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CLINICAL EVALUATION OF DRUGS FOR THE TREATMENT OF DIABETES

On Feb. 20, 1963, the Chairman of the Committee on the Use of Therapeutic Agents (hereinafter referred to as the Committee), in a letter addressed to the Food and Drug Administration, offered the services of the American Diabetes Association in connection with "problems arising with drugs already in use in the treatment of diabetes as well as drugs for which applications are pending or may be submitted in the future." At a meeting on June 12, the Committee considered a letter from Dr. Charles Weller of Larchmont, New York, a member of the American Diabetes Association, in which he requested that the Association establish uniform criteria for evaluating the effectiveness of hypoglycemic agents; the Committee agreed that this was a timely suggestion and that efforts to set up such criteria would be undertaken at its next meeting. Meanwhile, at a conference between Dr. Thomas P. Sharkey, President of the American Diabetes Association, and representatives of the FDA, Dr. Sharkey renewed the offer of this Association to be of assistance, on a consulting basis, in the evaluation of new drugs for the treatment of diabetes. It was agreed to hold a joint meeting between FDA representatives and the Committee at an early date.

Before the joint meeting, the Committee itself met to consider and draw up recommendations for the proper clinical testing of drugs used in the treatment of diabetes mellitus. The task was not too difficult. From examination of the literature, it was apparent to Committee members that it is important to avoid: poor selection of patients, improper experimental design, brevity of observations, and inadequacy of information on which effectiveness and toxicity could be judged. A start toward the establishment of standards had been provided by an editorial on the subject which appeared in DIABETES 8:472, 1959. At length the Committee, speaking only for itself but with the knowledge and consent of members of the Executive Committee of the American Diabetes Association who were present, was able to offer the FDA, and now offers to all others concerned, the following recommendations:

SELECTION OF SUBJECTS

The new drug should be tested in a few normal individuals.

For the most part those diabetic patients who, on the basis of experience and existing knowledge, are likely to respond should be chosen. In addition, but initially during hospital investigations only, some patients who are not likely to respond should be selected in order to define the limits of usefulness of the drug.

Patient cooperation must be assured.

There must be no complicating diseases which might interfere with evaluation of results.

Only patients with known diabetes of at least one year's duration and with demonstrated failure to respond to diet should be accepted for either inpatient or outpatient investigations. Recently discovered diabetes tends to improve with almost any kind of accepted treatment.

Among the suitable subjects as thus defined there should be some who have never received drug therapy for diabetes and, for purposes of comparing one drug

with another, some who have been treated with other hypoglycemic agents.

OBSERVATIONS IN HOSPITALIZED PATIENTS

A diet calculated to maintain the patient's present weight should be prescribed.

A control period of ten to fourteen days, or until a steady metabolic state is achieved, should precede any experimental period.

The experimental period should be of at least two weeks' duration for each drug tested.

A "recovery period" of at least two weeks should elapse between trials with successive drugs. Even this will be too short in many cases, for, especially in mild diabetes, the beneficial effects of one drug may last for many weeks and thus mask the effect of the next. Actually, it is doubtful that a succession of drugs should be tested in a patient who cannot stay in the hospital for as long as three months.

Use of placebos in control periods is advisable but not as important as in studies of ambulatory patients.

The patient should be weighed two or three times weekly. Daily determination of fasting and two- or three-hour postprandial blood sugar levels and of urinary glucose and ketone bodies in fractional and twenty-four-hour specimens is essential. Indices of lipid metabolism, such as serum cholesterol, triglycerides, and free fatty acids, should be obtained from time to time. More elaborate tests as, for example, respiratory quotient, nitrogen balance and studies with isotopes, will be added by those who have facilities for them.

Appropriate clinical and laboratory tests for toxicity are of course essential, not only with moderate, clinically effective doses of the drug but with doses as high as are likely to be used in practice.

Effectiveness should be determined first with the test drug alone and should be judged by changes in blood and urinary glucose and ketones, *not* by changes in "requirement" for insulin or other hypoglycemic agents; this is an untrustworthy guide.

The clinical pharmacology of a drug—absorption, metabolism, excretion, duration of activity, effective blood levels, and, to some extent, mode of action—can be studied only in a hospital, and should be.

OBSERVATIONS IN AMBULATORY PATIENTS

As with hospitalized patients, the diet should be designed to maintain present body weight, whether normal or abnormal. This is best accomplished by having the patient submit a quantitative record of his customary food intake for a week or more before observations are begun and at intervals thereafter.

The duration of the observations will vary with their purpose. In the investigation of a single drug, at least a year is usually necessary in each case for the accumulation of meaningful data respecting toxicity, side effects and late failures. In studies comparing one drug with another, a twelve-month period for each is not feasible and one must be content with three- or four-month periods but not less. For each drug tested in such short periods a minimum of six or eight sets of data for blood and urinary glucose and other determinations are necessary for proper evaluation.

Control and recovery periods should be of at least one month's duration and investigations, whenever possible, should be conducted with use of placebos and cross-over and double-blind technics.

Initially, office or outpatient visits should be made every one or two weeks, the patient bringing a record of his home urine tests made, if possible, four times daily with a copper reagent (not any of the glucose oxidase methods presently available) and a sample of a twenty-four-hour collection of urine for quantitative determination of glucose. For purposes of reporting, the home tests can be quantitated as the per cent of tests at each time of day showing o, + to ++, and +++ to ++++. Records of other drugs taken and illness or other untoward event should be required.

At each visit a urine specimen passed at that time should be examined for glucose, ketone bodies, and cellular elements. A fasting and a two- or three-hour postprandial blood sample for glucose should be obtained with the time since the last meal recorded. Body weight should be measured routinely.

Appropriate tests for toxicity should be made at intervals. It is in the long-term study of ambulatory patients that delayed manifestations of toxic reactions and side effects become apparent.

COMMENT

These recommendations are exacting. While they represent an approach to the ideal, they are at the same time practical. They are based on actual experience of Committee members in reviewing the original clinical reports of many physicians who have submitted to pharmaceutical firms data that would determine whether or not a given product would be acceptable to the FDA. In many cases the data have been less valuable than they might otherwise have been because procedures herein proposed have not been followed. The result may be that cooperating physicians may have to be asked to conduct further studies or supply missing information, not once but several times, and

approval of new remedies by FDA and their availability to the public may therefore be unduly delayed.

It is not expected that every investigator will be able to carry out all of the procedures that are desirable. Some physicians are equipped to perform one kind of investigation and some another. All who are involved have an obligation to themselves as well as to others to see that clinical studies of drugs are conducted in accordance with the aforementioned principles and practices.

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BOOK REVIEWS

ATHEROSCLEROSIS: MECHANISMS AS A GUIDE TO PREVENTION. *By Campbell Moses. $8.00, 239 pp., Lea and Febiger, Philadelphia, Pennsylvania, 1963.*

Campbell Moses has prepared an exceptionally fine compendium and digest which covers much of the abundance of multifaceted studies on arteriosclerosis that have been published in recent years. This superbly erudite presentation is clearly superior to other monographs of this type that have recently appeared. More than 1,300 papers are referred to in the bibliography. These have been grouped and pieced together in logical sequences and their contents reported briefly and accurately. This scholarly book should serve as an indispensable reference source for all investigators interested in this subject and save many hours of frustrating labor in the library over cumbersome cumulative indices. The informative chapters on the geographical and topographical distributions of arteriosclerosis prove conclusively that these have not deviated from the days of yore and should be useful to investigators who have had but little first-hand experience with the morbid anatomy of the human lesions.

It is understandable that the author should emphasize his own studies and those of other eminent notables. For the most part, however, the findings of various experimenters are presented with admirable objectivity. One consequence of this is that the author's own orientation does not emerge too clearly although in many instances a judicious evaluation of the work reviewed is included.

Moses appears to be equally impressed by the thesis that arterial thrombi (unlike the more ubiquitously prevalent venous and auricular ones) may undergo transmutation into atheromatous lipid masses and by the view that blood lipids play a fundamental role in the formation of intimal plaques. Unorganized thrombi in veins sometimes undergo puriform softening, a strictly nonatheromatous type of atheroma. The author is equally broadminded concerning other seemingly collisive speculations. The various regimes that have been recommended to retard the development of arteriosclerosis are discussed in considerable detail and with exquisite lucidity but their effectiveness seems obscured in a morass of incertitude.

The pathogenesis of this disease has been viewed from so many diverse directions and by such cunningly contrived approaches that the ordinary onlooker (such as this reviewer) ends up feeling that he has been encapsulated by a cloud enveloped in a fog even after reading this penetrating analysis. The only way to curb exuberant theoretical speculations concerning any disease is to develop an effective cure. This should serve as an added incentive to workers in this field, if any were needed.

CLINICAL METABOLISM OF BODY WATER AND ELECTROLYTES. *Edited by J. H. Bland. $16.50, 623 pp., W. B. Saunders Co., Philadelphia and London, 1963.*

It has recently been suggested that physicians can be divided into three loose groups—the very busy general practitioner, the specialty-trained, and usually more scientifically oriented practitioner, and the highly specialized research physician. It is largely to the second group that this book is directed and, although it occasionally hits above or below the mark, it accomplishes its purpose quite well. This new edition, although bearing the same title, is almost entirely a new book. Dr. Bland, having previously published competent, entirely self-written volumes, now believes that "one person can no longer encompass the field." He has chosen his coauthors well, reserving for himself the authorship of five of the twenty-two chapters, as well as the editorship.

As in any collaborative volume, some sections are more comprehensive than others. In two chapters, one on the transport of electrolytes and water and another on central nervous system control mechanisms, Joseph Cort takes us on a "lecture tour" of the scientist's critical mind. His clear presentation of the merits and limitations of current studies, and his analyses of more widely accepted hypotheses (and their still unresolved aspects) are at the highest level throughout.

Donald Oken, handling somewhat more familiar subject matter, also writes most effectively. He includes a lucid description of the countercurrent multiplier mechanism for urine concentration in a good general presentation of the most important aspects of recent work in renal physiology. These serve as a background for his discussion in another chapter of the pathophysiology and clinical aspects of renal failure. Oken wisely refutes the arguments for common use of low protein diets and sodium restriction in chronic renal disease, and takes an intelligent and practical approach to the limited but significant measures available for handling water and electrolyte imbalance, acidosis, etc., in renal failure. The chapter provides an excellent source of information for the student, the house officer and the physician struggling with this difficult problem.

Albert Behnke, the vigorous "grandfather" of the study of human body composition, draws on his personal studies and on those of others in presenting useful material on the