Clinical Pharmacology

Basic Principles in Therapeutics

SECOND EDITION

EDITED BY

Kenneth L. Melmon, M.D.

AND

Howard F. Morrelli, M.D.

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Macmillan Publishing Co., Inc.
New York

COLLIER MACMILLAN CANADA, LTD.
Toronto

BAILLIÈRE · TINDALL
London

MACMILLAN PUBLISHING CO., INC.
866 Third Avenue, New York, New York 10022

COLLIER MACMILLAN CANADA, LTD.

BAILLIÈRE • TINDALL, London.

Library of Congress Cataloging in Publication Data

Main entry under title:

Clinical pharmacology.

Includes bibliographies and index.
1. Pharmacology. I. Melmon, Kenneth L., (date)
II. Morrelli, Howard F., (date) [DNLM: 1. Drug therapy. WB330 C636]
RM300.C55 1978 615'.58 77–5690
ISBN 0–02–380230–8
ISBN 0–02–380270–7 pbk.
Baillière • Tindall SBN 07020 06750
Baillière • Tindall SBN 07020 0653X pbk.

Printing: 2 3 4 5 6 7 8 Year: 8 9 0 1 2 3 4

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 epidemiology of drug use (Chapters 24 to 26). Only in the last few years has consideration been given to therapeutic decisions affecting women of childbearing 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.

The contributors have demonstrated extraordinary diligence and patience in writing this innovative textbook. The editors thank their colleagues, fellows, house staff, and students for encouragement, criticism, and help during the long gestation period. They are greatly indebted for the thoughtful criticism and suggestions made by Arthur P. Grollman, Jr., M.D., associate professor of pharmacology and medicine, Albert Einstein College of Medicine, Bronx, New York. They are also indebted to Peggy Langston for editorial assistance in preparing the final manuscript.

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UNIT I

BASIC PRINCIPLES OF DRUG ADMINISTRATION

Chapter 1

DRUG CHOICE IN DISEASE STATES

William McFate Smith

CHAPTER OUTLINE

THERAPY AS A SCIENCE

Contemporary Therapeutics

This chapter historically and conceptually reviews the evolution of the discipline of clinical pharmacology, including the methods of therapeutic investigation and the proper evaluation of sources of information on the choice of drugs. There is a gap, of unknown but probably large size, between the quantity of available scientific information on drugs and their safe and effective uses in medical practice. One of the roles of a clinical pharmacologist is to narrow this gap.

Major purposes of this book are to develop awareness of therapeutic principles, to help promote transference of pharmacologic knowledge to bedside situations, and to convince the physician that therapy may be more effective and rewarding if objectivity is used to make and assess the results of a decision.

For centuries, man has applied logic to the major arts. One of the primary issues at debate has been whether scientific development is dependent upon inductive or deductive reasoning. In 1620, Sir Francis Bacon championed the inductive method, and this became a pillar of Newtonian mechanics. All scientific disciplines employ both inductive and deductive methods toward the realization of theory in practice. Logic has also been applied in the development of modern medicine, at least to diagnostic and laboratory activities. The same rigorous logic can and must be applied to therapeutics.

It is ironic that at a time when diagnostics has attained a sophisticated scientific state, therapeutic decisions often rest on impression, sentiment, tradition, or advertising. The enormity of the problem and the consequences of this paradox are readily appreciated when the underlying forces are considered. Each time we use drugs in man, we engage in an experiment for which the scientific approach is required, if maximum effectiveness and safety are to be achieved.

The 1973 edition of Webster's *New Collegiate Dictionary* defines "scientific method" as the "principles and procedures for the systematic pursuit of knowledge involving the recognition and formulation of a problem, the collection of data through observation and experiment, and the formulation and testing of hypotheses." These guidelines have served investigators in all branches of the arts and sciences whose quest is to know and to understand. The physician, in his consistent search for drugs to act upon the diseases of man, can certainly be served by the same guidelines. Since man is more than a hypothetical, intellectual puzzle, not just a principle, a curiosity, or a laboratory experiment, he confronts the physician with a challenge that is both intellectual and humanitarian. Successfully meeting this challenge is the skilled clinician's greatest achievement.

Feinstein emphasized that good clinical judg-

ment involves the scientific application of human capabilities. *An important aspect of clinical judgment is the selection and appraisal of therapeutic agents.* "The therapeutic decisions of clinical judgment require valid evidence, logical analysis, and demonstrable proof. Their scientific quality can be discerned, assessed, and improved by the same rational procedures used for any other act of experimental science" (Feinstein, 1967).

The rational choice of therapeutic agents is ideally predicated on: (1) an accurate diagnosis (2) thorough knowledge of the data related to the pathophysiology of the disease, (3) knowledge of the basic pharmacology and biochemistry of the drug and its metabolites, and the pharmacokinetics of the compound in normal and diseased man, (4) the ability to transfer such knowledge to effective bedside action, (5) reasonable expectations of the relation of pathophysiology and pharmacology so that the drug's effect can be anticipated, (6) a plan to make specific measurements that will reveal efficacy and toxicity and will set the course for continued therapy; and (7) knowledge and skill in the evaluation of claims of efficacy for empiric therapy (i.e., therapy based on observations of the apparent effect of a drug even when the pathophysiology of the disease or the pharmacology of the drug is unknown).

This description may imply a time-consuming process that is unrealistic for application in everyday decision making in medical practice. To the student or physician in training, it does require investment of considerable time. However, if the principles are understood, and if the results of their application are carefully assessed and objectively catalogued, like other acquired knowledge and skills, the process becomes swift and nearly automatic.

A pharmacologic "revolution" began during World War II, has advanced rapidly over the past 30 years, and is responsible for what has been called "the drug explosion" (Modell, 1961). The practicing physician must choose from among thousands of new drugs. The number of medicaments available in the early 1960s approached 200,000; 90% of those most commonly prescribed did not exist prior to World War II (Brown, 1955). Over 7000 new prescription products were introduced between 1948 and 1963; the current therapeutic arsenal includes at least 7200 drugs and drug combinations (American Medical Association, 1973). The development of drugs is so rapid that approximately 70% of them were unknown or were unavailable 15 years ago, when over half of all currently practicing physicians received their limited pharmacotherapeutic training. This pace slowed moderately during the 1960s, perhaps related to the new requirements of efficacy and safety for new drugs promulgated in the Kefauver-Harris legislation of 1962. Further slowing has occurred subsequent to the government-sponsored reviews of drug prescriptions, and now appears to have leveled off at around 70 new drug products per year (Task Force, 1968; *Final Report* of the Task Force on Prescription Drugs, 1969; Wardell, 1974; de Haen, 1975). This is down from over 200 between 1947 and 1958. Although less than 20% of these are newly synthesized entities, the remainder being minor chemical modifications, new formulations, or combinations, this number is still unlikely to be assimilated in a scholarly way into the physician's practice. The number alone creates a formidable challenge to rational therapeutics, even if each new drug were necessary, effective, and safe. Many are often poorly tested (whether or not current regulations for their development are met), and many are duplicates or combinations of two or more existing drugs. The credulity of physicians should have been taxed by claims that each of a number of nearly identical agents could be "best" for a given medical indication. Methods of discrimination are available that allow us to use preparations effectively, efficiently, and with a minimum of toxicity. Algorithms, both formal and conceptual, can guide us through the decision process, eliminating the need for rote memorization of the myriad facts about each drug. This thesis is initiated here and carried through in many subsequent chapters.

Unfortunately, the drug explosion took place against a backdrop of widespread therapeutic nihilism and a somewhat fragmented state of medical education, at least as far as therapeutics is concerned. Thus the senior physician's education has rarely equipped him with a critical approach to therapy, and he has not felt compelled to apply rigorous thought to therapeutic decisions.

The inadequacy of so much of the "investigation" related to drug evaluation further aggravates the situation. Much of this "investigation" is conducted by clinicians who have had no training in therapeutics, are unfamiliar with the requirements of the scientific method, do not have the means to properly interpret data, and have not been exposed to the intellectual rewards of new discovery or the academic consequences of sloppy work (Melmon, 1976). Literature on drug research is a rich teaching resource for examples of poor investigation and invalid conclusions.

Another aspect of the problem, which has important economic consequences, is the tendency for physicians to prescribe by brand name rather than by generic name. Generic prescribing is the ordering of chemically equivalent products that may cost considerably less than brand-named products, often as little as one-third. The physician's action is understandable; he is only responding to his most immediate source of drug information, the manufacturers' advertising (see Chapter 26). Moreover, for him to consider changing this pattern he must be reassured that *chemical* equivalence equals *therapeutic* equivalence, and this is not necessarily so (*Drug Bioequivalence*, 1974). This lack of *bioequivalence* has been seriously investigated only in recent years; although the studies are few and do not establish whether the cited instances are the rule or the exception, the problem is not hypothetical. The differing bioavailability of chemically equivalent drug products from different manufacturers, or even different batches from the same company, has been demonstrated to result in *therapeutic* inequivalence in some instances. Perhaps the best known examples of this are digoxin and corticosteroids (Lindenbaum *et al.*, 1971; *Drug Bioequivalence*, 1974).

Another uncertainty related to the standards of drug production must be considered a facet in therapeutic decisions. Is the assumption valid that the United States Pharmacopoeia (USP) or Good Manufacturing Procedures (GMP) guarantee product uniformity? Do the regulations really achieve their intent? A scholarly group has reviewed such questions and determined that the USP standards often have little scientific basis. Furthermore, they indicate that even if the USP standards were able to accomplish what they intend, an acceptable product that has uniform bioavailability, the GMP that regulate uniformity of drug product production are not based on scientific or sound statistical grounds sufficient to achieve their goal (*Drug Bioequivalence*, 1974). Lack of bioequivalence cannot be as readily extrapolated to all generic products as some would have us believe, but the clinical importance of lack of bioequivalence in some generic products is real.

In view of the foregoing, why has no crisis developed? Primarily because, for the majority of diseases, the margin of safety between the effective and toxic dose of a drug is enormous, and the disease may be self-limited. What must be guarded against is complacently attributing apparent safety and efficacy to the regulatory controls and failing to consider these factors as contributory whenever therapeutic failures or paradoxes related to drug administration occur.

The uncritical use of pharmaceutical agents and the trend toward irrational polypharmacy have informed society that iatrogenic disease is possible even though we do not know the incidence of drug-induced disease and its consequences (Modell, 1963; Lasagna, 1965; Moser, 1969; Melmon, 1971; Hewitt and Milner, 1974; Koch-Weser, 1974). Moreover, we do not know if drug-induced disease can be prevented without compromising the therapeutic effects of the drugs. The magnitude and consequences of the adverse drug reaction (ADR) problem are unknown at present because the data base is incomplete, unrepresentative, and uncontrolled (see Chapter 20). It also suffers from lack of uniform and reasonably rigorous operational definitions. Nonetheless, the potential for harm by the uncritical use of drugs is enormous. This state of affairs is not surprising given the size of the therapeutic arsenal and the drug-prescribing patterns that have evolved. Furthermore, the ADRs are by no means confined to the new drugs; ironically, most of the reported fatalities "caused" by drugs occur when older standard drugs are used. Digitalis preparations top the list.

In 1968, it was conservatively estimated that over one billion prescriptions were filled each year (Gosselin, 1968). In 1974, the number of prescriptions filled was over 2.7 billion, including hospital as well as outpatients (*Prescription Drug Data Summary*, 1976). Over 30 million patients are admitted to hospitals yearly, with those on medical wards of university hospitals receiving an average of 14 drugs during their stay (Cluff *et al.*, 1964). The amount of drug use in patients on other than "medical services" is lower, but whether drugs are overutilized on the medical services and are properly used or underutilized in other services has never been established. The frequency of adverse responses to drugs in hospitalized patients is variously reported to be between 1.5% and 35%. The deficiencies of the data base on ADRs must be noted, as well as the fact that most reports on this matter are based on events that occur on medical wards of acute care hospitals. Given the phenomenal level of drug prescribing, even with the acknowledged limitations of the data base, it would be surprising if the rate of untoward reactions had not increased in recent years. It is not known if "efficacy rates" are keeping pace with the increased prescribing of drugs.

Acute drug toxicity has become a common medical emergency. When intentional, we readily recognize it; drug overdosage is the most rapidly increasing means of suicide (see

Chapter 22). A more subtle problem must also be appreciated; even the well-intentioned, conscientious use of prescription drugs results in a number of hospital admissions for adverse drug reactions. We do not know how many of such admissions are due to the inevitable risk of proper therapeutic decisions or how many are due to the unfortunate consequences of thoughtless and useless administration of drugs. The data base on this problem suffers from the same limitations cited before, but ADRs have been reported to be responsible for 0.3 to 1.0% of general hospital admissions; even taking the 0.3% as the lower level of the problem, given today's costs of hospitalization, the economic consequences are still considerable (Smidt and McQueen, 1972; Karch and Lasagna, 1975).

This present state of contemporary therapeutics does not mean that physicians are basically careless, irrational, or ignorant, but as students, teachers, and practitioners of medicine we cannot escape our share of culpability. Whatever the true ADR rates turn out to be, we have all witnessed the consequences of suboptimal decisions and know that more attention needs to be paid to the education of the physician in the therapeutic decision process. If it is, the gap that exists between the teaching of pharmacology as a basic science and as a clinical science will be bridged. Keep in mind that no drug is devoid of toxicity, and that useful, potent drugs can cause serious morbidity and mortality. This problem is likely to be most dangerous if the therapist has little familiarity with the principles of controlled drug evaluation, if there is no effective professional program for continuing education in pharmacotherapy, if there are no objective, well-organized, and concise sources of drug information, and if we depend on the pharmaceutical industry to provide most of our information about therapy.

Drug advertisements are primarily promotional, not educational, and partly reflect the pharmaceutical firms' need to recover the cost of drug research, their desire to share in the market for a particular class of drug, and the brief duration of the potential market (often because therapeutic claims are not upheld or untoward effects are eventually recognized). Advertisements can place unreasonable pressure on undiscerning therapists, leading to irrational therapeutics (see Chapters 4 and 26). Similar claims may have encouraged Osler's observation that one should treat as many patients as possible with a new drug while it still has the power to heal. Furthermore, lack of advertisements, because a drug has come off of patent, can lead to underutilization of a perfectly good product.

Medicine has made great strides since Voltaire's satiric description of physicians as "men who prescribe medicine of which they know little, to cure disease of which they know less, in human beings of which they know nothing." And yet, the profession currently remains in danger of irrational and irresponsible therapeutic practices. Physicians are characteristically rational and responsible, but it is nearly impossible for them to appear so if they respond to the pressures of time, uncritical reading, industrial advertising, and the persuasion of "detail men" and patients to use the flood of new drugs without proper education in therapeutics and without sufficient knowledge about or rational expectations of each drug.

The yield from the drug explosion has exceeded the availability of competent clinical investigators to assess the efficacy and safety of new drugs. This does not mean, however, that the ability of practicing physicians to assimilate the essential knowledge of therapeutics and to develop competence in rationally prescribing drugs has been exceeded.

This book constitutes another acceptance of the challenge implied by those who cite the tragedy of declining education in pharmacology at a time when it is most needed. We make an effort to demonstrate the feasibility and desirability of teaching and learning rational therapeutics. The education of physicians in this matter cannot be left to chance or commercial enterprises. The authors agree that "our society's handling of the problems created by the pharmacologic revolution of the last quarter of the century leaves much to be desired" (Lasagna, 1964). But we hasten to add that the means are still at hand for mending our therapeutic ways. Encouraging events, such as the institution of clinical pharmacology units in a number of medical schools, constructive legislative initiatives that might mandate specific training in the therapeutic-decision process for all prescription writers, reorganization of data retrieval systems for gathering information on the utility function of new and old drugs (see below), and educational programs for the public to create realistic expectations of drugs as useful and harmful agents, are serving to awaken our concern about the proper use of drugs. We remain convinced that practicing physicians, teachers, and students can responsibly respond to these efforts to focus scholarly attention on the use of drugs in medical practice.