

The

Philosophical

Basis of

Psychology

FOURTH EDITION

**THE PHARMACOLOGICAL
BASIS OF
THERAPEUTICS**



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The Pharmacological Basis of Therapeutics

FOURTH EDITION

A TEXTBOOK OF
PHARMACOLOGY, TOXICOLOGY, AND
THERAPEUTICS FOR
PHYSICIANS AND MEDICAL STUDENTS

THE MACMILLAN COMPANY

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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 SMALL-CAP TYPE, usually immediately following the official or nonproprietary titles. Proprietary names of drugs also appear in the Index.

PREFACE TO THE FOURTH EDITION

The 30-year period since publication of the first edition of this textbook has witnessed an enormous change in the content, stature, and function of pharmacology; its role in the biomedical sciences; and its impact on the clinical sciences and rational therapeutics. The prefaces to the first three editions are reprinted herein, not only because they define the primary objectives of the textbook but also because they indicate the considerable changes that have occurred between editions. The new reader is particularly invited to read these prefaces; old friends of the book need not, since they are on familiar ground.

Quite by historical accident, each edition appeared at a strategic period. The first edition was written when basic pharmacology had not yet attained its present importance and was not fully accepted by clinical colleagues as a meaningful or relevant discipline. The appearance of that book did much to change the picture. An eminent pharmacologist, recently commenting on the first edition, stated that it provided a renaissance or perhaps more properly the *naissance* of the teaching and practice of pharmacology. The second edition, published in the mid-1950s, reflected the immense impact of the post-World War II burgeoning of biomedical research and the flood of new drugs that had not yet reached its crest. That edition provided a guide, to the perplexed student and clinician, for an easier and safer passage through the "therapeutic jungle." The third edition, published in the mid-1960s and written for the first time as a multiauthored work, appeared after the flood of new drugs had begun to ebb and when fundamental advances highly pertinent to rational therapeutics were being made by the many flourishing subdisciplines of pharmacology.

This fourth edition appears at a time when the above-mentioned advances are continuing and when, equally important, the impact of pharmacology not only on the practice of medicine but also on society itself is receiving increasing attention. The discipline has attained such stature that it is now a byword with legislators, public health officials, social scientists, legal authorities, ecologists, and many other specialists concerned with the welfare of the public and the quality of the environment. Three decades ago one would not have dreamed that the subject "drugs and society" would be a major public issue. In every appropriate chapter of this textbook, attention is paid to this aspect of pharmacology.

It is a source of gratification to the original authors, now editors, that for 30 years *The Pharmacological Basis of Therapeutics* has been known as the "blue bible" of pharmacology. The current edition has undergone a thorough updating of every chapter with respect to the mechanism of action and rational use of older therapeutic agents and the addition of important new drug entities. Readers of previous editions will again find themselves familiar with the organization and objectives of the textbook, and will recognize the smooth transition to multiple authorship first undertaken in the third edition. It is a source of great satisfaction to the editors that all but one of the 42 contributors to that edition were able and anxious to participate in the current undertaking.

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 Thomas for her editorial assistance, and once again we are delighted to express deep gratitude to Miss Joan Carolyn Zulch, Medical Editor, 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 task of preparing this fourth edition.

PREFACE TO THE FOURTH EDITION

LOUIS S. GOODMAN
ALFRED GILMAN

June, 1970

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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

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 application 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

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 sections and the use of drugs from the viewpoint of important advances in medicine, and the placing of emphasis on the application 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 Millican has supplied us with an appropriate paraphrase of Shakespeare's advice, given by Polonius to his son Laertes in *Hamlet*, as follows:

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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.

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