The Pharmacological Basis of Therapeutics

FIFTH EDITION

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

THE PHARMACOLOGICAL BASIS OF THERAPEUTICS

PREFACE TO THE FIFTH EDITION

THE 35-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. Only the Preface to the First Edition is reprinted herein, because it clearly states the three primary objectives that have guided the writing of all subsequent editions.

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, commenting on the first edition many years after its appearance, 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. The third and fourth editions were written as multiauthored works. Although the flood of new drugs had begun to ebb, fundamental advances highly pertinent to rational therapeutics were being made by the many flourishing subdisciplines of pharmacology. An authoritative textbook in such a diverse and active discipline could no longer be written by the two authors; however, as editors, they could devote their efforts to fulfill their original objectives.

It is possible in a preface to mention only a few examples of the major changes that appear in the present edition. Both the basic and applied aspects of pharmacokinetics have made impressive advances due to elegant analytical technics that can also be utilized clinically. The basic principles of pharmacokinetics are discussed separately as they relate to all drugs, and the practicing physician will find described valuable concepts now taught to the current generation of biomedical students. Applied principles are presented for individual drugs when altered biochemical disposition or impaired excretion requires changes in dosage regimens. In several cases the appropriate data are summarized in useful tabular form. Parallel advances have been made in the understanding of drug interactions. Again, the basic mechanisms of clinically relevant interactions are analyzed, and the applicable information is presented for individual drugs.

Studies on receptors for neurotransmitters, autacoids, hormones, and drugs have led to a better understanding of the mechanism of drug action and in certain instances to fruitful hypotheses or to more fundamental knowledge of the pathological physiology of disease states. An outstanding example is the inhibition of dopamine activation of adenylate cyclase by antipsychotic drugs in both the caudate nucleus and the limbic system. Indeed, discussion of the role of cyclic AMP as a "second messenger" and the effects of drugs thereon appears throughout the text. Prostaglandins are discussed both as primary drugs and as targets for the actions of drugs. In a similar manner the hypothalamic regulatory hormones are presented as primary therapeutic and diagnostic agents and in terms of mechanisms by which drugs can produce endocrinopathies. Needless to say, newly approved drugs are fully discussed as well as those that are still in the developmental stage but show considerable promise as future therapeutic agents. An outstanding example is the group of drugs that block the effects of histamine (and pentagastrin) on gastric secretion, the so-called H_2-receptor blocking drugs.

In order to prevent expansion of the present edition, less dynamic or outmoded areas have been condensed or eliminated, to allow adequate consideration of all important pharmacological and therapeutic advances. It is our estimate that well over one half of the text represents newly written or vigorously revised material.

Most of our contributors to the fourth edition were able and anxious to participate in the current undertaking, but it is with deep sadness that we record the untimely deaths of our

friends and colleagues, Drs. Robert D. Dripps, Don W. Esplin, James E. P. Toman, and Louis G. Welt.

For the fifth edition, we have sought the assistance of two associate editors who are also contributors—Alfred G. Gilman, M.D., Ph.D., and George B. Koelle, Ph.D., M.D., D.Sc.(Hon.), D.Med.(Hon.). The former, a representative of the younger generation of pharmacologists, is broadly trained in general pharmacology and clinical science with major interests in biochemical pharmacology, molecular pharmacology, and cell biology; the latter, a contributor since the third edition, is a teacher of broad experience with a background of research in neuropharmacology and many important editorial responsibilities.

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. However, special thanks are due to George E. Downs, Pharm.D., Assistant Professor of Clinical Pharmacy, Philadelphia College of Pharmacy and Science, who gave us expert editorial help with regard to those sections of the text related to pharmaceutical preparations and dosages. We also wish to acknowledge the invaluable editorial assistance of Lou Ann Thomas, Carol Bennett, and Eloise Gabel Smyrl.

The editors and authors owe a great debt to Miss Joan Carolyn Zulch, Medical Editor, Macmillan Publishing Co., Inc. This being her fourth edition of this textbook, she qualifies as an expert, self-taught pharmacologist—knowledge that superbly complements her editorial excellence and the patience and sense of humor vital to her job. 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 fifth edition.

LOUIS S. GOODMAN
ALFRED GILMAN

June, 1975

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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New Haven, Connecticut
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Introduction

CHAPTER
1 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 is essential for the subsequent study of the individual drugs. Many of these topics have been more extensively discussed in the textbooks by Melmon and Morrelli (1972), Levine (1973), and Goldstein and coworkers (1974).

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 processes, 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 clinician is interested primarily 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 and industrial poisoning as well as environmental pollution. His study of these substances is justifiably restricted to the general principles of prevention, recognition, and treatment of such toxicity or pollution. Finally, all physicians share in the responsibility to help resolve the continuing sociological problem of the abuse of drugs.

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 student and practitioner. At one time, it was essential for the physician to have a broad botanical knowledge, since he had to select the proper plants from which to prepare his own crude medicinal preparations. However, fewer drugs are now obtained from natural sources, and, more importantly, most of these are highly purified or standardized and differ little from synthetic chemicals. Hence, the interests of the modern clinician in *pharmacognosy* are correspondingly limited. Nevertheless, scientific curiosity should stimulate the physician to learn something of the *sources* of drugs, and this knowledge often proves practically useful as well as interesting. He will find the *history* of drugs of similar value.

The preparing, compounding, and dispensing of medicines at one time lay within the province of the physician, but this work is now delegated almost completely to the pharmacist. However, to write intelligent prescription orders, the physician must have some knowledge of the *physical and chemical properties* of drugs and their available *dosage forms*, and he must have a basic familiarity with the *practice of pharmacy*. When the physician shirks his responsibility in this regard, he invariably fails to translate his knowledge of pharmacology and medicine into prescription orders and medication best suited for the individual patient. The few details essential to the writing of correct prescription orders are summarized in the Appendix.

Pharmacokinetics deals with the *absorption, distribution, biotransformation*, and *excretion* of drugs. These factors, coupled with dosage, determine the concentration of a drug at its sites of action and,