Virchows Arch. A Path. Anat. and Histol. 388, 187–198 (1980)

Virchows Archiv A

Kidney Involvement in Behçet's Syndrome

A Report of 11 Cases Studied by Optic, Ultrastructural and Immunopathological Techniques

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Summary. The finding of a focal and segmental glomerulonephritis (GN) in a patient with a Behçet's syndrome led us to perform systematic renal biopsies in ten other patients with the disease. Renal biopsy specimens of 11 patients with Behçet's syndrome (followed for 6 months to 15 years) have been studied by light, electron and immunofluorescence microscopy. In all cases, blood pressure and renal function were normal. Proteinuria was present in five patients. By light and electron microscopy, amyloidosis could not be demonstrated in any case. In one patient, the focal and segmental GN was associated with fibrinoid, electron dense, mesangial and irregular subepithelial deposits. These deposits were also detected in seven other patients but to a lesser degree. Arteriolosclerosis was present in all cases. By immuno fluorescence, small scattered granules of C3 were observed in 10 patients in the mesangium and along the capillary basement membrane. They were diffuse in six cases and focal in four. Small focal deposits containing IgA and/or IgG, Clq were also observed in four cases. Circulating immune complexes found in six out of seven patients in whom they were sought. Rare cases of focal and segmental GN and amyloidosis have been reported in Behçet's syndrome. To our knowledge, glomerular C3 deposits have not been yet reported. These findings with the presence of circulating immune complexes suggest that renal symptoms occasionnally observed in Behçet's syndrome could be related to immune complex deposition.

Key words: Behçet's syndrome – Renal biopsy – Glomerulonephritis – C_3 deposits.

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0340-1227/80/0388/0187/$02.40

Introduction

Behçet's syndrome (BS) was originally characterized by a relapsing symptomatic triad: aphtous stomatitis, genital ulceration and iritis (Behçet 1937). Many other manifestations have since been added to these classical signs: cutaneous lesions (Nazzaro 1966; Sobel et al. 1973), arthritis (Mason and Barnes 1969; Strachan and Wigzell 1963), thrombophlebitis (Kansu et al. 1972), various neurological syndromes (O'Duffy and Goldstein 1976; Buge et al. 1977), cardiac and pericardial involvement (Godeau et al. 1972), gastro-intestinal manifestations (Empey and Hale 1972). Surprinsingly, renal involvement seems to be rare in such a systemic disease. The finding of a proteinuria during systematic investigation of a patient with BS and the presence of a glomerulonephritis (GN) on the renal biopsy led us to study the kidney of ten other patients with BS. Functional and microscopal observations including ultrastructural and immunopathologic techniques have been combined in this report.

Patients and Methods

Patients (Table 1). Eleven patients with BS have been studied. They were observed at the Department of Internal Medicine for a two and half years period (June, 1975 – December 1977). All patients included in this study fulfilled Mason and Barnes's criteria (Mason and Barnes 1969) for the diagnosis of BS: namely, either three major criteria (oral ulcers, genital ulcers, eye involvement and skin lesions) were present, or two of the major criteria were associated with two minor criteria such as arthritis, thrombophlebitis, cutaneous hyperreactivity, clinical manifestations of gastro-intestinal, cardiac and neurological involvement. All patients were male, seven were Arabs born in North Africa. The age at onset of the disease varied between 17 and 38 years (mean 33 years).

Functional renal evaluation included a pyelogram, urinary sediment, detection and quantitation of 24 h proteinuria and measurement of serum creatinine.

Severe criteria were required before considering kidney biopsy. Seven patients with an abnormal pyelogram, a suspicion of obstruction of the vena cava or under anticoagulant therapy were excluded. All renal biopsies were performed after informed consent by closed needle puncture by the same highly experienced physician without any morbidity.

Circulating immune complexes were investigated in sera by two methods: precipitation with polyethylene glycol and inhibition of complement-dependent lymphocytes EAC rosette formation. Details of these methods have been published elsewhere (Gluckman et al. 1978). Dosage of serum C_4, C_3 and C_3PA was done by radial immunodiffusion.

Morphological Methods. Two cores of renal tissue were available for study: one for light microscopy and one for immunofluorescence and electron microscopy.

Light microscopy examination: the renal fragments were fixed in Dubosq Brazil solution and subsequently in 15 per cent formalin, embedded in paraffin and cut at 2 or 3 μ. The following staining techniques were systematically used: Masson's trichrome, haematoxylin eosin, periodic acid – Schiff (PAS). Wilders reticulin, Thioflavine and Congo red with polarization microscopy. At least 30 different sections were examined in each case.

Electron microscopic examination: renal specimens with glomeruli were obtained from seven patients. Kidney tissue was fixed in osmium tetroxide, post fixed in glutaraldehyde and then embedded in epon. Ultra-thin sections were stained with uranyl acetate and lead citrate. The silver staining method was used to demonstrate the location of the deposits (Movat 1961).

Immunofluorescence microscopy: the renal biopsies were snap-frozen in liquid nitrogen and cut in a cryostat at $-25°$ C. Each section, briefly fixed in acetone, was washed in buffered phosphate at pH 7.3, covered with fluoreicein labelled anti-serum for 40 minutes, washed three times in buffered phosphate, and mounted in buffered glycerin. Antisera specific for human IgA, IgG, IgM, C_3,

Table 1. Clinical analysis of the cases

Case no.	Age at onset		Place of birth	Duration of follow-up (years)	Major criteria				Other criteria			
	Years	Sex			Aphtous stomatitis	Genital ulceration	Ocular lesions	Skin lesions	Joint involvement	Thrombophlebitis	Cutaneous hyperactivity	Other lesions
1	28	M	Algeria	5	+	+	+	+	−	−	+	−
2	38	M	France	0.5	+	+	−	+	−	+	−	−
3	17	M	Morocco	15	+	+	−	+	+	+	−	−
4	29	M	Senegal	1	+	+	+	+	−	+	−	[a]
5	30	M	Portugal	0.5	+	+	−	+	+	+	+	−
6	29	M	Algeria	3	+	+	+	−	−	−	+	−
7	28	M	Algeria	1	+	+	+	+	−	+	+	−
8	25	M	Turkey	2	+	+	+	+	−	−	+	−
9	38	M	Morocco	4	+	−	+	−	−	−	+	[b]
10	24	M	Algeria	1	+	+	+	+	−	+	−	−
11	29	M	Algeria	7	+	+	+	+	−	−	+	−

[a] Pericarditis
[b] Aseptic lymphocytic meningitis

albumin (goat serum Hyland Laboratories) and C_{1q}, C_4, fibrinogen (rabbit serum Behringwerke Laboratories) were used in each case. These antisera gave no fluorescence with normal renal tissue.

Results

Clinical and Biological Results (Table 1, 2). The duration of BS prior to the time of renal evaluation and kidney biopsy varied from 6 months to almost 15 years, with an average of 3 years 8 months.

Renal evaluation was performed during a relapse in five cases (no. 2, 8, 9, 10, 11). All patients were free of oedema and hypertension (blood pressure $\leqq$150–90 mm Hg). Proteinuria was observed in five patients: it was mild in four, (less than 500 mg/24 h) and reached to 2,000 mg/24 h in the fifth patient, who had developed a transient biological nephrotic syndrome (proteinemia 57 mg/100 ml, serum albumin 24 mg/100 ml) few weeks previously. Microscopic haematuria was not detected and plasma creatinine was normal in all patients ($n \leqq 124$ µmol/l). Complement (C_4, C_3, C_{3PA}) levels were found normal in the two patients studied (cases 2 and 3) although in case 2 it was tested during a relapse. Circulating immune complexes were detected in six patients, including the five patients in relapses, out of the seven tested.

Light Microscopy (Table 3). In all instances, the characteristic staining reactions failed to demonstrate amyloid depositions.

In one case (Fig. 1), the kidney biopsy specimen showed glomerular lesions which associated fibrinoid deposits and a focal and segmental glomerulonephritis (FSGN). Segmental lesions involving 30 per cent of glomeruli were characterized

Table 2. Biological data at the time of renal biopsy

Case no.	Proteinuria (g/24 h)	Urine sediment		Plasma creatinine μmol/l	Immune complexes	
		RBC (N≦3 per high power field)	WBC (N≦3 per high power field)		P.E.G.	R.I.
1	0	0	3	88	N.D	N.D
2	0	0	2	97	Pos.	Neg.
3	2	2	50	95	Neg.	N.D
4	0.25	1	2	115	N.D	N.D
5	0.20	0	3	86	N.D	N.D
6	0	3	3	62	Pos.	Neg.
7	0	0	2	71	N.D	N.D
8	0.20	2	0	94	Pos.	Pos.
9	0	1	2	87	Neg.	Pos.
10	0.40	0	45	65	Pos.	Neg.
11	0	0	3	63	Neg.	Pos.

N.D=not done; Pos.=positive, Neg.=negative

Table 3. Pathological findings

Case no.	Duration of illness prior to biopsy (years)	Optic microscopy		Immunofluorescence						Electronmicroscopy deposits	
		Amyloid deposits	Glomerular deposits	IgA	IgG	IgM	C_1q	C_3	Fibrinogen	Mesangial	Sub-epithelial
1	5	No	Yes	–	–	–	–	+4/8	–	No glomeruli	
2	0.5	No	No	–	–	–	–	+8/8	–	+	+
3	15	No	Yes+ FSGN[a]	+2/4[b]	–	–	–	+4/4	+1 crescent	+	+
4	1	No	Yes	–	–	–	–	+4/20	–	No glomeruli	
5	0.5	No	medulla	–	–	–	–	+5/5	–	No glomeruli	
6	3	No	Yes	+1/7	+2/7	–	–	+2/7	–	+	+
7	1	No	No	–	–	–	–	+12/12	–	+	+
8	2	No	Yes	–	–	–	–	+5/5	–	No glomeruli	
9	4	No	Yes	–	+2/15	–	–	+5/15	–	–	–
10	1	No	No	–	–	–	–	–	–	–	–
11	7	No	Yes	–	+2/8	–	+2/8	+8/8	–	+	–

[a] FSGN=Focal Segmental Glomerulonephritis.
[b] n/n=number of positive glomeruli/total number of glomeruli

by a proliferation of mesangial and epithelial cells. An area of fibrinoid necrosis was present in the mids of one segmental lesion. Other segmental lesions were fibrous with capsular adhesions and crescent formation. These segmental lesions were associated with deposits which were scattered, eosinophilic, located in the mesangium and on the epithelial side of the glomerular basement membrane (Fig. 2).

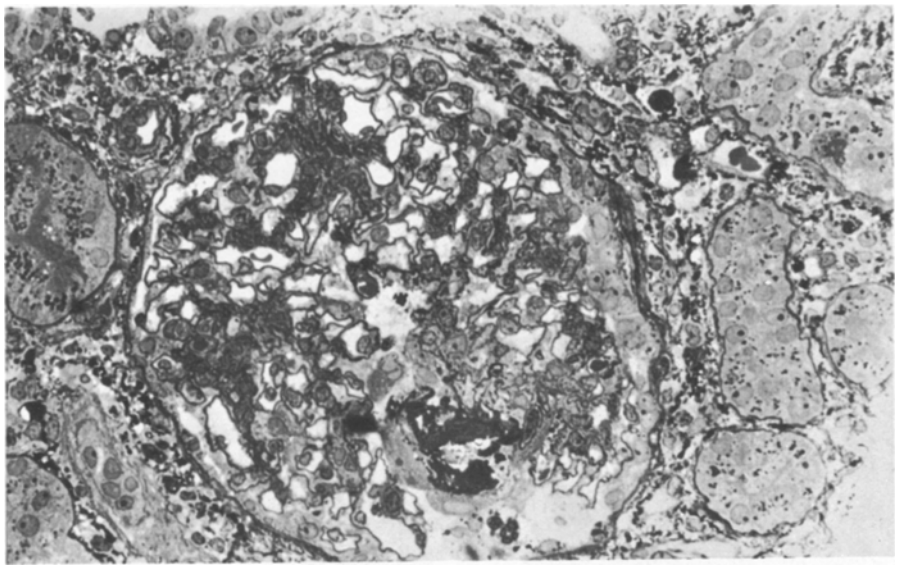

Fig. 1. Focal and segmental glomerulonephritis. Light photomicrograph of a silver methenamine-stained ultra-thin section. Case 3 (× 150)

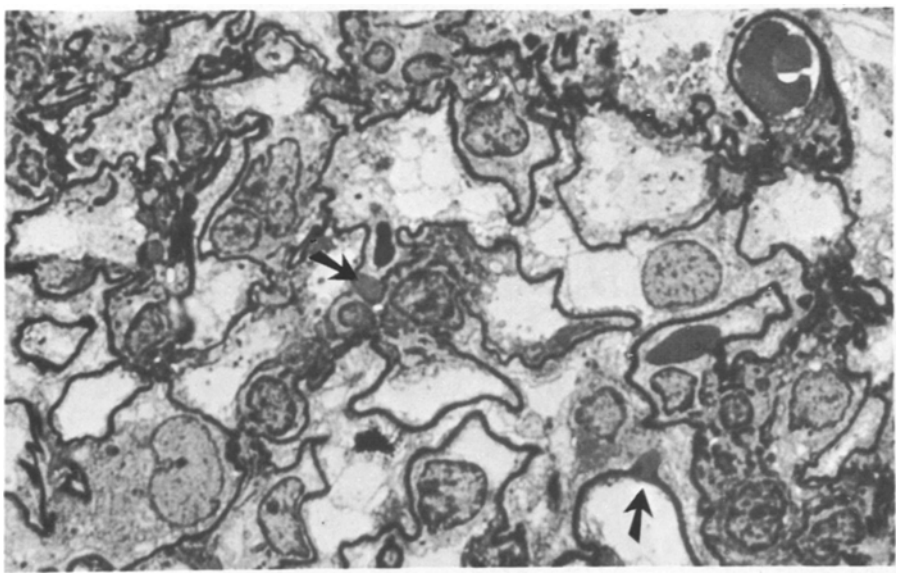

Fig. 2. Subepithelial deposits (*arrows*). Light photomicrograph of a silver methenamine-stained ultra-thin section. Case 3 (× 600)

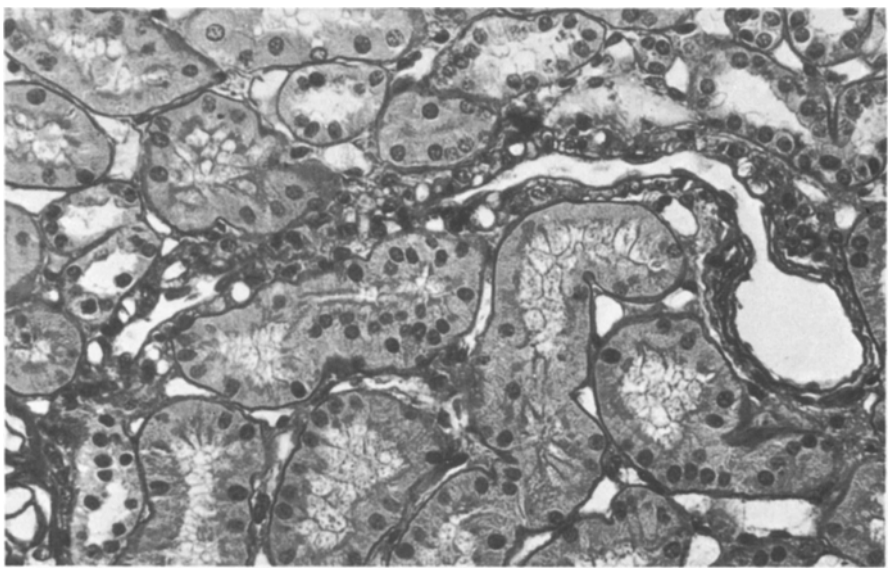

Fig. 3. Vacuolisation of muscular cells of a renal arteriole. Light photomicrograph. PAS. Case 10 (×150)

In the other patients, the glomeruli did not exhibit polymorphs, proliferative segmental lesions or mesangial matrix expansion, but there were deposits in seven cases. As in case 3, these deposits were scattered, eosinophilic and located in the mesangial area or on the external side of basement membrane, but they were scarce and hardly disclosed by light microscopy. Tubulo-interstitial lesions were present in only two patients. In case 3, numerous interstitial foci of fibro-oedema with few inflammatory cells were associated with some tubular loss or with tubules dilated and lined by a flattened epithelium. In case 11 there were few interstitial foci of acellular fibrosis with tubular atrophy.

Damaged vessels were observed in all the patients. Arterioles and small interlobular arteries showed intimal hyaline deposits or hyaline thickening of the walls associated with a fine vacuolation of muscular cells of some vessels (Fig. 3). Four patients (cases 2, 3, 4, 7) had greater than 50% of the vessels damaged. In only two cases (1, 3) were lesions located in larger vessels: they consisted of intimal thickening with reduplication of the internal elastic lamina. In spite of analysis of serial sections, we failed to observe arterial, venous thrombosis and vascular or peri-vascular cellular infiltration.

Immunofluorescence Microscopy (Table 3). Glomerular deposits of C_3 were observed in ten patients. This staining of C_3 had a irregular finely granular pattern along the capillary walls and within the mesangium (Fig. 4). The deposition of C3 was diffuse in six patients, focal and less intense in four. In six cases, C_3 staining was associated with IgA on two biopsies, with IgG on three biopsies and with C_{1q} on one biopsy. In these four cases, staining for immunoglobulins and for C_{1q} was focal and less intense than for C_3. In the patient with focal

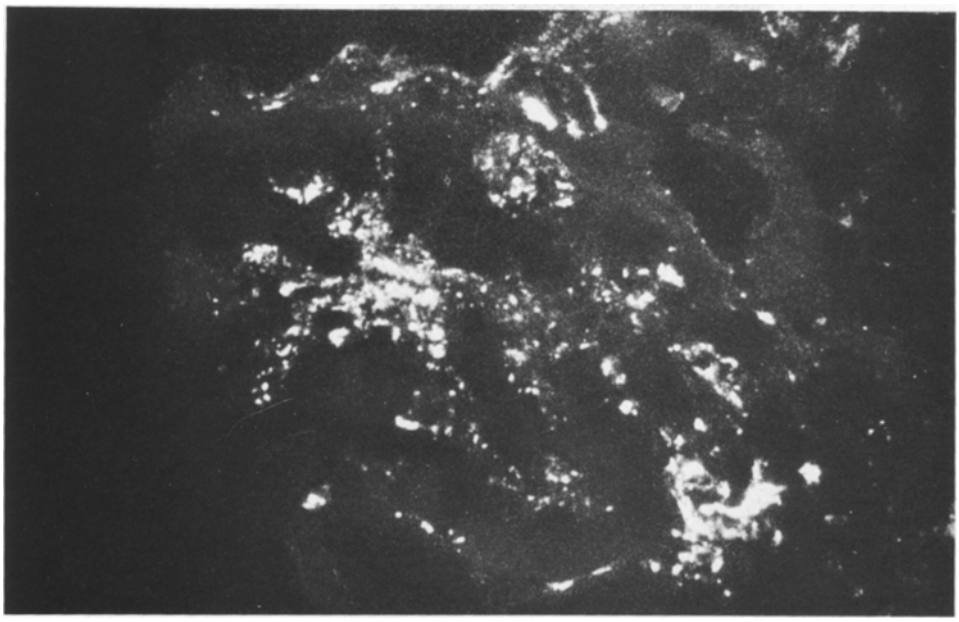

Fig. 4. Glomerular deposits of C_3 along the capillary walls and within the mesangium. Fluorescent micrograph of a section stained with anti C_3 globulin. Case 3 ($\times 200$)

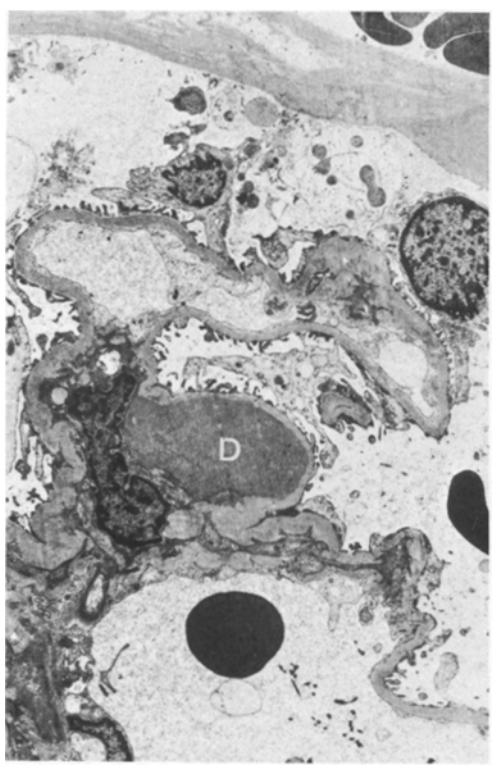

Fig. 5. Glomerular deposit in mesangial area (*D*). Electronmicrograph. Uranyl acetate and lead citrate stain. Case 6 ($\times 7{,}000$)

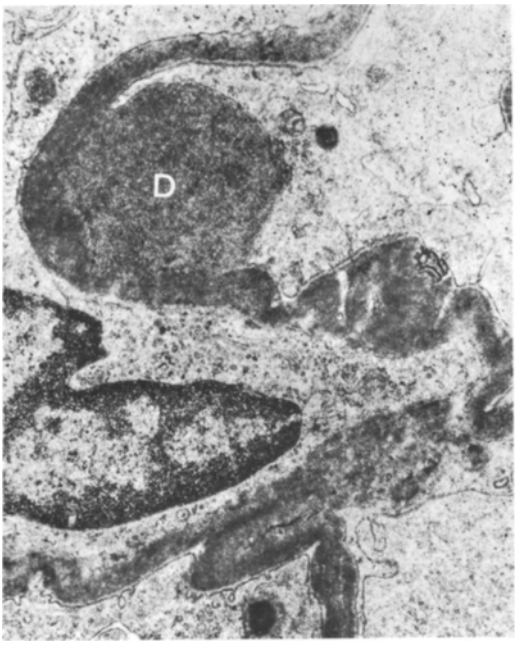

Fig. 6. Subepithelial hump-like glomerular deposit (*D*). Electronmicrograph. Silver stain. Case 7 ($\times 5{,}000$)

and segmental glomerulonephritis, one glomerulus with epithelial crescent stained with antifibrinogen serum. Staining with C_3 was also observed on arteriolar deposits.

Electron Microscopy (Table 3). The electron microscopic appearances confirmed the changes described above. In five of seven cases, in which electron miscropy was available with glomeruli, electron dense deposits were seen. These deposits were non argyrophilic, scarce and scattered in the mesangial matrix where they formed small round nodules (Fig. 5). An increase in the mesangial matrix or mesangial proliferation were not observed. In four cases the mesangial deposits were associated with finely granular subepithelial hump-like deposits (Fig. 6). In all cases amyloid deposits were absent in glomeruli and in blood vessels.

Discussion

Study of the kidney by renal biopsy demonstrated evidence of renal disease in ten patients. A mild proteinuria was noted in four. Only one patient had a major proteinuria with transient biological nephrotic syndrome. In no case was there obstruction of the vena cava and amyloid deposits were not observed by light or electron microscopy. Glomerulitis was characterized by fibrinoid deposits, located along the external side of basement membranes and in mesangial area; these deposits stained with C_3 and, in some cases, with immunoglobulins. In one patient, the deposits were associated with FSGN. These results

are strong evidence that BS can affect the kidney as other organs. Indeed, it was surprinsing that in a systemic disease renal manifestations seemed to be so unusual in BS and some authors have even claimed (Chajek and Fainaru 1975) that BS did not affect this organ. These authors did not observe any clinical and biological manifestation of renal involvement in 41 patients. Hamza et al. (1975) studied 22 cases of BS, out of whom only one case displayed, a macroscopic hematuria without proteinuria, for a few days. Renal function and pyelogram were normal. In contrast with these results a very slight proteinuria or microhaematuria was observed in 13 of 65 Japenese examined by Oshima et al. (1963) and more recently Rosenthal et al. (1978) found mild renal abnormalities consisting of proteinuria and/or microhaematuria in about 30% of their patients, but in no instance was renal biopsy performed. The incidence of proteinuria in our series is higher (5 of 11 cases) but leucocyturia, which was not detected by Rosenthal et al. (1978) without haematuria was observed.

Beside these results obtained on large groups of patients, isolated cases of renal involvement have been reported without pathologic study. In one case proteinuria associated with oedema was noted (Ota and Takayama 1969); in another an arterial hypertension with microscopic haematuria was discovered (Piers et al. 1977).

A survey of the literature has shown some isolated reports with pathological studies. Hamza et al. (1975) observed only vascular lesions on a renal biopsy performed one year after macroscopic haematuria. Kansu et al. (1972) reported a patient with inferior vena cava obstruction in whom percutaneous renal biopsy disclosed slightly increased cellularity in the glomeruli with minimal thickening of the basal membrane. These authors did not give information about biochemical renal abnormalities. At autopsy of a 39 year old patient, inflammatory, although non-specific changes were observed in kidneys (Noyan in O'Duffy 1978). In the series of Oshima et al. (1963), four cases, with urinary abnormalities, showed no renal dysfunction and their biopsy specimens disclosed no pathologic changes by light microscopy.

Apart from these cases with no or minimal lesions, two kinds of glomerular lesions have been described in BS: amyloidosis and FSGN. Nestor et al. (1970) and Beroniade (1975) reported three patients with nephrotic syndrome, in two of whom there was histologic proof of amyloidosis. Rosenthal et al. (1975) described systemic amyloidosis in three patients. Amyloidosis was expressed in as a nephrotic syndrome and in one by intermittent trace proteinuria. Two other cases of amyloidosis with nephrotic syndrome were also observed by Dilsen (in O'Duffy 1978).

In four instances a segmental and focal GN was described: in two cases (Yakohama et al. 1973; Mace and Jones 1978) on a postmortem examination. In one of these cases the renal manifestations were proteinuria and microscopic haematuria (Mace and Jones 1978). In the third case (Kansu et al. 1977) the patient had a proteinuria (1+) with microscopic haematuria and a normal renal function at admission. A few days later, the patient's serum creatinine level had risen to 7.8 mg/100 ml. A renal biopsy disclosed an acute focal necrotizing glomerulonephritis with early crescent formation. Electronmicroscopy showed the urinary space to be filled with epithelial cells and fibrinoid material

but failed to demonstrate any noticeable deposits of immune complexes. Immunofluorescent staining showed only fibrinogen in the blood vessels and glomeruli. In the fourth case (Gamble et al. 1979), the patient exhibited both renal and pulmonary involvement. Microscopic haematuria, leucocyturia, proteinuria (0.35 to 4.9 g/24 h), transient elevation of serum creatinine to 2.6 mg/100 ml were all associated with ill defined interstitial infiltrates involving the lungs. The lung biopsy revealed a vasculitis of the small pulmonary veins and alveolar septal capillaries. The renal biopsy showed a focal, segmental, necrotizing GN with variable crescent formation. Granular staining for IgG, C3, C4 and fibrinogen in the peripheral capillary walls of the affected glomeruli was substantiated by the finding of subendothelial electron dense deposits within the affected capillary walls.

In one case of our serie, the renal biopsy finding of FSGN was similar to the glomerular involvement reported previously, but we also observed glomerular deposits of C_3 (with gammaglobulins, in 4 cases) which had not yet been described. This was substantiated by the finding of mesangial and subepithelial electron-dense deposits. Except in acute or chronic glomerulonephritis and in some systemic diseases (endocarditis) glomerular deposits of C_3 are uncommon. Morel-Maroger et al. (1972) did not observe deposits of C_3 in cases of minimal changes or normal glomeruli in ninety-six patients who had a nephrotic syndrome or a proteinuria with or without microscopic haematuria.

A study of the kidneys of 303 patients obtained at autopsy revealed the presence of gamma-globulins and complement in only 21 cases (6,9%) with gamma-globulins alone in 12 cases (Sutherland et al. 1974).

The cause of BS is unknown but most of the evidence suggests some abnormalitie in the immune mechanisms. Usually complement components are not depressed or are at high levels (Kawachi-Takahashi et al. 1975; Adinolfi and Lehner 1976), but C_3, C_4 and C_2 can be significantly reduced before the onset of uveitis, suggesting that complement activation by the classical pathway can occur (Shimada et al. 1974). These abnormalities suggest that immune complexes may be involved in BS. In fact, circulating immune complexes were present in the serum of these patients (Williams and Lehner 1977) as in the serum of six of our patients. A significant correlation was four between the disease activity and the amount of immune complexes (Levinsky and Lehner 1978; Gupta et al. 1978). In the case of Gamble et al. (1979), the presence of these complexes was associated with glomerular deposits of IgG, C_3, C_4. Identical deposits were present in the lung within the wall of vessels affected of acute venulitis and septal capillaritis. Lehner also (unpublished observations, in Levinsky and Lehner 1978) have observed C_3 deposits in the vessel walls in biopsies from patients with BS. These findings suggest that immune complex mediated vasculitis is important in the pathogenesis of BS. In view of the correlations established with animal models this pathogenesis of BS could explain the rare occurence of patent renal involvement. In spite of the high levels of circulating class II immune complexes in animals displaying widespread vascular lesions, GN ordinarily does not develop. The reason for this unexpected finding is revealed by immunofluorescence microscopy which shows that the complexes are restricted to the glomerular mesangium (Germuth and Rodriguez

1973). Our study of 11 cases with immunofluorescence and ultrastructural microscopy, which showed glomerular deposits in 10, demonstrates that glomerular involvement is common in BS confirming the careful clinical studies of Oshima et al. (1963) and more recently of Rosenthal et al. (1978).

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Accepted May 28, 1980