At my request, on September 14, 1971, Dr. Thomas Chalmers, Associate Director of NIH for Clinical Care, invited the President of the Biometric Society, Professor B. Schneider, to appoint a committee to consider the biometric aspects of controlled trials of oral hypoglycemic agents. I am informed that the committee has now been appointed and that you have agreed to act as its Chairman.

The interest of NIH in this matter arises from the fact that approximately four million Americans have diabetes, as defined by an abnormal hyperglycemia and that seventy-five percent of these die of cardiovascular causes. Over 1.5 million diabetics are currently being treated with oral hypoglycemic agents. It is now about two years since the University Group Diabetes Program first reported that some oral hypoglycemic agents might increase the death rate from cardiovascular causes. Because of the wide clinical use of these drugs in the treatment of diabetes, it is important that the scientific aspects of the evidence concerning these agents be subjected to careful review.

Since the conclusion of the UGDP study depends in great measure on the biometric aspects of the investigation, I charge your Committee

1. to make an in-depth assessment of the scientific quality of the UGDP study and in particular of the biometric aspects of the design, conduct, and analysis of the trial;

2. to make a similar assessment of other controlled trials of oral hypoglycemic agents.

The committee is urged to utilize all the resources it needs to arrive at a satisfactory answer, and to prepare a report for publication. The Committee should feel free to obtain expert help in preparing this report and to call on representatives of pertinent disciplines as consultants. Although no prior approval by the NIH is required, we shall expect to be kept informed of the conclusions as they develop.

The committee was appointed by the President of the Biometric Society and now reports its findings.

The full committee met on six occasions during the period from August 1972 to October 1974. In addition, the European members met once as a group, and the US members did likewise. In the course of these meetings, discussions were held with others who are familiar with the clinical trials of oral hypoglycemic agents. Owing to limitations of time, the committee was able to hear only a few of the people who are knowledgeable in this field. It wishes to record special thanks for help given by Robert F. Bradley, MD, Jerome Cornfield; Alvan Feinstein, MD; R. J. Jarrett, MA, MD; Harry Keen, MD, FRCP; John B. O'Sullivan, MD; Stanley Schor, PhD; and Holbrooke Seltzer, MD.

The full committee visited the Coordinating Center of the UGDP at Baltimore and a subcommittee made a further visit to review the processes used in randomizing the allocation of treatments. Christian R. Klimt, MD, DrPH, the director of the Coordinating Center, and his staff provided extensive tabulations and original data of the UGDP trial. Harry Keen, MD, FRCP, also kindly made data available from the study that he and his colleagues conducted.

Subcommittee visits were paid to the centers at Boston and Cincinnati that participated in the UGDP trial.

Since the work of the UGDP is still in progress, it is not possible to assess the final outcome of the trial. In particular, much of the data on nonfatal events still remain unpublished. The committee saw as its main task the investigation of the excess cardiovascular mortality in the subjects who had received tolbutamide. It reviewed in detail reports of the UGDP on the design, methods, baseline data, and mortality results (*1, 2*); the original data on which these reports were based; and the commentary that has appeared in the literature up to the end of March 1973. The mortality data covered a period of approximately 8.5 years ending in October 1969; the committee has seen later overall figures, but since they were not final, the detailed data on which they were based were not studied. The preliminary report on phenformin (*3*) was considered in September 1973, but in view of the fact that the final report on that subject was still unpublished, the committee did not request the basic data on the effects of this treatment. For a similar reason it has given only limited attention to the findings on nonfatal events in the tolbutamide study. (*4*)

The committee has reviewed the published evidence available at the end of 1972 on other controlled trials of oral hypoglycemic agents. Some reference is made to all of these, but the main emphasis of this report is on the study by the UGDP and the Bedford study organized by Keen. (*5, 6*)

References at end of article.