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Editorial

Renal Changes in Diabetes

STUDIES on renal changes in diabetes have been advanced and accelerated by needle biopsy and the refinement of morphologic investigation by electron microscopy. Structural changes in the kidney have recently been described which occur prior to the development of a clinically recognizable diabetic state. Such lesions can be expected to play an important role in understanding the complex metabolic disorder of diabetes mellitus provided that their speicficity can be properly assessed.

The popular term "diabetic nephropathy" means different things to different people. Most commonly, it includes arteriosclerosis and arteriolosclerosis, pyelonephritis, papillary necrosis, certain types of glomeruloscleroses and tubular changes. Pyelonephritis is about ready to be removed from this group since substantial evidence has recently been presented which shows that its increased frequency in diabetes is more likely related to catheterization than to defective glucose metabolism.

Few lesions can be accepted as being indicative of diabetes when seen in histologic sections; of these, only two are generally considered specific: glycogen-filled epithelial cells in the straight, distal portion of proximal convoluted tubules, the so-called Armanni-Ebstein cells; and nodular glomerulosclerosis.

Ever since its birth, nodular glomerulosclerosis has had to fight for its existence. Initially, it was postulated that (1) it originated from the glomerular mesangium in the intercapillary region, (2) it was characteristic for diabetes, and (3) it was commonly associated with hypertension and a nephrotic syndrome.

Someone called it a "Johnnie-come-late-lesion"; perhaps this was the reason it was ignored for several years. When resurrected, it became involved in controversies, some of which are still alive. How do we stand today, after twenty-six years?

First, a group of investigators objected to its morphogenesis, namely, its origin from the intercapillary mesangium. Their temporarily persuasive argument was based on the conviction that there was no mesangium in normal glomeruli and that the nodules therefore must derive from endothelial cells. This concept could not account for the distinctive position of nodules in the axial region of the glomerulus. In recent years, there has been a gradual return to the original interpretation. Almost every investigator has given the cell group in the axial region his own designation, but all converge on the distinctiveness of this cell group which differs morphologically and functionally from capillary endothelium. After twenty-six years of aberration, we have come home to the intercapillary position of the nodular sclerosis specific for diabetes.

The second assault on intercapillary glomerulosclerosis during its infancy was the doubt raised against its specificity for diabetes. This controversy was fruitful because it led to the recognition of another lesion, namely, the diffuse form of glomerulosclerosis. This lesion, which involves the entire wall of the capillaries not just the intercapillary region, is found more often in diabetes than the nodular form. It can be distinguished from other types of glomerular sclerosing changes, but its features are not as distinctive as those of the nodular form. In fact, it can be safely recognized as "diabetic"

only if it is part of a composite picture. It becomes pathognomonic if associated with conspicuous deposits in the intercapillary region or with the nodular lesion. Characteristic changes in Bowman's capsule and in the basement membrane of proximal convoluted tubules or hyalinization of vasa efferentia of glomeruli are also helpful in establishing its identity. Once the diffuse type of diabetic glomerulosclerosis was carved out, it became clear that the nodular form remained the most reliable histologic manifestation of diabetes.

A third but valid criticism was directed toward the relationship of diabetic glomerulosclerosis to hypertension and the nephrotic syndrome. It has become quite clear over the years that hypertension and the nephrotic syndrome cannot be related to nodular glomerulosclerosis and that the nephrotic syndrome is more closely associated with the diffuse and mixed forms than with the nodular form.

It has been said that the specific glomerular lesions are extremely rare in diabetes secondary to destructive diseases of the pancreas or its removal. Consequently one is tempted to infer that diabetes due to lack of insulin does not bring about glomerulosclerosis. This thought is strengthened by the fact that, despite numerous attempts, no one has ever succeeded in producing the nodular lesion experimentally by removing or destroying the insulin-producing islets of Langerhans. There is the possibility then that glomerulosclerosis may be caused by the capacity of serum protein to bind insulin or by antigen-antibody reaction to either intrinsic or extrinsic insulin. Yet, attempts to produce glomerulosclerosis in this manner in animals have also failed.

The hypothesis has been advanced that most of the morphologic manifestions of diabetes, particularly those in the vascular system and kidney, are results of a metabolic defect of which the disturbance of glucose metabolism is only the earliest symptom recognizable with certainty. Whether this simultaneous nebulous disorder of protein-mucopolysaccharide-lipid metabolism affecting the vascular matrix is the basic defect, perhaps even preceding insulin lack or ineffectiveness, is conjectural at this point.

Equally speculative is the pathogenesis of nodular glomerulosclerosis itself. It is conceivable, although it has not been proven, that mucopolysaccharides are transferred into the glomerular filtrate and at least partially reabsorbed into the glomerular epithelial cells. After all, these cells are close kin to the tubular epithelial cells which are known to have the ability to excrete as well as reabsorb. In addition it has been demonstrated that glomerular epithelium absorbs protein, and studies with the electron microscope have disclosed that it reabsorbs identifiable particles which have passed through the basement membrane. It is a remarkable fact that the most specific lesions occur in the glomerular mesangium, in Bowman's capsule and in tubular basement membrane, three sites in which the epithelium is in juxtaposition to tissue which is capable of forming collagen, separated from it only by basement membrane. The only area in the glomerulus proper in which the epithelium is so situated is at the "waist" of capillary loops, the the intercapillary region, in which the basement membrane reflects from one loop of a capillary to another.

I am proposing that the glomerular epithelial cells are capable of transferring these substances into the urinary space as well as in the opposite direction, i.e., into the capillary lumen.

If this process occurs in the peripheral capillary loops, the substance, passing both ways through the basement membrane, may damage its fine structure without deposition of collagen. This may account for its increased permeability for protein and eventual thickening. This process would be equivalent to the diffuse form of glomerulosclerosis and would explain its frequent association with the nephrotic syndrome.

If, however, the reversed transfer takes place where the epithelial cells lie adjacent to the mesangium, these substances are deposited and accumulated at this site, thus accounting for the pathognomonic topography of nodular deposits in the mesangium in the intercapillary region.

To my knowledge, this hypothesis has not been advanced previously, perhaps it could be tested experimentally.

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