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PHARMACOLOGY  
AND  
THERAPEUTICS

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GROLLMAN

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SIXTH EDITION

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# PHARMACOLOGY AND THERAPEUTICS

*A Textbook for Students and Practitioners of Medicine  
and its Allied Professions*

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## Preface to the Sixth Edition

THIS new edition, for the first time, appears under dual authorship, an innovation which it is hoped will add to the vigor, authoritativeness and general excellence of the text. Both authors have scrutinized the entire volume and contributed to bringing it up-to-date.

Pharmacology during the present century has passed from a period of empiricism during which many (for the most part worthless) drugs were used, to an era of nihilism in which drug therapy was looked upon by the more critical as akin to charlatanism or at best as a form of placebo, to the modern age of spectacular specific chemotherapy. New preparations are constantly being added to the physician's resources with which the student as well as the practitioner of medicine must be well acquainted if he is to utilize to its maximum the advances of modern therapeutics. Pharmacology has assumed an important place in the medical curriculum, and the student must have an understanding of the science of drug therapy if he is to utilize intelligently, rationally and critically the drugs at his disposal. The advances in therapeutics which have made possible the accomplishments of modern medicine have also added to the responsibility of the physician who utilizes the potent drugs at his disposal. He can no longer be defined in the words of Voltaire as "the man in black who puts drugs he knows little about into a body he knows absolutely nothing about."

Each page of the present edition has been scrutinized critically and many parts of the book have been entirely rewritten. The book is so arranged that teachers, desiring to do so, may take up the subject in any order that they prefer. For example, many will postpone the consideration of the introductory Part I until the end of the course when it will be more readily comprehended by the student; others may begin with Part III since the basic mechanisms are best elucidated with the drugs described in this section. The ideal textbook of Pharmacology should serve the student not only during the period when this subject is taught in the school curriculum but also during his subsequent years of training and following his graduation. The present volume is intended to fulfil this need. Much of the more practical aspects of the subject which are covered in the text may be glossed over during the course in pharmacology when the student has had no practical experience but should prove useful later. By combining the basic principles with the practical aspects of the subject, a unity of presentation is attained which, from a pedagogic point-of-view, is far superior to relying on separately presented brief introductory and empirical practical treatises.

Since the primary purpose of the course in Pharmacology is to convey to the student the basic mechanisms of drug action, special attention has been devoted to this aspect of the subject. However, the teacher must not lose sight of the fact that the ultimate goal of the student is the practical



application of this knowledge to the patient. The failure to appreciate this is responsible for the fact that Pharmacology in most schools has not achieved the preeminence in the curriculum to which the phenomenal growth of drug therapy entitles it. Paradoxically, relatively less time is now assigned in the curriculum to the study of therapeutics than was the case a quarter of a century ago, despite the infinitely greater importance which this field has assumed in modern medicine. A textbook in pharmacology must meet this new obligation by serving not only for the brief time allotted to pharmacology in the curriculum, but also as a source of reference in the subsequent years of training.

The authors in the present volume have emphasized the basic mechanisms of drug action while orienting the subject towards its ultimate goal of practical therapeutics. An attempt has been made to explain the phenomena elicited in the therapeutic use of drugs in terms of normal body functions and to correlate these with the deviations from normal function encountered in disease. The pharmacologist is no longer content to observe the effects of drugs by acute experiments on animals or on isolated organs, but has turned with increasing frequency to a study of drug action at a molecular level and to explore their action more broadly on the basis of physiological and biochemical mechanisms. Despite this more fundamental approach, one cannot, except in a few cases, define with complete satisfaction the action of drugs at the enzymatic level.

The growth of Pharmacology and Therapeutics has made it a formidable task to satisfy the experimental pharmacologist whose interest lies in the broad theory of pharmacodynamics, the student who requires a basic course which will permit him to use drugs rationally and effectively, and the practitioner who wishes to keep abreast of developments in therapeutics. The first-mentioned must resort to the use of the original literature for his needs; it is for the latter two groups that the present volume is intended.

We are indebted to all who have offered valuable suggestions and criticism of the earlier editions; wherever possible, these have been incorporated in the present volume.

ARTHUR GROLLMAN  
EVELYN FRANCES GROLLMAN

DALLAS, TEXAS

## Preface to the First Edition

THE great advances which have been made in Pharmacology during the last few decades have made this subject one of the most important of the medical curriculum. No longer can it be said with Oliver Wendell Holmes that "if all the drugs of the Pharmacopœia be cast into the ocean, it would be to the hurt of the fishes and to the welfare of mankind." Nor can one deride therapeutics, as did Sir William Osler, by pointing out that only four drugs (iron, quinine, emetine, and mercury) have any specific virtue. The advances in drug therapy have made available to the physician a host of remedial agents with which he practices the art of modern medicine and which make possible its great accomplishments.

The present volume is not intended to be encyclopedic in scope, but rather a textbook adequate for the needs of the medical student and practitioner desirous of an up-to-date coverage of the subject. Although emphasis has been placed on the pharmacology of therapeutically important drugs, others of purely pharmacologic interest have not been neglected. For example, nicotine, muscarine, and strychnine are of little clinical usefulness but an understanding of their action is essential for any fundamental concept of the science of pharmacology. The purpose of the course in pharmacology is to acquaint the student with the scientific basis for the use of drugs in medicine; to do so, involves not only a consideration of the drugs commonly used in the clinic but also of the basic principles of the subject. The more practical minded may object to any attention paid to such drugs as muscarine or strychnine. However, a text in pharmacology should not be a mere handbook of therapeutics but should serve as a foundation for the rational and scientific use of drugs, without losing sight of the ultimate objective which is the application of drug therapy in disease. It is only if this be done that the subject merits a place among the basic disciplines of the preclinical sciences.

Since an extended bibliography would not be feasible, only selected references have been appended to each chapter. No attempt has been made in these to give recognition to all who have contributed to the subject, but rather to cite monographs, recent papers in which extended bibliographies may be found, and occasionally works of historical importance.

An epitome of prescription writing has been added as an appendix. This contains, it is believed, adequate information for the needs of the modern medical curriculum and may be taken up at any point of the course of study convenient to the instructor.

DALLAS, TEXAS

ARTHUR GROLLMAN

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## Part I

# Introductory Considerations

## 1. Introduction

### DEFINITIONS

**Pharmacology** may be defined simply as the science of drugs. It includes a study of their sources (*materia medica*), their action and fate in the animal organism (*pharmacodynamics*), their use in medicine (*therapeutics*), and their poisonous effects (*toxicology*). A drug is defined by the Food, Drug and Cosmetic Act to include "all medicines and preparations recognized in the United States Pharmacopeia and National Formulary for internal or external use, and any substance or mixture of substances intended to be used for the cure, mitigation, or prevention of disease of either man or other animals." More briefly stated, a drug is any substance used as a medicine. In actual practice, pharmacology does not limit itself to the study of drugs but includes the study of changes induced in living organisms by the administration in a state of minute division of all unorganized substances which do not act merely as foods. Thus, a study of the effects of many chemicals (*e. g.*, carbon monoxide, beryllium, muscarine, *etc.*) are included in pharmacology. The study of the action of such substances is of importance not only from a toxicological standpoint but also because of the light thrown by such studies on the reactions of the organism to drugs used to counteract the effects of disease or to reinforce the tissues in their struggle to maintain their functions when these are rendered abnormal. In a broad sense, pharmacology may be said to deal with any aspect of the interaction of chemical agents with biological systems. The latter include purified components of living systems as well as isolated tissues and intact animals. Pharmacology, accordingly, may be applied to the elucidation of fundamental physiological and biochemical mechanisms as well as for its primary objective, the application of chemical agents in the treatment of disease.

The art of applying drugs in disease is termed *therapeutics*. Many drugs, when used in excess or injudiciously, may cause undesirable, dangerous or fatal symptoms. Under such conditions they act as poisons, a term applied to substances having no value in disease but of practical importance because of the symptoms which they induce when ingested in quantity. The study of the effects of poisons, the diagnosis and the treatment of poisoning, and the methods of detecting the poison is termed *toxicology*.

It is impossible to distinguish between drugs and poisons since most remedies given in excess cause toxic symptoms, while many poisons are valuable remedies in small doses.

Pharmacy is closely allied to pharmacology; it concerns itself with the collection, standardization and preparation of drugs. *Materia medica*, the study of drugs from the standpoint of their botanical and chemical properties, as well as pharmacognosy, its modern counterpart, are now pursued chiefly by pharmacists. Although the preparation of drugs for therapeutic use is primarily the responsibility of the pharmacist, the physician ought to know those characters of drugs which are of importance in modifying their action and therapeutic application. Some general knowledge of the art of preparing drugs for therapeutic use is also indispensable. Many preparations are put up by the manufacturer in forms which require no further manipulation by the pharmacist. The latter, however, must be acquainted with the practical aspects of therapeutics, particularly the dose, method of administration, and toxicity of drugs. Like the student of medicine, dentistry, and their allied professions, he must have a thorough knowledge of pharmacology. The physician and others who utilize drugs must, in turn, be conversant with the composition and properties of the preparations which they prescribe.

## HISTORY

From the earliest times, tribal priests and medicine men have used various plants, minerals and animal organs, usually in association with prayers and incantations, to exorcise the evil spirits which they believed to be the cause of disease. Preparations containing alcohol, caffeine, cocaine, atropine, *etc.* have been used since before the earliest times of recorded history for their exhilarating effects. The earliest known prescriptions are recorded in a Sumerian tablet of 2100 B.C. which describes salves, ointments and medicines containing cassia, asafetida, thyme, sodium chloride and potassium nitrate. The Ebers Papyrus, discovered at Thebes, which dates from 1550 B.C., contains prescriptions of castor oil, opium, aloes, colchicum, squill and other drugs which are still in use. At a later date the temples of Esculapius and his disciples became the repositories of medical and pharmaceutical lore with prescriptions engraved on their pillars and doorposts.

The first recognition of disease as an abnormal reaction of the body rather than as a visitation from the Gods, was formulated by Hippocrates, who is supposed to have lived between 460 and 370 B.C. The Hippocratic concept, however, was soon lost and did not reappear until the renaissance. During this dark period the concepts of Galen (A.D. 131–201) and his dogmatic system of polypharmacy prevailed. Galen's name is retained in the term *galenical* for preparations of crude vegetable drugs. His many preparations included our presently used cold cream or rose water ointment (*Unguentum refrigerans Galeni*).

One of the outstanding leaders of the renaissance, which reintroduced free thought and critical inquiry, was Paracelsus (1493–1541) who attacked the Galenic system of polypharmacy and introduced the use of simple chemical

substances rather than the mixed vegetable preparations of Galen. Paracelsus introduced the use of mercurials in the treatment of syphilis. During his lifetime also the first official pharmacopeia was printed at Florence in 1497.

**Superstition** continued to prevail even after the renaissance with such concepts as "the royal touch" and the exploitation of numerous quack remedies. Although many drugs were in use, their adoption was fortuitous and the indications for their use were based on the prevailing theories of disease rather than any careful observation of their effects. The growth of chemistry during the nineteenth century led to the introduction of many new compounds in therapeutics which displaced the Galenic pharmacy which utilized preparations of crude drugs. It was only with the development of the science of physiology that the mode of action of drugs could be determined and pharmacodynamics developed. Advances in pathology and bacteriology in turn directed efforts to the therapeutic management of the derangements in the organism which these sciences showed to be the basis for different diseases.

**Pharmacology**, as a science, had its beginning in the latter half of the nineteenth century. At this time, Carl Binz, a pupil of Johannes Müller at Berlin, gave lectures on pharmacology and undertook a study of cyanide poisoning and of quinine. Rudolph Buchheim, a pupil of Ernst Weber of Leipzig, another prominent physiologist of the day, established in the basement of his home a laboratory for experimental pharmacology and was the occupant of the first chair of pharmacology at the University of Dorpat in 1849. Oswald Schmiedeberg, a pupil of Buchheim and Carl Ludwig, was the first occupant of a full time University Professorship in Pharmacology and is usually considered as the founder of modern pharmacology because of the many students whom he attracted and who continued his work.

The first full-time university professorship of pharmacology in the United States was established in 1890 at the University of Michigan with John J. Abel, a pupil of Schmiedeberg, as its first occupant. Prior to this time, *Materia Medica* and *Therapeutics*, which constituted the pharmacology of the medical curriculum, was usually taught by practitioners of medicine. Abel introduced the methods of Schmiedeberg with lectures and demonstrations and initiated the investigative spirit of modern pharmacology. Other pupils of Schmiedeberg including Mosso at Genoa, Gottlieb at Heidelberg, Haffter and Hubner at Berlin, Cloetta at Zurich, Pohl at Prague, Morphore at Padua, Morishima in Japan, and Cushny at Michigan (and subsequently at Edinburgh), and others throughout the world established pharmacology as an important part of the medical curriculum.

The earlier workers in pharmacology limited their observations for the most part to the action of drugs in animals or on isolated organs or tissues. As scientific medicine has grown, however, the pharmacologist has applied the methods of the various medical disciplines to his own field so that at present all methods available to the biological investigator are used by the pharmacologist to widen his sphere of knowledge. Any scientific efforts devoted to the elucidation of the nature and action of drugs may be considered as part of the pharmacologist's domain. The synthesis of new compounds,



their bioassay, the study of their physiological effects and fate in the body—in short, all methods of the biologist, biochemist, physiologist, chemist and pathologist are utilized to elucidate the effect of drugs in health as well as in disease.

Except for the discovery of anesthesia in the nineteenth century, which made possible modern surgery, pharmacology has had its greatest growth during the past half-century. The chemotherapeutic agents, hormones, vitamins, and innumerable synthetic drugs made their appearance during this period. As a consequence of empirical observations of the effect of chemicals on the organism as obtained by animal experimentation and clinical study, medicine has passed from the period of rapid advances in diagnosis which characterized the earlier part of the century to the present era of rapid advances in therapy. Technical advances in related fields have resulted in a flood of new drugs at a rate faster than they can be evaluated clinically. The need for such evaluation has opened a new field of clinical pharmacology. It is, moreover, now possible to undertake a systematic screening of related chemicals on the basis of the theoretical concepts which have been formulated. As a rapidly growing science, pharmacology has also broadened its interrelationships with other biological sciences. Current studies, for example, have not only added to the therapeutic armamentarium of psychiatry but have contributed to exploring the functions of the brain and its disorders.

## RELATION TO OTHER MEDICAL SCIENCES

Pharmacology originated as a branch of physiology with the goal of revealing physiologic function by a study of the reactions of living matter to chemical agents. As a science *sui generis*, pharmacology retains its close association with physiology but is also a branch of biology very closely related to the other sciences included by that term. It is neither possible nor advisable that the boundaries of these allied sciences should be too strictly limited. Consequently, though in the great majority of cases there need be little hesitation in deciding whether or not a substance is a "drug" and should, therefore, come under the scope of pharmacology, there is unavoidably some overlapping and some account must here be given of remedial agents which would not be regarded as "drugs" in the ordinary sense.

The greatest interest of pharmacology does not lie in its purely biological aspects, however, but in its relation to the treatment of disease. As long as we are ignorant of how a remedy acts in any disease, the treatment is purely empirical; when the mode of action is understood, much greater accuracy can be attained in the treatment. The object of pharmacology is to provide a scientific foundation for therapeutics and to increase the resources of the art of healing. The exact way in which a drug changes the diseased condition can often be followed only imperfectly in man, and recourse must be had to experiments on healthy or diseased animals to elucidate the principles on which it should be employed. Animal experimentation plays a vital role in the evaluation of new drugs and frequently demonstrates properties of new chemical bodies suggesting their possible