years. It is difficult to assemble totally appropriate age and sex matched control data, but in a recent study of normal males with no family history of diabetes (ages 22 to 28), the mean blood glucose one hour after a 50 gm. glucose load was 90.6±5.7 mg. per cent,[3] and in the studies of Neel et al.[4] the mean blood glucose one hour after a 100 gm. glucose load in patients with no family history of diabetes (ages 30 to 39) was 104.3±7.1 mg. per cent in males and 93.7±6.9 mg. per cent in females.* The data available would suggest that most of the patients in the UDPG study had persistently abnormal fluctuations in blood glucose concentration irrespective of the treatment prescribed. Although the UDPG study was a pioneer effort to improve the quality of clinical trials, it shares one of the common deficiencies of such studies in that it included no group of patients who had an essentially normal range of blood glucose fluctuation throughout the day.

Another frivolous aspect of the current controversy is the simplistic fashion in which the pathogenesis of the late complications of diabetes is viewed by most physicians. Each of the diverse clinical syndromes lumped into this unfortunate term has a very complex pathological basis, and in some instances a distinction must be made between processes responsible for acute symptoms and those which operate in the production of predisposing pathological lesions. There is little to support the widespread belief that each of the late complications is primarily a reflection of diabetic microangiopathy. There is no convincing evidence that alterations in capillary structure play a determining role in the pathogenesis of the common symmetrical peripheral neuropathic syndromes associated with diabetes mellitus,[5] nor is there convincing evidence that this process contributes to the increased frequency with which arterial occlusions occur in specific portions of the vascular system. In patients dying of diabetic nephropathy the pathological findings almost invariably include alterations other than those unique to diabetes mellitus; thus, arteriolosclerosis and intimal fibrosis of the renal arteries are often present.[6] Therefore, in any organ system, the pathological changes that are associated with diabetes mellitus may very well be subject to modification by independently determined genetic and environmental factors. However, this is rarely considered in efforts to evaluate the factors responsible for the clinical course in diabetics. As an example, although the recent studies of Hazzard et al.[7] would suggest that inherited abnormalities in lipoprotein metabolism are commonly associated with myocardial infarction, the distribution of patients with such abnormalities has not yet been assessed in clinical trials of diabetic therapy.

Another reason why caution must be exercised in the evaluation of clinical trials is the problem of asymptomatic but irreversible pathology in the patients studied. It is notoriously difficult to date the onset of an abnormality in glucose tolerance in adult-onset diabetics, and this problem is magnified by the recent realization that asymptomatic adult-onset diabetes may occur in children and young adults and does not appear to progress to the ketosis-prone type of the

* The effects of sex and increasing age on fasting blood glucose levels, and on the response to a 100-gm. oral glucose tolerance test in patients with no family history of diabetes have been well documented in patients up to age 39.