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cardiac events. During the first 12 months, 15 controls and six tolbutamide-treated patients died, so that in the early stages a significant difference in favor of tolbutamide became apparent. Thus, there appeared to be a beneficial effect of tolbutamide treatment on short-term survival after the acute episode of a first myocardial infarction. After five years, however, there was no significant difference in survival between the two groups. This study neither confirms nor contradicts the UGDP findings, as the population under consideration was not one of maturity-onset diabetics, and the patients taking tolbutamide had been exposed to a relatively small dose for a shorter time than that applied in the UGDP study.

4.3 Feldman et al. (19)

Research subjects in this study were 350 ambulatory patients with newly discovered asymptomatic diabetes, who were between the ages of 15 and 59 years, free of other diseases, and not taking drugs known to influence carbohydrate metabolism adversely. They were randomly assigned to tolbutamide (1 gm daily), phenformin (100 mg daily), or placebo treatment to test whether the orally given drugs were effective in preventing or postponing overt diabetes in these subjects. The study began in December 1964, and the published data cover the first 5.5 years of observation. The average age at admission was 44.4 years and there have been only two deaths. Consequently, the data are insufficient as yet to throw light on the relative mortality rates associated with the different treatments.

4.4 Tsagournis and Reynertson (20)

A prospective study of 137 patients with premature coronary artery disease was begun in 1965 to evaluate the influence of phenformin (50 to 100 mg daily) on mortality from cardiovascular disease. In a subgroup of 104 patients, randomized with respect to phenformin treatment, or to diet alone, nine deaths occurred among 50 control patients and six deaths.* * *

Persons known to have diabetes were excluded in this study, as were obese individuals, so that the generalization of these results to maturity-onset diabetes is dubious. It is also important to note that there were only about 50 patients in each group in this study. The small differences in the mortality rates for different treatments observed by the UGDP when there were about 200 individuals in each treatment group could not be detected with high probability when groups of 50 individuals are studied.

4.5 Summary

In reviewing as a whole the scope of the controlled clinical trials of oral hypoglycemic agents, we conclude that the only mortality data that are extensive enough for our purpose are those from the UGDP study and those from the Bedford trial.

5. CRITICISMS OF THE TRIALS OF ORAL HYPOGLYCEMIC AGENTS

These criticisms are essentially those that have been directed at the UGDP trial. The principal ones appear in papers by Feinstein, (21), Schor, (22), Seltzer, (23), and O'Sullivan et al. (24). In addition, there have been several editorials and commentaries about the UGDP trial, and they have relied mainly on these reports for source material. The criticisms have prompted the publication of two rejoinders. The first was by Cornfield, (17) who addressed himself to refuting the criticisms of Schor and also some criticisms that had appeared in the report by Feinstein. The second rejoinder article by Prout et al. (25) was specifically written to consider the many points raised in Seltzer's communication.

Many of the criticisms that are made in these articles would apply, sometimes even more strongly, to the Bedford study, but it was the UGDP trial that was challenged by the critics. The findings of this latter trial ran counter to prevailing ideas about the usefulness and safety of tolbutamide, and it is appropriate that these conclusions and the methods that led to them, should be carefully scrutinized.

In this section we restrict ourselves to the evaluation of published criticisms; a review of both trials by members of the committee will be included in subsequent sections.

References at end of article.