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DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
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BETHESDA, MARYLAND 20014

COPY

April 5, 1971

Charles C. Edwards, M.D.
Commissioner
Food and Drug Administration
Parklawn Building, Room 14-71
5600 Fishers Lane
Rockville, Maryland 20852

Dear Charlie:

As you are aware, we have been concerned for some time about the controversy raging over the report of the University Group Diabetes Program which suggested that the addition of tolbutamide to a diabetic diet not only does not prolong life but may be associated with an increased cardiovascular mortality. The scientific techniques of the collaborating investigators have had the enthusiastic approval of peer review groups and the Council, both initially and at the time of renewal of their grants four years ago. In addition, Dr. G. Donald Whedon, Director of the National Institute of Arthritis and Metabolic Diseases, has closely monitored the program for several years and has been confident of the validity of the group's conclusions.

Verbal report of the results at the annual meeting of the American Diabetes Association in June and their publication as a supplement to DIABETES in December of 1970 have resulted in a storm of criticism from diabetologists and from two biostatisticians. Because of the vehemence of these complaints, I asked Dr Thomas C. Chalmers, Associate Director for Clinical Care and Director of the Clinical Center, to spend all the time necessary to evaluate thoroughly the criticisms and the defense of the study by the investigators.

This Dr. Chalmers has done in the past month and he has satisfied me that the conclusions of the study are valid. The technical objections have been satisfactorily rebutted by the coordinating center of the study and by such eminent consulting biostatisticians as Dr. Jerome Cornfield of the University of Pittsburgh, Dr. Byron Brown of Stanford University, and Dr. Donald Reid of the University of London School of Tropical Medicine and Hygiene.

The objections of practicing diabetologists that they have seen no sign of an increased risk of cardiovascular deaths on tolbutamide is understandable in view of the fact that they would have had to be able to detect an increment in cardiovascular death rate of 1% per year over an expected rate of less than 1% per year. Obviously, this small but real risk could only be demonstrated by a long-term controlled trial.

The results of this study have important implications, not only for diabetics now being treated, but also with regard to the pathogenesis of the vascular complications of diabetes and the place of controlled trials in the treatment and prevention of chronic diseases.

The proposed package insert on tolbutamide seems to us to be a fair representation of the state of our knowledge. There remains the problem of whether or not asymptomatic hyperglycemia should ever be treated, and it is hoped that future studies may answer that question.

Sincerely yours,

/S/ Robert Q. Marston
Robert Q. Marston, M.D.

cc:
Henry Simmons, M.D.

TCChalmers:ajk