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DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
NATIONAL INSTITUTES OF HEALTH

Date: August 19, 1970

Reply to Attn of: NIH-A-DIR

Subject: Progress report on tolbutamide study

To: Director, NIH
THROUGH: Deputy Director for Science, NIH

Several items of interest in relation to this multi-clinic study of the first oral drug for diabetes:

1. On July 29, 1970, in Chicago I attended a meeting between members of the AMA Council on Drugs and representatives of the University Group Diabetes Program (UGDP). Representing the AMA Council were Dr. John Adriani of New Orleans, chairman, Dr. Daniel Azarnoff of Kansas City and Dr. C. Alvin Paulsen of Seattle. Also attending on the AMA side were Dr. William Barclay, Director of Division of Scientific Activities, Dr. John Lewis, Dr. Richardson and Dr. Thomas Hayes, Director of the Department of Drugs. Dr. William Best of Hines VA Hospital attended as an independent observer and participated actively in the discussion. Representing the UGDP were Dr. Max Miller, chairman, Dr. Klimt, Dr. Meinert and Dr. Knatterud of the Coordinating Center at the University of Maryland, Dr. Ted Schwartz, Presbyterian-St. Luke's, Chicago, Dr. Robert Osborne, MGH, Boston and Dr. Bo Boshell, University of Alabama. In essence, the questions, particularly of Doctors Azarnoff, Paulsen and Best, were specific, detailed and on the mark. The careful and detailed answers of the UGDP group were responsive and quite clearly satisfied the questioners. The discussion lasted about five hours and specific details can be supplied from my notes if desired. About 3 p.m. the UGDP group (and I) left the meeting and the AMA people went into executive session to decide on their report. This will probably be made in October, and there is little doubt in my mind that it will mainly, if not entirely, support the findings of the UGDP study.

2. The paper submitted for publication to the journal Diabetes has been reviewed, comments received from the reviewers by the authors, their replies sent back to the journal, and the message has been received that the paper is basically acceptable and will be published in October.

3. Dr. Klimt tells me that the American Diabetes Association (ADA) has appointed a special review group (in addition to the reviewers of the paper for the journal) which will meet with representatives of the UGDP in mid-September following which the ADA will plan to prepare a position statement which will be more definitive than the vapid one at their annual meeting in June. Issuance of this statement is also scheduled for October.

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4. Dr. Klimt tells me that the FDA remains firmly in support of the UGDP study and its results but that Dr. Simmons believes that it would be better to hold up issuance of new guidelines, package insert language or any other pronouncements until October following the publication of the paper and issuance of the statements of the AMA Council on Drugs and the ADA.

5. Attached are copies of the inserts in the Senate Appropriations hearings record requested by Senator Magnuson on the UGDP.

G. Donald Whedon, M.D.
Director, NIAMD

Attachments

bcc (w/attachments):
Dr. Burton
Dr. Bernstein
Dr. Remmert
Dr. Roth
Mr. Baylis
Dr. Klimt

SUMMARY OF RESULTS OF THE UNIVERSITY GROUP DIABETES PROGRAM STUDY OF THE ORAL DRUG, TOLBUTAMIDE

A ten-year study of the effects of anti-diabetic drugs conducted by 12 leading medical centers (University Group Diabetes Program or "UGDP") with research grant support from the National Institute of Arthritis and Metabolic Diseases of the National Institutes of Health, has demonstrated that Tolbutamide ~~(brand name "Orinase")~~ is no more effective than diet alone in the treatment of mild, adult-onset diabetes mellitus except insofar as it lowers blood glucose, and indeed is less effective than diet or diet and insulin in reducing mortality from heart disease and related conditions in such patients.

The UGDP study was carried out in 12 different locations throughout the United States at 12 university medical centers with well established diabetes clinics. Patients were divided into four groups of about 200 each. All patients were placed on a diabetic diet. One group received, in addition, 1.5 grams daily of the oral drug Tolbutamide; a second group received, in addition to the diet, insulin at a fixed level of 10 to 16 units per day; a third group was given insulin at a variable level sufficient to control blood glucose for best possible clinical control; and the last group received an inactive tablet (placebo) in addition to the diet. The 823 patients, all recently diagnosed to have mild, symptomless adult-onset diabetes, were assigned at random to the four study groups.

The objective of the study was to ascertain the effectiveness of these four methods of treatment in prevention, or long-term postponement, of the onset of the blood vessel-related complications of diabetes (heart disease, kidney degeneration, blindness, and others) which make this disease a serious disorder once they make their appearance.

During the study, ten cardiovascular deaths have occurred among the patients treated with the sham or placebo tablet (in addition to the diabetic diet which all groups received). Twelve patients died in the group which received insulin injections in doses adjusted to maintain normal blood sugar levels. Thirteen patients died in the group treated with a fixed dosage of insulin. Twenty-six patients died in the group treated with Tolbutamide. The

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increased number of deaths in the tolbutamide group over those occurring in the other groups took place in a majority of the twelve clinics.

The duration of the study, well beyond the standard periods for drug testing, was of critical importance. During the first three years the data showed no differences between the groups, but in the fourth year of use, for reasons still unknown, the death rate in the tolbutamide group began to rise, and continued to increase thereafter.

Throughout this 10-year study, results were reviewed semiannually by all the medical investigators involved. In 1966, the entire study was reviewed in depth by diabetes and internal medicine experts not involved in the study, in connection with the decision for continuation of the funding of the research by the National Institute of Arthritis and Metabolic Diseases of the National Institutes of Health; the validity of the design and conduct of the study was reaffirmed by these outside experts. In addition, in June 1969, the accumulated data were carefully reviewed by three biomedical statisticians of national reputation who confirmed the findings of the study:

(1) No evidence was found that the combination of diet and tolbutamide therapy used for treatment of mild non-insulin dependent diabetics is more effective than diet alone except insofar as it lowers blood glucose.

(2) The findings suggest that tolbutamide and diet is less effective than diet alone or than diet and insulin at least insofar as cardiovascular mortality is concerned.

In trying to determine a basis for the difference in mortality experience, the investigators carefully scrutinized the characteristics of the various treatment groups at baseline (entry into the study) and were unable to find any differences in the composition of the groups to account for differences in mortality. Age, sex, race and level of blood glucose were not different at conventional levels of statistical significance in comparing the tolbutamide and control groups. Except for serum cholesterol, no significant differences were found on examination of 13 cardiovascular risk factors at time of entry. Adherence to treatment was similar in the control and tolbutamide groups. Changes in blood glucose during the course of the study were unrelated to the mortality findings.

It has not been proven that Tolbutamide is the sole factor responsible for the difference in mortality experienced, but the study clearly indicates that there is a need for careful re-evaluation of current management of patients with adult onset diabetes who are not insulin dependent.

The results of this ten-year study were presented at the annual meeting of the American Diabetes Association, June 14, 1970, in St. Louis, and have been submitted for publication to Diabetes, the journal of the American Diabetes Association.

Study of another oral anti-diabetic drug, Phenformin (DBI), now in its eighth year, is being continued by the University Group with support from the National Institute of Arthritis and Metabolic Diseases.

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MARTON GRANT [illegible]

The University Group Diabetes Cooperative Project was initially funded in Fiscal Year 1961 at $153,206. In 1964 by which time all 12 cooperating clinics had joined the study along with the coordinating center at the University of Maryland, the total for the 13 grants was $537,074. Since then annual funding has been between 500,000 and 600,000, averaging approximately $45,000 annually per clinic. Total funding to date is $4,818,427; this total covers the studies still in progress on the oral drug phenformin, as well as the studies on tolbutamide just reported.