of its possible toxic effect is highly relevant. Moreover, the problem of whether a subject with mild diabetes who would not normally take any hypoglycemic drugs can avoid some vascular complications of the disease by doing so is one that the trial was designed to illuminate or solve. We do not already have the answer to this; what is understood well is that certain patients require hypoglycemic drugs for current needs. It is another question as to whether these patients, and those with milder disease, can produce a prophylactic effect against vascular abnormalities by taking hypoglycemics in an attempt to maintain strict control of their disease. This is a matter for research and not for the simple implementation of current therapeutic practice.

5.5 *Discontinuation of tolbutamide and phenformin in the UGDP study*

The action of the UGDP in discontinuing the use of tolbutamide and phenformin has been criticized by those who believe that the trial of these treatments should have been continued in order to obtain more definitive results. It would have been easier to interpret the findings if there were more data on mortality. We recognize that the precise point at which suspicion of toxicity outweighs the need for scientific information is uncertain and that the choice might have been made differently by another equally qualified group of observers. Although we are not in a position to defend the timing of the UGDP decision in this matter, it is clear that ethics would dictate that a decision about withdrawal had to be made before all important questions concerning the effect of the drug were resolved. We do not criticize the UGDP investigators for having made the decision when they did. Nevertheless, the result of that decision is to leave us with some residual uncertainty about the meaning of the findings, a point that is well understood by the UGDP investigators themselves.

6. DATA FROM THE UGDP AND BEDFORD TRIALS

The directors of the UGDP and Bedford trials have kindly made available certain data that we requested from them in order to review evidence concerning the death rate of subjects taking part in controlled trials of oral hypoglycemic agents. In the case of the UGDP, the data of interest extended to the time at which the drug was discontinued. Events subsequent to that would cast light on the effects, if any, of previous use of the drugs—a question to which we do not propose to address ourselves. In the case of the Bedford trial, data are still being accumulated, and we have examined those available up to June 1972. These must, of course, be regarded as provisional. In both trials the data bear on many questions of great interest that we did not consider since they had limited relevance, if any, to our charge.

A simple method of studying data from a long-term clinical trial is to estimate failure rates for various population groups. Failure may be taken to be any adverse event; commonly, as in the present context, it is interpreted as death. The failure rate for a group after a certain length of follow-up is the rate at which the survivors are then dying. If the failure rate for a group is constant throughout follow-up (so-called exponential survival), its value, Y, may be estimated by $Y=k/t$, where k is the number of deaths in the group and t, the number of persons-periods at risk, each subject contributing a survival period or, if death has not occurred, a period of observation.

Approximately, log Y may be regarded as normally distributed with a mean of $\ln Y$ and a variance of $1/k$.

The failure rate takes into account the length of time for which each subject has been exposed to risk and can be made specific both for demographic characteristics of the subjects and for risk factors of interest. In the present context we have chosen a three-month period as an appropriate unit of time in calculating exposure to risk.

Simple and informative as the failure rates are in many cases, they become unwieldy and increasingly variable as subjects are cross-classified in more and more ways. We have therefore made use of the logistic model in order to carry out a more detailed analysis of the UGDP and the Bedford data.

6.1 *UGDP data*

In this section, we consider a problem relating to randomization and we present our analyses based on failure rates and on the multiple logistic model. We also report analyses designed to take into account the extent of adherence to treatment.