INTERCAPILLARY GLOMERULOSCLEROSIS *

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In 1936, Kimmelstiel and Wilson [1] described eight instances of a renal lesion which consisted of hyaline thickening of the intercapillary connective tissue of the glomeruli, associated with arteriosclerosis. They termed the lesion "intercapillary glomerulosclerosis." Of their eight patients, seven gave a history of diabetes mellitus. Clinical data on the eighth were lacking. Anson [2] reported six additional cases in 1938. Newburger and Peters [3] tabulated the data of these reports, adding four autopsied cases of their own. According to them, the clinical syndrome associated with intercapillary glomerulosclerosis included diabetes mellitus, hypertension, widespread edema, albuminuria, hyposthenuria, nitrogen retention, hypo-albuminemia, retinal arteriosclerosis and, occasionally, heart failure and anemia. The syndrome as outlined by Porter and Walker [4] is essentially similar.

It is the purpose of this paper to point out that, although intercapillary glomerulosclerosis in its more advanced state is seen only in cases of diabetes, it is not of necessity associated with a particular clinical syndrome which includes diabetes mellitus.

The clinical histories, autopsy protocols and microscopic sections of all cases of diabetes and of arteriolar nephrosclerosis autopsied since 1909 at the Presbyterian Hospital, New York City, were reviewed. Satisfactory microscopic preparations were available from 144 cases in the former group and from 126 in the latter. Intercapillary glomerulosclerosis was noted in 33 of the 144 cases of diabetes mellitus, an incidence of 22.9 per cent (Fig. 1). Thirty-two instances, or 25.4 per cent, were found among the 126 cases of arteriolar nephrosclerosis without diabetes (Fig. 2).

The microscopic sections of the kidneys of 199 cases of glomerulonephritis autopsied during the same period were reviewed. Among these, 13 instances were found in which the lesions of many of the glomeruli were indistinguishable from those of intercapillary glomerulosclerosis (Fig. 3). Nine additional examples of this lesion were found among 81 cases of generalized arteriolar sclerosis without associated diabetes or renal disease (Fig. 4).

The incidence of intercapillary glomerulosclerosis in these various conditions is summarized in Table I.

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One additional instance of early intercapillary glomerulosclerosis (autopsy no. 13545) was accidentally encountered in a female, 47 years old, with cirrhosis of the liver and Banti's syndrome who died following splenectomy. A few sclerotic arterioles were found in the kidney and pancreas of this case.

The age incidence of intercapillary glomerulosclerosis varied somewhat in the different groups. The average age at death of the patients with diabetes was 59.6 years; of those with arteriolar nephrosclerosis, 45.2 years; of those with generalized arteriolar sclerosis, 61.7 years, and of those with glomerulonephritis, 27 years. It is of interest that 82 per cent of the patients with both diabetes and intercapillary glomerulosclerosis were females, whereas only 54 per cent of the entire group of patients with diabetes were females. No such disproportion in sex distribution was noted in any of the other groups.

The pertinent clinical and pathologic data of these 88 cases of intercapillary glomerulosclerosis are summarized in Table II, according to the various categories of disease in which they were classified.

TABLE I

Incidence of Intercapillary Glomerulosclerosis

	Total no. cases	Intercapillary glomerulosclerosis	
		No. cases	Per cent
Diabetes mellitus	144	33	22.9
Arteriolar nephrosclerosis	126	32	25.4
Generalized arteriolar sclerosis (without diabetes or renal disease)	81	9	11.1
Glomerulonephritis	199	13	6.5

TABLE II

Intercapillary Glomerulosclerosis. Summary of Clinical and Pathologic Features

	Diabetes mellitus	Arteriolar nephrosclerosis	Generalized arteriolar sclerosis	Glomerulonephritis	Total
Intercapillary glomerulosclerosis (number of cases)	33	32	9	13	88
	(*per cent*)	(*per cent*)	(*per cent*)	(*per cent*)	(*per cent*)
Albuminuria	83*	97	57	100	86
Hypertension (systolic pressure greater than 150 mm. Hg)	50*	94‡	67	77	71
Nitrogen retention	48†	93*	0*	92	70
Edema	30	47	22	38	36
Heart failure	42	56	22	15	41
Anemia (Hgb. less than 75%)	47*	78	0	77	59
Cardiac hypertrophy (greater than 400 gm.)	38‡	91	78	85	68
Arteriolar sclerosis, generalized	94	94	100	46	86
Arteriolar sclerosis, renal	100	100	100	100	100
Arteriosclerosis	94	88	78	31	80

* Data not recorded in 3 cases.
† Data not recorded in 12 cases.
‡ Data not recorded in 1 case.

Discussion

The results of serum protein determinations and of retinal examinations were available in too few cases to permit inclusion of these data. In our cases edema, except in glomerulonephritis, was generally dependent upon the presence of cardiac failure; and the anemia was usually secondary to renal decompensation. The clinical features which have been regarded as characteristic of intercapillary glomerulosclerosis are lacking in an appreciable proportion of these cases, among patients with diabetes as well as in the group as a whole. It is evident that the clinical signs and symptoms are not specific.

Herbut [5] and Allen [6] emphasized the specificity of the lesion of intercapillary glomerulosclerosis and suggested its use by the pathologist as a criterion for the morphological diagnosis of diabetes mellitus.* On the other hand, Kimmelstiel and Wilson,[1] in their original paper on glomerulosclerosis, called attention to the occurrence of identical lesions in the early stages of intercapillary glomerulonephritis unassociated with diabetes. Newburger and Peters [3] also studied a case of subacute glomerulonephritis without diabetes or generalized vascular disease in which the renal lesions were suggestive of intercapillary glomerulosclerosis. Our material includes 13 cases of glomerulonephritis, 10 chronic and 3 subacute, in which glomerulosclerosis was noted.

Our study indicates, further, that intercapillary glomerulosclerosis occurs not infrequently in association with conditions other than diabetes and glomerulonephritis, notably arteriolar sclerosis and arteriolar nephrosclerosis.

The case of cirrhosis of the liver, in which early lesions were seen associated only with mild arteriolar changes, is evidence that the study of routine sections of kidneys, with the possibility of glomerulosclerosis in mind, may lead to the discovery of other instances not associated with diabetes or renal disease.

It is important to note, however, that in every case where glomerulosclerosis was widespread or marked, review of the case record revealed a history of diabetes mellitus.

The frequency of arteriosclerosis and arteriolar sclerosis in patients with diabetes is well known. It has often been commented upon in association with intercapillary glomerulosclerosis as well. Nevertheless, the most striking finding emerging from our study is the extremely

* Since this paper was submitted for publication, the material upon which Dr. Allen's presentation was based has been published in the Archives of Pathology (So-called intercapillary glomerulosclerosis—a lesion associated with diabetes mellitus. Morphogenesis and significance. *Arch. Path.*, 1941, 32, 33–51.)

high incidence of arteriosclerosis and arteriolar sclerosis in these 88 cases of intercapillary glomerulosclerosis, and, in particular, the occurrence of sclerosis of renal arterioles in every instance. Newburger and Peters [3] suggested that the primary lesions were those of the arterioles, and that the diabetes and hypertension, as well as the renal changes, might be secondary.

Seventy of our cases of diabetes mellitus also showed generalized arteriolar sclerosis. The diagnosis of intercapillary glomerulosclerosis was made in 31 of these, an incidence of 44.3 per cent. Furthermore, diabetes and nephrosclerosis occurred together in 22 instances and, of these, 13, or 59.1 per cent showed the lesions of intercapillary glomerulosclerosis. Anson [2] noted the presence of nephrosclerosis in all of his six cases.

Attempts to correlate these glomerular changes with hyalinization of the islets of Langerhans and with the specific therapy of diabetes were fruitless. Of 42 of our patients with diabetes dying before the introduction of insulin, 3 cases showed the lesions of intercapillary glomerulosclerosis.

Summary

The autopsy records of 550 patients with diabetes mellitus, arteriolar nephrosclerosis, generalized arteriolar sclerosis and glomerulonephritis have been reviewed. Among them, 87 instances of intercapillary glomerulosclerosis were found. In its advanced form, this condition was always associated with diabetes mellitus, and was present in 59.1 per cent of the cases of diabetes with arteriolar nephrosclerosis. Less severe degrees of glomerulosclerosis were found with equal frequency in cases of arteriolar nephrosclerosis without diabetes, and somewhat less often in cases of generalized arteriolar sclerosis and glomerulonephritis. One additional instance was encountered in a case of cirrhosis of the liver without diabetes, renal disease or generalized vascular disease. Sclerosis of renal arterioles has been found to be invariably associated with intercapillary glomerulosclerosis.

Note: We are indebted to Dr. Walter W. Palmer and to Dr. Allen O. Whipple for permission to use the clinical records of the patients included in this study.

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DESCRIPTION OF PLATE

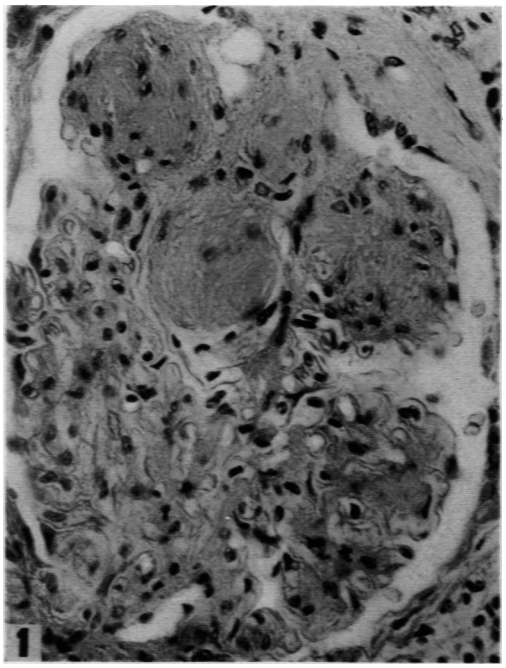
PLATE 14

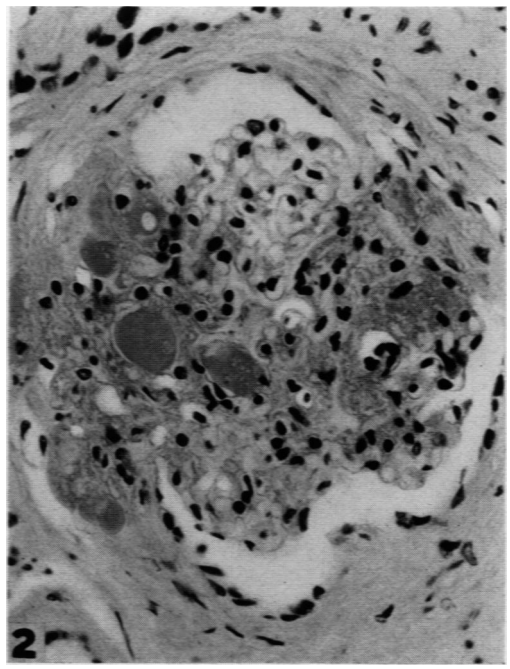
FIG. 1. Glomerulus from a case of diabetes mellitus (autopsy no. 13,286). Hematoxylin and eosin stain. × 394.

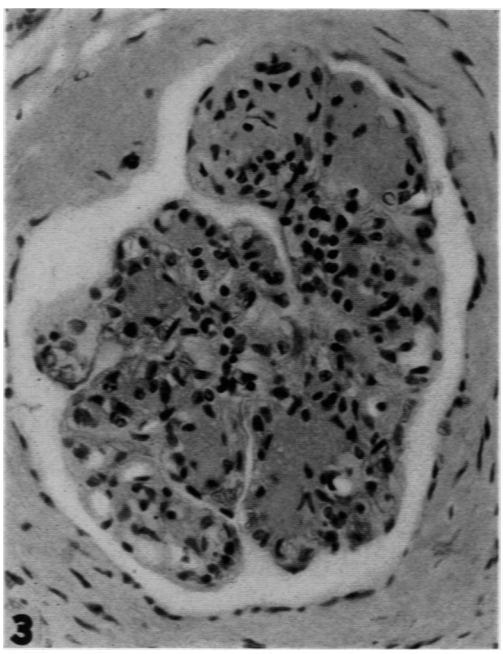
FIG. 2. Glomerulus from a case of arteriolar nephrosclerosis without associated diabetes (autopsy no. 11,757). Hematoxylin and eosin stain. × 394.

FIG. 3. Glomerulus from a case of subacute glomerulonephritis without associated diabetes (autopsy no. 11,459). Hematoxylin and eosin stain. × 394.

FIG. 4. Glomerulus from a case of generalized arteriolar sclerosis without associated diabetes or renal disease (autopsy no. 11,730). Hematoxylin and eosin stain. × 394.







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