THE YEAR BOOK *of* DRUG THERAPY 1970

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of
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1970

EDITED BY

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There are twenty YEAR BOOKS in various fields of medicine and one in dentistry. Publication of these annual volumes has been continuous since 1900. The YEAR BOOKS make available in detailed abstract form the working essence of the cream of recent international medicoscientific literature. Selection of the material is made by distinguished editors who critically review each year more than 500,000 articles published in the world's foremost journals.

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The material covered in this volume represents literature reviewed up to August, 1969.

PUBLISHERS' NOTE

With the publication of the preceding volume, Dr. Harry Beckman relinquished his editorship of the YEAR BOOK OF DRUG THERAPY, a position he had held for 20 years. Doctor Beckman has been a close friend and valued adviser during these years, and the publishers wish to thank him for his astute editing and outstanding cooperation. Inasmuch as Harry is an avid fisherman and ardent baseball fan, we sincerely hope that he will find time to pursue—with relish—these extracurricular activities.

We have, indeed, been fortunate to secure the services of Dr. Dale G. Friend to assume the editorship of this volume. Doctor Friend is well qualified, through years of experience and inherent ability, to assume the post of Editor of this YEAR BOOK, and we wish him well. We know that the reader will benefit immensely from the qualities that Doctor Friend brings to his new position—qualities that will be in the finest tradition of the YEAR BOOKS.

EDITOR'S PREFACE

It is a most difficult task to take over as editor of the YEAR BOOK OF DRUG THERAPY after the excellent tenure during the past 20 years of my old friend and colleague, Harry Beckman. As one who has long been an enthusiastic reader of the YEAR BOOK, I never ceased to be stimulated and at times amused by his penetrating analysis of the current therapeutic scene. He will be missed by all of us.

It is apparent to everyone that the role of drugs in medicine is rapidly becoming far more important than it has ever been in the past. Not only do we have more and better drugs, but the use of them is becoming more complex and hazardous. It is absolutely necessary, as many leaders in medicine are beginning to recognize, that we devote much more attention to the training of physicians in the proper use of drugs. Our ability to treat many diseased states hinges on the successful use of drugs already available. Oftentimes, agents must be used in situations and in ways that require thorough knowledge and skill if they are to succeed in their mission without producing serious adverse effect.

It is obvious to those of us who have been closely observing the field of adverse drug reporting that a very high percentage of reactions to drugs is predicated on their improper or unskillful use. Physicians all too often use drugs without thoroughly understanding their basic properties and potentials for harm. All too frequently, new drugs are used on the advice of agents or advertising of the firm manufacturing the drug. Although much of the advertising and information supplied is good, it by nature of its source invariably has some bias. It is absolutely imperative that physicians seek independent, objective information before replacing an old agent or prescribing a new agent. Unfortunately, it is often difficult for him to do so. Because original articles appear in such a variety of journals, it is nearly impossible to have individual access to much of the information.

Although several publications have appeared which are useful in helping the physician in his therapeutic endeavors, there needs to be much more done in this field. Furthermore, the physician should be able to see the original material and a critical analysis of it, such as is attempted in the YEAR BOOK.

There is another aspect of drug therapy that needs much more attention than it is presently being given. Although the Drug Review Board of the National Academy of Sciences has done a monumental job in sorting over and recommending the status and correcting claims for drugs appearing between 1938 and 1962, there still remain thousands of questionable preparations on which there is equivocal or little objective information. These agents add to confusion in therapy and in many instances are either useless or of limited relative value. For example, there are some sixty preparations for the treatment of angina pectoris: any knowledgeable physician knows that there are fewer than three or four that can really be of sufficient merit to warrant his attention. This same situation holds for many other therapeutic classes.

Finally, we must all be more critical not only in selecting our agents, but we must see that our patients get the most value for the money they spend on drugs. They must not only be protected from spending their money for useless or questionable agents, but they must be given the most effective, highest quality drug at the lowest price available. This can only be done by a fully informed physician with not only knowledge concerning the best drug to use in the situation but one who also possesses information as to relative cost of equally effective agents.

Because the editor considers the above points so important, he is including an introduction that briefly outlines the principles and practices necessary for good drug therapy. It is his hope that readers will find it helpful in their desire to better understand, select and use the best drug available with the least hazard to their patients.

INTRODUCTION

Principles and Practices of Good Drug Therapy

It is evident as information has been compiled on adverse drug effects that there is a definite need for physicians to be much more critical in their selection and use of drugs in therapy. Often, success in treating disease depends not so much on the drug as on the skill of the physician using it. Furthermore, if the serious incidence of adverse effects is to be reduced significantly, it will be due to the wiser use of drugs.

Unfortunately, very little concerning drug therapy is taught in medical schools, and much of what is taught is given long before the student is in a position to use it in handling patients. Consequently, much of what has been given is forgotten or totally inadequate when the physician begins prescribing drugs.

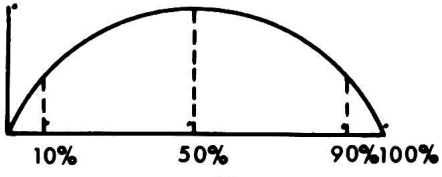
Because of this weakness in drug therapy education, there is urgent need for much more effort in the medical school and hospital training to properly equip physicians to practice drug therapy wisely.

All too often at present, physicians are so poorly prepared to handle drugs that they are uncritical, confused, use questionable drugs, prescribe them improperly and know so little about them that they are in no position to secure the maximum benefit from them or recognize the early signs of impending adverse effect.

This introduction has been prepared as an aid to the practicing physician in the hopes that the principles set down will help him to make the decisions wisely that he alone can make in the best interest of his patients.

The first and most important principle is to fit the dose of

Fig. 1.



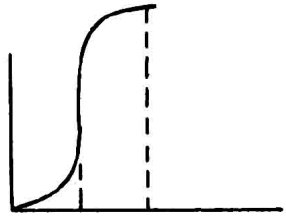


Fig. 2.

the drug to the needs of the individual patient at the particular time in his illness. In other words, the dose must be titrated to the needs of the patient if best results are to be obtained. There are two basic factors operating when a drug is given to a patient: the normal distribution curve of patient response applicable to any large group of individuals and the dose response curve of the drug.

The distribution curve can be illustrated by a simple bell-shaped curve (Fig. 1). It can be readily seen from the curve that most individuals will fall in the 80 percentile group in their reaction to the effects of an average dose of a drug. However, there remain approximately 10% who are oversensitive and who will find the dose too much and develop an adverse effect. At the other end of the curve is another 10% who will find the average dose inadequate and will receive little benefit from the medication.

The dose response curve can be illustrated by an S-shaped curve (Fig. 2). From the curve, it can be seen that most drugs exert a maximum effect over a rather narrow range. Once the correct dose for the individual has been found, there is little to be gained by pushing the dose higher. It is therefore most important to determine an adequate dose for the individual and adjust the dose as needed to fit the patient's progress.

Many factors influence the dose of a drug in any individual patient: the speed of absorption and elimination, the degree of absorption, metabolism and factors influencing it, the route of elimination and any impairment of it, the role of metabolites, secondary pharmacologic actions and, finally, genetic factors in the patient, any of which may change the dose pattern. Since these are so important to successful therapy, they will be discussed in more detail.

It is important that the physician know all he can about the absorption and elimination of a drug. Drugs that are only partially absorbed should receive critical attention especially if they are potent agents capable of causing serious toxic effect should too much be absorbed. Usually the mechanism behind the inability of the intestinal tract to absorb 100% of a drug is not understood. Unquestionably, there are many factors influencing the situation, any one of which might be altered in such a way as to decrease or increase absorption. Therefore, drugs in this category should be suspect and dosage adjusted carefully with frequent observation clinically, or, when feasible, chemically, to ascertain the situation for each patient receiving the drug. Furthermore, the physician must be alert to recognize any sudden alteration in absorption pattern and compensate as needed to maintain the desired effect.

It must be borne in mind there are many factors that influence absorption other than characteristics of the absorption pattern. Foods, alkalies, metal-containing preparations such as aluminum and magnesium, calcium, certain resins, mineral oils, bulk-producing substances and various agents capable of chelating certain drugs all may influence the degree of absorption. These factors and their influence on the drug being given should be known or the drug should be given in their absence until such information is available or the desired therapeutic effect is obtained with one or more of them operating.

Metabolism of a drug once it is absorbed varies with the individual drug. Some are readily split into inactive metabolites rather promptly, others are only slowly broken down in the body, whereas still others are acted on by tissues to give metabolites that may be more or less active than the parent drug. Often the metabolism of a drug is dependent on intact liver, kidney, other tissues or serum enzymes. For most drugs, the liver is the prime source of metabolic activity with the liver microsomes playing a most important role. Drugs that are quickly metabolized are usually short acting and must be frequently renewed if a steady effect is to be obtained. On the other hand, drugs that are slowly metabolized are frequently long acting, and, if there is impairment of the liver, excessive amounts may accumulate. Drugs that are metabo-

lized slowly are prone to accumulate in elderly patients when liver and kidney reserve is lost with increasing age. Occasionally drugs are split into metabolites that are active and which may or may not be readily handled by the tissues. Therefore, as much as can be learned about the metabolic degradation of a drug should be available before prescribing it.

Route and time necessary to eliminate a drug is important information and should be available to guide the physician. Drugs excreted by the kidney are dependent on an intact renal excretory system. Drugs that are readily excreted are less likely to cause adverse effects through accumulation than are those that are excreted slowly. Here, too, the elderly may have difficulty eliminating an agent which is excreted with difficulty.

It must be remembered that nearly all drugs have pharmacologic effects other than the principal or desired effect. Usually drugs are selected which exhibit the maximum degree of desired effect with as little as possible of secondary effect which may be undesirable. It is in these other effects that an adverse action often develops. Whereas, for example, one can tolerate dry mouth caused by atropine and its derivatives, the severe sedation produced by certain antihistamines or antidepressant drugs may be intolerable. It is therefore important that the physician thoroughly understand the nature of these secondary pharmacologic actions and be guided accordingly.

Recently, considerable interest is being generated in molecular biology and diseases created by genetic inherited defects. Certain individuals, it has long been recognized, are prone to acquire allergies to a variety of agents. Although we do not know for certain, it does seem that heredity may play a role in this situation. Recently there have been discovered enzymatic defects in the red blood cells, liver-produced enzymes and other tissues that cause the individual to react in an abnormal way to drugs not otherwise toxic.

The development of new drugs with specific actions has led to the use of several drugs often given at the same time to correct various physiologic abnormalities. This practice has created new complications. Certain drugs are incompatible, either causing an enhanced effect of one or both or a reduced or no effect of one or the other. Adverse reactions increase

rapidly as the number of agents given at one time increase. It is therefore important for the physician to be constantly alert to this phenomenon and ascertain the possible effect of adding another drug to one already being administered. There are already long lists of drug incompatabilities or interactions, and the number is growing rapidly.

Physicians should develop more interest and knowledge about the cost of drugs to their patients. Often a well-designed therapeutic program fails because the patient cannot afford to pay for the drugs involved.

At present, physicians do not readily have access to drug price lists and are often shocked when patients complain of the cost of their medicine. The local pharmacist can readily supply such information. It is the editor's contention that drug advertising should also supply this information. Expensive drugs should be avoided if cheaper ones are as effective. Prescriptions written in generic terminology may or may not result in reduced cost to the patient, and it has the disadvantage of turning over an important aspect of drug selection to the pharmacist. In view of the present controversy over therapeutic equivalence with serious differences in blood levels being found for several important drugs, it is wise to stick with a known effective agent until it is certain that another brand is as effective.

Because all of these factors are operating each time a drug is prescribed to a patient, it is exceedingly important for the physician and his patient to work closely together whenever a drug is used in therapy. The physician should know all he can about the drug from reliable independent literature, and, based on this thorough knowledge, make his patient a partner in the treatment program. This means that the patient should know the name of the drug, what the physician hopes to accomplish, important signs that may herald the onset of some adverse effect and be closely followed by the physician and urged to report immediately anything he may consider important. Furthermore, any warning so reported should be taken seriously by the physician. Finally, it is absolutely necessary that the physician carry out any recommended precautions, examinations or laboratory procedures suggested.

It must be remembered that every time a foreign molecule enters the human body a new experiment is under way, and all the care and thought as well as controls should be exercised, as would be the case in any study. If this approach is taken, there will be much more successful therapeutic results with considerable reduced incidence of adverse effects.

D. G. F.

Acne

Adult Acne is discussed by Naomi M. Kanof[1] (Georgetown Univ.). Acne in adults who had had no overt evidence of the disease in adolescence is most correctly designated as postpuberal or adult acne. Lesions of adult acne appear only on the face, particularly on the lower part of the sides of the cheeks, along the jawline and on the chin. Comedones are absent or sparse. Erythematous papules, the predominant lesions, are fewer than in adolescent acne but are more likely to become nodular and cystic. Residual discoloration is often prolonged. Seborrheic erythema and scaling are frequent concomitants in adults, especially between the brows, on the chin, and around the nares. The time of appearance of the lesions relative to the menstrual cycle varies. Duration of acne in adults is indeterminate and unpredictable, but few patients seek treatment between middle and old age.

Treatment is influenced by the type and intensity of the eruption. Many women seeking treatment are on estrogen-progestogen regimens. If flare-ups are unrelated to this therapy, sequential estrogen for the first part of the cycle and combined therapy for the latter part is probably best. Treatment should be discontinued if not beneficial within 3 or 4 cycles. Intralesional steroid is reserved for unresolving large nodules and cysts. Variously indicated measures, as in adolescent acne, include dietary restrictions, use of a suitable soap and drying lotions, antiseborrheic remedies, topical steroid lotions combined with antibiotics, oral broad-spectrum antibiotics and sulfonamides, oral vitamin A, acne surgery and irradiation. Irradiation can be used more liberally than

(1) Cutis 5:428-430, April, 1969.

in younger patients. It is difficult to assure adults with acne that the condition will be resolved either spontaneously or therapeutically.

► [A truly annoying condition which is, at times, distressful. Some women with this condition who take oral contraceptives which contain both progestins and estrogen report good results. Others must stop these drugs. Tetracycline in small doses occasionally does surprisingly well. Loss of weight when obesity is present is also helpful. – Ed.]

Aggravation of Acne Vulgaris by Topical Application of Corticosteroids under Occlusion. The use of full-strength steroid formulations is increasing, especially for the cystic forms of acne. James E. Fulton, Jr., and Albert M. Kligman[2] (Univ. of Pennsylvania) report an experience with strong topical steroids, used under occlusion to treat acne, that was at first rewarding and then disturbing. Eight males and 4 females with severe acne were selected for occlusive topical therapy with high-strength steroid. Lesions on the left side of the face were counted at weekly visits. The test preparation was 0.5 or 1% triamcinolone acetonide cream or solution. The steroid was applied nightly to the left side of the face and occluded with polyethylene film. In the morning it was again applied to the same side, but without occlusion. Ten patients were immediately pleased with the results; the erythema and pain lessened and the papules and cysts decreased in size. Seven patients, however, had severe flares in the next 2-6 months, often with a striking rise in the closed comedone count and then the development of small inflammatory papules. Sometimes this process was gradual, but occasionally severe aggravation occurred in as little as 1 month.

These patients with severe acne showed an initially favorable reaction to treatment with topical triamcinolone under occlusion, but then in many serious flares developed in their acne. This is the same pattern produced experimentally in normal subjects by steroids under occlusion. The topical treatment of acne with full- or high-strength steroids, particularly under occlusion, cannot be recommended.

► [One wonders why this flare-up occurred. Could it be that occlusive dressings made a more suitable situation for bacterial growth? – Ed.]

Use of Lincomycin in Dermatology. In a double-blind study, John H. Hall, John P. Tindall, J. Lamar Callaway and J. Graham Smith, Jr.[3] (Duke Univ.) studied the efficacy of lin-

(2) Cutis 4:1106-1108, September, 1968.

(3) South. M. J. 61:1287-1294, December, 1968.