RENAL BIOPSY IN GOUT

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The association of renal disease with gout is well recognized, but the pathogenesis of the kidney disorder has never been defined clearly, and urate deposits, pyelonephritis, "interstitial nephritis," and a high incidence of "nephrosclerosis" have all been held responsible.

When tubular atrophy and interstitial fibrosis with chronic inflammatory cell infiltration have become pronounced, it is usually impossible to determine whether the initial lesion was vascular, infective, or due primarily to tubular atrophy. This study of renal biopsy specimens was made to determine if any early lesions could be identified and if they could be correlated with the clinical state of the patients.

Patients and Methods

Eleven men and one woman agreed to renal biopsy. Their ages ranged from 40 to 69 years. The diagnosis of gout was based on a history of typical attacks of monarticular arthritis and the finding of a raised serum uric acid on one or more occasions (6 mg./100 ml. and 5 mg./100 ml. being taken as the upper limits of normal for men and women respectively). The duration of the attacks of gouty arthritis varied from 4 to 38 years.

Renal function was estimated by measurements of the blood urea, maximum urine-urea concentration, phenol-sulphophthalein (P.S.P.) excretion, and endogenous creatinine clearance. These estimations were made in the clinical laboratories of the London Hospital.

Renal biopsy was performed by the method of Kark and Muehrcke (1954) with minor modifications (Ross and Ross, 1957). No complications occurred. The renal tissue was fixed in formol-saline and/or alcohol. Sections cut 6 microns thick were stained with haematoxylin and eosin, combined van Gieson's and elastic stain, and Heidenhain's azan stain. An attempt was made to demonstrate urates by the method of Schultz and Schmidt and by Lillie's ferric ferrocyanide method for reducing agents. The sections were prepared in the Bernhard Baron Institute of Pathology.

TABLE I.—Clinical and Biochemical Features

Case No.	Sex	Age	Duration of Gout in Years	Family History of Gout	Gouty Tophi	Blood-pressure in mm. Hg	Proteinuria	Serum Uric Acid, mg./100 ml.	Renal Function at Time of Biopsy			
									Blood Urea, mg./100 ml.	Max. Urine Urea, g./l.	P.S.P. % Excretion at 2 hrs.	Creatinine Clearance, ml./min.
1	M	55	38	+	0	105/75	+	6.2	37	21.6	61	85
2	M	40	6	+	0	140/80	0	7.0	38	19.2	50	71
3	M	46	12	0	0	130/80	0	6.0	30	24.6	65	84
4	M	45	13	+	0	140/100	+	6.0	30	22	63	94
5	M	60	16	+	0	140/90	0	7.2	38	18.6	46	75
6	M	43	4	0	0	160/110	+	7.5	38	19.2	36	78
7	M	53	14	0	0	130/80	(present in 1 of 4 tests)	6.9	45	16.8	51	70
8	F	45	10	0	0	130/80	0	7.5	39	18.6	45	69
9	M	51	10	+	0	120/80	(only 1 test)	7.7	39	16.8	57	73
10	M	69	30	+	0	130/80	0	9.4	60	22.8	45	81
11	M	65	75	0	0	210/120	+	6.0	54	16.4	—	—
12	M	66	12	0	+	140/70	+	10.7	195	7.8	—	—

TABLE II.—Histological Features

Case No.	Glomeruli (No. in Brackets)	Tubules	Interstitial Tissue	Medulla	Arterioles	Urates	Culture from Biopsy Needle
1	(15) Normal	Normal	Normal	Normal	Normal	None	Sterile
2	(4) "	"	Slight diffuse increase, probably normal for juxta-medullary cortex	"	Normal arcuate	"	—
3	(17) "	"	Normal	None	Normal	"	Sterile
4	(21) "	"	Very fine collagen between tubules, probably normal	"	Slight medial hypertrophy	"	—
5	(9) 5 normal, 3 with tenuous capsular adhesions, 1 with shrunken tuft and capsular thickening	Focal atrophy	Diffuse slight increase of collagen, more marked focally. No inflammatory cells	"	Medial hypertrophy of arcuate	"	Sterile
6	(9) Normal	Normal	Slight focal periglomerular and perivascular fibrosis	"	Slight medial hypertrophy of interlobulars	"	"
7	(14) "	"	Slight cellular and fine collagenous increase. No inflammatory cells	"	Normal	"	"
8	(26) Normal except 1 with slightly thickened capsule	"	Very slight diffuse increase with fine collagen	"	Slight medial hypertrophy of interlobulars	"	Staphylococcus saprophyticus
9	(13) Normal apart from occasional capsular adhesions	"	Slight diffuse cellular and collagenous increase. No inflammatory cells	"	Normal	"	Sterile
10	(5) Normal; 1 fibrohyaline	Occasional dilated tubules with eosinophil casts	Moderate increase. No inflammatory cells	"	"	"	—
11	(7) 4 hyalinized, 3 with shrunken tufts and capsular fibrosis	Atrophy and dilatation with eosinophil casts	Diffuse increase, with focal dense chronic inflammatory cell infiltration	"	Medial hypertrophy and subintimal hyalinization in interlobulars	—	—
12	(32) 8 present as fibrohyaline disks. Remainder atrophic, with solid or shrunken tufts and capsular fibrosis	Atrophy only, marked focally	Diffuse collagenous increase, severe focally, with chronic inflammatory cell infiltration	"	Medial hypertrophy with some subintimal collagen in interlobulars	None	Sterile

Results

The clinical and biochemical findings are summarized in Table I. Proteinuria was found in six patients (Cases 1, 4, 6, 9, 11, and 12), three of whom (Cases 4, 6, and 11) were the only patients with hypertension. The urine in all cases was sterile at the time of renal biopsy, and the urinary deposits showed no abnormalities except a slight excess of leucocytes in six cases (Nos. 3, 5, 8, 9, 11, and 12).

Four patients (Cases 1, 2, 3, and 4) had completely normal tests of renal function. Two (Cases 11 and 12) had renal failure with nitrogen retention—one with proteinuria and hypertension and the other with proteinuria but a normal blood-pressure. The other six patients had slight and doubtfully significant impairment of maximum urine-urea concentration or of P.S.P. excretion or of both tests; the blood-urea concentration was raised in only two of this group (Cases 7 and 10).

Histological Findings

The histological findings are summarized in Table II. Glomerular, tubular, and interstitial lesions were found

FIG. 1.—Case 12. (Haematoxylin and eosin. $\times 80$.)

FIG. 2.—Case 3. Normal glomerulus and tubules. No increase of interstitial tissue. (Heidenhain's azan. $\times 180$.)

in four patients (Cases 5, 10, 11, and 12). In two of these (Cases 11 and 12) renal failure was present; the other two were in the group with impairment of renal function of doubtful significance. The glomerular lesions were all atrophic or "ischaemic" in character, identical with those found in pyelonephritic or arteriosclerotic kidneys, and presumably due to impaired blood supply (Fig. 1). Atrophy and/or dilatation of tubules was present in these four specimens, but in no other cases. No thickening of glomerular capillary basement membranes, as described elsewhere in one case (Fiaschi *et al.*, 1959), was noted. One patient (Case 12) died in uraemia six months after biopsy. The post-mortem histology of the kidneys was similar to that of the biopsy material; a few urate deposits were noted macroscopically but were not seen in sections.

Three biopsy specimens were normal in all respects (Cases 1, 2, and 3, Fig. 2) and one was normal except for slight medial hypertrophy of arterioles (Case 4, with hypertension). Two of these patients (Cases 1 and 4) had proteinuria but normal renal-function tests, and two (Cases 2 and 3) had no clinical or biochemical renal abnormality.

Four specimens (from Cases 6, 7, 8, and 9) showed changes intermediate between the above groups. There was slight collagenous and/or cellular increase of cortical interstitial tissue without associated inflammatory-cell infiltration (Fig. 3). No tubular abnormality was found and the glomeruli were normal except for a slightly thickened Bowman's capsule in Case 8 and occasional capsular adhesions in Case 9. One of these specimens was from a patient with hypertension (Case 6), and the perivascular and periglomerular distribution of the collagen suggested that vascular lesions might be responsible for the interstitial change. The other three members of this intermediate group had normal blood-pressure. In these cases the degree of interstitial fibrosis was more than might be expected from their ages (53, 51, and 45 years). In the hypertensive patient and one other (Case 8) the arterioles showed slight medial hypertrophy.

No urate deposits were seen in any of the sections, but medullary tissue, the usual site of deposition, was present in only two specimens.

FIG. 3.—Case 8. Normal glomerulus. Tubules separated by fine collagen. (Heidenhain's azan. $\times 195$.)

Table III shows the relationship between the clinical and histological features in the 12 cases.

Discussion

Two patients (Cases 11 and 12) were known from previous observation to have proteinuria and evidence of renal impairment. The other 10 were not admitted for this investigation because of any known disturbance of renal function, but because, out of a larger group of out-patients with gout, they agreed to renal biopsy.

It was interesting, therefore, to find that of these 10 cases of gout eight had proteinuria and/or some impairment of renal function, and that six had disorders of renal structure. Admittedly impairment of renal function was in some cases very slight and was estimated by relatively crude tests. Moreover, renal biopsy specimens are not necessarily representative of renal structure. There is the further possibility that the minor disorder of renal structure—slight interstitial-tissue increase—could be regarded as a normal finding in older patients, especially in the juxtamedullary zone. Nevertheless, a comparison with ischaemic renal lesions and renal-function tests in non-gouty patients suggests that these changes are more than might be expected.

Several authors have described defects of renal function in gout. Schnitker and Richter (1936) found proteinuria in almost half, and impaired renal function in 17 of 55 patients. Coombs *et al.* (1940) found some evidence of defective renal function in 18 out of 22 patients. He noted that inability to concentrate was the earliest abnormality, and considered that neither the duration of the arthritis nor the level of serum uric acid could be the sole factor determining renal damage. McQueen (1951) reported albuminuria in about half and urinary casts in about a quarter of 65 cases. Gutman and Yü (1957) found that 65 out of 300 gouty patients had overt renal damage, assessed by routine urine analysis, the urea concentration test, P.S.P. excretion, and serum N.P.N. estimation. These patients were, however, in older age-groups than the present series, and the authors doubted whether their renal impairment was greater than that of non-gouty subjects of the same age. Modern and Meister (1952) believe that there is a distinct renal clinical syndrome in gout, characterized by slight albuminuria, no hypertension, great impairment of renal function, and a prolonged course. This clinical picture could, however, be produced by chronic pyelonephritis alone.

The description of renal lesions in gout has previously been confined to necropsy material. Most authors agree on the final picture of gross tubular atrophy and

interstitial fibrosis, sometimes with terminal abscess formation (Schnitker and Richter, 1936; Brown and Mallory, 1950; Modern and Meister, 1952; Fineberg and Altschul, 1956; Lichtenstein *et al.*, 1956). The part played by urate deposition and tubular obstruction in the production of this picture has been the subject of controversy. Schnitker and Richter (1936) did not regard the urate deposits in the kidneys as important, having noted them to be present in otherwise relatively normal tissue. Spitz *et al.* (1949) also noted heavy infiltration of the kidneys in a patient who had had no renal failure. In this context, the phrase "benign gouty nephrosis" has been used (Sokoloff, 1957). Brown and Mallory (1950), however, thought that their necropsy findings supported the view that the main cause of renal failure in gout is tubular blockage by uric acid. There is no doubt that massive excretion of uric acid, such as follows the irradiation of leukaemic patients, can cause tubular obstruction and even fatal renal insufficiency (Greenbaum and Hope Stone, 1959), but it is uncertain whether this bears any relation to the pathogenesis of the gouty kidney.

Our study does not provide any conclusive evidence about the production of gouty nephropathy. The most advanced lesions which were found in the two patients with renal failure (Cases 11 and 12) were of the type described in necropsy material. Such lesions are usually interpreted as being caused by chronic pyelonephritis, but it is impossible to know if tubular and interstitial changes preceded or followed infection or even progressed independently of infection. Possibly the old term "interstitial nephritis" is applicable. Perhaps the fine interstitial fibrosis which we have noted as the only abnormality in some of our cases is the earliest structural defect. It is possible that the metabolic disorder of gout promotes slowly progressive tubular changes, undetectable by simple histological stains, but accompanied by interstitial reaction. In time tubular atrophy would develop with or without coincidental infection and produce the final picture of "interstitial nephritis."

Summary

Twelve patients with gout have been studied by renal biopsy. Two were known previously to have renal failure. Eight others had proteinuria and/or impairment of renal function and six had disorders of renal structure.

It is suggested that the earliest renal lesion is tubular damage with subsequent interstitial reaction.

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TABLE III.—*Relationship Between Clinical and Histological Features*

Cases	Clinical Features	Histological Features
2, 3	Normal	Normal
1	Proteinuria only	Arteriolar hypertrophy only
4	" and hypertension	
7	Slight impairment of renal function	Interstitial tissue increase only
9	Proteinuria and slight impairment of renal function	
6	Hypertension, proteinuria, and doubtful impairment of renal function	Interstitial tissue increase and arteriolar hypertrophy
8	Slight impairment of renal function only	
5, 10	" " "	Scanty atrophic glomerular lesions. Tubular dilatation or atrophy. Interstitial tissue increase
11	Hypertension, proteinuria, and renal failure	Atrophic glomerular lesions. Tubular atrophy. Interstitial tissue increase. Arteriolar hypertrophy
12	Proteinuria and renal failure	