

A χ^2 analysis of these data indicated that there were differences, not statistically significant, in the proportion dead from all causes, but the tolbutamide-treated group had a significantly greater proportion of deaths from cardiovascular causes than did the placebo-treated group. Analysis by the life table method confirmed these results. Since there were differences in the base-line characteristics of the patients in the various treatment groups, however, the question arose as to whether the differences in cardiovascular mortality rates might be adequately explained by differences in the incidence of risk factors. The conclusions from the use of the logistic model (17) indicated that the expected number of deaths due to cardiovascular causes in the tolbutamide group if it indeed had the same cardiovascular mortality as the placebo group, was only 10.7, whereas 26 cardiovascular deaths had been observed. Further confirmation of these analyses was obtained from the Monte Carlo monitoring procedure and the likelihood calculations. Hence, the investigators concluded that there was an excess of cardiovascular deaths in the tolbutamide group—an excess group that could not be explained by differences in the base-line variables.

A closing date of Jan. 6, 1971, was used for the analysis of mortality data in the group receiving phenformin and those receiving other treatments at the phenformin clinics. A total of 47 deaths occurred, of which 37 were due to cardiovascular causes. The treatment groups in this case are the groups in the clinics where phenformin was used. The number of patients and the percent dead in the various treatment groups (3) are given in the bottom portion of Table 1.

The investigators concluded that there was an excess of cardiovascular deaths in the phenformin group, and further analysis showed that the excess could not be explained by baseline differences in the groups at risk.

The relatively few published findings on nonfatal untoward events in the UGDP trial show only minor differences among the treatment groups (3) and these data will not be considered further in this report.

In 1969, a decision was made to discontinue treatment with tolbutamide. In contrast to the controversy that this action of the UGDP investigators provoked, there has been relatively little discussion of the decision, taken in 1971, to discontinue treatment with phenformin, and this latter step is not considered in detail in the present report.

4. OTHER STUDIES OF HYPOLYCEMIC AGENTS

In this section, four other controlled studies of hypoglycemic agents will be reviewed. Uncontrolled studies will not be discussed because it is extremely difficult to tell which of the effects observed in such cases are due to the treatment and which are due to the selection of patients and their assignment to the treatment groups. The studies under discussion are identified by their authors.

4.1 Keen *et al.* (5, 6) (*The Bedford Study*)

The subjects for this trial were people in whom the capillary blood glucose level, measured two hours after a 50-gm glucose load, was between 120 and 200 mg/100 ml. Of the 248 persons identified in this way, 228 were recruited through a screening program and 20 from a glaucoma study. The subjects are described as being borderline between normal and diabetic, and presumably had milder disease, on the average, than those included in the UGDP study. The latter had an average two-hour blood glucose level of 229 mg/100 ml, but this was not necessarily strictly comparable to that obtained in the Bedford study since the glucose load and conditions of the test were not identical in the two studies.

The subjects studied by Dr. Keen and his colleagues included 129 males and 119 females, so that the percentage of females was 48, considerably lower than the 71% in the UGDP study. The average age of the males was 55.4 and of the females 58.9 years. These ages were higher by 1.3 and 6.8 years, respectively than those of the corresponding groups in the UGDP. All subjects entered the trial, effectively, on one of two dates, June 1, 1962 or Jan. 1, 1964, and all were studied at one center.

Half of the subjects were treated with tolbutamide, 0.5 gm twice daily, and the other half with placebo tablets. In addition, one half of each of these groups was recommended to limit carbohydrate intake to 120 gm daily and the other