DRUGS OF CHOICE 1984 1985

Edited by

Walter Modell, M.D.

DRUGS OF CHOICE 1984 1985

Edited by

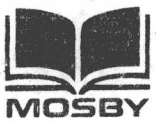
Walter Modell, M.D.

Emeritus Professor of Pharmacology,
Cornell University Medical College,
New York, New York;
Consultant to the Surgeon General of the Army;
former Member, Board of Directors,
United States Pharmacopeia;
Editor, *Clinical Pharmacology and Therapeutics;*
Editor, *Rational Drug Therapy*

Illustrated

THE C. V. MOSBY COMPANY

St. Louis Toronto 1984



A TRADITION OF PUBLISHING EXCELLENCE

Editor: Samuel E. Harshberger
Assistant editor: Anne Gunter
Editing supervisor: Elaine Steinborn
Manuscript editors: Ivie Davis, Connie Povilat, Dale Woolery
Book design: Gail Morey Hudson
Cover design: Suzanne Oberholtzer
Production: Barbara Merritt

1984-1985 edition

Printed in the United States of America

The C.V. Mosby Company
11830 Westline Industrial Drive, St. Louis, Missouri 63146

The Library of Congress cataloged this serial as follows:

Drugs of choice, 1958/59—
St. Louis, C.V. Mosby Co.
v. 26 cm.
Editor: 1958/59— W. Modell
Includes bibliography.

1. Pharmacology. 2. Therapeutics. 3. Drugs. I. Modell, Walter, 1907— ed.
RM101.D75 615.1 58-6889
ISBN 0-8016-3523-3

C/VH/VH 9 8 7 6 5 4 3 2 1 01/C/080

Contributors

MOHAMMAD AMIN, M.D.

Professor and Chairman, Section of Urology, Department of Surgery, University of Louisville School of Medicine, Louisville, Kentucky

KENNETH A. ARNDT, M.D.

Associate Professor of Dermatology, Harvard Medical School; Dermatologist-in-Chief, Department of Dermatology, Beth Israel Hospital, Boston, Massachusetts

JOSEPH F. ARTUSIO, Jr., M.D.

Professor and Chairman, Department of Anesthesiology, Cornell University Medical College; Anesthesiologist-in-Chief, The New York Hospital, New York, New York

J. WELDON BELLVILLE, M.D.

Professor of Anesthesia. University of California at Los Angeles, School of Medicine, Los Angeles, California

HYLAN A. BICKERMAN, M.D.

Clinical Professor of Medicine (Ret.), Special Lecturer, College of Physicians and Surgeons, Columbia University; Attending Physician, Presbyterian Hospital, Columbia-Presbyterian Medical Center, New York, New York

JEROME B. BLOCK, M.D.

Professor of Medicine and Chief, Division of Medical Oncology, Harbor General Hospital, UCLA Medical Center, Torrance, California

JOHN J. BONICA, M.D., D.Sc., F.F.A.R.C.S.

Chairman Emeritus and Professor of Anesthesiology; Director, Multidisciplinary Pain Research Center, University of Washington School of Medicine, Seattle, Washington; Immediate Past President, International Association for the Study of Pain

RUBIN BRESSLER, M.D.

Professor and Head, Department of Internal Medicine; Professor of Pharmacology, Health Sciences Center, University of Arizona, Tucson, Arizona

ROWAN T. CHLEBOWSKI, M.D., Ph.D.

Assistant Professor of Medicine, Division of Medical Oncology, Harbor General Hospital, UCLA Medical Center, Torrance, California

KENNETH A. CONRAD, M.D.

Associate Professor, Departments of Internal Medicine and Pharmacology, Health Sciences Center, University of Arizona, Tucson, Arizona

WILLIAM W. COON, M.D.

Professor of Surgery, University of Michigan, Ann Arbor, Michigan

JOHN M. DAVIS, M.D.

Assistant Professor of Surgery, Cornell University Medical College; Assistant Attending Surgeon, The New York Hospital Cornell Medical Center, New York, New York

†ARTHUR C. DeGRAFF, M.D.

Professor of Therapeutics, New York University, School of Medicine; Visiting Physician, Bellevue Hospital; Attending Physician, University Hospital, New York University Medical Center; Senior Consultant in Cardiology, Manhattan Veterans Administration Hospital, New York, New York

†Deceased

PETER DINEEN, M.D.

Professor of Surgery and Director of Surgical Microbiology Research Laboratory, Cornell University Medical College; Attending Surgeon, The New York Hospital, New York, New York

JO-DAVID FINE, M.D.

Assistant Professor and Director of Research, Department of Dermatology, The University of Alabama, Birmingham, Alabama

FREDERICK R. FRANKE, M.D., D.Sc. (Med.)

Clinical Professor of Pharmacology, School of Pharmacy, University of Pittsburgh; Cardiologist, Western Pennsylvania Hospital, Pittsburgh, Pennsylvania

RAY W. GIFFORD, Jr., M.D.

Chairman, Department of Hypertension and Nephrology, The Cleveland Clinic Foundation, Cleveland, Ohio

I. WILLIAM GOLDFARB, M.D.

Clinical Instructor, Department of Surgery, University of Pittsburgh School of Medicine; Director, Nutritional and Metabolic Support Service, Western Pennsylvania Hospital, Pittsburgh, Pennsylvania

KENNETH GOLDSTEIN, M.D., F.A.C.P., P.C.

Associate Clinical Professor of Medicine, The George Washington University Medical Center, Washington, D.C.

LAWRENCE M. HALPERN, Ph.D.

Associate Professor of Pharmacology and Member, The Pain Clinic, University of Washington School of Medicine, Seattle, Washington

WILLIAM D. HAUGER, M.D.

Associate Program Director, Internal Medicine Residency Program; Program Director, Intensive Care Program, Conemaugh Valley Memorial Hospital, Johnstown, Pennsylvania; Assistant Professor of Internal Medicine, Temple University School of Medicine, Philadelphia, Pennsylvania

ROBERT E. HODGES, M.D.

Professor, Departments of Internal Medicine and Physiology; Chief, Nutrition Section, Department of Internal Medicine; Attending Physician, University of Nebraska Hospital and Clinic and Omaha Veterans Administration Hospital, Omaha, Nebraska

LEO E. HOLLISTER, M.D.

Senior Medical Investigator, Veterans Administration Medical Center; Professor of Medicine, Psychiatry, and Pharmacology, Stanford University School of Medicine, Palo Alto, California

RICHARD B. HORNICK, M.D.

Professor and Chairman, Department of Medicine, University of Rochester School of Medicine and Dentistry, Rochester, New York

MELVIN HORWITH, M.D.

Clinical Professor of Medicine, Cornell University Medical College; Attending Physician, New York Hospital, New York, New York

DONALD W. HOSKINS, M.D.

Clinical Associate Professor of Medicine, Cornell University Medical College, New York, New York

CRAIG M. KESSLER, M.D.

Associate Professor of Medicine, Division of Hematology and Oncology, George Washington University Medical Center, Washington, D.C.

NEIL A. LACHANT, M.D.

Assistant Professor of Medicine, Division of Hematology, Harbor General Hospital, UCLA Medical Center, Torrance, California

CHI-WAN LAI, M.D.

Associate Professor, Department of Neurology, The University of Kansas College of Health Sciences and Hospital, Kansas City, Kansas

LOUIS LASAGNA, M.D.

Professor and Chairman of Pharmacology and Toxicology; Professor of Medicine, The University of Rochester School of Medicine and Dentistry. Rochester, New York

IRVING H. LEOPOLD, M.D., D.Sc. (Med.)

Professor and Chairman, Department of Ophthalmology, University of California, Irvine, Irvine, California

LAWRENCE S. LESSIN, M.D., F.A.C.P.

Professor of Medicine and Pathology; Director of Hematology and Oncology, The George Washington University Medical Center, Washington, D.C.

ROBERT LICH, Jr., M.S. (Path.), M.D.

Professor Emeritus of the Section of Urology, Department of Surgery, University of Louisville School of Medicine, Louisville, Kentucky

FLETCHER H. McDOWELL, M.D.

Professor of Neurology, Cornell University Medical College, New York, New York

WALTER MODELL, M.D.

Emeritus Professor of Pharmacology, Cornell University Medical College, New York, New York; Consultant to the Surgeon General of the Army; former Member, Board of Directors, *United States Pharmacopeia;* Editor, *Clinical Pharmacology and Therapeutics;* Editor, *Rational Drug Therapy*

JOHN H. MOYER, M.D., D.Sc.

Professor of Medicine, Temple University School of Medicine, Philadelphia, Pennsylvania; Clinical Professor of Medicine, Milton S. Hershey Medical Center, Hershey, Pennsylvania; Vice-President and Director of Professional and Educational Affairs, Conemaugh Valley Memorial Hospital, Johnstown, Pennsylvania

PHILIP S. NORMAN, M.D.

Professor of Medicine, The Johns Hopkins University Hospital School of Medicine; Physician, The Johns Hopkins Hospital and The Good Samaritan Hospital, Baltimore, Maryland

STEPHEN A. PAGET, M.D., F.A.C.P.

Associate Professor of Clinical Medicine, Cornell University Medical College; Associate Attending Physician, The New York Hospital and The Hospital for Special Surgery, New York, New York

HERBERT RAKATANSKY, M.D., F.A.C.P.

Physician, Miriam Hospital; Associate Physician, Rhode Island Hospital, Providence, Rhode Island

JACK L. SMITH, Ph.D.

Swanson Professor of Biochemistry; Director, Division of Medical Nutrition Education, School of Allied Health Professions, College of Medicine, University of Nebraska Medical Center; Deputy Director of the Swanson Center for Nutrition, Inc., Omaha, Nebraska

W.D. TIGERTT, M.D.

Professor of Pathology, University of Maryland School of Medicine, Baltimore, Maryland

LEROY D. VANDAM, M.D.

Emeritus Professor of Anesthesia, Harvard Medical School; Anesthesiologist, Brigham and Women's Hospital, Boston, Massachusetts

WILLIAM J. WISHNER, M.D.

Pasadena Diabetes and Endocrinology Medical Group, Pasadena, California; Assistant Professor of Medicine, University of Southern California School of Medicine, Los Angeles, California

DEWEY K. ZIEGLER, M.D.

Professor of Neurology, University of Kansas School of Medicine, Kansas City, Kansas

Preface

This book is a practical guide to the selection of the best drug for a particular therapeutic problem. Because of the extremely fertile mating of the synthetic chemist and the pharmaceutical manufacturer, in the recent past new drugs appeared on the market almost too quickly for the physician to learn the names, to say nothing of distinguishing which were the same drugs with different proprietary names. It was a herculean job to learn enough about them to evaluate their relative therapeutic merits. The present decline in the drug birth rate has made learning their names simpler, but some of the latest additions are so new and some so very complex in their pharmacologic and toxicologic actions that it requires substantial information to choose them well and to use them safely. In addition, so much more is being learned about interactions of drugs with other drugs, with environmental contaminants, and with foods that the choice of new drugs is still a difficult matter. Yet the choice of the right drug will determine whether the patient receives the most judicious therapy. The proper use of the drug may also determine the outcome of the patient's condition.

There are obvious advantages in choosing the best drug for the clinical problem at the outset of treatment. For the seriously ill patient, time may be precious, and if the first choice is the best drug for the situation, that irretrievable commodity is not wasted. Something short of the best may provide incomplete relief, no relief at all, untoward effects, or disaster. The patient is likely to assume, and perhaps he also has the right to expect, that the physician will provide the optimum drug for his condition the first time a prescription is written. It is understandable that, having endured a period of unsatisfactory treatment, the patient may be reluctant to continue an obvious trial-and-error process. For the physician's part, it is not feasible to plead that there is no other way of determining the best drug.

A bad initial impression of a drug often leads to enduring and unshakable prejudice and causes the physician to avoid using it in situations in which it is eminently useful and safe. Nothing is more likely to lead to a bad first impression than ignorance of limitations and interactions; conversely, nothing is more likely to lead to appropriate first impressions of a new drug than the knowledge that enables the physician to select the best drug for the therapeutic target; that is to say, the *drug of choice.* Yet there is almost nowhere for the physician to turn for the kind of help needed—certainly no place where unbiased, authoritative, and definitive information bearing on this problem is brought together and made easily available. This volume is designed to satisfy this need by bringing together knowledge that is presently spread through the various specialties, and, if published at all, published separately. It is a volume of expert *opinion* designed to provide the American physician with a comprehensive source of clear, concise, authoritative, and practical answers to the continually recurring question of which drug in a rapidly changing scene is, at the critical moment, the drug of choice for an actual therapeutic problem.

Many experts and educators in medicine have participated in the preparation of this book. Each was requested to express *his own opinion* of the drugs in cur-

rent use in his field based on his specialized knowledge and experience. Controversy was avoided, because to be fairly explored controversy must be considered in great detail. Such discussions in the usual format of the review article often leave the reader still seeking the clear and definitive answer. Although the existence of controversy may be indicated, the issues will not be argued here, since such argument would defeat our purpose.

The warm reception given the thirteen previous editions of *Drugs of Choice* has proved that the medical profession recognizes the present urgent need for authoritative and unbiased information on the choice of a particular drug for a particular clinical situation. This has been most gratifying to the contributors, who work very hard to make an up-to-date book of this type possible. A well-timed revision is, however, essential if the book is to remain useful by being sufficiently up to date.

Trial has shown that a 2-year interval between revisions is a satisfactory one. A shorter period would be too brief for substantial experience with the drugs introduced in the interval, and there would be too few new drugs to merit a new edition, whereas a longer period would allow the current edition to become badly dated before a new one was available.

Recent legal and quasi-legal actions of the F.D.A. have created new and special problems and responsibilities for the practitioner. These are discussed in detail in the Introduction, which is recommended as practical as well as protective reading.

Many of the drugs available have not been mentioned in the text. Failure to discuss a new drug may be interpreted to mean that the drug was introduced too recently to provide sufficient clinical experience for a truly substantial opinion by my standards. Failure to discuss an older drug may be interpreted to mean that it is not a drug of choice, and in my opinion, it is not of sufficient importance to merit discussion.

Walter Modell, M.D.

Contents

Legal complications in the clinical use of new drugs

Walter Modell, M.D.

Tozer and Kasik, experts in medicolegal developments, believe that in his own defense the physician in general practice would be wise to tell all his patients about their diseases and drugs prescribed in detail to enable them to give a truly informed consent and that it would be wise also to record a careful resume of the conversation.

In addition, to minimize the risk of suit for an injury caused by a drug, Tozer and Kasik say that the physician first "might consider whether he should prescribe any drug with which he is not thoroughly familiar; familiar, that is, with its chemistry, mode of action, contraindications, side effects and the means of treating whatever adverse reactions it might precipitate.

"Second, he should know his patient in relation to the proposed drug. The pertinent history must be taken and recorded and any suggested tests for sensitivity and pre-disposition to reactions must be performed.

"Third, he must be able to justify the use of the drug with its dangers, as opposed to other drugs and other methods of treatment. . . .

"Fourth, he should watch for, and follow up, all symptoms and signs which might indicate an adverse reaction and he should stop treatment with the drug when such symptoms appear unless there is some, overriding consideration.

"Finally, he might consider keeping a diary in which to record the names of all patients who have received each drug so that when he receives a new warning from a detail man or a revised product card or a 'Dear Doctor' letter he can pass the warning on to every patient taking that drug without having to make a major search of his files to discover their names."

There is also the question of whether in the case of every drug he prescribes he should have at hand and be prepared to apply the proper emergency treatment for a reaction.

Many aspects of the F.D.A.'s attitude deeply concern the medical profession and the practice of medicine.

Information on the proper use of drugs develops with continued clinical experience. Package inserts, when prepared shortly before a new drug is released, cannot provide a final account of a drug. By the very nature of the drug problem, even if an insert is written by an unbiased expert, it must contain many statements that will have to be altered as experience accumulates. For every single drug the determination of actual efficacy, proper dosage, and safe use requires substantial experience by the general practitioner as well as by the expert. "It is held by many that it takes about five years before a truly definitive statement can be made about a drug. This implies that there must be free and unrestricted expression of opinion and publication of experience with drugs already officially described and delimited in F.D.A. inserts if progress is to be made in therapeutics and if errors by the

F.D.A. are to be promptly published and rectified."

We are afraid of therapeutic regimens that are guided by legal rather than clinical considerations. We are also afraid of "defensive" therapy. To those who want to use the best drug in the best way for each patient in each instance, I offer this book whose contributors are recognized authorities in their respective fields. They have had clinical experience with the drugs they write about. They have seen the dosage regimens they recommend work in their patients. They have had the experience necessary to recommend the drugs they do. Expertise and experience and nothing else—no other considerations dictate the drugs and dosages recommended here.

SELECTED REFERENCES

Modell, W.: FDA censorship: Congressional Record, Senate, June 8, 1967, p. S7884; Clin Pharmacol. Ther. **8**:359, 1967; Med. Tribune, p. 1, June 15, 1967.

Tozer, F.L., and Kasik, J.E.: The medical-legal aspects of adverse drug reactions, Clin. Pharmacol. Ther. **8**:637, 1967.

CHAPTER 1

Principles for the choice of drugs

Walter Modell, M.D.

To judge whether a drug is useful in a specific clinical setting or, when there is more than one drug available, to decide which is preferable requires two kinds of pharmacologic information: (1) data obtained through studies in the laboratory and (2) data developed through studies in man, that is, its clinical pharmacology, a body of information on drugs more heard about now than ever before.

ESSENTIAL PHARMACOLOGIC INFORMATION

In the choice of a drug, the laboratory investigations that supply information and the proper interpretation of the data they provide are basic because knowledge about the actions of a drug, its potency, and its toxic effects gives the initial clues to its therapeutic potential and its dangers. Most of the important drugs in modern use have come by way of the research laboratory, for example, penicillin; only a handful, for example, digitalis, atropine, and morphine, have been inherited from ancient times, have survived the improvements and changes forged by the synthetic chemist, and are still to be found in today's pharmacopeias.

Bearing of experimental data on clinical utility of drugs

This is an appropriate place to make clear that there is no conflict between the data of the laboratory and the clinic. If properly selected, laboratory findings are more often directly applicable to the clinical situation than many clinicians admit. That a disparity should sometimes exist generally arises through neglect of pertinent laboratory data or through their improper interpretation or application.

Chemists and drug manufacturers have an understandable tendency to make assumptions of drug utility in advance of the long period of experience essential to establish unquestionable clinical utility. The newspapers and television, too, along with unsettling stories, try to make news by disclosing unverified information on drugs that have a suggestive design or pharmacologic action and presenting them as panaceas.

Such publicity frequently is followed by public pressure on the medical profession to use insufficiently understood drugs. More often than otherwise, trials of drugs in man fail dismally to fulfill the hopeful predictions made or even remotely to satisfy the need for which, on the basis of superficially examined laboratory experiments, the drugs appeared to be suited. Too often such failures are interpreted as evidence of lack of compatibility between laboratory data and clinical application and as implying that the former are of limited utility in the evaluation of drugs for man. No matter how effective governmental and industrial controls and trials may be, it is the practicing physician who will still have to make choices of drugs on the basis of information somehow obtained. We hope that the principles of choice will not change because of legislation or F.D.A. fiat.

It is of the greatest importance to realize that it is the initial observation of the pharmacologic properties of new drugs in the laboratory animal that gives the clue to utility as well as makes possible their safe exploration in man. Thus the animal, the experiment, and in fact, the pharmacology laboratory are basic to progress in therapeutics. The difficulties with tranylcypromine (Parnate) could have been avoided by using information already developed in the laboratory; so, too, the MER/29 reactions would have been avoided if the early animal experiments had been fully reported. Truly important recent discoveries such as the modern treatment of gout, hypertension, and hyperlipidemia were direct results of animal experiments.

The pharmacologic properties of drugs as seen in the animal are likely to apply to man when laboratory experiments are carefully analyzed and applied only to those clinical situations that really correspond. Although species differences are sometimes striking, it is often possible to avoid disparity by the choice of the appropriate laboratory animal. When appropppriate associations are regularly made, there will be far less time and effort lost in the futile trial of drugs that do not apply to the conditions for which they are tested. The well-designed laboratory investigation should provide precise information essential for determining the applicability of a drug to clinical problems, the physiologic functions altered by the drug, the nature of toxic reactions, and the likelihood of significant species differences in relation to drug tolerance as well as pharmacodynamic action. Such data also provide clues to possible serious drug interaction. Carcinogenic and teratogenic potentialitities may defy the laboratory—often only long clinical experience completes the tale.

The nature and extent of the physiologic dysfunction in man to be rectified by therapy must be borne in mind and compared with the condition of the experimental animal in which the drug was tested, or a mismatch will inevitably result. Notable examples of such mismatches can be cited. Respiratory stimulation can be induced in the cat with several drugs, but it may not be automatically assumed that such drugs will stimulate respiration when it is depressed because of intoxication or disease. In fact, respiratory stimulants in clinical use usually do not induce the same degree of stimulation in the depressed respiratory center seen in the laboratory animal. That there should be clinical depression of respiration despite decreased oxygen and increased carbon dioxide content of the blood, both excellent stimulants of a reactive center, is strong evidence that the respiratory center is not only depressed but also resistant to stimulation. The reason why the

respiratory analeptics now in use are disappointing is *not* that the respiratory center of the normal cat differs significantly from that of man but rather that the normal respiratory center examined in the laboratory is in a *different reactive state* from that in clinical depression of respiration.

The pharmacologic actions of drugs can usually be trimmed down to very simple and precise terms since, fundamentally, drugs either stimulate or depress some physiologic function. Pharmacologic actions include toxic and undesirable as well as potentially useful effects. When drug actions seen in the animal are analyzed on such a basis, one can compare the experimental and clinical setting to decide whether there is sufficient similarity between them to hope for clinical utility. A drug that anesthetizes a normal cat is very likely to anesthetize a patient because the physiologic settings in both are similar, that is, before anesthesia is induced the central nervous system of the patient is usually as normal as that of the cat. The action of antidotes in the acutely poisoned animal is also likely to correspond with that in man because the type of action called for and the setting are much the same in both.

There are, of course, instances of disease or dysfunction in man for which there is no laboratory duplicate in which to test a drug. The psychotropic drugs may be cited as outstanding examples, but when clinical situations with their physiologic dysfunctions are carefully evaluated, comparable laboratory-induced states in animals are usually possible. Sometimes the association between laboratory and clinical states can be made out of piecemeal consideration of the disturbance in man. Where it is a fact that there is no laboratory counterpart, the deficiency on the part of the laboratory must be reckoned with, and in such a case it may be that only evaluation in the patient will provide basic as well as practical information on clinical utility.

Finally, there are the unanticipated spin-offs of the experiences with new drugs in man and unanticipated therapeutic uses (acetazolamide in glaucoma, chloroquin in psoriasis, the "pill" in rheumatoid arthritis). Only experience brings these out into the open. Such serendipity is fortunately not rare.

Nature of chemical relationships of drugs to clinical use

Our understanding of structure-activity relationships of many drugs has progressed to a point where the pharmacologist can often design a chemical structure and predict its pharmacologic action and toxic effects with amazing assurance. The genius of synthetic chemists is such that they ply the pharmacologist with new drugs with interesting and challenging actions. Their ability to make these new drugs threatens our present capacity for their careful clinical evaluation.

When new drugs are considered, knowledge of previously investigated congeners is important as a basis for speculation and prognostication. It is equally important to recall that new drugs may or may not have all the particularized actions of the mother substance or, in rare instances, may block one or more of these actions. In the transformation the drugs may have lost some facets of action or gained entirely new ones. It is important to recognize that some new drugs are therapeutically inferior to or more toxic than the old ones for which they are offered as a substitute. Alterations are not invariably improvements nor, for that matter, is a change in potency per se an accomplishment of much real clinical importance. Despite our highly developed talent for predicting the pharmacologic actions of freshly synthesized drugs, only examination in the animal and long trial in man tell the complete story.

The probable incidence of reactions caused by drug allergy, intolerance, idiosyncrasy, and drug interaction cannot be determined by preclinical investigation in animals or even in man. These are rare events that are identified and

measured after a large and broad general clinical experience in man. Under our present system it usually takes 3 to 5 years of clinical use before the full potential for harm as well as the limits of utility are realized. It has been suggested that a probationary period of about that length of time be considered by the medical profession for all new drugs, sometimes called "phase IV," and recently proposed for legal status in national legislation.

Patterns of drug action

The parameters of drug action provide the practical considerations that determine whether a drug with an attractive pharmacodynamic design will prove useful. Potency, time-action characteristics as well as absorption and elimination all play decisive roles in determining when a drug may be used and, in the end, whether, despite eminently desirable pharmacologic actions, it can be used well or at all. Not only are pharmacodynamic effects important, but even when drugs possess the most desirable of actions, administration by an acceptable route in the circumstances that exist must be feasible, and the desired effects must be producible within an acceptable time period and maintainable at a desirable level of effectiveness for useful end results. Well-tailored pharmacodynamic actions are useless unless they can be induced soon enough and last long enough. Token effects, no matter how appropriate, are without merit. Excessively long action may be more of a hazard than the drug action is worth. A new and complex subspecialty, pharmacokinetics, sheds light on this aspect of drug behavior as well as its target in the body and how it is apportioned.

Potency. The potency of a drug, namely, the amount of substance by weight necessary to induce an effect, is of obvious practical importance, since it determines the absolute amount that will have to be given to induce an effect, but beyond this it is not a very telling bit of information. Provided it is possible to induce effects of equal intensity with other drugs, absolute potency per se is not invariably, or even usually, a determinant in drug choice. For example, since it is possible to reproduce all the effects of 1 mg. of digitoxin on the heart with digitalis leaf, which is 1/1,000 as potent, merely by giving a 1 GM. dose, the difference in absolute potency provides in itself no basis for a choice between them.

In some instances the potency of drugs is expressed in the literature so as to become truly misleading. For example, there are barbiturate drugs for which the average hypnotic dose for man is appreciably smaller than that of the usual barbiturate and less than the common capsule containing 100 mg. Such a barbiturate has been recommended as safer than others of which more has to be used for similar effects. The implication here is that the smaller absolute dose is less likely to cause difficulties. On the other hand, less potent barbiturates that require more drug per hypnotic dose than the usual 100 mg. have been put forward as preferable because a larger than usual amount is required for toxic effects. The implication here is that difficulties are less likely to be encountered because a larger than usual amount of drug is needed to cause toxicity. Obviously both arguments cannot be correct, but what is more important is that, as generalizations, *both are wrong.*

This sort of spurious claim has also been made currently for antihistaminics, phenothiazines, benzodiazepines, and benzothiadiazine diuretics. The outstanding feature is that there is no evidence at all that either potency range is advantageous. The fallacies in these cynical claims have escaped many, and few are sensitive to the fact that relative potency is not nearly so important as relative differences in therapeutic ratios and therapeutic ceilings. There is an argument that increased absolute potency has an advantage in that a smaller mass of foreign materials needs to be used to induce a pharmacologic effect. The validity of this assumption has never been examined or quantitated. It is certainly the