Our view of this criticism of the UGDP findings is that it has some weight (although we do not interpret it as a criticism of the action of the UGDP) and that the toxic effect of the oral hypoglycemics cannot be affirmed with the certainty that would be present if total mortality were significantly different.

b. The excess mortality appears clearly in only a few of the clinics. This might suggest a peculiarity or defect connected with the study methods employed there, and this would have to be understood before any reasonable interpretation of drug effects could be made. We have considered the question of whether the differences in results between clinics are such as to cast doubt on the meaning of the UGDP findings. We recognize that a clinic in a middle class suburban area is likely to have patients different in many ways from those of an inner city environment, so the fact that clinics differ is in itself not at all surprising. It would at least call for an explanation, nonetheless, if a toxic effect were clearly discernible in one set of clinics and a contrary effect in others. We present data in section 6 (Table A.3) that bears on this point. Looking at the failure rates for females and comparing placebo with tolbutamide groups, we note that there were seven clinics in which there was at least one cardiovascular least in one group or the other. The patients receiving tolbutamide had the higher rate in six of these. In the case of males, the tolbutamide rate was the higher in five of seven instances. We conclude that the excess mortality is not in fact confined to a few clinics and that this * * *

As mentioned previously, the study of Paasikivi gave findings that cannot be appropriately transferred to the UGDP population in view of the differences in dosage of tolbutamide, duration of study, and population at risk.

The study of Keen and his colleagues, however, deals with a population of borderline diabetics somewhat comparable to the UGDP group except that they were mostly ascertained by screening. Since the investigation is still under way, we can consider only the findings currently available. Keen (*5*) found that the death rates for all causes and for cardiovascular causes were essentially the same in the tolbutamide and placebo groups, but that the various pathological outcomes that he designated collectively as cardiovascular events were significantly less common among low risk subjects receiving tolbutamide than among comparable subjects receiving placebo.

The resources available in the Bedford study did not permit as thorough an investigation as was possible in the UGDP. The randomization of patients was carried out without the detailed attention to documentation that a major trial demands. There was restricted coverage of background variables, and all the usual safeguards for the maintenance of "blindness" could not be ensured. Finally, as the work is unfinished, a definitive analysis has still to be produced. The provisional data that Dr. Keen has kindly sent us are reviewed in section 6 and do not throw doubt on the UGDP findings in regard to deaths from cardiovascular causes. We have regarded the data on deaths as more relevant for comparison with the UGDP and also more clearly defined than the data on cardiovascular events.

d. A fourth criticism that has figured prominently in the literature is that the randomization did not succeed in allocating to the treatment groups patients who were comparable with respect to base-line risk factors. Since we have had access to the original data, we have been able to carry out an anlysis that was designed to test whether in fact the differences in mortality in the tolbutamide and placebo groups could be explained by the base-line differences. Our findings, which are given in section 6, take into account the differences between centers and the differences in length of treatment, as well as the base-line variables. They support the view of Cornfield (*17*) that there is no evidence that the base-line differences arising from the randomization contributed in any important way to the finding of adverse effects from tolbutamide.

5.4 *Failure to adapt dosage of drugs to individual need*

Feinstein (*21*) has noted that the oral drugs "were given in unsatisfactory dosage to many people who did not need them," and others have made a similar criticism. It is true that the use of a fixed dose of drug, which was also the approach adopted by Feldman et al (*19*) and Keen et al,(*6*) limits the generalization that can be made about therapeutic effects, but since the dose of tolbutamide is about equal to the average recommended for therapeutic use, an evaluation

References at end of article.