The PHARMACOLOGICAL BASIS *of* THERAPEUTICS

Second Edition

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

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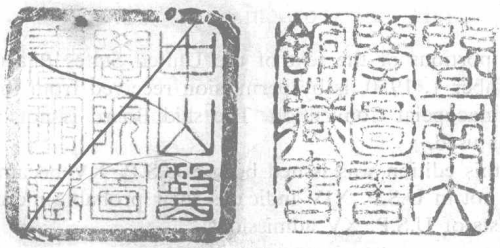

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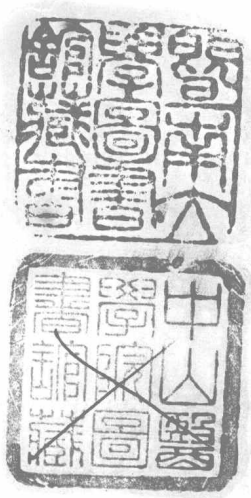

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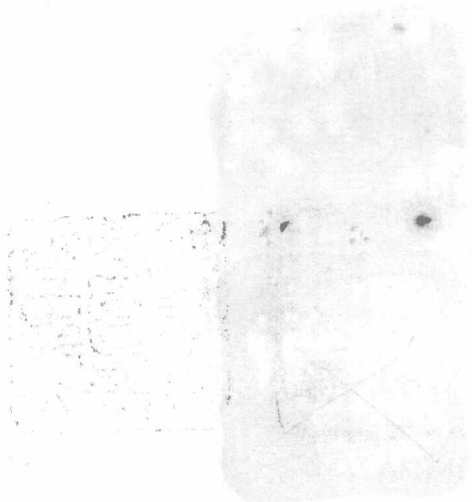

PREFACE TO THE SECOND EDITION

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. Futhermore, 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
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New Haven, Connecticut
November 20, 1940

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SECTION

I

INTRODUCTION

CHAPTER

1

GENERAL PRINCIPLES

SCOPE OF PHARMACOLOGY

The subject of pharmacology is a broad one and embraces the knowledge of the source, physical and chemical properties, compounding, physiological actions, absorption, fate and excretion, and therapeutic uses of drugs. A *drug* may be broadly defined as any chemical agent which affects living protoplasm, and few substances would escape inclusion by this definition.

For the medical student and physician, however, the scope of pharmacology and the number of substances to be regarded as drugs are more restricted than indicated by the above definition. The physician is concerned with actions and uses of drugs in the therapy of disease. Obviously his attention is directed toward fields of interest different from those of the pharmacist who compounds drugs, the chemist who synthesizes new medicinals, or the botanist and microbiologist who study the mechanisms by which plants, bacteria, and moulds form potent therapeutic agents. Therefore, the study of pharmacology should be approached with specific aims in mind. Before individual drugs are discussed, it is fitting to consider the component parts of pharmacology in order to appreciate how best to approach the subject from the standpoint of the interests and requirements of the medical student and practitioner.

The subject of pharmacology in its entirety may be divided into pharmacognosy, pharmacy, pharmacodynamics, pharmacotherapeutics, and toxicology.

Pharmacognosy is that branch of pharmacology which deals with the physical characteristics of crude drugs. It is purely a descriptive science. Inasmuch as most crude drugs are of plant origin, pharmacognosy deals largely with the botanical sources of drugs and the characteristics of the plants from which they are obtained. The interests of the physician in pharmacognosy are limited. At one time it was essential for a member of the medical profession to have a broad botanical knowledge, for it was then within his province to select the proper plants and to make from them crude drug preparations. If William Withering had not possessed training in botany, the introduction of digitalis into medicine might have been long delayed. Fortunately, the physician today is not confronted with the problems of pharmacognosy. For him, the drugs of the world are gathered, manufactured, and marketed in forms which permit economy, stability, uniformity, and ease of administration. However, scientific curiosity should stimulate the physician to gain some conception of the sources of the medicinals which he employs, and often this knowledge proves both interesting and helpful.

Pharmacy deals with the art of preparing, compounding, and dispensing medicines. This work at one time lay within the province of the physician, but now it is delegated almost completely to the pharmacist. However, the physician must have a basic knowledge of the art of pharmacy in order to write intelligent prescriptions. He must know the form in which a drug is best administered,

what solvents are suitable for a particular medicinal agent, whether two drugs can be placed in solution together without incompatibility, etc. Too often the physician shirks his responsibility in this regard, and resorts to the practice of prescribing "ready-made" mixtures of drugs sold by pharmaceutical houses under trade names. Often the proportion of drugs in such a prepared mixture is not exactly that which is desired. Trademarked products are also likely to be expensive. The physician gives up his prerogative of individual treatment and does not favor the best interests of his patient when he fails to translate his knowledge of pharmacology into a prescription best suited for the needs of a particular individual. It requires little additional effort in the study of pharmacology to master the few details essential to the correct writing of prescriptions.

Pharmacodynamics is the study of the actions of drugs on the living organism. It is one of the youngest of the experimental medical sciences and dates back only to the latter half of the nineteenth century. Pharmacodynamics is a border science. It borrows freely both from the subject matter and technics of physiology, physiological chemistry, pathology, and bacteriology. It is unique only in that attention is focused on the physiological responses to drugs. As the name implies, the subject is a dynamic one. The student who studies it in a static manner, who merely memorizes the actions of drugs, is foregoing one of the best opportunities for correlating the entire field of preclinical medicine. For example, the mechanism of action of diuretic drugs and their therapeutic indications and limitations can only be fully understood when one has a basic understanding of the physiology of the kidney and the pathological physiology of edema formation. Yet no greater insight can be gained into the physiology of the kidney than that obtainable from a study of the actions of diuretics. As an even more striking example may be cited the action of digitalis on the heart. The study of the cardiac effects of digitalis leads to a better understanding of the physiology of conduction in cardiac muscle, the factors controlling heart rate, diastolic size and cardiac output, and the alterations in the functions of the heart and vascular system secondary to congestive heart failure. The pathological physiology of cardiac decompensation can be more thoroughly appreciated by observing the restoration of cardiac function by digitalis and the rapid reversal of events which proceeded slowly over a period of months or years. Again, no better understanding of the physiology of the autonomic nervous system can be obtained than by studying the actions of drugs which prevent the responses of effector organs to nerve impulses, and drugs which mimic the effects of nerve impulses. Conversely, the laborious task of learning the numerous actions of a score or more of autonomic drugs is rendered unnecessary by correlating a basic knowledge of the manner in which these drugs alter the functional activity of structures innervated by autonomic nerves with the known responses of the same structures to nerve stimulation.

Pharmacodynamics also deals with the absorption of drugs, their fate in the body, and the mechanism of their excretion. Here a number of principles of physiological chemistry can readily be applied to an understanding of the metabolism of substances foreign to the body.

There are many phases of pharmacodynamics which are of minor interest to the physician, among which is *comparative pharmacology*. From an academic point of view, the action of a drug on frogs may be just as important as its effect on man. The physician, however, is interested in the actions of drugs which are useful in therapeutics, and to him comparative pharmacology is important only in so far as the results obtained have clinical application. Striking advances have occurred in the field of human pharmacology, largely as a result of new methods of experimental approach. When digitalis was first studied, the frog heart was utilized. Much basic information was gained, but the modern interpretation of the actions of the drug on the human cardiovascular system was forthcoming only after the effects of digitalis had been studied in man by means of special technics for measuring cardiac size and output, circulatory velocity, venous pressure, peripheral resistance, and changes in conduction in cardiac muscle. As a result, many of the earlier conceptions

were discarded or revised. Numerous other instances could be cited in which it was necessary to change the older concepts of the actions of drugs obtained from animal experimentation when the drugs were restudied in man. Therefore, in the following pages, emphasis is placed on human pharmacology.

The subject of comparative pharmacology, however, is not to be neglected. Some of the most esoteric observations on the actions of drugs in lower species can be applied to human pharmacology. For example, the fact that a chicken is anesthetized by barbital for an indefinite period because of an inability to excrete the drug has a clinical counterpart in the patient with inadequate renal function who receives a barbiturate which depends upon renal elimination for its duration of action. The responses of the gastrointestinal tract of a primitive fish, the tench, to certain autonomic drugs permit broad interpretations which help to clarify the basic mechanism of action of these drugs on smooth and striate muscle.

Another ramification of pharmacodynamics is the correlation of the action of drugs with chemical constitution, hereafter referred to as "structure-activity relationship." This is a basic field which has resulted in some of the greatest contributions of pharmacology to medicine. Structure-activity relationship is discussed in connection with the individual drugs. This is done with the realization that many students and physicians have only a superficial interest in this subject. It is hoped, however, that an occasional reader will be stimulated by its inclusion to a deeper interest in pharmacology.

Pharmacotherapeutics is the study of the uses of drugs in the treatment of disease. Pharmacotherapeutics is no longer practiced in an empirical manner, but rather rational drug therapy is based wherever possible upon a correlation of the pharmacological actions of drugs with the pathological physiology or microbiological aspects of disease. Only in rare instances are drugs still used on an empirical basis. The drugs employed in pharmacotherapy can be divided into two main classes. A large number are used for their actions on the host. They stimulate or depress physiological or biochemical functions in a manner so predictable that they can be employed to alter the course of a disease. Drugs of this type may be designated as *pharmacodynamic agents*. Other drugs are administered to the host for the purpose of destroying parasites. These are known as *chemotherapeutic agents*. An effective chemotherapeutic drug should possess minimal pharmacodynamic and maximal parasiticidal action. The word "chemotherapy" was introduced by the famous German pharmacologist, Paul Ehrlich. It was Ehrlich's goal to find a specific drug for the treatment of each infectious disease. His most conspicuous successes were the trypanocidal dyes and the antisyphilitic arsenicals. Today Ehrlich's goal has largely been achieved. Drug therapy can now cure or control the vast majority of parasitic diseases caused by invading organisms, which range from viruses to helminths.

In the medical curriculum, pharmacodynamics and the principles of chemotherapy are usually taught before the student has had clinical courses. For this reason pharmacotherapeutics is often neglected in the teaching of pharmacology on the false premise that the student does not have the necessary clinical background. This is true only if one has empirical therapy in mind. It is during the study of pharmacodynamics and chemotherapy that the student has the best opportunity to correlate the actions of drugs with the knowledge that he has already gained of pathological physiology of disease, microbiology, and parasitology.

Toxicology is the science of the noxious effects of drugs. This broad aspect of pharmacology is discussed separately (*see* Appendix II).

MECHANISMS OF DRUG ACTION

One of the most fascinating and difficult fields of pharmacological research is that which deals with the mechanisms of drug action. In a few instances, the fundamental manner in which a drug produces a given effect is evident. For example, an osmotic cathartic such as magnesium sulfate is effective because the magnesium and sulfate ions are poorly absorbed and therefore exert an osmotic force which retains water in the lumen of the bowel. No ready explanation is avail-