argue, therefore, that the target population was unsuitable. Such a claim, however, overlooks the important but ill-understood prophylactic aspect of the trial, in which certain treatments were given to patients who, initially at least, could safely go without drugs, in order to test whether the common vascular complications of diabetes could be prevented. The issue was the testing of certain possibly preventive treatments rather than the implementation of certain standard therapeutic regimens.

Question. Was the decision to include phenformin in the study justified?

Answer. In the event it proved to be, since valuable information was obtained about the limitations of that drug. Its use, however, greatly complicated an already difficult study. It is clear that one of the problems of a long-term clinical trial is that potentially interesting therapies may develop while the trial is in progress, and the natural desire to include them may divert resources.

The omission of a history of smoking was a blunder.

7.2 *Conduct of the study*

This was necessarily a lengthy and complex trial, and a substantial pioneering effort was needed to mount it successfully. We have raised a question of whether the randomization was properly carried out. The only evidence that it might not have been is the data on the allocation of treatments according to the sex of the patient. Against this possibility are two * * *

7.3 *Methods of analysis*

The UGDP investigators sought to examine their data from a number of different points of view, and in so doing they made use of some relatively unfamiliar and exploratory statistical techniques. In some cases these methods would not necessarily have been chosen by other groups of statisticians faced with the same situation, but since the results of all the analyses tended to point in the same direction, there would be little advantage in discussing at length the weight to be attached to the different analyses.

The likelihood calculations seem to us to add very little to the other analyses. The results are rather difficult to grasp and require rather arbitrary weighting to be given to the likelihood of different hypotheses. The method does not take concomitant variables into account.

The Monte Carlo monitoring procedure was a major attempt to overcome the selective effect of a sequential analysis of the mortality data. The investigators were concerned lest they had paid undue attention to contrasts between treatments at a particular moment when extreme fluctuations might have occurred. Their method was ingenious, and although minor points of criticism may be raised, we do not think that these materially affect the issue. (Some of these points might be (1) the use of national mortality data, with death rates higher than those in the study population; (2) the use of an "average" survival curve for all patients in the simulation; (3) the adding of life table death rates at different ages to obtain the death rates during intervals; and (4) the arbitrariness of the linear boundaries. For an alternative approach to the sequential analysis of survival data, using internal comparisons only, see Breslow and Haug.(*29*)) The detailed outcome of such a monitoring procedure is of no great importance. The decision to stop the use of tolbutamide must have depended on considerations of various sorts, among which the monitoring procedure provided a contribution—no more than that.

The UGDP did not try to determine whether interactions were present in their data. This criticism was raised by Feinstein and is valid.

7.4 *Findings*

Although we have concerned ourselves almost entirely with issues related to the possible toxicity of tolbutamide, we wish to point out that one of the valuable aspects of the completed UGDP trial will be the provision of data on the long-term treatment of adult-onset diabetes with insulin. It is already clear that the benefits from this treatment are not dramatic, and the only worthwhile information about them will have to come from the relatively precise methods of a controlled clinical trial. In this sphere, the UGDP trial has no competitor. Indeed, we would generalize from this and point out the * * *

On the question of cardiovascular mortality due to tolbutamide and phenformin, we consider that the UGDP trial has raised suspicions that cannot be dismissed on the basis of other evidence presently available.

We find most of the criticisms levelled against the UGDP findings on this point unpersuasive. The possibility that deaths may have been allocated to car-

References at end of article.