EDITORIALS

The Editorial Board of this Journal, the Committee on Scientific Publications and the Council of the American Diabetes Association share the loss of our distinguished Editor, scientist and friend, Dr. William C. Stadie, with his family, his colleagues at the University of Pennsylvania and the scientific community of the world. Elsewhere in this issue our able President, long-time friend and co-worker of Dr. Stadie, has presented a story on his life.

The Editorial Board and his Associate Editor are grateful for the few years he was able to serve the Journal and the American Diabetes Association. As Editor, his impeccable scientific standards and gentle but firm leadership have left an imperishable mark in the history of the Journal.

THE CLINICAL TESTING OF ORAL HYPOGLYCEMIC AGENTS

The chief requirements of any oral preparation for the treatment of diabetes are two: (1) it must be safe and (2) it must be at least as good as insulin for patients who need therapy in addition to diet. Specifically, we shall interpret the second requirement to mean that the oral agent must be as capable as insulin of maintaining the blood sugar below 150 mg. per 100 cc. and the urine free of sugar or nearly so with the patient on a diet appropriate to his ideal body weight and activity.

Although the responsibility for evaluating new remedies rests originally with their industrial developers and ultimately with the Food and Drug Administration, there is an in-between stage in which the fate of such products depends upon the results of preliminary clinical trial. It is, after all, the judgment of the physician that labels a drug safe or toxic, effective or useless. The decisive importance of his observations demands that he employ experimental designs as foolproof, and criteria as rigid, as those of the laboratory worker.

From this point of view, the office- or clinic-treated diabetic makes a poor test subject. Variations in food intake, activity, emotional stress and motivation almost preclude the controlled conditions that ought to surround the exploration of a new form of treatment. These variables account in part for the unreliability of some of the first reports on the sulfonylureas by clinicians who worked mainly with ambulatory patients. Such patients have their place in clinical trials, but that place is later rather than earlier.

The first clinical testing of a new drug for diabetes is best done in the hospital, preferably the metabolic ward. Even here, special precautions must be observed. Of first importance is the selection of cases. Obese patients should be avoided, for the vast majority of them, when placed on a proper diet in the hospital, will be found not to need insulin even though they have seemed to at home; and the purpose of the study is to determine whether the drug in question can replace insulin that is actually required. Patients with newly discovered diabetes, who tend to improve with any kind of treatment, or those whose tolerance for carbohydrate is changing for other reasons such as a recent illness or surgical operation, should not be chosen. The ideal subject is the otherwise healthy individual with diabetes of one year's duration or more, a well established requirement for insulin, an unchanging body weight and a stable emotional make-up.

Diet, obviously, must be constant. The caloric allowance should be calculated to maintain the customary body weight in the condition of reduced activity that hospitalization entails.

Except in special circumstances, insulin should be withdrawn rather than reduced, for withdrawal, but not reduction, will tell whether insulin was necessary at all and, if so, whether the oral drug can completely replace it. There is not much point in ascertaining whether the test preparation can compensate for the loss of 10 units out of a customary 20 unit dosage, for example, because, first, the apparent ability to alter that elusive entity, "insulin requirement," is an unreliable measure of a drug's activity and second, because there is little to be gained by using an oral supplement in the routine management of patients for whom some insulin is necessary.*

The withdrawal of insulin should be followed not by the immediate administration of the test substance but

* The claim, not fully established, that some oral hypoglycemic agents minimize the fluctuations of the blood sugar in patients with labile diabetes might be considered an exception to this statement.

by a *control period* of at least ten days during which fractional and twenty-four-hour urine specimens are analyzed daily for glucose and, if positive, for ketone bodies and both fasting and postprandial blood sugar levels are determined each day. If blood and urinary glucose remain within acceptable limits as defined above, the patient needs neither insulin nor oral drug and has proved himself an unsuitable subject.

If hyperglycemia and glycosuria appear or continue during the control period, the drug to be tested is added to the regimen, with no other change, for the next ten days (*test period*), during which comparable data are collected and signs of toxicity watched for.

A *recovery period* of similar length terminates the observations.

If during the test period normal or nearly normal glucose levels are achieved, it can be concluded that the compound is effective for the patient in question and possibly for others of a similar type. If good control is not obtained, the compound is not as good as insulin for this patient and the opposite conclusions can be drawn.

Ideally, a period with a placebo instead of the test substance should follow the recovery period, but this adds materially to the time required and is far less important in hospital than outpatient observations.

Obviously, this elaborate and time-consuming kind of study is not suitable for large numbers of patients or for the determination of long-term toxicity. Its purpose is to provide unassailable data on the effect of a given preparation in a few carefully selected subjects with diabetes of various types and degrees of severity. Only after the accumulation of this sort of information should the base of clinical testing be broadened to include ambulatory cases.

With respect to office or clinic patients, we are not concerned here with single-dose response tests of a few hours' duration but with the effectiveness and safety of drugs on a maintenance basis. The procedure follows the general scheme just presented but with two important modifications: Insulin must be withdrawn slowly rather than abruptly in order to guard against ketosis, and the "double-blind" method of administering the test drug and a placebo is imperative. The inherent difficulties of this kind of observation are mitigated to some extent by longer control, test and recovery periods; weekly visits at which blood sugar and quantitative (twenty-four-hour) urinary glucose are determined; written records of home urine tests made four times daily; and measurements of body weight.

Short-cuts in these procedures have been taken too often in the past, and the tendency to take them is currently increasing with the successive introduction of new forms of the sulfonylureas and other hypoglycemic agents. The fact that a new drug differs from its predecessor by only an atom or two is no guarantee that either its biologic activity or its safety is identical. Witness the example of carbutamide, in which merely the substitution of a methyl for an amino group converted that compound to one (tolbutamide) which is appreciably less toxic and lacks bactericidal properties while retaining essentially the same hypoglycemic potency. In the interest of sound medical practice and public safety, and despite the pressure of commercial competition, each new compound, however similar to others, deserves the same careful clinical testing as if its close relatives had never been heard of.

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THE TUBERCULOUS DIABETIC

The publication of a report on the management of the tuberculous diabetic by Luntz[1] has prompted this comment. Its purpose is to emphasize again a concluding statement by Luntz, to wit, "Acute bilateral pulmonary tuberculosis in a diabetic is a serious complication to be regarded as a medical emergency. It calls for immediate treatment in a special hospital unit with an effective dosage of combined chemotherapy for the tuberculosis and the stabilization of the diabetes as a matter of great urgency."

The validity of these conclusions cannot be questioned by any one who has had the opportunity to observe these cases. The tragic consequences of neglect of both diseases and, per contra, the remarkable success of combined therapeutic efforts in the past twenty years testify to the correctness of the conclusions.

The experience of Luntz was based, it is true, on only a short (one year) follow-up of eighty-four cases. He noted the usual sequence, tuberculosis complicating pre-existent diabetes in the majority of instances. The age distribution was also the usual one, with two peaks of predominance, twenty to thirty-nine and forty-five to sixty-four years, the first seeming to correspond to the maximal incidence of tuberculosis, the latter to the maximal incidence of diabetes. It would seem unnecessary to remind any practitioner again, in these days of mass X rays, of the dictum of at least yearly chest X rays in all diabetic patients and in particular in those with a break in tolerance or poor or difficult control. Such vigilance is imperative in the light of Luntz's finding of bilateral