DRUGS OF CHOICE 1972-1973

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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 synthetics chemist and the pharmaceutical manufacturer, in the recent past new drugs had 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 had been 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 very new 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 drug interaction with other drugs, with environmental contaminants, and with foods that the choice of new ones is still a difficult matter. Yet the choice of a drug will determine whether the patient will receive the most judicious therapy.

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 his physician will provide the optimum drug for his condition the first time he writes a prescription. It is understandable that, having endured a period of unsatisfactory treatment, the patient may be reluctant to continue an obviously trial-and-error process. For his part, it is not feasible for the physician 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 uses, limitations, and dangers, and, conversely, nothing is more likely to lead to appropriate first impressions of new drugs 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 he needs—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 current 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 seven 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 two-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 FDA have created new and special problems and responsibilities for the practitioner. These are discussed in detail in the Introduction, a short new feature of this book, which is recommended as practical reading.

In order to provide fresh insights and a forum for different points of view, the authorship of a few chapters, especially those on controversial issues, has been changed in each edition. During recent years there has been a relative lull in the rate of new drug development, which provided a good opportunity for substantial reevaluation of opinion. Accordingly, all chapters have been thoroughly revised and five of them entirely rewritten, two by the old authors and three by new ones. This edition therefore represents an extensive revision. The number of contributors now stands at forty-one.

As in previous editions, a single alphabetically arranged, all-inclusive, and up-to-date Drug Index appears at the end of the book. For ease in reference it is distinguished from the text by the tint of the paper. The Drug Index *will not help the reader make his choice.* Recommendations of authors are to be found only in the text itself. The Drug Index, limited in size by practical considerations, is a representative list of drugs in common use. Many obsolete and obviously irrational medicaments have been excluded, but many drugs with limited utility are included simply because they are still being used. Where the number of proprietary names for a single drug is so large as to make their complete listing an unrewarding undertaking, many of the proprietary names have been omitted.

In this edition a list of tables is included in the preliminary matter. In addition, an outline survey with page references appears at the beginning of each chapter.

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

Walter Modell, M.D.

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Introduction

Legal complications in the clinical use of new drugs

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Tozer and Kasik, experts in medico-legal 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 résumé 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."

Many aspects of 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 stuffers, which are usually prepared shortly before a new drug is released, cannot provide a substantial account of a drug. By the very nature of the drug problem, even if it is written by an unbiased expert, a stuffer 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. stuffers if progress is to be made in therapeutics and if errors by the F.D.A. are to be promptly published and rectified."

By evading the most important charge of the Kefauver-Harris legislation, that of ensuring drug effectiveness, the F.D.A. is emasculating the provision most important to good medicine. The F.D.A. has reduced upper limits for drug use on the basis of safety in some cases by arbitrarily limiting dosage. It does not assure, as the Food and Drug Amendments require, that drugs in commerce must also be clinically effective. And there can be no question about the meaning of the law: it means effective in the dosage recommended.

The Editor takes the position that the actions of the F.D.A. have made a volume such as *Drugs of Choice* more acutely needed than heretofore.

We are afraid of therapeutic regimens that are guided by legal rather than clinical considerations. To those who want to use the best drug in the best way, for each

patient in each instance, the Editor offers this book whose contributors are recognized authorities in their respective clinical 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.

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Chapter 1

Principles for the choice of drugs

Walter Modell, M.D.

Let's hurry, hurry, use the new drug before it stops curing.

Attributed to Trousseau

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, an aspect 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 laboratory, for example, penicillin; only a handful, like digitalis, quinine, and morphine, have been inherited from ancient times and have survived the improvements and changes forged by the synthetic chemist and are still to be found in the modern pharmacopeia.

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 seem to 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 before the long experience that is essential to establish unquestionable clinical utility is completed. The newspapers, too, along with unsettling news stories, try to reassure by disclosing unverified information on drugs that have a suggestive design on pharmacologic action and presenting them as some kind of panacea.

Such publicity frequently is followed by public pressure on the medical profession to use insufficiently understood drugs. More often than otherwise, trial of drugs in man fails dismally to fulfill the hopeful predictions made for them or even remotely to satisfy the need for which, on the basis of superficially examined laboratory experiments, they 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 he somehow obtains. The principles of the 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 which 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 that already had been 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 current discoveries (1968) such as a one-shot treatment of a chloroquine-resistant malignant malaria was the direct result of animal experiment.

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 very striking, it is often possible to avoid such a disparity by the choice of the appropriate laboratory animal. When appropriate 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 will also provide clues to possible serious drug interaction.

The nature and extent of the physiologic dysfunction in man to be rectified by therapy must be borne in mind and compared with that in 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 produce the same degree of stimulation of 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 is significantly different from that of man but that the normal respiratory center examined in the laboratory is in a *different reactive state* from that in clinical depression of respiration. The same type of mismatch leads to the constant ebb and flow of new antianginal drugs.

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. They include toxic and undesirable actions 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; for example, 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 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 against which to test a drug. The psychotropic drugs may be cited as outstanding examples of the exception to the rule. However, when the 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 information on clinical utility. In any event, if the findings in the latter are to be applicable to the needs of the former, careful and precise analysis of the disturbance caused by disease as well as that of the situation in which a drug is examined is essential.

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 the synthetic chemist is such that he plies the pharmacologist with new drugs with interesting and challenging actions. His 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. In the transformation they 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 alone a property 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 2 or 3 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.

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 curve, characteristics of absorption, and elimination all play decisive roles in determining where a drug may be used and, in the end, whether, despite eminently desirable pharmacologic actions, it can be used well or at all. This is to say, 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