Summary of Discussion

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Considerable evidence was presented in both the formal presentations and during the discussion for a role of arterial injury in the pathogenesis of atherosclerosis. A variety of induced injuries have been shown to accelerate atherosclerosis development in experimental animals. These include endothelial denudation with indwelling catheters or by balloon damage, chemical damage by compounds such as homocystine, hemodynamic factors, viral damage, damage by antigen antibody complexes, etc. It is not clear, however, whether the exacerbation of atherosclerosis in diabetes is secondary to some form of enhanced arterial injury, or due to other factors such as metabolic differences in the arterial wall or differences in blood borne constituents such as hormones, lipoproteins, etc. An answer to these important questions would be markedly facilitated by the availability of an appropriate animal model that showed exacerbation of atherosclerosis by diabetes. It was apparent from the discussion that rabbits and monkeys when treated with insulin may be appropriate for investigating the effect of diabetes on atherosclerosis in type I (insulin-dependent) diabetes, but there still is no appropriate animal model for type II (non-insulin dependent) diabetes. There is also the very interesting and unexplained observation that chemically-induced diabetes in rabbits, rats, and chickens is associated with less atherosclerosis than intact animals. With insulin treatment, however, atherosclerosis is markedly enhanced over that of intact animals, suggesting a role of exogenous insulin in atherosclerosis enhancement in diabetes.

The belief was expressed by a number of the discussants that there must be more to the exacerbation of atherosclerosis in diabetes than simply enhanced arterial injury, as there is such a predominance of small vessel disease as well as macrovascular disease. This may point to alterations in the metabolism of basement membrane constituents such as glycosaminoglycans and certain collagen types. Further evidence of potential differences in the pathogenesis of atherosclerosis in diabetics is the much greater extent of calcification seen in diabetic arteries. Again, this may reflect important differences in connective tissue metabolism.

Central to the injury theory of atherogenesis is the role of enhanced smooth muscle cell proliferation. Platelets contain a powerful mitogen for smooth muscle cell proliferation that is believed to be released at the site of endothelial injury. There also appear to be other factors in diabetic serum that, though less potent than the platelet factor, further enhance smooth muscle cell proliferation and, as such, could play a role in the enhanced atherosclerosis in the diabetic. Dr. Ledet's studies suggest that one such factor is growth hormone. This is supported by the observation that patients with acromegaly have accelerated atherosclerosis. Additional studies are needed, however, to carefully determine if there are differences in serum constituents from type I and type II diabetics as well as to distinguish the effect of growth hormone from the reported stimulation of cell proliferation by insulin itself. There was also discussion of the various tissue culture systems used to test for stimulation of cell proliferation with some concern that the primary explant system may not be the most appropriate due to the difficulty in distinguishing independent effects on cell migration from cell proliferation.

It was clear from the discussion that we know very little of the pathogenesis of the exacerbation of atherosclerosis by diabetes. Further studies in this area are critically needed in order to determine whether future clinical interventions should concentrate on reducing plasma risk factors (such as lipoproteins, glucose, etc.) or might better concentrate on factors expressed at the level of the arterial wall, such as an enhanced susceptibility to endothelial injury, local metabolic changes, or a direct effect on the arterial wall of exogenous insulin or of insulin antibody complexes formed against the heterologous insulin.

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