

# Renal Lesions of Subacute Infective Endocarditis

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## Summary

This paper gives an account of five patients with glomerulonephritis complicating subacute infective endocarditis. In three patients with focal (segmental) glomerulonephritis granular deposits of immunoglobulin and C3 and reduced serum complement suggested an immune-complex aetiology; but in two patients with a diffuse proliferative glomerulonephritis no Ig or C3 was detected in the diseased glomeruli and the pathogenetic mechanism remained undetermined. Four of the five patients developed renal failure needing dialysis.

## Introduction

Infective endocarditis has long been known to cause glomerular disease though this is rarely of serious clinical significance (Baehr, 1921). Most workers have distinguished two morphological patterns of injury—a diffuse and a focal glomerulonephritis (Gutman *et al.*, 1972; Heptinstall, 1966)—though there has been no agreement on the pathogenesis or interrelationship between them. We describe here the clinical and immunopathological findings in five patients with glomerulonephritis complicating subacute infective endocarditis. In three patients there was evidence that nephritis was due to antigen-antibody complexes but in two patients no immunoglobulin or complement could be detected in the diseased glomeruli. These patients were also unusual in that four developed severe renal failure needing dialysis.

## Case Reports

**Case 1.**—In October 1970 a 60-year-old man had an attack of bronchopneumonia. This responded to antibiotics but he continued to have recurrent episodes of fever each responding temporarily to short courses of ampicillin. In April 1971 mitral incompetence was diagnosed and he was treated with ampicillin and cloxacillin for six weeks though blood cultures were sterile. He improved again for a short period but symptoms recurred and in November 1971 he was admitted to Hammersmith Hospital. On examination he had signs of mitral regurgitation, lymphadenopathy, and hepatosplenomegaly. Proteinuria fluctuated between 0.9 and 7.7 g/24 hours and creatinine clearance was reduced to 26 ml/min. Out of 15 blood cultures five grew *Actinobacillus actinomycetemcomitans*. Despite treatment with penicillin and gentamicin for six weeks, renal function deteriorated and he needed peritoneal dialysis for three weeks. Renal biopsy three weeks after the start of treatment showed 10 glomeruli, in two of which there were crescents. Most of the glomeruli showed extensive proliferation within the tufts but in the least-affected glomeruli damage was segmental (figs. 1 and 2). Because the renal lesion was so severe and blood cultures sterile he was given prednisolone 60 mg/day but this had to be stopped because of gastrointestinal haemorrhage. Renal function gradually improved and on discharge the blood urea was 52 mg/100 ml and the 24-hour urine protein 0.5 g.

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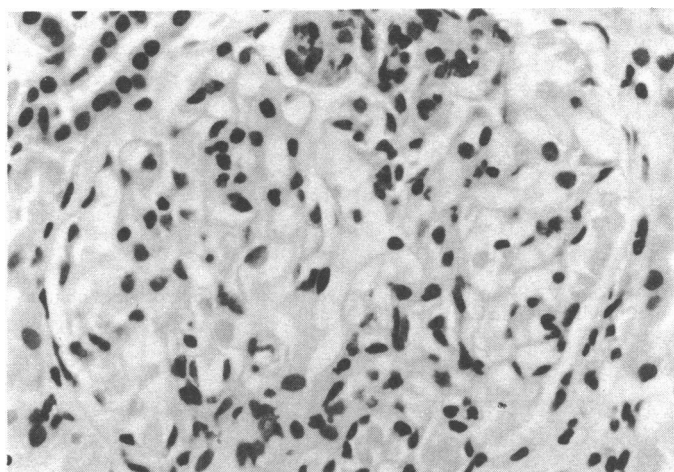


FIG. 1—Case 1. Least affected glomerulus showing segmental sclerosis. (H. and E.  $\times 320$ .)

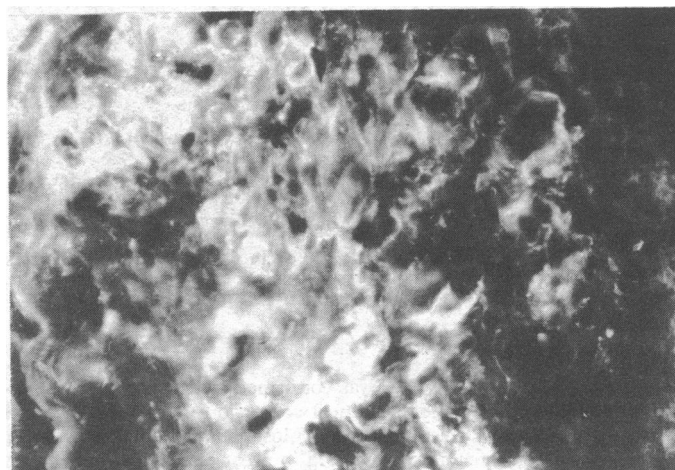


FIG. 2—Case 1. Immunofluorescent appearances of typical glomerulus showing scattered deposits of C3 along capillary walls. (Fluoresceinated anti-C3.  $\times 340$ .)

**Case 2.**—A 57-year-old man with rheumatic aortic valve disease presented with a 12-month history of increasing dyspnoea and malaise; six months earlier he had had a short febrile illness. On examination there were signs of aortic regurgitation, hepatosplenomegaly, finger clubbing, and persistent fever. The serum creatinine was 2.0 mg/100 ml and the urine contained red cells but no protein. Repeated blood cultures were sterile but a high titre (1:1,024) of complement-fixing antibody to psittacosis/lymphogranuloma venereum (L.G.V.) antigen was detected. A diagnosis of psittacosis endocarditis was therefore made and treatment with tetracycline and rifampicin was begun. A renal biopsy five days later showed minor focal proliferative changes (figs. 3 and 4). The serum creatinine fell progressively to 1.5 mg/100 ml. He improved temporarily but four months later, because of a return of fever, increasing aortic regurgitation, and a fall in C3 concentration, recurrent infection was diagnosed and the aortic valve replaced. At operation a bicuspid aortic valve was found to be covered in vegetations. Postoperatively his serum creatinine was 1.4 mg/100 ml and 6 months later the antibody titre to psittacosis/L.G.V. antigen had fallen to 1:16. He has continued on tetracycline and rifampicin.

**Case 3.**—The patient was a 25-year-old man in whom a heart murmur had been discovered at the age of 4 months and the clinical

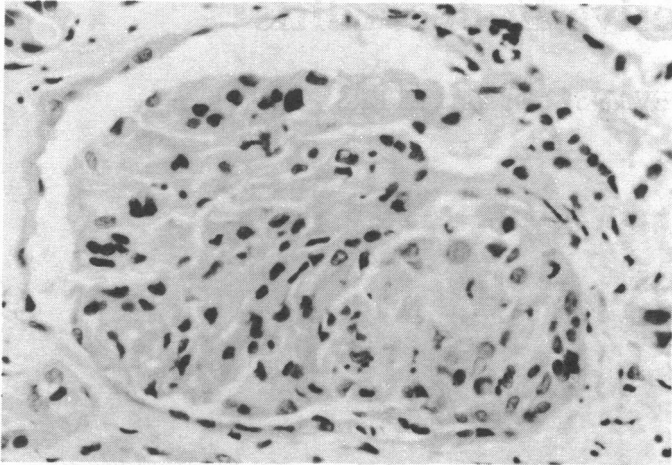


FIG. 3—Case 2. Segmental proliferative lesion showing localized obliteration of capillary lumina. (H. and E.  $\times 380$ .)

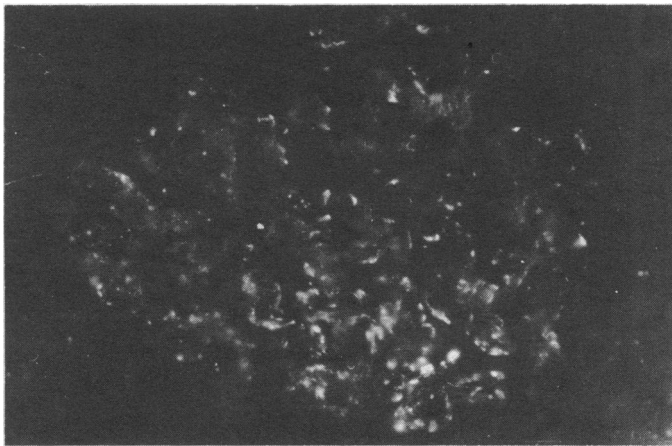


FIG. 4—Case 2. Immunofluorescent appearances of typical glomerulus showing extensive granular deposition of IgG along capillary walls and in mesangial regions. (Fluoresceinated anti-C3.  $\times 310$ .)

diagnosis of tetralogy of Fallot was confirmed by cardiac catheterization at the age of 13. A total surgical correction performed the next year, leaving a small residual ventriculoseptal defect and a minor degree of pulmonary stenosis, resulted in great clinical improvement. He continued well for nine years but then became tired and unwell and was found to be anaemic (haemoglobin 9 g/100 ml). One month later he had a haematemesis and was admitted to hospital, where he was found to have renal failure (blood urea 400 mg/100 ml). Blood cultures grew *Streptococcus viridans*. He was transferred to Hammersmith Hospital, where treatment with peritoneal dialysis and penicillin was started. Renal biopsy 27 days later showed seven out of eight glomeruli entirely sclerosed; the eighth showed a segmental proliferative glomerulonephritis. No improvement in renal function occurred over a period of three months and he ultimately died of staphylococcal septicaemia. At necropsy friable vegetations were present on the mitral and tricuspid valves and on the suture line of the patch in the pulmonary artery. The kidneys were of normal size. Ninety per cent. of the glomeruli were sclerosed and the remainder showed adhesions between capillary loops and Bowman's capsule.

*Case 4.*—This patient was a 54-year-old Persian man with rheumatic disease of the aortic and mitral valves. These had been replaced by Starr-Edwards prostheses in May 1972. The blood urea had been 28 mg/100 ml when he was discharged from hospital on the 10th postoperative day. Two months later he had rigors and was found to have atrial fibrillation. An unsuccessful attempt at cardioversion was followed by gastrointestinal bleeding. From that time he continued to have intermittent fevers. On investigation in Teheran the blood urea was 96 mg/100 ml and the urine contained protein (3 g/24 hours), red cells, and casts. He was readmitted to Hammersmith Hospital in November 1972 when the blood urea was 212 mg/100 ml, though it had been only 62 mg/100 ml 10 days earlier. The haemoglobin was

4.7 g/100 ml. Three blood cultures grew *Staphylococcus albus*. He was treated by peritoneal dialysis for 16 days and with gentamicin, rifamicin, and lincomycin for six weeks. Renal biopsy seven days after the start of treatment showed histological evidence suggesting acute tubular necrosis and diffuse mesangio-proliferative glomerulonephritis without neutrophil polymorph infiltration. When discharged from hospital the blood urea had fallen to 34 mg/100 ml and the urine was free of protein.

*Case 5.*—A 62-year-old man presented with a short history of fever and proteinuria. On admission to hospital he was thought to be dehydrated but on rehydration remained oliguric and was found to be uraemic. On transfer to Hammersmith Hospital he was confused and suffering from severe congestive heart failure. Despite assisted ventilation and peritoneal dialysis he deteriorated and died the next day. At necropsy the mitral valve leaflets were found to be thickened and the chordae shortened. There were small vegetations along the line of valve closure and an ulcer (4 x 2 mm) on the anterior cusp. Histological examination showed an acute inflammatory reaction with sheets of Gram-positive cocci within the valve. The kidneys were of normal size but microscopy showed a diffuse lobular proliferative glomerulonephritis (fig. 5).

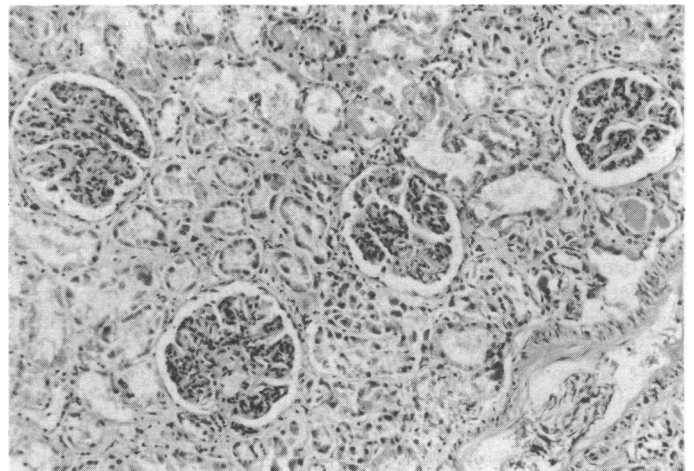


FIG. 5—Case 5. Necropsy kidney specimen showing diffuse mesangial proliferative glomerulonephritis. (H. and E.  $\times 145$ .)

## Methods

The serum concentrations of the complement components C3, C4, C1q, glycine-rich beta glycoprotein (GBG), and properdin were measured as described previously (Williams *et al.*, 1973). The methods and antisera used for immunofluorescence have been described previously (Evans *et al.*, 1973) as have the methods used for light microscopy (Macanovic *et al.*, 1972). In two patients (cases 1 and 2) whose glomeruli contained immunoglobulins there was sufficient biopsy material to attempt identification of antigen. The IgG fraction of convalescent serum from Case 1 was fluoresceinated by standard techniques (Nairn, 1969) and shown to react with the organism by direct immunofluorescence. Fluoresceinated serum was then layered on cryostat sections which were untreated and prewashed in citrate buffer (pH 3.2) and then in phosphate-buffered saline. Biopsy material from case 2 was eluted with citrate buffer (pH 3.2) according to the method of Feltkamp and Boode (1970). The eluate was neutralized and tested for psittacosis antigen and antibody by a micro complement fixation test (Meyer *et al.*, 1969) and for antibody by indirect immunofluorescence.

## Results

Renal biopsy findings are summarized in table I (see also figs. 2 and 4). Attempts to find antigen or specific antibody in the glomeruli of the patients in cases 1 and 2 failed. Complement studies are summarized in table II. Low C3 concentrations were

TABLE I—Renal Biopsy Findings in five Patients with Subacute Infective Endocarditis

Case No.	Light Microscopy	Immunofluorescence				Thin Section
		IgG	IgA	IgM	C3	
1	Extensive proliferative glomerular changes with segmental distribution in least affected glomeruli	Diffuse granular parietal	0	Diffuse granular parietal	Diffuse granular parietal	Badly damaged glomerulus. Subendothelial deposits?
2	Mild segmental and focal proliferative glomerulonephritis	Diffuse granular parietal and mesangial	0	Diffuse granular parietal and mesangial	Diffuse granular parietal and mesangial	Subendothelial and mesangial deposits
3	Segmental proliferation in one glomerulus. Remaining 7 glomeruli sclerosed	0	Diffuse granular parietal and mesangial	Diffuse granular parietal and mesangial	Diffuse granular parietal and mesangial	Subendothelial and mesangial deposits
4	Diffuse mesangial proliferative glomerulonephritis	0	0	0	0	No deposits seen
5	Diffuse mesangial proliferative glomerulonephritis	0	0	0	0	No deposits seen

TABLE II—Serum Complement Levels of four Patients with Subacute Infective Endocarditis before and after Treatment. Figures are Percentages of Pooled Normal Serum

		Case No.				Normal Ranges	
		1	2		3		4
			a*	b*			
C3	Before	60	55	55	25	100	68-116
	After	100	90	100	100	120	
C4	Before	72	35	40	52	100	50-210
	After	100	45	52	100	135	
Clq	Before	106	100	100	200	100	60-136
	After	66	170	100	170	170	
GBG	Before	200	100	74	100	100	40-210
	After	100	74	100	74	100	
Properdin	Before	100	100	100	100	100	40-210
	After	70	100	Not done	60	100	

found in three of four patients and they returned to normal with treatment (see fig. 4). In case 2 the C3 concentrations fell again during relapse and returned to normal after excision of the infected valve. C4 concentrations were persistently low in case 2 and rose to the lower limit of normal after excision of the infected valve. The other two patients with low C3 concentrations had C4 concentrations of 52% and 72%, which rose to 100% after treatment. Clq, GBG and properdin concentrations were normal in all patients.

## Discussion

Three features of interest emerged from our studies of these patients: evidence for an immune complex nephritis in three patients with segmental histological changes, our failure to identify the pathogenetic mechanism in the two patients with diffuse proliferative glomerulonephritis, and the severity of renal involvement in four of the five patients.

Evidence suggesting that glomerular disease was the result of circulating antigen-antibody complexes was present in all three patients with focal (segmental) nephritis. The reduction in the concentrations of C3 and C4 suggested activation of the classical complement pathway and deposits of immunoglobulin and C3 were found in their glomeruli. These deposits were subendothelial in the patients in cases 1 and 2 (see fig. 5) and mainly mesangial in case 3. Studies of experimental immune complex nephritis (Germuth *et al.*, 1972) have shown that the site of deposition within the glomerulus depends on the size of the immune complexes. It seems that relatively small complexes formed in antigen excess localize in a subepithelial position and are associated with a diffuse proliferation, whereas larger complexes formed in antibody excess deposit on the inside of the glomerular basement membrane or in the mesangium and are accompanied by a focal nephritis. These findings suggest that complexes were formed in antibody excess in cases 1-3. It is

interesting that in the preantibiotic era death from renal failure associated with bacterial endocarditis most often occurred in patients in whom blood cultures were repeatedly sterile—the so-called bacteria-free stage. Such patients had a chronic illness sometimes lasting decades associated with massive splenomegaly, lymphadenopathy, and profound anaemia (Libman and Freiberg, 1948). Probably these patients had prolonged circulation of immune complexes formed in antibody excess accounting for the sterile blood cultures and the hyperplastic reticuloendothelial system. In acute endocarditis, however, infected blood cultures, indicating excess antigen, are associated with diffuse proliferative glomerulonephritis (Heptinstall, 1966) and immunofluorescent and ultrastructural studies (Gutman *et al.*, 1972; Tu *et al.*, 1969) have shown subepithelial deposition of complexes.

Our attempts to show the antigens of the infecting organisms in the glomerular deposits—that is, to provide direct evidence of immune-complex nephritis—were unsuccessful. Other workers, however, have occasionally succeeded in identifying antigens or eluting specific antibody. Cocksackie B4 antigen was shown to be present in the glomeruli of a patient who had viral pancarditis (Burch *et al.*, 1969), and antibody to enterococci was eluted from the kidney of another patient with endocarditis due to this organism (Levy and Hong, 1973). Studies of experimentally induced immune-complex nephritis (Wilson and Dixon, 1971) have shown that antigen becomes obscured to immunofluorescent reagents by further deposition of antibody and complement, particularly in the mesangial deposits formed in antibody excess (Germuth and Rodriguez, 1973). Previous immunofluorescent studies (McIntosh *et al.*, 1971; Berman and Myers, 1972; Gutman *et al.*, 1972) in subacute infective endocarditis have usually shown evidence of immune-complex deposition in both the focal and diffuse forms of glomerulonephritis: Morel-Maroger *et al.* (1972) found granular deposits of C3 in the biopsies of patients who had no clinical evidence of renal involvement and Gutman *et al.* (1972) found deposits of IgG and C3 six months after treatment when the patient was clinically well. These studies suggest that immune complex deposition is the most common cause of both focal and diffuse proliferative glomerulonephritis.

We cannot explain the pathogenesis of diffuse glomerulonephritis in cases 4 and 5. No evidence of immune-complex deposition was obtained by immunofluorescent or ultrastructural studies. One other patient with subacute infective endocarditis whose biopsy did not contain immunoglobulins or C3 has been reported (Morel-Maroger *et al.*, 1972). This patient had no clinical evidence of renal involvement but a renal biopsy showed focal nephritis. Proliferative nephritis associated with polyarteritis nodosa (Berger *et al.*, 1971; McIntosh *et al.*, 1971) and, more rarely, Goodpasture's syndrome (Berger *et al.*, 1971) have also been described without deposits of immunoglobulin or C3 in the affected glomeruli. The mechanism of glomerular injury in these situations remains to be identified.

Immunological studies of these patients were clinically valuable. Immunofluorescent studies help in differentiating the focal nephritis of subacute infective endocarditis from the histo-

logically similar appearances seen in polyarteritis nodosa, Goodpasture's syndrome, Henoch-Schönlein syndrome, and idiopathic focal nephritis associated with mesangial IgA/IgG deposits (Berger, 1969; Berger *et al.*, 1971). Serial determinations of serum complement were valuable in assessing activity of the immune-complex disease and its response to therapy, and in one of our patients the fall in plasma C3 concentration was helpful in diagnosing relapse.

Even before the advent of antibiotics renal failure in subacute infective endocarditis was unusual (Baehr, 1921). It was, however, a striking feature in this group of patients, four of whom needed peritoneal dialysis. Two of these patients recovered good renal function, one died of cardiac failure shortly after admission, and the fourth patient, with extensive glomerular destruction, had irreversible renal failure. In one of the patients who recovered there was also clinical and histological evidence of acute tubular necrosis but in the remaining patients renal failure was due solely to glomerulonephritis. The striking improvement in renal function after eradication of infection emphasizes the importance of persistence of antigen in the progression of nephritis and the degree of recovery that is possible unless widespread glomerular scarring has already occurred. The importance of early diagnosis and effective treatment is evident.

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# Response to Propranolol and Diazepam in Somatic and Psychic Anxiety

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## Summary

A total of 12 chronically anxious psychiatric outpatients were treated with racemic propranolol (Inderal), diazepam (Valium), and placebo for one week each, using a balanced cross-over experimental design. Six patients had predominantly somatic anxiety, complaining mostly of bodily symptoms, and six had mainly psychic anxiety, complaining primarily of psychological symptoms. Clinical ratings of anxiety were made by patient and psychiatrist after each treatment. Though diazepam was in general more effective than propranolol or placebo in relieving anxiety, propranolol was more effective than placebo in patients with somatic anxiety but not in those with psychic anxiety. We suggest that propranolol should be reserved for patients whose anxiety symptoms are mainly somatic.

## Introduction

Granville-Grossman and Turner (1966) were the first to suggest that beta-adrenoceptor blockade might be effective in the treatment of pathological anxiety. Some more recent reports support this view (Wheatley, 1969; Conway, 1971; Bonn *et al.*, 1972; McMillin, 1973). Nevertheless, neurotic anxiety is not commonly treated with beta-blocking drugs and there are no clear indications for their use. Granville-Grossman and Turner (1966) found that only autonomically mediated symptoms were significantly improved by propranolol; anxiety, tension, and irritability were not. In view of the known peripheral effects of beta-adrenoceptor blockade these findings were not unexpected, but to what extent a reduction in autonomic symptoms creates clinical improvement is debatable (Ramsay *et al.*, 1973). Anxious patients vary greatly in their emphasis on the somatic or the psychological aspects of their anxiety. We took this into account in planning the present investigation of the effects of propranolol compared with those of diazepam and placebo in anxious patients.

## Patients and Methods

Outpatients attending the Maudsley Hospital with a primary diagnosis of chronic anxiety state (continuous symptoms for at least four months) were considered for the trial. Patients with cardiac disease and asthma were excluded. Out of 15 patients selected one group suffered mainly from somatic anxiety, placing most emphasis on bodily symptoms, and another group

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