EDITORIALS

DIABETIC MICROANGIOPATHY

It may be surprising to some students of the diabetic syndrome that new and basic information concerning diabetes mellitus should be derived at this late date from morphologic studies. However, this is certainly the case as indicated by the considerable attention recently shown in the concept of "diabetic microangiopathy." "Microangiopathy" refers to diffuse capillary disease consisting chiefly of widening of the basement membrane of capillaries found in various tissues. These changes have been reported in the renal glomerulus,[1] in retinal capillaries,[2] muscle capillaries[3] and subcutaneous capillaries[4] of diabetic subjects. The term "basement membrane" may be confusing to many who may recall that in the lexicon of the light microscopist, the basement membrane is "a condensation of the intercellular substance of the connective tissue at the surface of its contact with the epithelium.[5] However, electron microscopists use the term more generally to denote the layer of amorphous material of moderate electron density which is found external to the plasma membrane of numerous cells including endothelial, skeletal muscle and many epithelial cells.

Vascular abnormalities in diabetic patients have been known for a long time. Early interest in diabetic vascular disease centered on the large vessels because of easily recognized severity and high incidence of atherosclerosis in these patients. It seems generally agreed that there is an increased incidence of atherosclerosis in diabetic patients and that this disease occurs earlier in diabetic patients than in normal individuals or in patients with other diseases. It is extremely unusual if significant atherosclerosis is not found in the major vessels during a postmortem examination of a diabetic patient. The era of insulin therapy and low fat diet has not significantly reduced the incidence of atherosclerosis in diabetic patients. Large vessel disease, particularly coronary atherosclerosis and peripheral occlusive disease of the extremities contributes a significant portion of the morbidity and mortality of the diabetic syndrome.

Pioneering work by Woltman and Wilder[6] in 1929 drew attention to abnormalities in the smaller vessels of diabetic subjects. Two types of abnormal small vessels have been described. The first abnormality consists of endothelial proliferation whereas the second and more characteristic change consists of widening of the capillary basement membrane.

Description of the nodular lesion in diabetic glomerulosclerosis by Kimmelstiel and Wilson[7] and later description of diffuse changes by Bell[8] called attention to the renal capillary lesion. Staining with PAS helped to clarify the renal capillary changes but the electron microscope was necessary to demonstrate widening of capillary basement membranes and the nature of the nodules. Subsequently, electron microscopy has shown similar basement membrane widening in retinal,[2] muscle[3] and subcutaneous capillaries.[4]

A major question concerns the significance of this lesion in capillaries of varying structure in the diabetic patient. Abnormal capillaries in the glomeruli appear to be of major importance since the basement membrane of glomerular capillaries seems to play an important role in filtration. Similarly in cutaneous and muscle capillaries, significant increase in the amount of investing basement membrane may interfere in the exchange of gases and metabolites. Although there are considerable data to gather before a definite conclusion may be drawn, it seems likely that diffuse capillary disease may be responsible for many of the "complications" (retinitis, nephropathy and neuropathy) of diabetes mellitus.

Still to be clarified are questions concerning the cause of the basement membrane changes, the chronology of their development and the relationship, if any, to insulin therapy and clinical "control." There is evidence that the glomerular capillary changes occur before chemical diabetes is well established whereas in our experience with a group of muscle biopsies from diabetic patients, we were unable to find basement membrane widening in a juvenile diabetic or in two prediabetic individuals.[9] The degree of basement membrane widening failed to correlate well with age, duration of diabetes, or severity as judged by the requirement for insulin and clinical indications. Only a tentative conclusion was possible: Some duration of chemical diabetes is required to produce the muscle capillary lesion. However, it is possible that there may be qualitative differences in the diabetic syndrome from one individual to another.

It should be stressed that capillary basement mem-

brane widening can be demonstrated without use of the electron microscope. For several years we have obtained satisfactory muscle biopsies without difficulty from the vastus medialis by open biopsy or by needle biopsy using a specialized thoracotomy needle. However, any biopsy site would be expected to be suitable. These biopsies fixed in osmium, embedded in plastic and sectioned at 0.5-1μ, may be examined by phase contrast microscopy. Such preparations clearly show basement membrane abnormalities if they are present. Indeed, when we reviewed our paraffin sections stained by the periodic acid Schiff method, we were able to recognize the thick-walled interstitial muscle capillaries. However, in these preparations, one cannot distinguish the basement membrane from endothelial cytoplasm. With phase contrast microscopy this distinction can be made.

Now that morphologic studies have demonstrated the basement membrane changes, the attention of biochemists has been drawn to this problem. Recently, Lazarow[10] has shown that the glomerular capillary basement membrane contains little polysaccharide and large amounts of proline and hydroxyproline suggesting a chemical similarity to collagen.

Although the origin of the basement membrane material, its structural composition and its possible relation to the biochemical lesions of diabetes mellitus are problems for the future, this chapter in the history of the study of diabetes mellitus well illustrates that there is still much to be learned by those who are prepared to relate changes in structure with new information concerning cell physiology.

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*PREGNANCY AND DIABETES**

The combination of diabetes mellitus and pregnancy poses more controversial and provocative problems than almost any other problem appearing in gravid women. Although adverse effects of each upon the other are recognized clinically, these are poorly understood. The wide differences of opinion referable to practically every aspect of diabetic pregnancies illustrate the magnitude of the perplexities and the extensive fields for medical research.

Current studies exploring various genetic aspects of diabetes offer new concepts and the promise of solving some of the mysteries now harassing internist, obstetrician, and pediatrician alike. Causes for the frequent first appearance of diabetes during the gestation period, the alterations in insulin requirements for patients with pre-existing disease, the marked propensity toward hydramnios and toxemia, choice of the optimal time for delivery, and the route of delivery most favorable are moot issues. The most puzzling and distressing phenomenon is the profound, potentially fatal effect upon the fetus, an effect not infrequently in operation during the earliest stage of maternal disease. The type of islet cell hyperplasia observed in stillborn infants and those that die early in the neonatal period, the excessive size of these infants, and their proneness to respiratory distress are features indistinguishable in deadborn or sick infants of mothers predisposed to diabetes and those with long-established disease.

Fragments of new information are gradually accumulating from laboratories in many parts of the world. It appears certain that gaps in knowledge are narrowing as these are applied to clinical situations. Dr. Kyle, whose thought-provoking monograph accompanies this number of the *Annals* as Supplement 3, renders a valuable and needed service in his painstaking scrutiny of every angle of the problem. Unquestionably, benefits will be derived from the mustering together of all pertinent current views and the results of recent, important clinical and laboratory investigations.

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