Summary of Discussion

KALEVI PYÖRÄLÄ

The review by Keen on the relationship of clinically manifest diabetes and impaired glucose tolerance (IGT) to atherosclerotic vascular disease (ASVD) indicated that diabetes is without any doubt associated with an increased occurrence of ASVD, whereas there still is some controversy with respect to the association between IGT and ASVD.

It was noted in the DISCUSSION that further studies are still needed for a better definition of the quantitative increase in the risk of ASVD in patients with different clinical types of diabetes. Furthermore, risk factors may operate with different force in different populations. Interesting recent observations of Pyke and co-workers on chlorpropamide-alcohol flushing and its relationship to large-vessel and small-vessel disease in patients with non-insulin-dependent diabetes were briefly discussed. The finding that diabetics with a positive response in a chlorpropamide-alcohol flushing test, particularly those in whom flushing can be prevented by indomethacin (a prostaglandin synthesis inhibitor) show a relative protection from vascular disease awaits confirmation in other series of patients. If confirmed, it will be strong evidence for the importance of individual, genetically determined differences in the reaction of the vascular wall of diabetics.

Keen drew attention to differences between ethnic groups in the occurrence of ASVD in diabetics. Grabauskas, on behalf of the multi-national group of investigators, gave a report on the main results of the Multi-National Study of Vascular Disease in Diabetics coordinated by WHO (Jarrett et al., Diabetes Care *1*:175—201, 1979; basic data to be published as Internal WHO Document NCD/OND/79.4). This study comprised a total of 6,695 diabetics selected from 14 populations with widely different geographic, ethnic, and cultural backgrounds. The study confirmed the low prevalence of ASVD in diabetics from Japan and Hong Kong, where the population frequency of ASVD is known to be low. In contrast, the prevalence of diabetic retinopathy and proteinuria was not particularly low in the diabetics from Hong Kong and high in those from Japan.

The question was raised as to whether any threshold level of blood glucose could be defined, below which the increased risk of ASVD would not occur. Keen's interpretation of the data available from prospective population studies was that, in contrast to the risk of small-vessel disease, which, on the basis of Bedford and Pima Indian studies, is small in subjects with a fasting blood glucose less than 130–140 mg/dl (7.2–7.8 mmol/L) or 2-h blood glucose less than 200 mg/dl (11.2 mmol/L), there may be no clear-cut threshold blood glucose with respect to the risk of ASVD. In those prospective studies that have found a relationship between blood glucose and ASVD, the increased risk of ASVD has been found to occur at considerably lower levels than the threshold level found for small-vessel disease. In the London Civil Servant Study, a doubling of coronary heart disease mortality occurred when 2-h blood glucose was more than 96 mg/dl (5.4 mmol/L). Since people with IGT form a heterogeneous group, including many who will not develop frank diabetes, the findings from the Bedford Study (Keen) and the Helsinki Policeman Study (Pyörälä), that subjects with impaired glucose tolerance have an increased risk of ASVD, are of practical as well as theoretical significance.

In the discussion related to the review by Stout on the role of insulin in atherosclerosis, Pyörälä reported that in the Helsinki Policeman Study population high plasma insulin levels showed, in addition to their association with increased coronary heart disease risk, also an association with an increased risk of cerebrovascular disease. Pyörälä reported preliminary results concerning the relationship of plasma insulin and coronary heart disease in an ongoing study designed to compare the prevalence of ASVD in newly diagnosed non-insulin-dependent diabetics and in a randomly selected control population of the same age. Plasma insulin levels, both fasting and post-glucose, were found to be higher in diabetics with coronary heart disease than in those without coronary heart disease. A similar relationship was observed between post-glucose plasma insulin and coronary heart disease in nondiabetic controls.

From the Department of Medicine, University of Kuopio, Kuopio, Finland.

Pyörälä commented on the findings from three population studies indicating that plasma insulin response to glucose load appears to be a more sensitive indicator than glucose tolerance in the prediction of ASVD risk. This may be explained by the fact that precursor stages of non-insulin-dependent diabetes are characterized by hyperinsulinemia rather than by insulin deficiency. Hyperinsulinemia may be present for a long time before the actual impairment of glucose tolerance becomes evident. Reaven stated that this concept is well-compatible with the finding that the relationship between blood glucose and insulin responses to an oral glucose load in normal subjects and patients with varying degrees of hyperglycemia is "horse-shoe"-shaped (Reaven and Miller, Diabetes *17*:560–69, 1968). This finding has been corroborated by analyses of the relationship of blood glucose and insulin levels after oral glucose load in the Pima Indian population (Savage et al., Diabetes *24*:362–68, 1975), the Nauru Island population (Zimmet et al., Diabetologia *15*:23–27, 1978), and the Busselton population (Welborn and Wearne, Diabetes Care *2*:154–60, 1979). However, this "Starling-curve" relationship may apply to populations, and may not necessarily indicate the metabolic evolution of individuals.

The possible significance of high circulating insulin levels in insulin-treated diabetics in relation to atherogenesis is unsolved. Studies of free insulin levels in insulin-treated diabetics in relation to the development of ASVD would be needed. On the other hand, it is not fully clarified whether or not antibody-bound insulin is of any importance in this respect. In this context, St. Clair mentioned the interesting, new observations of Alexander and Clarkson (Fed. Proc. *40*:1–335, 1981) in rabbits immunized with injections of insulin and Freund's adjuvant. Diet-induced atherosclerosis was found to be more severe in these rabbits having antibody complexes to heterologous insulin than in control rabbits.