

depressing PIF production by the hypothalamus (10). Apparently when the two lower doses of estradiol were injected, the action of the ME implant on AP prolactin predominated. However, the largest dose of estradiol given, 10 μ g, was able to completely counteract the effect of the ME prolactin implant on AP prolactin levels. This dose of estradiol may have acted both at the AP and hypothalamic levels. It is of interest that AP weight was equally increased by the 10- μ g dose of estradiol in both the control and ME prolactin implanted rats.

Several workers have reported on estrogen uptake by the hypothalamus and AP. Eisenfeld and Axelrod (11) observed that administered estradiol-³H was approximately 5 times as concentrated in hypothalamic tissue and approximately 60 times as concentrated in AP tissue as in plasma. This may indicate a specific affinity by the AP and hypothalamus for estrogen. It would be of interest to determine to what extent uptake of estrogen by these two tissues may be modified by an ME implant of prolactin. The present findings, as well as the observation that high circulating levels of prolactin can depress AP prolactin levels in rats (12), suggest that circulating levels of prolactin may normally alter the actions of estrogen on the AP and hypothalamus.

Summary. A median eminence implant of prolactin significantly lowered anterior pituitary prolactin content and concentration in female rats. Injection of 1.0 μ g of estradiol benzoate daily for 5 days was unable to counteract this action of the ME implant of pro-

lactin, whereas 5 μ g was only partially effective. However, injection of 10.0 μ g of estradiol benzoate daily was as effective in increasing anterior pituitary prolactin levels in the presence as in the absence of an ME implant of prolactin. These results suggest that circulating levels of prolactin, by acting on the hypothalamus, may be able to modify the action of estrogen in promoting prolactin secretion.

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Glomerular Lesions in a Strain of Genetically Diabetic Mice* (33433)

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Glomerular lesions, similar to those found in human diabetes mellitus were observed in nonobese, genetically determined, spontaneously diabetic mice (1). The lesions were not found in pen-bred Swiss albino control ani-

mals under the same laboratory conditions.

The hereditary diabetic mice of the KK

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strain were found in Japan by Kondo and his associates in 1957 (2). The diabetic characteristics described by Nakamura (3) included: glycosuria, elevated glucose-tolerance curves, higher than normal pancreatic insulin activity, and hypertrophy and hyperplasia of the pancreatic islets. Dulin (4) found higher plasma insulin levels and a diminished insulin response of diaphragm and fat pads in the KK mice, when compared with the similar tissues from nondiabetic animals.

Materials and Methods. Thirty-nine KK diabetic mice and 30 Swiss albino control animals were studied. Two oral glucose-tolerance tests were performed in each animal by giving 3 g of glucose per kilogram of body weight. Blood samples were collected from the tail with micro collecting tubes. Concentrations of serum glucose were determined with the Technicon autoanalyzer microtechnique, using 0.025 ml of blood. The Uristix paper strip was used for determination of glucose and proteins in the urine. Levels of serum insulin were obtained by our modification of the double antibody immunoassay using a microtechnique (5).

KK and control mice were sacrificed at the ages of 1 (5 animals), 2 (6 animals), 4 (5 animals), 6 (6 animals), 9 (6 animals), 12 (5 animals), and 16 (6 animals), months. The Swiss albino controls were matched in age distribution. The kidneys were removed, bisected, and fixed in 10% neutral formalin. After paraffin embedding, sections were cut at 3–4 μ and stained with hematoxylin and eosin (H&E), periodic acid-Schiff (PAS), and chromotrope silver methenamine (C-SM).

Results. In all the KK mice studied, diminished tolerance to glucose, elevated levels of immunoreactive insulin in serum and in pancreatic extracts, as well as hypertrophy and hyperplasia of the islets of Langerhans, were found. Glycosuria and proteinuria were intermittent in the diabetic animals, varying between 0 and 4+ (6).

On light microscopy, the glomerular lesions consisted of an increase of the mesangium leading to nodular lesions, exudative lesions, segmental thickening of the basement membrane, and proteinaceous deposits.

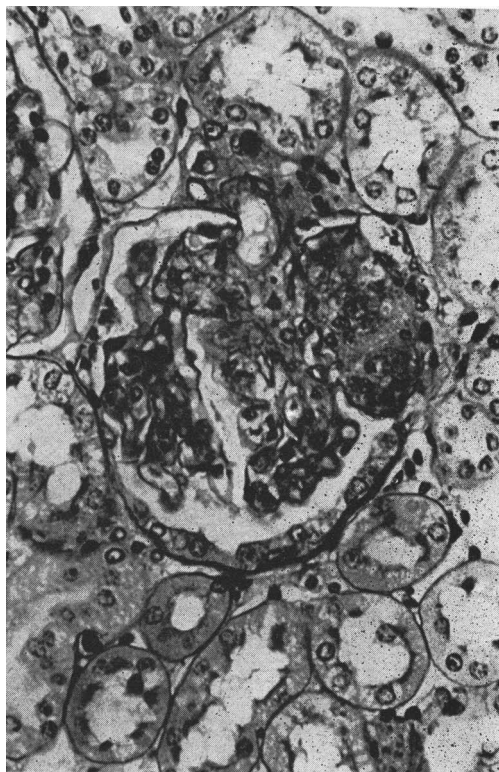


FIG. 1. Nodular and diffuse type of advanced glomerulosclerosis. There is compression of capillaries. Some capillary walls are thickened. 15-month-old animal PAS stain. $\times 800$.

The increase of mesangial matrix and cells was both diffuse and focal. In the diffuse variety, there was an increase of matrix and cells, beginning in the stalk area and resulting in a moderate widening of the mesangial space in the more severely affected glomeruli. The nodular lesions (Fig. 1) seem to be derived from the mesangium and were also made up of matrix and cells, causing a greater segmental widening of the mesangial space. In the larger nodular lesions, the matrix predominated, cells were few in number and usually located at the periphery of the nodules. Nodules consisting of matrix without cells were rarely seen. Nodules were generally found near the hilus, occasionally impinging on the efferent arteriole and only rarely in the periphery of the glomerular tuft. Exudative lesions (Fig. 2) were noted in the glomerular tuft within capillaries, never in Bowman's capsule. Some were large, distending into



FIG. 2. Large exudative lesions apparently distending capillary lumina. There is moderate increase in mesangial matrix and cells and striking segmental thickening of capillary walls. 15-month-old animal, C-SM stain. $\times 800$.

capillary loops, while others were small and multiple in a single capillary tuft. The capillary wall (Fig. 3) showed segmental thickening of mild to moderate degree. In 6 animals, a membranous transformation of some of the glomerular loops was occasionally noted in C-SM-stained sections examined under oil immersion. These transformations consisted of irregularity of the epithelial surface of the basement membrane, either nodular or in the form of thin, elongated projections (spikes), having the same staining characteristics as the basement membrane. Occasional small rounded red-staining deposits were noted in association with the projections. With C-SM stain, red proteinaceous deposits were sometimes found in the mesangium. Vascular lesions were absent, except for rare hyalinization of efferent arterioles.

The lesions were grouped as to severity

and their occurrence in the different age groups was noted. The diffuse increase in mesangial cells and matrix became significant in 6 to 9-month-old KK animals and was severe by 16 months. The nodular lesions also significantly increased in animals more than 9 months of age. A slight increase in mesangium and nodular lesions were occasionally found in animals as young as 4 months. Two 16-month-old mice, however, showed only slight increase of mesangium and only occasional inconspicuous nodular lesions. The exudative lesions were seen only in animals 9 months and older and were considerably increased in 12 to 16-month-old mice. Three of the animals in this group, however, did not have any of these lesions. The segmental thickening of the basement membrane was seen only in animals 16 months of age. Focal wrinkling of capillary

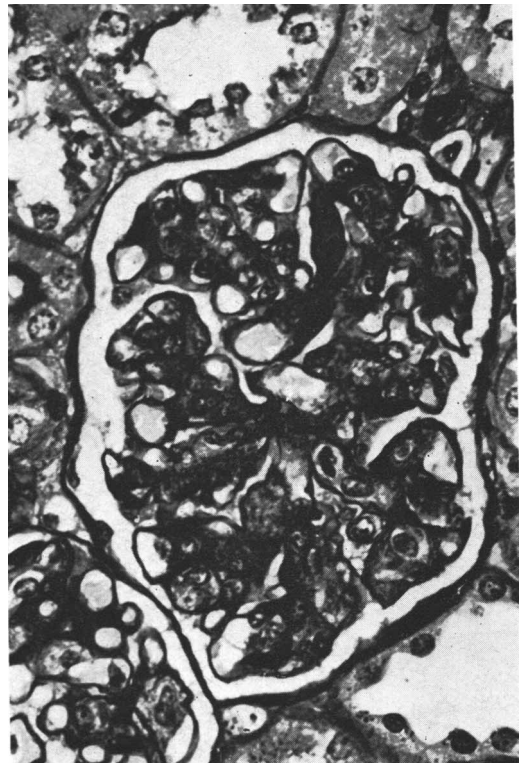


FIG. 3. Moderately severe, diffuse glomerulosclerosis, increase in mesangial matrix and cells, with widening of the mesangial space. Moderate thickening of capillary walls. 15-month-old animal PAS stain. $\times 800$.

walls and obsolescence of glomeruli were noted in older animals with more severe mesangial lesions. In glomerular obsolescence, there was collapse of the capillary loops and severe sclerosis. In the control animals, the mesangium increased with age. In the older animals from 12 to 15 months of age, sclerosis was occasionally as severe as that of the KK mice; however, nodular lesions were absent. In mice younger than 12 months, the increase of mesangium was mild or absent. Unlike the group of KK mice, none of the young control animals showed severe focal glomerular lesions. Exudative lesions and a membranous transformation were also never seen in the control mice.

The diffuse increase in mesangium and the nodular and exudative lesions increase in number and severity with the age of the KK animals and are rarely encountered under 6 months. The diffuse mesangial changes first seen in the younger animals apparently evolved into the nodular lesion in older mice.

Discussion. The striking glomerular lesions in the KK mice bear a certain similarity to those described in human diabetic nephropathy consisting of: diffuse increase in mesangium, terminating in a nodular lesion, exudative lesions, segmental thickening, and irregularity of the basement membrane as well as focal membranous transformation (7). The occurrence of some of these glomerular lesions in young animals and the relatively early sclerosis and collapse of glomeruli in the older age group may also be considered as points of similarity. The following dissimilarities were found in comparison to human changes: sclerosis of arterioles is not quantitatively significant. The nodules vary from the typical human lesions in two

respects. They are rarely entirely free of cells and are generally located near the hilus rather than at the periphery of the lobule. The exudative lesions are more numerous and much larger, and never seen in Bowman's capsule.

These glomerular changes may represent a model of diabetic glomerular sclerosis in mice and therefore may become a useful investigative tool to study the pathogenesis and progression of glomerular lesions in diabetes mellitus.

Summary. In a strain of genetically determined, spontaneously diabetic mice (KK mice) lesions similar to those seen in human diabetic nephropathy were found in the glomeruli. These lesions increased with age and consisted of diffuse and nodular mesangial changes, exudative lesions, and alterations of the basement membranes.

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