Modern Pharmacology

Second Edition

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MODERN PHARMACOLOGY

SECOND EDITION

EDITED BY

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PREFACE TO THE SECOND EDITION

Updating and expanding *Modern Pharmacology* in its Second Edition has become a surprisingly welcome task. It has given the editors a chance to deepen a collaboration and friendship that began in 1961, a friendship that shows no signs of coming unraveled despite the passage of almost 25 years. With the considerable help of our colleagues, we have prepared this expanded Second Edition.

We have added three new chapters (Pharmacokinetics, The Calcium Channel Blockers, and Immunomodulating Drugs), which we believe are reflective of important new directions in medical thought. The chapter on pharmacokinetic principles is, perhaps, more detailed than is absolutely necessary for students' needs. However, it provides a theoretical framework to underlie the rational approach that the physician can now apply to drug dosing for individual patients, including those with impaired liver and kidney function. The chapter on calcium channel blocking drugs pulls together information that was just beginning to emerge at the time the first edition was written and greatly expands our knowledge of the many areas in basic and clinical medicine in which these drugs are exerting profound influence. The addition of a chapter on immunopharmacology is especially timely since the use of agents to suppress or modify immune responses during organ transplantation has recently assumed considerable importance in therapeutics.

All the remaining chapters have received careful attention and appropriate modification. We are most grateful for the past contributions of the authors of the first edition who, for various reasons, could not lend their active support in this new venture, and also happily welcome our association with several new colleagues.

In ancient Egypt it was recommended that to relieve a constipated child one should boil an old book in oil and apply half of it on the stomach to start evacuation. We sincerely hope that this updated edition of *Modern Pharmacology* no longer qualifies for "old book" status, and that it will continue to serve a wide variety of pharmacological uses.

C. R. C.
R. E. S.

PREFACE TO THE FIRST EDITION

Modern Pharmacology was conceived as a teaching text, that is, a text written, organized, and edited specifically to fill needs identified by faculty and students in the health sciences. In determining the extent of detail and depth of analysis with which any topic would be treated, the editors have been guided by their conviction that, unlike a reference work or a supplementary manual, a teaching text should simultaneously fulfill two obligations:

1. To focus attention on the underlying principles of the discipline in order to facilitate and encourage a student's subsequent understanding of more specialized topics; and
2. To make easily and clearly accessible the most current and authoritative information on major issues in the field.

In *Modern Pharmacology,* readers will find the discussion of therapeutic agents sufficiently detailed to ensure accuracy and clarity without a counterproductive proliferation of detail. The extensive introductory section on general principles is intended to guarantee that the student's understanding of specific drugs will be grounded in the fundamentals of receptor theory, pharmacokinetics, and toxicology. In addition to the emphasis on general principles in the introductory section and throughout individual chapters, we felt that certain other topics needed to be covered in more detail than is usually the case in textbooks of pharmacology. For example, we have found that the role played by α and β adrenoceptors, both in normal autonomic regulation and following modulation by sympathetic agonists and antagonists, often involves concepts that initially are difficult for students to grasp. We have, therefore, discussed these receptors from a number of viewpoints in different chapters within Parts II (Drugs Affecting the Autonomic Nervous System) and III (Cardiovascular Drugs). The functioning of receptors in normal sympathetic nervous system control is covered in Chapter 9 (Introduction to the Autonomic Nervous System); their activation by drugs is discussed in Chapter 11 (Sympathomimetic Drugs); their blockade is examined in Chapter 12 (Adrenoceptor Antagonists); and, finally, their modification by antihypertensive agents is thoroughly analyzed and summarized in Chapter 23 (Pharmacological Treatment of Hypertension). We feel that such reemphasis, especially when placed in the conceptual framework of physiological *and* pharmacological control and intervention, will allow the student to fully comprehend the importance of these receptors in the clinical management of disease. Furthermore, the underlying mechanisms responsible for the appearance of certain side effects (e.g., orthostatic hypotension, gastrointestinal hypermotility and hypomotility, augmented salivary and pulmonary secretion, etc.) will be appreciated more easily.

Other areas that we believe have not received sufficient discussion in other texts include antiarrhythmic agents, antihypertensive drugs, contemporary drug abuse, antiasthmatic drugs, topical drug use, antirheumatic and antiinflammatory compounds, the principles underlying cancer chemotherapy, and new methods of drug delivery. These areas have been singled out for comprehensive discussion either in expanded chapters (Chapter 18, Pharmacology of Antiarrhythmic Drugs;

Chapter 23, Pharmacological Treatment of Hypertension; Chapter 42, Contemporary Drug Abuse; Chapter 56, The Rational Basis for Cancer Chemotherapy) or in separate chapters that have unified material that other texts have discussed only briefly in disparate chapters (Chapter 6, Bioavailability, Dosage Regimens, and New Delivery Systems; Chapter 69, Pharmacological Control of Asthma; Chapter 70, Antiinflammatory and Antirheumatic Agents; Chapter 71, Drugs Used in Dermatological Disorders). The latter approach is especially well illustrated in Chapter 71, which begins with a description of normal skin anatomy and physiology, progresses to the general principles of percutaneous drug transport, analyzes the utility of local versus systemic therapy, and then discusses the specific topical applications of previously mentioned classes of therapeutic agents. Chapters developed in this way provide an emphasis and focus not often evident in more general discussions of pharmacological activity.

In writing this textbook we have been guided by our view, which is consistent with that of other faculty in the United States as well as in other countries (most recently expressed at The Teaching and Learning in Pharmacology Symposium at the 1981 Eighth International Congress of Pharmacology in Tokyo), that there was still a need for a textbook of pharmacology, in addition to those currently available. Many teachers of pharmacology felt that such a book must avoid two pitfalls. It must not be so detailed that students are overwhelmed by the volume of material to be mastered, and it must not be so brief and simplistic that students are deprived of the fundamental background material (e.g., general principles and reviews of appropriate basic physiology) necessary for a broad understanding of drug therapy.

The contributors to *Modern Pharmacology* were chosen for their ability to balance the need for brevity, clarity, and accuracy without sacrificing essential depth. In general, each chapter has been written by individuals who teach *and* do research in the areas they have written about. In addition, each chapter has been reviewed and evaluated for completeness and relevance by other prominent authorities on that particular topic.

We hope that both faculty and students find that we have achieved our goals and that this book is an aid in learning about drugs currently available and in providing the background for the evaluation of compounds yet to be discovered.

C. R. C.
R. E. S.

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We acknowledge the efforts of many of our colleagues for taking the time to carefully review various sections of this manuscript. In particular, we are indebted to the thoughtful and thorough reviews of Drs. Tai Akera, Marion Anders, Carl Buckner, William Berndt, Sue Duckles, William Fleming, Desmond Gourley, Joe Hume, Abnash Jain, Rashida Khakoo, Robert Mueller, Arthur Raines, Charles Rutledge, George Spratto, Frank Standaert, Mary Wimmer, and Steve Young.

We also acknowledge the assistance of the editorial staff of Little, Brown and Company. Nancy Coon, Medical Editor, provided leadership and cooperation at every stage of the project. Katharine Tsioulcas, Senior Book Editor, worked with us by phone almost on a daily basis during the arduous but enjoyable editing process.

In addition, we would like to thank our hard-working office staff: Virginia Lewis, Elessa Kramer, Debra Beery, Louise Shepherd, and Tom McBee; the Medical Illustration Department of West Virginia University School of Medicine, including Virginia S. Swecker and Marianne Peterson; and Dr. Arthur Jacknowitz of the University's Drug Information Center.

Last, we acknowledge the contribution of Margaret Craig and Judith Stitzel, who took time from their own busy professional lives to provide continued encouragement and support through the writing of this Second Edition.

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CONTENTS

PART I

GENERAL PRINCIPLES OF PHARMACOLOGY

NOTICE

The indications and dosages of all drugs in this book have been recommended in the medical literature and conform to the practices of the general medical community. The medications described do not necessarily have specific approval by the Food and Drug Administration for use in the diseases and dosages for which they are recommended. The package insert for each drug should be consulted for use and dosage as approved by the FDA. Because standards for usage change, it is advisable to keep abreast of revised recommendations, particularly those concerning new drugs.

CHAPTER 1

DEVELOPMENT OF PHARMACOLOGICAL THOUGHT

ROBERT E. STITZEL

To understand a science, one has to know its history and development. It should be useful, then, and we hope entertaining, for students to understand the background and underlying assumptions of *pharmacology,* a discipline that defines itself in simple yet all-encompassing terms: the study of the interaction of chemicals with biological systems.

One of the earliest concerns of humankind was a desire for protection against the evils of disease and suffering. Since the conquering of these afflictions often determined survival and since the current state of knowledge did not permit the rational use of *drugs* (chemical entities, both endogenous and foreign, that are capable of reacting with biological systems), it should not be surprising that additional help was sought from supernatural powers. This was especially true of the ancient Greeks, who believed that it was by whim that the gods dispensed prosperity or pestilence. Thus, early in human history a natural bond was formed between religion and the use of drugs. Those who became most proficient in the use of drugs to treat disease were the "mediators" between this world and the spirit world, namely, the priests, shamans, holy persons, witches, and soothsayers. Much of their power within the community was derived from the cures that they could effect with drugs. It was believed that the sick were possessed by demons and that health could be restored by identifying the demon and finding a way to cast it out.

Originally, religion dominated its partnership with *therapeutics* (the application of chemical substances in the diagnosis, prevention, and treatment of disease, or, additionally, the use of drugs for the intentional modification of normal physiological and biochemical function) and divine intervention was called upon for every treatment. However, the use of drugs to effect cures led to a profound and drastic change in both religious thought and structure. As more became known about the effects of drugs, the importance of divine intervention began to recede, and the treatment of patients effectively became a province of the priest rather than the gods whom the priest served. This process of cultural evolution, brought about at least in part by the growing understanding of the curative powers of natural products and decreasing reliance on supernatural intervention, forever altered the relationship between humanity and its gods. Furthermore, when the priests began to apply the information learned from treating one patient to the treatment of other patients, the religious approach began to lose most of its remaining proponents: There was at last a recognition that a regularity prevailed in the natural world that was independent of supernatural whim or will. Therapeutics thus evolved from its roots in magic to a foundation in experience. This was the cornerstone for the formulation of a scientifically based practice of medicine.

People began to believe that nature alone could provide the means to remove pain and disease, and thus they sought remedies in nature, that is, in

plants, minerals, and animals. A variety of medicinal agents were collected on the basis of their symbolic qualities as well as on astrological signs and portents. For example, since the sword symbolized strength and power, the early Greek physicians attempted to use iron therapy against weakness and anemia. The observation that the horn of the rhinoceros is powerful led Chinese physicians to propose it as a potent aphrodisiac (with subsequent intensive hunting and near extinction of rhinoceroses).

While it is often tempting to dwell on the more bizarre, and possibly absurd, therapeutic practices of the ancients, it should always be kept in mind that these practitioners brought forth their explanations in good faith. Furthermore, many of their "drugs" were added to the therapeutic armamentarium only after considerable trial and error and application of clinical judgment. We should not automatically brand their explanations as silly and as having no basis by today's "rational" standards. We must assume that these early drug users were just as intelligent as we are and that they had good reasons, *in light of the facts then available,* for what they said and did. The answer to the question What did they consider good reasons? is not a simple one: It must take into consideration their entire intellectual, ethical, and cultural background.

CONTRIBUTIONS OF MANY CULTURES

The Indian cultures of Central and South America, although totally isolated from the Old World, developed drug lore and usage in a fashion almost parallel to that of the older civilization. The use of drugs played an intimate part in the rites, religions, history, and knowledge of the South American Indians. The knowledge of medicinal remedies possessed by the Aztecs probably was accumulated both during their migration into the valley of Mexico and through their commerce with the Mayans to the southeast, the Zapotecs to the south, and the Tarascans to the west. These contacts greatly expanded their knowledge of the abundant flora of these regions, much of which was believed to be of medicinal value. As we have already seen for European medicines, New World medicine was also closely tied to religious thought. All the Indian cultures treated their patients with a blend of religious rituals and herbal remedies. Incantations, charms, and appeals to various deities were as important as the appropriate application of poultices, decoctions, and infusions.

The early drug practitioners both in Europe and South America gathered herbs, plants, animals, and minerals and often blended them into a variety of foul-smelling and ill-flavored concoctions. The fact that many of these preparations were so distasteful led to an attempt to improve on the "cosmetic" properties of these mixtures to ensure patient use. Individuals who began to search for improved product formulations were largely responsible for founding the disciplines of *pharmacy* (the science of preparing, compounding, and dispensing medicines) and *pharmacognosy* (the identification and preparation of crude drugs from natural sources).

At a very early stage in the history of pharmacology there were attempts to codify and standardize remedies. The records that have come down to us from China, India, Sumeria, Egypt, and Greece are frequently concerned with the accumulation, development, and recording of local drug lore; this was an integral part of each culture. Many of these writings, some dating as far back as 4000 B.C., contain numerous dietary suggestions and recipes extolling the benefits of virtually every known variety of fruit, vegetable, grain, grass, or bulb. This codification of drug lore was based on information that had been accumulated during earlier centuries.

The Chinese medical papers were written quite early and were extensive. The *Pen Tsao*, for instance, was written about 2700 B.C. and contained classifications of individual medicinal plants as well as compilations of plant mixtures to be used for medical purposes. The Chinese *Doctrine of Signatures* (like used to treat like) enables us to understand why medicines of animal origin were of such great importance in the Chinese pharmacopoeia. Ancient Egyptian medical papyri con-