Why Control Diabetes?

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The definition of diabetes control varies widely among specialists of the disease. Proponents of "good" control believe that the goals of appropriate therapy for diabetes should include an all-out effort to obtain levels of fasting and postprandial blood glucose as close to those in the non-diabetic as possible. Certainly, good control has been proven to accomplish the following:

1. Prevention of ketoacidosis
2. Prevention of severe hypoglycemia
3. Decrease in perinatal mortality and morbidity
4. Promotion of normal growth and development of the juvenile diabetic
5. Prevention of, or inhibition of, infection

The evidence that hyperglycemia is responsible for vascular complications, particularly microvascular disease, and that good control will prevent or inhibit the rapidity of the development of this pathologic process, or even reverse it, is the basis of this presentation.

At the outset, however, it must be appreciated that retinopathy, nephropathy, neuropathy, and large vessel disease may be the presenting manifestations of diabetes, and that it is possible to have extensive vascular complications in the presence of relatively mild glucose intolerance. Furthermore, 20% of juvenile-onset type, ketosis-prone diabetics of more than 25-years duration with continuous hyperglycemia do not have clinically impressive retinopathy or nephropathy. Also, it has been noted that large vessel disease or neuropathy is absent in 20% to 40% of insulin-dependent diabetics.

The evidence for good control is largely based on the following observations:

1. Clinical studies
2. Animal studies
3. Histologic and electron microscopic data
4. Biochemical studies
5. Altered coagulopathy, viscosity, and hypoxia

Recent studies in well-controlled juvenile diabetics indicate that serial biopsies of quadriceps muscle have demonstrated "thinning" of previously thickened capillary basement membrane, in contrast to persistent and increasing thickening of capillary basement membrane in poorly controlled diabetic patients. In addition, it has recently been demonstrated that diabetic vascular lesions developed in normal kidneys transplanted into patients with diabetes mellitus after a period of two years, while transplanted kidneys in non-diabetic control patients of the same age and type remained unaffected; this also gives great support to the concept of good control.

Animal studies with diabetic Chinese hamsters, mice, rats, dogs, and monkeys have indicated that good control with insulin therapy or islet transplantation prevents or reverses lesions in the eyes, kidneys, or nerves.

Histologic and electron microscopic studies of capillary basement membrane of muscle have given conflicting results. One group of observers indicates that basement thickening is already genetically predetermined, while other investigators relate capillary basement membrane thickening to the duration of diabetes. Methodology of technique, the patient's age, unknown duration of existing diabetes, and cri-

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teria for the diagnosis of diabetes have to be clarified before coming to definitive conclusions.

Biochemical studies indicate that hyperglycemia or insulin deficiency produces alteration in vascular basement membrane composition, as well as accumulation of glucose-derived substances, such as sorbitol in the lens of the eye, Schwann's cell, and aorta. Recently, an elevation of glycolysated hemoglobin (HbAIc) has been noted in the blood of diabetic mice as well as human diabetics. The glycolysation of hemoglobin appears to be a post-synthetic modification of HbA which is dependent on the degree and duration of hyperglycemia.

Recent data reveal that platelet aggregation is more intense in diabetic patients, with increased sensitivity of platelets to aggregation from adenosine diphosphate (ADP) and epinephrine. This sensitivity correlates with elevated levels of Von Willebrand factor, which in turn appears to be influenced by growth hormone. Also, platelets from diabetic subjects are more sensitive to arachidonic acid-induced aggregation, which can be abolished by aspirin, which is a prostoglandin synthetase-inhibitor.

Spontaneous fibrinolytic activity of the blood is abnormally low in persons with diabetes mellitus, and implies a poor defense mechanism against fibrin deposits in the vessel walls, which conceivably may contribute to the development of diabetic microangiopathy. Increased red blood cell aggregation and alterations in plasma protein changes in diabetics, with their effects on blood viscosity and flow, may also play a role in accelerating the rate of progression of diabetic microangiopathy.

In addition, the decreased reactivity of HbAIc with 2,3 diphosphoglycerate might impair oxygen unloading in diabetes, and contribute to tissue hypoxia, which may have pathogenetic implications in the development of diabetic angiopathy.

Whether reversal of hyperglycemia, as well as the use of agents to inhibit some of the above-described adverse effects of the diabetic milieu, may affect the development of diabetic microangiopathy is far from settled. Consideration must be given to more intense regulation of dietary factors; use of the newer oral hypoglycemic agents; administration of insulin three or four times daily for better control; long-term studies on the use of aspirin, and other platelet-aggregating inhibitors, as well as phosphate supplements; availability and effectiveness of growth hormone inhibiting agents; the use of substances which can interfere with the post-ribosomal steps of basement membrane assembly; and finally, improvements in the delivery of insulin, whether it be by better biomechanical engineering or by increased knowledge of immunologic and other biologic defenses in the use of islet or organ transplantation.