# Pharmacology:
## Drug Actions and Reactions

Second Edition

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Little, Brown and Company Boston

Second Edition



Library of Congress Catalog Card No. 77-81491

ISBN 0-316-52226-0(C)
ISBN 0-316-52227-9(P)

Printed in the United States of America

# FOREWORD

The mode of action of drugs is not generally understood by people outside certain health professions. However, public awareness and concern about the intermittent or daily exposure of large segments of the population to drugs and other chemicals is greater today than ever before. Interest in drugs now extends far beyond their therapeutic use in the treatment of disease. For the first time, a large population of normal people receive drugs over long periods, as illustrated by the oral contraceptives. Recently, the dramatic increase in the use of street drugs and drugs of abuse in all age groups has greatly expanded public awareness of drugs. In addition, increasing numbers of chemicals appear in our environment as food additives, economic insecticides, and fertilizers and as industrial pollutants in air, water and food. It is abundantly clear that the science of pharmacology has relevance to a growing number in our society.

There is an obvious need for an authoritative book covering the general aspects of pharmacology and addressed to individuals of diverse backgrounds and occupations who wish to acquire an understanding of how chemical agents affect living processes. Such a book should be useful not just to students in the health professions but to biologists, chemists, public health officials, lawyers, legislators, administrators, science instructors and intelligent laymen as well.

*Pharmacology: Drug Actions and Reactions* is the consummate result of an earnest, scholarly and pioneering effort to present an explanation of the science of pharmacology in terms of general concepts and principles governing chemical-biologic interactions. This is a logical approach to cover the multitude of chemical agents and the diversified interests of the intended reader; the principles will endure even though today's drugs may change. With the background provided by this book, one will be prepared to understand the actions of most individual drugs. In addition, a sufficient number of important, specific examples are included to illustrate the application of the principles.

Much of the material presented in the book is oriented toward therapeutic agents, but the concepts and principles apply equally to most nontherapeutic and toxic chemicals; furthermore, specific attention is given to toxicology. Great effort has

been expended in making the text self-contained and understandable. The style is straightforward and lucid. The carefully selected illustrations and examples are simple and clear.

The author of this book is well known for her many research contributions in pharmacology over the years and for her thorough understanding of the subject. She has been a dedicated scholar and teacher of students in the health professions and in recent years has been a lecturer to nonprofessional groups as well. It was my pleasure to have guided her doctoral studies and to have collaborated in research with her during my tenure as chairman of the Department of Pharmacology at Tufts University School of Medicine.

The above was written as the foreword to the first edition. It is still relevant in its entirety, since the present edition incorporates additional and new material without changing the approach that has proved to be so successful in presenting the general aspects of pharmacology. The new chapter on drug actions affecting the fundamental properties of all cells and those influencing the autonomic nervous system, as well as the appended details of the pharmacology of various important classes of drugs, will, moreover, greatly enhance the reader's understanding of the mode of action of drugs. The thought-provoking questions newly provided at the end of each chapter will guide the serious student in mastering the fundamental principles of the interaction of drugs and living organisms.

Byron B. Clark

# PREFACE TO THE SECOND EDITION

The philosophy guiding the writing of this textbook, as stated in the preface to the first edition, was to present a comprehensive and coherent explanation of the science of pharmacology in terms of its basic concepts and principles. The text's wide acceptance by college students majoring in diverse fields as well as by students in medicine, nursing and veterinary medicine affirms that this was a logical approach to use. I am most grateful for this favorable reception. That the guiding concept was also realistic is evident from the fact that, despite rapid advances in the medical sciences, no revisions have been needed in these aspects of the original text. The text and references have been updated, however, to reflect advances in our understanding of receptors, of kidney function and of various other processes, and to indicate the changes in environmental and occupational toxicology and in new drug development brought about by recent legislation. Since students have indicated the usefulness of the Glossary, this portion of the book has also been amended to include additional terms in current usage. But it is the wholly new sections which have been added that clearly distinguish the present edition from its predecessor.

The textbook has been enlarged by addition of a new chapter and study guide questions at the end of each chapter, and by new appendixes prepared to meet the needs of students who wish to supplement their knowledge of the basic principles of drug action with more specific information about some of the therapeutic agents currently in widespread use. These sections were developed originally as teaching aids in my own undergraduate course in pharmacology. Their proved usefulness to several hundred students and the favorable comments of many colleagues have encouraged the incorporation of these teaching materials into the textbook itself.

The new Chapter 13, How Drugs Alter Physiologic Function: A Recapitulation, is a summary of the various mechanisms by which drugs may influence and alter physiologic functions and biochemical processes. The major portion of this chapter is concerned with the general aspects of the anatomy, physiology and biochemistry of the autonomic nervous system and with the ways in which drugs affect autonomic nervous system activity.

The approach used in the presentation of Appendixes 1-6 is both descriptive and

operational. The material presented is, however, only introductory; comprehensive sources such as those listed in Chapter 2 should be consulted for more detailed information about the drugs discussed as well as those that are not included. Appendix 1 deals with two groups of nonprescription drugs widely used by the laity – the antacids and laxative-cathartics. Appendix 2 is a synopsis of drugs that influence kidney function, a topic chosen primarily because the action of these drugs can be so well identified and characterized in terms of known physiologic functions and processes. Appendix 3 summarizes some important aspects of the use of chemotherapeutic agents in the treatment of parasitic and neoplastic diseases. Appendix 4 discusses the nature of pain and the principal classes of drugs used to treat pain: local anesthetics, nonnarcotic analgesics, narcotic analgesics, and general anesthetics as exemplified by alcohol. Appendix 5 continues the discussion of central nervous system depressants by summarizing the actions of drugs used as sedatives and hypnotics. Finally, Appendix 6 deals briefly with drugs used in the treatment of mental disorders.

I want to express my gratitude to my publishers, Little, Brown and Company, whose careful editing and sound judgment added immeasurably to the success this text has enjoyed. In addition to acknowledging again my debt to all those who helped launch the first edition of this book, my thanks are due to the many students and readers whose enthusiastic reception of the first edition encouraged and promoted the preparation of this new one.

R. R. L.

Boston

# PREFACE TO THE FIRST EDITION

Pharmacology is the unified study of the properties of chemical agents (drugs) and living organisms and all aspects of their interactions. So defined, it is an expansive science encompassing areas of interest germane to many other disciplines. The specific pharmacologic knowledge needed by the physician, who uses chemicals as therapeutic agents, differs from that of the biochemist or physiologist, who uses chemicals as tools in research. Likewise, this knowledge is different for the ecologist or legislator, who is sensitive to the consequences or responsibilities inherent in the widespread use of chemical agents. There is, however, a body of information dealing with the basic concepts and principles that is fundamental to understanding the actions of drugs in every aspect of this science, theoretical or applied, and at any level of complexity.

The purpose of this book is to provide a concise source of that core of pharmacologic knowledge that can be shared by all wishing to acquire an understanding of how chemical agents affect living processes. The emphasis is placed, therefore, on fundamental concepts as they apply to the actions of most drugs. In order to illustrate the underlying principles, some agents that are in general use or are subjects of public concern are singled out for fuller discussion. Certain therapeutic conditions are also discussed in order to provide an understanding of the basis of drug therapy. The nontherapeutic or toxicologic aspects of drug action are given special attention since the widespread exposure of living organisms to a multitude of chemicals is of grave public significance.

This book is written for individuals of diverse backgrounds who have in common a working knowledge of general chemistry and biology. The biochemical and physiologic principles needed to understand pharmacologic principles form an integral part of the text. In order to provide more coherence and greater ease in reading, individual statements have not been scientifically documented with references to the pertinent literature. At the end of each chapter, however, some specific as well as some general references are listed for those who desire more extensive information. And in the body of the text certain words or phrases are printed in boldface type to indicate that a fuller explanation of the term is contained in the Glossary. The Glossary of

more than one hundred entries also provides a handy reference for most terms defined throughout the text.

I have tried to prepare a text that alone will provide the nonprofessional with a basic understanding of pharmacology but that may also serve as an introduction for those who will be professionally concerned with the interactions of drugs and living organisms. I hope, too, that this book will serve the further purpose of implementing the presentation of pharmacology in nonprofessional schools so that students in biology, chemistry, psychology, physical education, and premedical programs as well as those in other fields will have the opportunity to acquire some training in one of the youngest of the experimental medical sciences – pharmacology.

R. R. L.

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# CONTENTS

# 1. THE HERITAGE OF PHARMACOLOGY

An acquaintance with the history of a subject frequently reveals the true nature of the subject. Tracing the growth of pharmacology, then, from its earliest beginnings will give us a sharper perspective of the scope of the field and a clearer understanding of what distinguishes pharmacology today as an orderly science in its own right. In the words of the Nobel laureate Albert Szent-Györgyi, "If we want to see ahead we must look back."

## THE BEGINNINGS

Man's use of medicinals is as old as man himself, since his need to find measures to combat sickness has always been as important to his survival as his need for food and shelter. Early man's efforts in dealing with disease, colored as they were by his superstitious concepts of the causes of illness, led him to search for animate and inanimate objects in his environment with which to drive away the evil spirits. But the successes of science frequently have their roots in the absurdities of magic, and some of our important drugs were discovered through primitive man's experiments with the plants that grew around him. The use of alcohol and opium to ease pain, of cinchona bark (the source of quinine) to treat malaria and of ipecac for amebic dysentery can be cited as examples of early man's therapeutic successes despite his ignorance of the causes of these ailments. Some of his failures can also be called valuable discoveries, since drugs like curare, veratrine and ouabain, known only as fatal poisons by primitive cultures in various regions of the world, have now become valuable therapeutic agents when used in proper amounts. Thus the accumulation of this primitive medical lore and its dissemination and use by midwives, priests, witch doctors and other practitioners were the beginnings of **materia medica**,[1] medicine and toxicology.

### Egypt and Babylonia

The Egyptians are to be credited with handing down to us the oldest known records of medicine, even though the medical systems of Sumaria, Babylonia and India are

[1] Terms appearing in **boldface type** are defined in the Glossary.

probably of equal antiquity. The most ancient of the records devoted entirely to medicine is the Medical Papyrus of Smith (ca. 1600 B.C.E.).[2] It clearly indicates that the Egyptians had developed a codified and conventionalized form of therapy for a great variety of diseases and had differentiated between those clinical conditions that could be treated successfully and those that could not. The Ebers' Papyrus (1550 B.C.E.), the largest of the Egyptian medical papyri, lists more than seven hundred remedies and describes in detail the procedures for their preparation and administration for specific ailments. Many of these prescriptions plainly show their magical origins in the inclusion of incantations together with ingredients such as lizard's blood, an old book boiled in oil, the thigh bone of a hanged man and excreta or organs of various domestic animals. But there is also reference to liver as a remedy for anemia and to modern drugs, such as castor oil, squill and opium. This close alliance of medicine and religious beliefs was to continue for many, many centuries and even today has not been completely broken.

As Egyptian medicine developed, it gave rise to great physicians and surgeons whose knowledge was unsurpassed even by the famous Greek physicians who came later. The Egyptians not only advocated professional standards of conduct that were to influence the Hippocratic code of medical ethics but also developed medical specialization. For example, some physicians limited their practice to obstetrics, gynecology or gastric disorders. For the first time the patient was given the choice of witch doctor or which doctor. The Egyptians can also take credit for some of the earliest concerns about public health in their promotion of public sanitation through a system of copper pipes for the collection of rainwater and the disposal of sewage.

The known contributions of the Babylonians to medicine appear to be fewer and of lesser consequence than those of the Egyptians. This may be related to the differences in their religious philosophies. The Egyptian had a comforting mythology that made him feel secure in his world; he believed that the supernatural powers were concerned with promoting his welfare. The Babylonian, on the other hand, lived in a hostile world in which demons were everywhere and were always ready to descend upon a victim in the form of sickness. Although the code of Hammurabi (2123–2081 B.C.E.) established the profession of physician as separate from that of clergy, with doctors' fees set by law, the highly superstitious populace demanded the irrational treatment purveyed by the sorcerers. Yet despite this contrast in medical culture between the Egyptians and the Babylonians, it was the latter who transmitted the foundations of medicine to India and Greece and even supplied the names of many Greek drugs.

### Greece and India

In both the Greek and Indian cultures, the earliest records disclose that secular medicine was practiced but still had to compete with that of the priesthood. For even though disease was treated by both medicinals and charms, the most common

[2] B.C.E.: before the common (Christian) era; C.E.: common era.

place for treatment was the temple. In Greece, with its luxuriant mythology and its plethora of deities, separate temples were built to Asclepius, the God of Healing, and these became virtually sanatoriums or hospitals for the sick. The greatest of these temples was built atop a high mountain peak at Epidaurus, to which people flocked from all parts of the Mediterranean area. Near the present-day ruins of this temple-sanatorium is an almost perfectly preserved theater built in the fourth century B.C.E. and paid for by the fees and largess of the temple's patients.

Secular medicine was fostered by and developed around the celebrated centers of learning. In India, the universities at Taxila (present-day Pakistan) and Benares, famous for their medical schools, and in Greece the four prestigious schools at Cos and Cnidus (in Asia Minor), Crotona (in Italy) and Acragas (in Sicily) produced some of the most illustrious men associated with the medical sciences of antiquity.

Sushruta (ca. 500 B.C.E.), one of the renowned names of Hindu science, was professor of medicine at the University of Benares. He described and laid down elaborate rules for many surgical procedures and was also probably the first to graft skin from one portion of the body to another and to attempt aseptic surgery by sterilization of wounds. Sushruta also recommended diagnosis by inspection, palpation and auscultation for the detection of the 1,120 diseases he described.

In the sixth century B.C.E., vaccination for smallpox was known and probably practiced in India. Evidence for this appears in writings attributed to one of the earliest Hindu physicians, Dhanwantari (550 B.C.E.): "Take the fluid of a pock on the udder of the cow . . . upon the point of a lancet, and lance with it the arms between the shoulders and the elbows until the blood appears; then, mixing the fluid with the blood, the fever of the small-pox will be produced." Yet vaccination for smallpox and the aseptic surgery practiced by Sushruta were unknown in Europe for another two thousand years. It may well be that there were still other advances that the Hindus could have contributed to Europeans, if the latter had had wider acquaintance with the culture of India and if there had been better transmission and acceptance of Indian knowledge.

The impact of the Indians on the advancement of medicine depends on whether one speaks about their contributions to European medicine or about the practice of medicine in India itself. In contrast, the preeminent Greek physicians of this period had a far-reaching effect on medicine and pharmacy; their influence was to pervade the ensuing years.

*Development of Medical Ethics*

It was the great teacher Hippocrates (460–377 B.C.E.) and his successors who really freed medicine from mysticism and philosophy and made it reliant upon rational therapy. Hippocrates taught the doctrine that disease stems from natural causes and that knowledge is gained only through study of the natural laws; he sought to explain Nature in Nature's terms. Since Hippocrates believed that the body has ample natural resources for recuperation and that the role of the physician was to remove or reduce the impediments to this natural defense, he made little use of drugs. He relied mainly upon fresh air, good food, purgatives and enemas, blood-letting,

massage and hydrotherapy, and used sparingly only a few of the four hundred drugs mentioned in his writings. However, Hippocrates is known as the Father of Medicine not just for his rational doctrine but mainly for his emphasis on medical ethics. The famous oath attributed to him did much to ennoble the medical profession by setting a standard of professional conduct to which subsequent generations of physicians have sworn fealty.

The emancipation from religious beliefs and the setting of high standards of ethics were the two most important contributions that the Greeks made directly to medicine; the art itself was not advanced to any degree beyond that achieved by the Egyptians of a millenium earlier. The Age of Greece did contribute to some important progress, however, in pharmacy, anatomy and physiology.

*Development of Pharmacy*

Theophrastus (372–287 B.C.E.), in his classic treatise *The History of Plants*, provided a summary of all that was known about the medicinal properties of plants. This work was later used by Dioscorides (57 C.E.), Nero's surgeon, in the preparation of a materia medica which scientifically described six hundred plants, classified for the first time by substance rather than by disease. It remained the chief source of pharmaceutic knowledge until the sixteenth century, and Dioscorides is honored as the Father of Materia Medica.

*Development of Anatomy and Physiology*

Herophilus, perhaps the greatest anatomist of antiquity, and Erasistratus, probably the most outstanding physiologist of ancient times, were contemporaries of Theophrastus. They developed their respective disciplines to heights which would be attained only once again before the Renaissance. Herophilus carried out remarkable dissections, named various parts of the human body and even understood the role of nerves, differentiating for the first time between sensory and motor nerves. He understood so completely the function of the artery that he might well be credited with the discovery of the circulation of blood nineteen centuries before Harvey.

Erasistratus also made noteworthy advances in dissection and in understanding the function of arteries, veins and nerves as well as some of their interrelationships. Although Hippocratic medicine developed the rational approach to therapy, it was Erasistratus who rejected the final ties of medicine to mystical entities. Hippocratic medicine was bound to the doctrine of so-called humors, the composition of the body being blood, phlegm, yellow bile and black bile, and illness or pain being brought about by a change in the proportion of these humors. Erasistratus abandoned this humoral theory and tried to account for all physiologic phenomena on the basis of natural causes. Unfortunately, it was the Hippocratic theory which became the heritage of medicine, being ultimately discarded only in the nineteenth century.

**The Roman Era**

After the conquest of Greece, the heritage of Greek medicine migrated to Rome. With their great sense of order, the Romans organized medicine, trained physicians

in state schools, built military and private hospitals and provided for public sanitation. But their most useful contribution was the compilation of encyclopedic summaries of knowledge which prepared the way for future advances. In medicine, the foremost was that of Aurelius Celsus (first century B.C.E.); when rediscovered in the fifteenth century, his *De Medicina* played a major role in fostering the reconstruction of medicine.

Although the Romans formulated and applied their borrowed medicine in able fashion, they contributed little of real significance to the development of Western medical science. Even the one outstanding original scientist of this period – Galen (131–201 C.E.) – was a Greek physician.

Galen was one of the first true experimental physiologists. For example, in neurology he performed experiments by which, in serial sectioning of the spinal cord, he was able to distinguish the sensory and motor functions of each segment of the cord. Galen also made many contributions to the field of pharmacy; most noteworthy are his extensions of the work of Dioscorides, introduction of a complicated polypharmacy and origination of the use of **tincture** of opium and preparations of vegetable drugs, still known as "**galenicals.**"

Galen missed anticipating the science of pharmacology, however, since he did not carry over the experimental approach to the study of the drugs he used. He further tarnished his record as an experimentalist by ignoring the work of Erasistratus and adopting and enlarging the Hippocratic doctrine of the origin of human illness. Galen added the four elements – earth, air, fire and water – to the four humors – blood, phlegm, yellow bile and black bile – and ascribed the cause of all diseases to derangement of these elements and humors. In Galen's voluminous writings (of the five hundred books reputed to him, one hundred eighteen have survived), he set forth his ideas and his system of medicine and pharmacy with such authority and conviction in his own invincibility that he profoundly affected medicine for fifteen hundred years. Unfortunately, to the detriment of medieval medicine, it was the serious errors embodied in Galen's system of the cause of disease which went uncriticized; these far outweighed in influence his valuable contributions as an accurate observer and experimentalist.

**The Middle Ages**

In the long span of years between the distinguished Greek physicians and Paracelsus (1493–1541) there were no significant new advances in medical science. This is not to say, however, that progress was not made during the Dark Ages. While the medical sciences were marking time in Europe, the wealth of knowledge that had been accumulated and preserved in the Roman manuscripts passed to the East. Sustained and enriched in turn by the Arab and Jewish physicians, this medical knowledge came back to Europe with the Western movement of the Arabs and the travels of the Crusaders. The diligence of the Christian religious orders in copying manuscripts and in making their monasteries the repositories of all the learning of the past also helped in preserving this knowledge. Notable among those responsible for maintaining the continuum of medicine during the Dark Ages were the Moslem physicians