reports have demonstrated persisting abnormalities in cholesterol, free fatty acids, and triglycerides in individuals who were receiving a sulfonylurea, but on close inspection of the data, "control" was determined only by measurements of fasting blood glucose levels, and even these were persistently elevated. However, abnormalities in circulating lipids associated with imperfect management of diabetes using oral hypoglycemic agents have been shown to be reversible by the addition of sufficient insulin to improve blood glucose levels.[28] This observation has been one of the factors which have supported the use of more rigid blood glucose criteria as an objective in treatment with oral hypoglycemic agents, be they sulfonylureas or biguanides. Thus far there is no clear-cut evidence that blood lipid abnormalities due to relative insulin deficit are more or less likely to be preventable or reversible at comparable blood glucose levels whether insulin or oral hypoglycemic agents are used.

A real problem has been the tendency for physicians to use oral hypoglycemic agents not in an ideal manner, but rather for the sake of convenience, with too little emphasis upon diet, adequate choice or dosage of the agent used, or proper selection of the patient. In such situations, obviously, the performance of oral hypoglycemic agents should be less effective than that of insulin, assuming that control of blood glucose and lipid abnormalities are indeed important in slowing down progression of macroangiopathy.

The above observations are critical in evaluating studies such as the University Group Diabetes Program (UGDP), which recorded more cardiovascular deaths in patients receiving tolbutamide or phenformin than in those treated with diet and placebo, diet and standard dose of insulin, or diet and a variable dose of insulin. The results may be interpreted as follows: (1) If it is true that tolbutamide, as a result of an inotropic effect upon the myocardium[29] or via some other mechanism, and an unrelated compound such as phenformin, through some unidentified mechanism, actually contribute to cardiovascular death, the seriousness of this particular end point would weigh so heavily that the use of these oral hypoglycemic agents should be summarily discontinued. (2) On the other hand, if these oral agents were seemingly less effective because of their improper use, the question is whether the results would be improved by correct usage and what the criteria should be for such usage. (3) The third possibility is that inadvertent significant differences in baseline cardiovascular risk factors accounted for the less favorable cardiovascular mortality experience in those treated with tolbutamide or phenformin and that the study does not prove or disprove lack of effectiveness for tolbutamide up to the time it was discontinued from the study (October, 1969) or for phenformin (discontinued January, 1971). The latter is more than a mere possibility, for the interpretations of UGDP results by the investigators, the American Diabetes Association,[30] the Council on Drugs of the American Medical Association,[31] and the U.S. Food and Drug Administration[32] are based upon statistical grounds that do not take into account the clinical background of knowledge concerning coronary heart disease in the diabetic. The many flaws in the UGDP study make any extrapolation of the results to the diabetic population at large extremely hazardous, and a number of objections remain apparent to the clinician:

1. In placebo treated patients not a single myocardial infarction was recorded among the cardiovascular deaths.