diovascular causes preferentially in the groups receiving oral therapy exists, and, in view of the "nonsignificance" of differences in total mortality, some reservation about the conclusion that the oral hyperglycemics are toxic must remain. Nonetheless, we consider the evidence of harmfulness moderately strong. The risk is clearly seen in the group of older women as shown in Table A.2. Whether it acects all subgroups of patients cannot be decided on the basis of the available data. owing to the small number of deaths involved in these subgroups.

There remains the question of generalization of these findings. As has been frequently pointed out, the conditions of drug use in this study were, to some extent, abnormal. Tolbutamide dosage is varied in practice, and the patient unable to maintain adequate control with tolbutamide could be shifted to insulin. A good deal rests, then, on the matter of whether tolbutamide is actually toxic. If this should be admitted, it is hard to see how it could be regarded as a reasonable therapy, even when given in variable rather than fixed dosage.

If, however, this finding is rejected, there remains the question of whether tolbutamide, although ineffective in this fixed-dose regimen, might be an effective therapy as ordinarily used. The UGDP gives no direct answer to this question, but the dose of tolbutamide ordinarily employed varies only moderately.

There is also the question of the extent to which the UGDP subjects reasonably represent the population of maturity-onset diabetics who are candidates for oral therapy. Little of the commentary available to us raises questions on this point, and we assume that the UGDP population is representative of a large fraction of the maturity-onset, non-insulin-dependent diabetic population.

In conclusion, we consider that in the light of the UGDP findings, it remains with the proponents of the oral hyperglycemics to conduct scientifically adequate studies to justify the continued use of such agents.

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