KRANTZ & CARR'S

Pharmacologic Principles of Medical Practice

EIGHTH EDITION

Domingo M. Aviado

Pharmacologic Principles of Medical Practice

A TEXTBOOK ON PHARMACOLOGY AND THERAPEUTICS FOR STUDENTS AND PRACTITIONERS OF MEDICINE, PHARMACY AND DENTISTRY

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Eighth Edition

Foreword by

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Dedicated to
Algernon B. Reese
and
Harold G. Scheie
From the grateful father of a patient

FOREWORD TO EIGHTH EDITION

In the previous editions the important determinants for preparation of another edition included the introduction of new drugs, expanded knowledge of the mechanism of drug action and metabolism, and more precise clinical pharmacology. In this, the Eighth Edition, many new and fascinating elements have been added while the time-tested values of this standard and popular textbook on pharmacology have been retained. Most important is the introduction of a new author, Professor Domingo M. Aviado, of the Department of Pharmacology at the University of Pennsylvania. Dr. Aviado brings youthful freshness, enthusiasm, broad and deep knowledge of drugs, drug action, physiology and clinical medicine, and a tremendous interest and effectiveness in medical student teaching. Dr. Aviado is very much a contemporary man and his recognition of the changing pattern of medical education has led him to rewrite and to organize the vast knowledge of pharmacology contained in the Seventh Edition of Krantz and Carr's textbook as well as to add information on new drugs and their clinical application.

Dr. Aviado has done this in such a manner that the Eighth Edition will be of great value to students in the health professions, to young health professionals during their post-degree training period, and to professionals in the practice of medicine, pharmacy and dentistry. This textbook for all seasons of a person's professional life provides the basic pharmacological principles of clinically important drugs grouped according to their major therapeutic effect on organ systems. A perusal of the table of contents will entice the novice into the rich and readable text lured by such section titles as "Pharmacology of Blood Cells and Blood Plasma," "Pharmacology of the Reproductive System," "Pharmacology of the Respiratory System," or Chapter headings such as "Antidotes and Clinical Toxicology," "Habitual Use and Abuse of Drugs," "Uropharmacology" and many others. At the same time the professional in training or in practice will be quickly guided to the section and chapter for his particular continuing education where he can learn of the appropriate drugs, their dosages, absorption, fate and excretion, mode of action, adverse reactions, contraindications and drug interactions. Of particular value to the thoughtful and conscientious physician, pharmacist and dentist is the inclusion of the evaluation of drug efficacy made by panels of distinguished clinicians and pharmacologists under the sponsorship of the National Academy of Science—National Research Council. Thus the new author has fulfilled in an innovative and creative fashion the objective of *A Textbook on Pharmacology and Therapeutics* which was so successfully begun by the original authors.

There is another noteworthy touch which should be mentioned. Dr. Aviado has dedicated this edition to Dr. Algernon B. Reese and Dr. Harold G. Scheie, two outstanding American ophthalmologists who are legends in their own time. Dr. Reese, Professor of Ophthalmology at Columbia University's College of Physicians and Surgeons, is nationally and internationally acclaimed for his work in retinoblastoma, which has led to ever improved methods of treating this childhood tumor thereby saving the vision and lives of countless children throughout the world. Dr. Harold G. Scheie, Professor of Ophthalmology at the University of Pennsylvania, renowned Surgeon to persons from all parts of the globe, teacher of teachers, has made notable contributions to our understanding and better treatment of glaucoma. It is fitting that this Eighth Edition which will bring much knowledge and understanding to its readers should be dedicated to our two friends who have done so much for vision.

Alfred Gellhorn, M.D., Sc.D. (Hon.)
Dean of the Medical Faculty
University of Pennsylvania

PREFACE TO THE EIGHTH EDITION

When *Krantz and Carr* wrote the first edition of *Pharmacologic Principles of Medical Practice*, the age of miracle drugs had just begun. The sulfonamides and the antibiotics, penicillin and streptomycin—all were changing the outlook in the treatment of microbial diseases. The following drugs were about to be introduced in rapid succession, unprecedented in the history of therapeutics: alkylating agents and antimetabolites for treatment of neoplasms, ganglionic and adrenergic blocking drugs for essential hypertension, carbonic anhydrase inhibitors and thiazides as diuretics, antipsychotics, anti-anxiety agents and antidepressants for mental illness, and corticosteroids and oral antidiabetics as substitutes for hormones. In the 1950's new drugs were introduced at a rate of 50 to 90 yearly.

In the face of constantly changing available drugs, pharmacology was taught by emphasizing general principles. A group of drugs was selected and the generalities were formulated on the basis of observations on several drugs. Because information regarding a single drug was insufficient, observations on various drugs were combined to formulate a complete picture of the pharmacology of the group of drugs. The student had sufficient time to perform laboratory exercises demonstrating pharmacologic principles of biological assay, dose-response curve and margin of safety. The time available was not adequate for the teaching of details relative to the clinical use of drugs, and dosages were omitted. The size of pharmacology teaching staffs was limited in number and therefore the responsibility for teaching was dependent on a few instructors who had to master several topics to enable them to be helpful to students who were eager to learn about drugs.

The present author joined the Department of Pharmacology at the University of Pennsylvania in 1948, a year prior to the publication of the first edition of Krantz and Carr's textbook. With the guidance of Carl F. Schmidt, the author participated in the teaching of medical students and started his research involving reflexes induced by veratrum alkaloids originating from the heart and lungs. This was the era of the physiologic approach to the investigation of drugs, so the perfusion technique was used for the identification of sensory receptors. However, this experimental approach was not completely successful because of the premature appearance of edema in the perfused lung, cardiac arrhythmia in the perfused heart and shock in the animal with perfused systemic vessels. These complications in turn led to the author's interest in the search for new drugs to treat pulmonary edema, pulmonary emphysema, bronchial asthma, systemic shock, essential hypertension, angina pectoris and cardiac arrhythmias. For the last-mentioned disorders, chloroquine and congeners were investigated which led to the study of new agents for the treatment of drug-

resistant malaria. This was about to lead to research in the areas of chemotherapy of pulmonary helminthiasis and neoplastic disease when Williams & Wilkins invited the author to prepare the eighth edition.

The eighth edition has been written under circumstances entirely different from those surrounding the first. As in other medical schools, the teaching personnel in Department of Pharmacology at the University of Pennsylvania has increased fourfold, and consequently teaching by a particular instructor has become limited in scope. Research has gradually occupied an increasing amount of time, although teaching has continued to be the primary responsibility of those who work in educational institutions. The ever-changing scene of available drugs has been curtailed, as only a dozen drugs are introduced a year. The amount of time allotted to the teaching of pharmacology in the medical curriculum has been reduced to half the original, and in some schools pharmacology is taught in conjunction with basic or clinical sciences or both by integration in organ systems or diseases.

Like other teachers, the author has failed to successfully assess the effectiveness of teaching pharmacology. He has found himself bearing increasing responsibilities to his family, to his profession and to society in general, and thus it has been almost impossible for him to adequately perceive the changes in the attitudes of students, the relative importance of drugs in therapeutics and the rising cost of medical care and drugs. Based on conversation with recent graduates, there are major shortcomings in the current teaching of pharmacology. Graduates who have been taught in generalities may find themselves unable to make a reasonable selection of a drug to use in practice. They learned in pharmacology courses that barbiturates in general induce the formation of hepatic enzymes which metabolize other drugs, and therefore they tend to avoid their use and rely on other, less effective hypnotics and sedatives. The graduate was not completely informed that the phenomenon of enzyme induction has only been shown unequivocally to pertain to three barbiturates administered in rats. The emphasis on teaching by means of drugs instead of diseases has its limitations. The graduate might not recall the use of epinephrine in the treatment of glaucoma but would remember its mydriatic effect. Likewise, it has been easy for graduates to list the uses of the sulfonamides while forgetting to consider these drugs when faced with a patient suffering from dermatitis herpetiformis.

At the same time, the recent graduates who have received the same generalized form of instruction find themselves relying heavily on drug information supplied by monographs on diseases, the abbreviated material collected in postgraduate seminars and the elaborate advertisements of manufacturers. An examination of marketing reports indicates that most practitioners prescribe a few selected drugs; 75% of the dollar value of the drug market is accounted for by 30 drugs which are covered in about 1/10 of a pharmacology course in a sketchy manner. Generalities learned as a student do not help in the choice of a drug.

The preparation of the eighth edition provided an opportunity for the author to incorporate some changes which might ease the burden of teaching and studying pharmacology. The major change is to reduce generalities and emphasize details of a few selected drugs. More information on specific drugs is now available, so that it is no longer necessary to form a composite picture derived from observation of other drugs.

There are six features which appear for the first time in the eighth edition.

First: the selection of 100 prototypes representative of drugs which are likely to be used for the treatment of disease. This selection is based on the clinical efficacy of the drug, on its popularity among practitioners and on its appeal as a tool for teaching pharmacologic principles. Each of the 100 prototypes is discussed in terms of the usual dosages, indications, mode of action, contraindications and adverse reactions. The recent interest in drug interactions has resulted in a separate entry for each prototype. The table of contents lists these prototypes and includes digoxin, ephedrine and chloroquine and 47 others which have been in use since before 1948, and 50 introduced since 1949. Of the latter, only 10 of the 100 prototypes were introduced since 1963.

Second: the selection of 100 alternatives which would supplement the 100 prototypes. The alternatives include drugs introduced since the seventh edition appeared and are labeled as *new* in the table of contents. The drugs were introduced as follows: 12 in 1968, 12 in 1969, 17 in 1970, and 8 in 1971; 4 additional drugs introduced in late 1971 and 2 in early 1972 could not be included in the present edition. Alternates introduced prior to 1968 have been discussed in previous editions and deserve some consideration in the present edition because they are used to treat the diseases for which the prototypes are not indicated.

Third: the use of 230 categories of drug usage to help students recognize differences in potency, duration of action, mode of administration and extent of usefulness of pharmaceuticals. In the classical tradition, instruction in the barbiturates has been given in accordance with the categories of long-acting, intermediately-acting, short-acting and ultrashort-acting drugs, and it should be remembered that there are important differences, not so much in duration of action as in metabolism and clinical usefulness. The digitalis glycosides have not been taught in a similar manner, and thus most students forget the availability of intravenous preparations produced on account of the poor oral absorption of this group of drugs. An alphabetical list of the categories appears in the appendix (p. 1214).

Fourth: the use of new titles to emphasize the multiple applications of drugs. Epinephrine normally would be discussed in a chapter on "Sympathomimetic Drugs." In the present edition it is included also in the following chapters: "Drugs for the Treatment of Bronchial Asthma," "Ophthalmic Pharmacology," "Drugs for the Treatment of Disorders of the Heart Beat," "Treatment of Shock" and "Pharmacologic Aspects of Allergy." Another example is dexamethasone, which is discussed not only under "Adrenal Corticosteroids" but also under "Pharmacologic Aspects of Arthritis," "Ophthalmic Pharmacology," "Dermatologic Pharmacology" and chapters devoted to the treatment of bronchial asthma, increased intracranial pressure and trichinosis.

Fifth: the new arrangement of topics in Sections I to XVIII on organ systems, in Section XIX on special topics and in an Introductory Section on general pharmacology. The appendix contains the results of a survey of teaching of pharmacology conducted by the author, and a compendium of drug preparations, dosages and prescriptions prices compiled by my colleague, Harry Salem. To allow cross references among various sections and with the appendix, the drugs have been numbered with a roman numeral for the section and arabic numbers for its place in a section. The use of numerals has revealed the following statistics: there are 1365 drugs listed in this book, 85% of which are com-

mercially available in the United States. The 15% or 193 drugs which are not available comprise the following: 64 which are now obsolete but are included for historical reasons and to record the drugs which have received *ineffective* ratings (see below); 62 which are sold in Europe but have not been introduced in the United States; and 67 that are under clinical investigation here and abroad. Most of the drugs belonging to the last two groups are in the categories of drugs influencing the autonomic nervous, respiratory and cardiovascular systems and antiparasitic drugs. These topics have been the subject of research investigation by the author for the last 25 years and it is a great personal disappointment for him to note that no drug belonging to these categories has been introduced since 1968 and only 3 since 1962. It is important for the student to realize that the lack of new drugs in these areas does not reflect a lack of interest or a need for them.

Sixth: the inclusion of Drug Efficacy Study Implementation (DESI) ratings. The results of review by panels appointed by the National Academy of Science—National Research Council of drugs introduced from 1938 to 1962 have appeared in the Federal Register since 1967. No compendium of these ratings has been published and they are being summarized for the first time in the eighth edition. Ratings reported up to June 15, 1972, are included in this edition. The author has taken the attitude of accepting the adequacy of 99% of the ratings because there has been no time to examine the reasons for the panels reaching their conclusions and making their recommendations. In 1% of the instances, the author has disagreed with them and the reasons for this are mentioned.

The illustrations were selected for their teaching value. Techniques used in the laboratory and in the clinical investigation of drugs were selected, not only those in current use but also those of historical interest. There is one figure corresponding to each category of drugs. The author wishes to acknowledge the help received from the authors who supplied the glossy prints and the permission of the publishers to use them.

The author also wishes to express his thanks to the professors of pharmacology of the schools of medicine, pharmacy and dentistry, who, in exchange for his own, furnished him with lecture schedules, lecture notes and laboratory manuals, which he has examined. It would be advantageous to receive any comments, suggestions and corrections relating to the text from them, as well as from their students and practitioners.

Portions of the text have been examined by the following reviewers: Nathan B. Eddy, Samuel L. Fox, Howard W. Jones, George B. Koelle, Peter J. Snyder and Harry Wollman. Their suggestions have been of great assistance. The previous authors have examined the entire text. The present author desires to thank each of these individuals for his generous cooperation.

Appreciation is expressed for the assistance received from my associates at the University of Pennsylvania: Dean Gellhorn for his foreword, Dr. Harry Salem for the Appendix on Drug Preparation, Dr. Miroslaw Belej for reviewing the chemical structures, Mr. Jerome Rauch for his library facilities, Barbara Ewing for her art work, and Patrice Kindle, Janet Oswald, Barbara Ashworth, Robin Robertson, Richard Haynes and Henry Reutter, Jr. for the preparation and proofreading of the manuscript.

It is a pleasure to acknowledge the help of several staff members of The Williams & Wilkins Company and the Waverly Press, who have made a number of innovations in the production of this edition, each one contributing a personal touch: Dick M. Hoover, Vice President; Jon Paul Davidson, Editor; Dick Griffin, Production Editor; Norman Och, Book Designer; and the following redactors: Maryalice Ditzler, Elaine Rice, Lydia Cooperstein and Nancy Slaughter.

My wife and four children helped with the typing and in the sorting of hundreds of references and thousands of trade names needed for the book. During the final months of completing the manuscript, there were times when they could not understand that, for the author, writing a textbook is more difficult than doing research. Now that the book has been completed, the author can remain with his family on weekends and resume planning his next perfusion experiments.

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