals, the pharmacist who compounds drugs, the pharmacognosist or microbiologist who studies the biosynthesis of therapeutic agents, the biochemist or physiologist who uses drugs as tools for the advancement of his own discipline, or the toxicologist who is concerned with the potential hazards of drugs. Primarily, the physician is interested only in drugs that are useful in the prevention, diagnosis, and treatment of human disease, or in the prevention of pregnancy. His study of the pharmacology of these drugs can be reasonably limited to those aspects that provide the basis for their rational clinical use. Secondarily, the physician is also concerned with chemical agents that are not used in therapy but are commonly responsible for household, environmental, or industrial intoxication. His study of these substances is justifiably restricted to the general principles of prevention, recognition, and treatment of such toxicity.

A brief consideration of its major subject areas will further clarify how the study of pharmacology is best approached from the standpoint of the specific requirements and interests of the medical stu-