5.1 *Main issue in criticisms of the UGDP trial*

The primary issue of concern in the published criticism of the UGDP is whether or not the evidence pointing to toxicity of the oral agents is valid. Thus, in Seltzer's discussion of the design of the trial,(*23*) all of the nine points he raised bear on this question to an important degree. In the following account, most attention is therefore given to the UGDP mortality findings, but in addition, reference is made to the selection of patients, the dosage schedule adopted, and the decision to discontinue the use of tolbutamide and phenformin in the UGDP study.

5.2 *Selection of patients*

The first point raised by Seltzer, and also discussed by others, concerns the selection of patients. Criticism of the criteria used embraces the recruitment of subjects known to have concurrent disease (including cardiac disease), the inclusion of some who did not have diabetes, the exclusion of those judged (on somewhat vague criteria) to have a life expectancy of less than five years, and the inevitable arbitrary exclusion of those who proved uncooperative.

The determination of criteria for admission to the study depended on ethical as well as many practical considerations, and was inevitably, to some extent, arbitrary. It is almost never practicable, and rarely desirable, to make treatment comparisons in a strictly random sample from some defined population of subjects. To be useful for clinical purposes, however, the study patients should be so well described as to be identifiable by the clinician and should also be among those for whom the competing therapies are used or considered.

The choice of specific selection criteria adopted by the UGDP was a responsibility that was shared with medical experts and is not a topic on which this committee as a whole claims primary competence. It is important to recognize, however, that criticism of the choices made is largely irrelevant to the primary issue raised by the critics. For example, the concern about possible tolbutamide toxicity would not really be lessened if it could be shown that the study group contained some nondiabetics. A drug found toxic in such subjects would not likely be counted safe for persons with well-documented mild diabetes either. The criteria for inclusion or exclusion do influence the efficiency of the study, and the extent to which its findings can be generalized, but have little bearing on the issue of toxicity. We turn to criticisms that are more important in this regard.

5.3 *The UGDP mortality findings*

The implication of the UGDP mortality results is that the oral hypoglycemics are responsible for an increase in cardiovascular mortality, but that they do not affect mortality from other causes. Several kinds of criticisms have been raised about this interpretation, of which we consider the following to be the most important.

a. Although the total death rate was higher in the tolbutamide group than in those receiving placebo, the difference was not significant. Correspondingly, the death rate from noncardiovascular causes was higher in the placebo group than in the tolbutamide group. As O'Sullivan et al (*24*) have commented, "Interpretation of a study showing no increased risk of * * *

If there were subtle cues that could lead to somewhat different recording of signs and symptoms for different groups, it is conceivable that deaths of uncertain cause might be more likely to be assigned to a cardiovascular cause in the tolbutamide and phenformin groups than in the others. It will be appreciated that the review panel used in the UGDP study had no independent access to primary "objective" data, but depended on data already structured and to some extent interpreted by the clinic physician. Under these circumstances it is not too surprising that in only 2 of 89 cases was there a major disagreement between the panel and the clinic physician. The use of a review panel was an indispensable choice, especially for monitoring possible differences in procedure among clinics. However, its independent contribution to the actual assignment of cause of death should not be thought of as large. The UGDP took unusually strong measures to minimize the possibility of biased evaluation and took care to use well-defined end points in arriving at a diagnosis of cause of death. Nonetheless, the possibility of this sort of biased recording cannot be ruled out completely.

References at end of article.