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MELMON and MORRELLI'S

临床药理学 Clinical Pharmacology

Fourth Edition



S. George Carruthers
Brian B. Hoffman
Kenneth L. Melmon
David W. Nierenberg



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M E L M O N A N D M O R R E L L I ' S

CLINICAL PHARMACOLOGY

BASIC PRINCIPLES IN THERAPEUTICS

F O U R T H E D I T I O N

EDITORS

S. GEORGE CARRUTHERS, M.D.

Richard Ivey Professor and Chair, Department of Medicine, Professor, Department of Pharmacology and Toxicology, London Health Sciences Centre and University of Western Ontario, London, Ontario, Canada

BRIAN B. HOFFMAN, M.D., F.R.C.P.(C)

Professor of Medicine and Molecular Pharmacology, Stanford University and Veterans Affairs Palo Alto Health Care System, Palo Alto, California

KENNETH L. MELMON, M.D.

Professor of Medicine and Molecular Pharmacology, Associate Dean for Postgraduate Medical Education, Stanford University, Stanford, California

DAVID W. NIERENBERG, M.D.

Edward Tulloh Krumm Professor of Medicine and Pharmacology/Toxicology, Chief, Division of Clinical Pharmacology, Associate Dean for Medical Education, Dartmouth Medical School, Hanover, New Hampshire

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In 1932 Albert Einstein said "The scientist finds his reward in what Henri Poincaré calls the joy of comprehension, and not in the possibilities of application to which any discovery may lead." (Albert Einstein from the Epilogue to Planck, "Where Is Science Going?" 1932, p 211.) Our editors concur but add that the thoughtful physician has the advantage over the basic scientist in that he or she can experience the joy of comprehension in both the discovery and application phases of rational therapeutics.

This book is dedicated to the recognition that scientific achievement applicable to people requires the output of many collaborating and working in sequence often in silence, often without tangible reward. This book is dedicated to the proposition that ordinarily little can be accomplished by one. In this instance, the editors note that the task of succeeding editions has become increasingly and remarkably more complex. The first edition compiled the work of 19 authors; each edition has needed more and this edition required 89 contributors.

This book is dedicated to those who tenaciously and effectively collaborate in order to develop and to pass on wisdom.

*This book is dedicated in gratitude to those in
biology and therapeutics
Who are of the past,
Who are involved in the present,
And who are invested in any way in the future
of human health.*

Contributors

John A. Abisheganaden, M.R.C.P. (UK) Associate Consultant, Department of Respiratory Medicine, Tan Tock Seng Hospital, Singapore
Chapter 2

Moir L. Aitken, M.D., F.R.C.P. Associate Professor of Medicine, Division of Pulmonary and Critical Care Medicine, Department of Medicine, University of Washington School of Medicine, Seattle, Washington
Chapter 2

J. Malcolm O. Arnold, M.D. Professor of Medicine, Pharmacology and Toxicology, University of Western Ontario, Division of Cardiology, London Health Sciences Centre, Victoria Campus, London, Ontario, Canada
Chapter 1

Christopher M. Barnard, M.D. Clinical Assistant Professor of Dermatology, Stanford University School of Medicine, Monterey, California
Chapter 11

David W. Bates, M.D. Associate Professor of Medicine, Harvard Medical School; Chief, Division of General Medicine, Brigham and Women's Hospital, Boston, Massachusetts
Chapter 24

Neal L. Benowitz, M.D. Professor of Medicine, Psychiatry and Biopharmaceutical Sciences, Division of Clinical Pharmacology and Experimental Therapeutics, University of California, San Francisco, California
Chapter 17

Joseph R. Bertino, M.D. Chairman, Program of Molecular Pharmacology and Therapeutics, American Cancer Society Professor of Medicine and Pharmacology, Memorial-Sloan Kettering Cancer Center, New York, New York
Chapter 13

Brian G. Birdwell, M.D. Clinical Assistant Professor of Medicine, University of Oklahoma Health Sciences Center, Oklahoma City, Oklahoma
Chapter 1

Terrence F. Blaschke, M.D. Professor of Medicine and Molecular Pharmacology, Chief, Division of Clinical Pharmacology, Stanford University School of Medicine, Stanford, California
Chapter 26

Homer A. Boushey, M.D. Chief, Asthma Clinical Research Center and the Division of Allergy and Immunology, Professor of Medicine, Department of Medicine, University of California, San Francisco, California
Chapter 2

D. Craig Brater, M.D. Professor of Medicine, Chairman, Department of Medicine, Director, Division of Clinical Pharmacology, Indiana University School of Medicine, Indianapolis, Indiana
Chapter 6

Peter Brooks, M.D. Professor and Executive Dean (Health Sciences), The University of Queensland Royal Brisbane Hospital, Herston, Queensland, Australia
Chapter 10

Christopher P. Cannon, M.D. Associate Physician, Cardiovascular Division, Brigham and Women's Hospital, Assistant Professor of Medicine, Harvard Medical School, Boston, Massachusetts
Chapter 1

S. George Carruthers, M.D. Richard Ivey Professor and Chair, Department of Medicine, Professor Department of Pharmacology and Toxicology, London Health Sciences Centre and University of Western Ontario, London, Ontario, Canada
Chapter 1

David Coffey, M.D. Associate Professor of Medicine (Neurology) and Psychiatry, Section of Neurology, Dartmouth-Hitchcock Medical Center, Lebanon, New Hampshire
Chapter 7

Paul E. Cooper, M.D., F.R.C.P.C. Associate Professor of Medicine, University of Western Ontario, Chief, Clinical Neurological Sciences, St. Joseph's Health Centre, London, Ontario, Canada
Chapter 7

Richard Day, M.D., F.R.A.C.P. Professor of Clinical Pharmacology, University of New South Wales, Director Clinical Pharmacology and Toxicology, St. Vincent's Hospital, Darlinghurst, New South Wales, Australia
Chapter 10

B. M. Demaerschalk, M.D. Fellow, Stroke Service, Department of Clinical Neurological Sciences, University of Western Ontario, University Campus, London Health Sciences Centre, London, Ontario, Canada
Chapter 7

George C. Ebers, M.D. Professor, Department of Clinical Neurology, University of Oxford, Radcliffe Infirmary, Oxford, England
Chapter 7

Kevin R. Forward, M.D. Associate Professor, Chief, Division of Microbiology, Dalhousie University, Halifax, Nova Scotia, Canada
Chapter 14

Raymond R. Gaeta, M.D. Associate Professor of Anesthesiology, Director, Pain Management Service, Stanford University Medical Center, Stanford University School of Medicine, Stanford, California
Chapter 15

Sean P. Gaine, M.D. Assistant Professor of Medicine, Director, Pulmonary Hypertension Center, Division of Pulmonary and Critical Care Medicine, Johns Hopkins Hospital, Baltimore, Maryland
Chapter 2

Gabriel Garcia, M.D. Associate Professor of Medicine, Stanford University School of Medicine, Stanford, California
Chapters 3, 4

Lewis R. Goldfrank, M.D. Associate Professor of Clinical Medicine, New York University School of Medicine, Director, Emergency Medicine, Bellevue Hospital Center/New York University Medical Center, New York, New York
Chapter 18

Marc E. Goldyne, M.D., Ph.D. Clinical Professor of Dermatology, Department of Dermatology, University of California, San Francisco, California
Chapter 11

Jerry H. Gurwitz, M.D. The Dr. John Meyers Professor of Primary Care Medicine, University of Massachusetts Medical School, Executive Director, Meyers Primary Care Institute, Fallon Healthcare System and University of Massachusetts Medical School, Worcester, Massachusetts
Chapter 21

Gordon Guyatt, M.D., M.Sc. Professor of Medicine and Clinical Epidemiology and Biostatistics, McMaster University, Hamilton, Ontario, Canada
Chapter 29

Vladimir Hachinski, M.D., F.R.C.P.C., M.Sc., D.Sc. Richard and Beryl Ivey Professor and Chair, Chief, Department of Clinical Neurological Sciences, London Health Sciences Centre, University Campus, London, Ontario, Canada
Chapter 7

Malcolm Handel, M.D. Arthritis and Inflammation Program, Garvan Institute of Medical Research and University of New South Wales, Darlinghurst, New South Wales, Australia
Chapter 10

Andrew R. Hoffman, M.D. Professor of Medicine and Molecular and Cellular Physiology, Stanford University School of Medicine, Chief, Medical Service, VA Palo Alto Health Care System, Palo Alto, California
Chapter 9

Brian B. Hoffman, M.D. Professor of Medicine and Molecular Pharmacology, Stanford University and VA Palo Alto Health Care System, Palo Alto, California
Chapter 1

Paul Hoffman, Ph.D. Professor of Microbiology, Dalhousie University, Halifax, Nova Scotia, Canada
Chapter 14

Leo E. Hollister, M.D. Clinical Professor of Medicine, Research Director, Harris County Psychiatric Center, University of Texas Medical School, Houston, Texas
Chapter 8

Zhuo Wei Hu, M.D., Ph.D. Senior Research Pharmacologist, Stanford University School of Medicine, Division of Endocrinology/Gerontology and Metabolism, Department of Medicine, Palo Alto, California
Chapter 12

John C. Hunter, Ph.D. Head, Department of Analgesia, Neurobiology Unit, Roche Bioscience, Palo Alto, California
Chapter 15

Lawrence R. Jenkyn, M.D. Associate Professor of Neurology and Psychiatry, Department of Neurology, Dartmouth-Hitchcock Medical Center, Lebanon, New Hampshire
Chapter 7

B. Lynn Johnston, M.D. Associate Professor, Infectious Diseases, Dalhousie University, Halifax, Nova Scotia, Canada
Chapter 14

Lori D. Karan, M.D. Assistant Professor of Medicine, Division of Clinical Pharmacology and Experimental Therapeutics, University of California, San Francisco, California
Chapter 17

Gideon Koren, M.D., F.A.C.C.T., F.R.C.P.C. Head, Population Health Science Program, Director, Division of Clinical Pharmacology/Toxicology, Professor of Pediatrics, Pharmacology, Pharmacy Medicine, and Medical Genetics, The CIBC World Market Children's Miracle Foundation, Chair in Child Health Research, University of Toronto, Toronto, Ontario, Canada
Chapter 20

Fredric B. Kraemer, M.D. Chief of Endocrinology, VA Palo Alto Health Care System, Associate Professor of Medicine, Stanford University, Division of Endocrinology, Stanford, California
Chapter 9

Lucian Leape, M.D. Adjunct Professor of Health Policy, Department of Health Policy and Management, Harvard School of Public Health, Boston, Massachusetts
Chapter 24

Spencer Lee, Ph.D. Professor of Microbiology, Dalhousie University, Halifax, Nova Scotia, Canada
Chapter 14

Steven A. Lieberman, M.D. Associate Professor, Division of Endocrinology, Department of Internal Medicine, The University of Texas Medical Branch, Galveston, Texas
Chapter 9

- David J. Liepert, M.D.** Clinical Assistant Professor of Anesthesiology, University of Calgary College of Medicine, Calgary, Alberta, Canada
Chapter 16
- Richard Lin, M.D.** Assistant Professor of Medicine, Division of Clinical Pharmacology, Department of Pharmacology and Medicine, University of Texas Health Sciences Center, San Antonio, Texas
Chapter 12
- Ronen Loebstein, M.D.** Division of Clinical Pharmacology and Toxicology and Department of Medicine A, The Chaim Sheba Medical Center, Hashomer, Israel
Chapter 20
- Richard D. Mamelok, M.D.** Internist-Clinical Pharmacologist, Consultant to Industry, Palo Alto, California
Chapter 27
- Robert Marcus, M.D.** Professor of Medicine, Stanford University School of Medicine, VA Palo Alto Health Care System, Palo Alto, California
Chapter 10
- Thomas J. Marrie, M.D.** Professor and Chair, Department of Medicine, University of Alberta, Edmonton, Alberta, Canada
Chapter 14
- Mervyn Maze, M.D., Ch.B., F.R.C.P., F.R.C.A.** Sir Ivan Magill Department of Anaesthetics, Imperial College School of Medicine, Chelsea and Westminster Hospital, London, England
Chapter 15
- Richard S. McLachlan, M.D.** Professor, Departments of Clinical Neurological Sciences, Medicine, and Physiology, University of Western Ontario, Neurologist, London Health Sciences Centre University Campus, London, Ontario, Canada
Chapter 7
- Kenneth L. Melmon, M.D.** Professor of Medicine and Molecular Pharmacology, Associate Dean for Postgraduate Medical Education, Stanford University, Stanford, California
Part 1
- Naseema B. Merchant, M.D.** Pulmonary Fellow, Division of Pulmonary and Critical Care Medicine, Yale University School of Medicine, West Haven, Connecticut
Chapter 2
- Urs A. Meyer, M.D.** Professor of Pharmacology, Chairman, Department of Pharmacology, Biozentrum, University of Basel, Basel, Switzerland
Chapter 22
- Thomas Michel, Ph.D., M.D.** Associate Professor of Medicine, Harvard Medical School, Chief, Cardiology Section, West Roxbury VA Medical Center, Physician, Brigham and Women's Hospital, Boston, Massachusetts
Chapter 1
- Jeffrey Wells Miller, M.D.** Senior Clinical Pharmacologist, Lilly Laboratory for Clinical Research, Eli Lilly & Co., Inc., Indiana University Hospital and Outpatient Center, Indianapolis, Indiana
Chapter 9
- Stanley Nattel, M.D.** Director, Research Center, Montreal Heart Institute, Professor of Medicine, University of Montreal, Montreal, Quebec, Canada
Chapter 1
- Lewis S. Nelson, M.D.** Assistant Professor of Clinical Surgery (Emergency Medicine), New York University School of Medicine, Fellowship Director, New York City Poison Control Center, New York, New York
Chapter 18
- Michael W. Nicolle, M.D., F.R.C.P.C., D. Phil.** Assistant Professor of Medicine, University of Western Ontario, Director, Myasthenia Gravis Clinic, Department of Clinical Neurological Sciences, London Health Sciences Centre, University Campus, London, Ontario, Canada
Chapter 7
- Michael S. Niederman, M.D., F.A.C.P., F.C.C.P., F.C.C.M.** Chief, Department of Medicine, Winthrop University Hospital, Mineola, New York
Chapter 2
- David W. Nierenberg, M.D.** Edward Tulloh Krumm Professor of Medicine and Pharmacology/Toxicology, Chief, Division of Clinical Pharmacology, Associate Dean for Medical Education, Dartmouth Medical School, Hanover, New Hampshire
Part 1
- Paul W. Noble, M.D.** Associate Professor of Medicine, Yale School of Medicine, Pulmonary Section Chief, VA Connecticut Healthcare System, West Haven, Connecticut
Chapter 2
- Owen A. O'Connor, M.D., Ph.D.** Clinical Assistant Attending Physician, Department of Medicine, Memorial-Sloan Kettering Cancer Center, New York, New York
Chapter 13
- Ronald G. Pearl, M.D., Ph.D.** Chairman and Professor of Anesthesia, Department of Anesthesia, Stanford University School of Medicine, Stanford, California
Chapter 16
- David Quinn, M.B.B.S., F.R.A.C.P.** Director of Clinical Training and Lecturer, Department of Clinical Pharmacology and Toxicology, University of New South Wales and St. Vincent's Hospital, Darlinghurst, New South Wales, Australia
Chapter 10
- Stephen I. Rennard, M.D.** Larson Professor of Medicine, Pulmonary and Critical Care Medicine, Department of Internal Medicine, University of Nebraska Medical Center, Omaha, Nebraska
Chapter 2

G. P. A. Rice, M.D. Professor, Department of Clinical Neurological Sciences, London Health Sciences Centre, University Campus, London, Ontario, Canada
Chapter 7

David Robertson, M.D. Elton Yates Professor of Medicine, Pharmacology and Neurology, Autonomic Dysfunction Center, Vanderbilt University, Nashville, Tennessee
Chapter 1

Dan M. Roden, M.D. Professor of Medicine and Pharmacology, Director, Division of Clinical Pharmacology, Vanderbilt University, Nashville, Tennessee
Chapter 1

Irwin H. Rosenberg, M.D. Professor of Nutrition and Medicine, Director, USDA Human Nutrition Research Center on Aging, Tufts University, Boston, Massachusetts
Chapter 5

Elizabeth M. Ross, M.D. Assistant Professor, Tufts University School of Medicine, Assistant Physician, Divisions of Clinical Nutrition and General Internal Medicine, New England Medical Center Hospital, Boston, Massachusetts
Chapter 5

Peter C. Rubin, M.D. Department of Medicine, University Hospital, Queens Medical Centre, Nottingham, England
Chapter 19

Jane M. Rutherford, D.M., M.R.C.O.G. Department of Feto-Maternal Medicine, Queens Medical Centre, Nottingham, England
Chapter 19

David L. Sackett, F.R.S.C., M.D. Trount Research and Education Centre at Irish Lake, Markdale, Ontario, Canada
Chapter 29

Daniel S. Sitar, Ph.D. Professor and Head, Department of Pharmacology and Therapeutics, Professor, Department of Internal Medicine (Clinical Pharmacology Section), Professor, Department of Pediatrics and Child Health, University of Manitoba, Winnipeg, Manitoba, Canada
Chapter 23

Kathryn L. Slayter, Pharm. D. Infectious Diseases Pharmacist, Queen E II Health Sciences Centre, Halifax, Nova Scotia, Canada
Chapter 14

Peter H. Stone, M.D. Associate Professor of Medicine, Cardiovascular Division, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts
Chapter 1

Brian Strom, M.D., M.P.H. Professor of Biostatistics and Epidemiology, Medicine, and Pharmacology, Chair, Department of Biostatistics and Epidemiology, Director, Center for Clinical Epidemiology and Biostatistics, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania
Chapter 30

Arturo Tamayo, M.D. Clinical Stroke Fellow, Department of Clinical Neurological Sciences, University of Western Ontario, London, Ontario, Canada
Chapter 7

Mark R. Tonelli, M.D., M.A. Assistant Professor of Medicine, Division of Pulmonary and Critical Care Medicine, University of Washington, Seattle, Washington
Chapter 2

Claire Touchie, M.D. Assistant Professor, Infectious Diseases and Microbiology, Dalhousie University, Halifax, Nova Scotia, Canada
Chapter 14

John Urquhart, M.D., F.R.C.P. (Edin) Professor of Pharmacoepidemiology, Department of Epidemiology Maastricht University, Maastricht, Netherlands
Chapter 28

Robert E. Vestal, M.D. Senior Medical Director, Early Clinical Development, Covance Inc., Walnut Creek, California
Chapter 21

Sunita Vohra, M.D., F.R.C.P.C., M.Sc. Clinical Epidemiologist, Population Health Sciences, The Hospital for Sick Children Research Institute, Scientific Consultant, Division of Clinical Pharmacology and Toxicology, The Hospital for Sick Children, Assistant Professor of Pediatrics, University of Toronto, Toronto, Ontario, Canada
Chapter 20

Thomas N. Ward, M.D. Associate Professor of Medicine (Neurology), Dartmouth-Hitchcock Medical Center, Lebanon, New Hampshire
Chapter 7

Mark S. Weinfeld, M.D. Assistant Professor of Medicine, Washington University School of Medicine, Washington University Cardiology Consultants, St. Louis, Missouri
Chapter 1

Thomas L. Whitsett, M.D. Professor of Medicine and Pharmacology, Department of Medicine, Cardiovascular Section, University of Oklahoma Health Sciences Center, Oklahoma City, Oklahoma
Chapter 1

Kenneth Williams, B.Sc. (Hons), Ph.D. Associate Professor, Deputy Director, Department of Clinical Pharmacology and Toxicology, St. Vincent's Hospital and University of New South Wales, New South Wales, Sydney, Australia
Chapter 10

James M. Wright, Ph.D. Associate Professor, Department of Medicine and Department of Pharmacology, University Hospital, University of British Columbia, Vancouver, British Columbia, Canada
Chapter 25

Preface to the Fourth Edition

The prompt and accurate diagnosis of many diseases has been facilitated in recent years by technological advances in medical imaging and clinical chemistry. At the same time, the clinician's ability to treat disease has also been enhanced by the development of many useful new medications; the conduct, publication and widespread communication of major clinical trials; the development of useful clinical guidelines and critical paths; and the ready access to other sources of information: MEDLINE, Web sites, professional societies, and many others.

Despite these advances in diagnostic capabilities and availability of information, prescribing drugs optimally has not become correspondingly easier. Modern health-care management has often increased expectations that primary-care physicians will assume more direct responsibility for the comprehensive medical management of patients with a wider range of diseases. Access to prompt consultation with subspecialists is sometimes restricted.

There has been a proliferation of new drugs within established drug classes and discovery of new classes of drugs as well. These newer agents often exhibit greater efficacy or reduced toxicity. However, they sometimes are accompanied by new (even unknown) adverse effects; and they are often extremely expensive. Many new drug-drug interactions (involving new drugs and older agents) are also important to consider. Under these circumstances, it might be anticipated that "information overload" could challenge the physician's ability to select an optimal drug, dose, and duration of treatment for the individual patient.

Consequently, a major focus of the fourth edition of this text is to provide a solid foundation of information and skills useful for physicians interested in optimizing their use of drugs over a broad range of common and important therapeutic problems. In this edition, the editors and contributors have tried to tie recommendations for pharmacotherapeutic decisions in common major diseases to the best available evidence, as presented in such primary forms as clinical trials, meta-analyses, or structural reviews. Such evidence is often very reliable and is rooted in the careful assessment of experience in hundreds or thousands of patients with a specific disease. While it is true that personal experience and anecdotal information sometimes may have an important role in pharmacotherapy, especially when good evidence is not available, we

as a profession have learned that it is a serious mistake to use such impressions instead of objective observations. A major theme of this book is that difficult therapeutic decisions are most likely to succeed when they are generally based on the results of well-planned and well-performed clinical trials.

This edition emphasizes at the same time that it is important to recognize that the best available evidence is often derived from studies conducted in groups of patients who do not completely resemble the specific (really unique) patient sitting before the physician. For example, there may be extensive evidence that may suggest an optimal approach to the drug choice in the management of a serious staphylococcal infection in a group of otherwise healthy patients or to the management of essential primary hypertension in otherwise healthy adults. However, the careful physician may need to modify these recommendations after considering the factors that make his or her patient unique. Some examples of these patient-specific factors discussed in this book are patient gender, age, renal function, hepatic function, prior history of adverse drug reactions or drug allergies, pregnancy or desire to breast feed, genetic predisposition to alterations in drug clearance or drug action, use of concomitant medications, or the presence of other medical problems. This book has been created to help emphasize therapeutic principles so that the careful, thoughtful physician can adapt the "best available evidence" to suit the specific needs of each individual patient.

Physicians are becoming increasingly aware that judging the quality of their therapeutic decisions requires them to consider more clinical endpoints than merely "Did the drug work?" We need to consider a number of clinical outcomes on at least four "axes," including asking the following questions:

1. How has this treatment improved the patient's functional status (e.g., ameliorated the headache, epistaxis, and shortness of breath associated with hypertension)?
2. How has the treatment altered the course of the disease (e.g., controlled the blood pressure, improved renal function, lessened LVH, lowered overall mortality etc.)?

3. What are the direct and indirect costs of the treatment chosen (e.g., cost of medication, cost of monitoring, cost of adverse reactions, cost of doctor visits, etc.)?
4. What is the level of the patient's overall satisfaction with the treatment provided (e.g., the patient is delighted that his blood pressure has been lowered, but his drug-induced erectile dysfunction or depression is just not worth the benefit obtained)?

The editors hope that the approaches described in the book will help the prescriber (whether medical student, resident house officer, or experienced physician) practice

clinical pharmacology in a manner that delivers greater overall quality of care to patients. We also have the conviction that personal efforts aimed at understanding the principles of rational drug therapy will help physicians to maintain competence in a rapidly changing and advancing medical environment, as well as making therapeutic decisions more reliable and decision-making more interesting.

We are grateful to all the contributors to this fourth edition for their hard work in elaborating the important themes outlined above in preparing chapters aimed at meeting these goals. We acknowledge the patience and support of Ms. Barbara Ordway, our editorial consultant, and the staff of McGraw-Hill for their ongoing support.

S. GEORGE CARRUTHERS
BRIAN B. HOFFMAN
KENNETH L. MELMON
DAVID W. NIERENBERG

Preface to the Third Edition

The goals and objectives for revising this book were not only to update material previously covered, but also to deliberately shift emphasis to deal with most of the therapeutic decisions commonly made by practicing physicians. We hope that this edition attracts the student and practitioner into wanting to learn core facts, skills, and the most basic principles of clinical pharmacology by drawing them into the subject via discussions of routine as well as difficult therapeutic decisions encountered in the practice of medicine. We have tried to avoid the Charybdis of cookbook practicality and the Scylla of excessive dry theory.

We present what we believe is mandatory to know about decisions about drugs in brief introductory form in the first chapter. The rest of the first section of the book builds on these principles in specific clinical settings to ensure that most common therapeutic problems are discussed. To learn what the most common decisions were, we reviewed the list of 100 most used drugs and 100 most common diagnoses for which prescriptions were written in North America and Western Europe. The list for the

United States was obtained from IMS America. It probably covers about 80% or more of the volume of prescription drugs used in North America and Europe today. Individual authors were assigned to cover each of those diagnoses and the drugs used to treat them. All are covered in the first section of the book as minimum subject matter. Thus, this section should be more useful as a reference text to clinicians than were the previous editions. For heuristic purposes, essential principles are highlighted throughout the text as they have been in previous editions.

Section II contains the basic subject material that is the core of clinical pharmacology without reference to specific diseases. Chapters in Section I consistently refer to chapters in Section II as the basis of most therapeutic decisions. This book continues to be a supplement to, not a substitute for, the basic textbooks of medicine and pharmacology.

The editors are very grateful for the editorial and secretarial assistance, patience, and dedication of Wallace Waterfall and Dana O'Neill.

KENNETH L. MELMON
HOWARD F. MORRELLI
BRIAN B. HOFFMAN
DAVID W. NIERENBERG

Preface to the Second Edition

The objectives of this book have not changed since the first edition. *Clinical Pharmacology: Basic Principles in Therapeutics* is designed to illustrate a consistency of approach to qualitative and quantitative decision making in therapeutics. Its use should allow the therapist to distinguish drug-related events from spontaneous alterations in disease and provide general knowledge about objective therapeutics that will allow him/her to individualize therapy. The text is written with medical, osteopathy, pharmacy, and allied health students uppermost in mind; such students are the best candidates to evolve therapeutics from an "art" to a rational and objective science.

Readers might legitimately ask why a textbook of "principles" requires revision, since true principles remain constant. In short, the editors are students in a rapidly evolving and novel discipline. Although a number of useful principles were identified in the first edition, some that were designated as principles were not fundamental concepts and, because the field of clinical pharmacology has grown rapidly in recent years, a number of new principles have evolved. Many factors that now impact on therapeutic decisions were not known in 1972, nor were data related to the psychology of the doctor-patient "therapeutic contract" necessarily widely available or easily summarized (Chapter 4). The science of pharmacokinetics was not as aggressively applied to man as it has been in the last 5 to 10 years. Furthermore, the mathematical concepts necessary to make precise and therefore biologically useful decisions during use of high-risk drugs had not been tested in therapeutic settings (Chapters 2 and 3). Clinical pharmacologists had not developed a useful, defensible, and systematic approach about placebos, about how to make therapeutic decisions in circumstances of uncertainty, or about the economic factors that overtly or covertly influence therapeutic decisions and the epidemiol-

ogy of drug use (Chapters 24 to 26). Only in the last few years has consideration been given to therapeutic decisions affecting women of child-bearing age, pregnant women, the fetus, and the neonate (Chapter 5). Patients with dermatologic disorders can be rationally as well as empirically approached (Chapter 19). The therapeutics of some hepatic, respiratory, endocrine, and inflammatory disorders have become much more specific and effective, and this has allowed the description of new "principles."

The organization of this second edition is similar to that of the first edition. Unit I presents general principles that apply to all therapeutic decisions; Unit II emphasizes the specific factors about a disease and a drug that justify the setting of therapeutic objectives in their coordination; and Unit III stresses the obvious and less overt factors that impact on therapeutic decisions and the observations that can be made and attributed to the drug per se. Unit IV has been deleted from this revision; although the programmed cases were popular, they were too individualized in some respects to justify the space they occupied.

As in the first edition, successful use of this book requires knowledge of both pharmacology and medicine. It should serve as a supplement to, rather than a replacement of, the basic textbooks of medicine and pharmacology. We hope that *Clinical Pharmacology: Basic Principles in Therapeutics* will not foster dogma, recipes, or folklore about drugs, but will help to stimulate scholarly and rational thought about therapeutics that is applicable to individualized settings.

We deeply appreciate the persistent, imaginative, and sometimes exciting writing of our contributors as well as the assistance of our editors, Elyce Melmon and Emma Ponick. We also gratefully acknowledge the thoughtful suggestions made by our fellows and students, and the secretarial help of Ms. Vivian Abe.

KENNETH L. MELMON
HOWARD F. MORRELLI

Preface to the First Edition

Even in medicine, though it is easy to know what honey, wine and hellebore, cautery and surgery are, to know how and to whom and when to apply them so as to effect a cure is no less an undertaking than to be a physician.

Aristotle, *Nicomachean Ethics*, Vol. IX

Detailed pharmacologic knowledge stands alone as a basic science, but successful therapeutics requires application of this information to disease-induced abnormalities in individual patients. Aristotle did not claim that physicians were successful, only that they attempted to be. There is abundant information that physicians generally are poor therapists, despite their detailed knowledge of the pathogenesis of disease and the pharmacology of specific drugs that can alter a disease. The consequences of poor therapy include both toxic reactions to drugs and unchecked or even exacerbated disease. No longer can it be said, "The diagnosis is always more important than the treatment." Therapeutics must not continue to lag so far behind pharmacology, physiology, biochemistry, and pathophysiology, which serve as its foundation. Much information must be applied to clinical settings to allow major improvements in the management of disease and decreases in the incidence, morbidity, and mortality of drug toxicity.

This textbook was written (1) to help medical students understand how to approach the problems of administration of drugs to man, and (2) to show house staff and practicing physicians who learned therapeutics in a "hand-me-down" fashion that this instructional approach at best fosters mediocrity in therapeutics and should be replaced by a more efficacious and satisfying method. A consistent approach to therapeutic settings is possible, and the organization of the book generally describes the rationale for therapeutic decisions. An underlying principle herein is that the pathophysiology of disease and basic facts of pharmacology must be interdigitated in order to select drugs and establish therapeutic objectives. Once a category of drug is considered, the therapist must recall and use the basic principles of drug administration (Unit I); then the specific factors of disease and drug that justify bringing them together must be contemplated, so that the dynamics of pharmacology and pathophysiology can be

put into perspective in the therapeutic plan (Unit II). Once the therapeutic objectives have been set, a plan must be made and implemented to observe, recognize, and evaluate the effects of drug administration (Unit III). The student may then evaluate his ability to recognize and apply principles in programmed problem-solving situations, taken from actual cases of the clinical pharmacology consultation service, University of California Medical Center, San Francisco (Unit IV).

Successful use of this book requires knowledge of both pharmacology and medicine. It does not replace the basic textbook in either discipline; rather, it is a supplement to both. Unit II does not include all, or even most, of the important diseases or drugs that might be discussed. The approach described in each chapter—physiology, pathophysiology, pharmacology, and, finally, the integration of these subjects—is consistent, can be applied at the bedside, and constitutes what the editors consider to be active clinical pharmacology. Such an approach can be subdivided into guidelines (principles), and some clinical states lend themselves more readily than others to illustration of principles that can be applied broadly. We hope the reader will find that principles applicable to one disease also apply to other disorders, for that is what makes them principles. They should help to stimulate thought rather than to propagate dogma or provide further recipes for therapeutics.

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KENNETH L. MELMON
HOWARD F. MORRELLI

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