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RENAL PATHOLOGY IN HYPERTENSION AND THE EFFECTS OF TREATMENT

PRISCILLA KINCAID-SMITH

University of Melbourne, Department of Medicine, Royal Melbourne Hospital, Parkville, Victoria 3050, Australia

A consideration of the renal pathology in hypertension must take account of two separate aspects. The changes which result from hypertension must be considered separately from the pathology of underlying renal disease in secondary hypertension.

1. Renal pathology due to the effects of the hypertension

Hypertension causes few well documented lesions in the glomeruli and tubules in the kidney. Even in its most aggressive form namely, malignant hypertension, there may be surprisingly little evidence of parenchymal damage in the kidneys of some patients who have run a fulminating course to a uraemic death (Kincaid-Smith *et al.*, 1958).

(a) *Parenchymal lesions*

The mean weight of the kidneys in patients who have died of malignant hypertension is only reduced by approximately 25% from a mean of 350 g to 260 g.

Microscopic examination reveals preservation of the glomeruli, the major abnormality being ischaemic tubular atrophy in nephrons distal to severely narrowed interlobular arteries (Kincaid-Smith *et al.*, 1958).

Ischaemic atrophy of tubules may be mild in some cases and may be difficult to detect unless tubules are measured and carefully compared with the normal for the age of the patient. Glomeruli may shown wrinkling of the basement membrane but this is not a uniform change and there is little evidence of loss of glomeruli.

Benign hypertension causes little if any alteration in the appearance of the renal parenchyma. There was no significant reduction in renal weights in a consecutive series of 131 patients in whom there had been careful documentation of blood pressure and retinal findings. The blood pressure had been consistently above 180/110 mmHg and no retinal haemorrhages or exudates or papilloedema had been observed. The mean left renal weight was 162.9 g and the mean right renal weight was 159.7 g (Kincaid-Smith, 1975a). Within this series there was no evidence of excessive sclerosis of glomeruli in patients with benign hypertension. The number of sclerosed glomeruli and the degree of tubular atrophy correlated with the age of the patient, not the severity or duration of hypertension.

(b) *Vascular lesions*

Malignant hypertension The major impact of hypertension in the kidney is seen in the blood vessels.

In malignant hypertension, the fulminating progression to renal failure is accompanied by and correlates with, the degree of rapid occlusion of interlobular arteries in the kidney. Fibrin deposition is the first abnormality and subsequent proliferation of myointimal cells in a concentric pattern produces the classical 'onion layer' lesion (Kincaid-Smith, 1975b, 1980a). The factors which may contribute to this process and create the vicious circle are set out in Figure 1.

Arterioles in malignant hypertension may show deposits of fibrin on the intima and proliferation of myointimal cells within the intima but more commonly they show occlusion by fibrin or the so-called 'fibrinoid necrosis' in the wall of the arteriole due to insudation of fibrin.

Effect of treatment on vascular lesions in malignant hypertension There is striking alteration in the character of the vessel lesions in malignant hypertension following treatment.

The most rapid alteration occurs in areas of so-called fibrinoid necrosis or in fibrin deposits within the lumen. Florid fibrin deposits which are a feature in interlobular arteries and arterioles before treatment are replaced by hyaline intimal deposits within a few days of treatment. Biopsies carried out in patients with malignant hypertension support observations in experimental animals that fibrin disappears in 3–4 days.

The fresh cellular proliferation of myointimal cells which is also characteristic of the lesions in the un-

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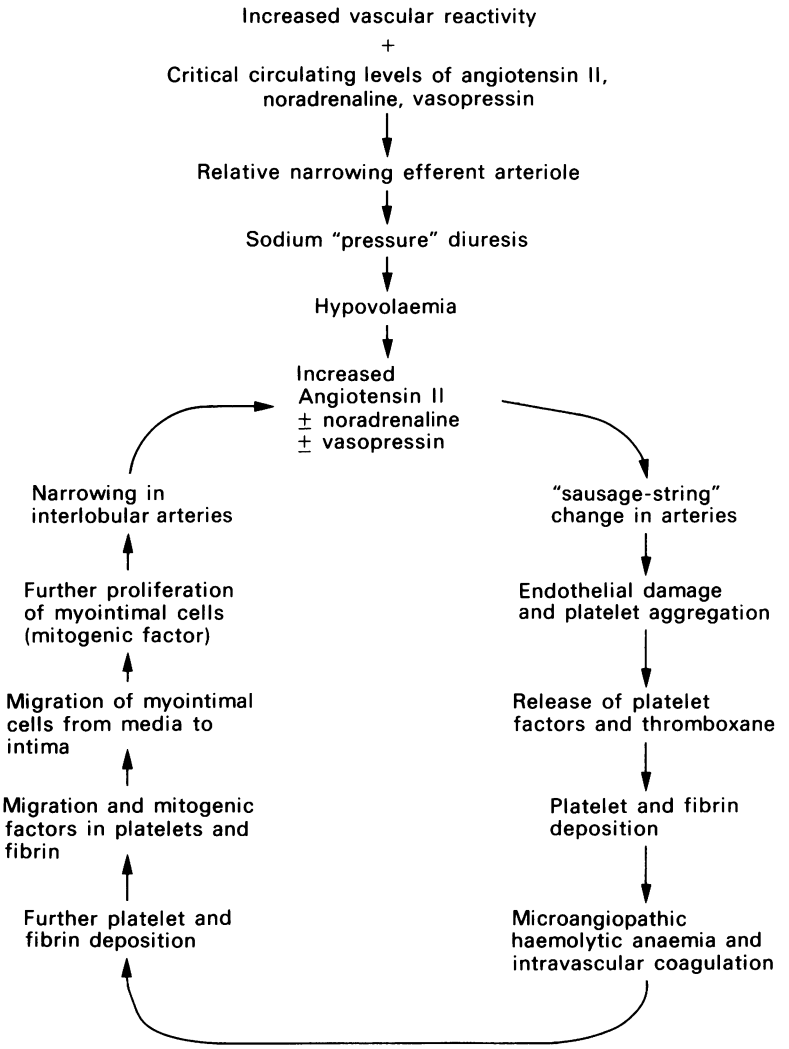

Figure 1 Proposed factors which may contribute to the vicious circle in malignant hypertension and the 'onion layer' lesion in interlobular arteries.

treated malignant hypertension is replaced after treatment by collagen and elastic fibres so that the lesions in interlobular arteries come to resemble those seen in benign hypertension except that the degree of narrowing is greater. These modifications in interlobular arteries which occur following treatment may not be accompanied by any increase in the size of the lumen. Severely narrowed interlobular arteries almost certainly do not improve and parenchyma distal to these arteries undergoes severe ischaemic atrophy and scarring. The nephrons supplied by interlobular arteries of normal calibre may undergo enormous hypertrophy over a period of years following treatment of malignant hypertension in patients with steadily improving renal function (Kincaid-Smith, 1976). From such observations it seems likely that the degree of narrowing which is present when treatment is started persists but that the character of the intimal thickening changes, concentric fibroelastic layers replacing the cellular myointimal proliferation.

Vascular lesions of benign hypertension In benign hypertension, the wall of renal arterioles is thickened and the ratio of the size of the lumen to the thickness of the wall decreases. Interlobular arteries may show

Table 1 Diagnosis in 49 patients with malignant hypertension or grade II hypertensive retinopathy presenting over a 5 year period

		Percent
Glomerulonephritis	18	37.5
Renal artery stenosis	9	18.7
Reflux nephropathy	6	12.5
No secondary cause detected	5	10.4
Renal papillary necrosis	4	8.3
Scleroderma	3	6.2
Gouty nephropathy	2	4.1
Polycystic	1	2
Polyarteritis nodosa	1	2

thickening of the wall due to an increase in media and due to concentric layers of fibroelastic intimal tissue. The lumen may be narrowed, however individual variation is great. The lumen may show no obvious reduction in size even after very prolonged and severe hypertension (Kincaid-Smith, 1975a).

2. Renal pathology relating to the underlying disease process which has caused hypertension

The importance of underlying renal disease as a cause of hypertension is well accepted in malignant hypertension where more than half the patients have an underlying renal cause (Gudbrandsson *et al.*, 1979; Kincaid-Smith *et al.*, 1958; Kincaid-Smith, 1980a).

With the more widespread treatment of hypertension in the past 25 years, only patients with more refractory hypertension develop the malignant phase and at the present time almost 90% of patients referred to me with malignant hypertension have an underlying cause (Table 1).

Essential hypertension which accounted for 44% of patients dying of malignant hypertension at the Royal Postgraduate Medical School in the 1950s, has now become a rarity, accounting for only 10.4% of patients whom I see. However, most of these patients have been referred as malignant hypertension and not with the label of the renal disease subsequently discovered following investigation. The reduction in cases with essential hypertension may reflect the greater ease with which hypertension is now treated and the fact that most patients with essential hypertension are treated well before they reach the malignant phase. Malignant hypertension often melted in the 1950s with methods of treatment such as a single night dose of hexamethonium bromide and with modern drugs, it is a very rare event for malignant hypertension to develop during treatment. Patients with renal hypertension are perhaps more likely to be resistant to treatment and perhaps more likely to present with malignant hypertension in 1981. The underlying renal diseases in 43 of 49 patients with malignant hypertension whom I have seen over 5 years are shown in Table 1.

Table 2 shows how my own experience in this field has changed over the past 20 years, but also shows a marked difference between my findings and those of a recent report from Scandinavia (Gudbrandsson *et al.*, 1979). There is a clear discrepancy between the 9% of patients with glomerulonephritis in Gudbrandsson's study and 37% in my own series. This difference is reflected in the percentage with essential hypertension, thus only 10% of our patients were diagnosed as essential hypertension against 37% in Gudbrandsson *et al.* (1979) study. The similar distribution of renal disease in other sub groups such as reflux nephropathy and renal artery stenosis suggests that my series is not heavily slanted by an excess number of patients with renal disease because of referral patterns but that our diagnostic criteria for glomerulonephritis are different from those of the Scandinavian group.

The prevalence of underlying renal disease in patients with benign hypertension has not been as well documented but it is likely tht renal disease is frequently overlooked in patients with benign hypertension. Because investigation of patients with severe hypertension is more exhaustive, underlying renal disease is more likely to be overlooked in mild or moderate hypertension than in severe hypertension.

(a) *Glomerulonephritis*

Glomerulonephritis is probably the commonest renal disease in the community. Many patients with

Table 2 Underlying renal disease in malignant hypertension.

	Kincaid-Smith et al. *(1958)* (118)	*Gudbrandsson* et al. *(1979)* (39)	*Kincaid-Smith (1981)* (49)
Essential	44%	37%	10%
Glomerulonephritis	20%	9%	37%
Reflux nephropathy	27%	9%	12%
Renal artery stenosis	4%	24%	19%
Other	5%	14%	22%

Table 3 Renal biopsy findings in healthy army recruits found to have urine abnormalities

	Persistent proteinuria	*Microscopic haematuria*
No obvious lesion	3 (8.6%)	16 (15.0%)
Focal glomerulonephritis	2 (5.7%)	5 (14.3%)
Mesangial proliferative glomerulonephritis	30 (85%)	85 (80%)
Total	35	106

Information derived from Pwee *et al.* (1978).

glomerulonephritis may have microscopic haematuria in the absence of proteinuria and only careful evaluation of the urine deposit will permit recognition of such cases.

Screening studies of apparently healthy young adults have demonstrated that proteinuria with or without associated microscopic haematuria is present in 1%–2% (Pwee *et al.*, 1978; Robinson *et al.*, 1961). Only a few biopsy studies have been carried out in screened populations. The only recent study has revealed glomerular disease in most cases (Table 3). This is also the only screening study carried out since fluorescent microscopy has been available. In this study, 56% of healthy subjects with urine abnormalities had mesangial IgA nephropathy (Pwee *et al.*, 1978). Perhaps the most revealing aspect of this study is the fact that on follow up three years later, 8.4% of these healthy army recruits had developed hypertension and 7.4% had developed uraemia. This study is relevant because it demonstrates a clearcut difference in prognosis between subjects with glomerulonephritis and asymptomatic subjects with essential hypertension (Report Management Committee, 1980). This prognostic difference alone is sufficient reason to detect patients with glomerulonephritis particularly as a simple test namely, careful urine microscopy is necessary to differentiate the two groups. Glomerular findings may be minor and may well be missed on light microscopy unless special stains, fluorescent and electron microscopy are performed.

While the Singapore study could reflect a particular problem with geographic or racial connotations, mesangial IgA nephropathy is by far the commonest glomerular lesion encountered in hypertensive patients in Melbourne. The distribution of glomerular lesions in a consecutive series of 60 patients with hypertension and proteinuria or microscopic haematuria presenting over a 3 year period is shown in Table 4. Patients presenting with hypertension and urinary abnormalities show a similar distribution of glomerular lesions to that found in normotensive patients with glomerulonephritis (Kincaid-Smith, 1981).

When the character of the urinary red cells suggests glomerular disease (Figure 2), (Fairley, 1980; Fairley & Birch, 1979; Fairley & Birch, unpublished), we would normally carry out a renal biopsy. The different prognosis in different categories of patients with glomerulonephritis (Cameron, 1979; Pwee *et al.*, 1978) as well as significant benefits of treatment demonstrated in controlled trials in some categories

Table 4 Renal biopsy findings in 60 patients with hypertension and proteinuria with microscopic haematuria (47) or microscopic haematuria alone (13)

	The character of the urinary red cells suggested glomerular disease in all cases		
Morphological category of glomerular lesion	*Proteinuria and microscopic haematuria*	*Microscopic haematuria alone*	*Mesangial IgA nephropathy*
Minor change with mesangial deposits of immunoglobulins	2	3	2
Membranous	1	0	0
Mesangial proliferative	9	5	6
Diffuse (> 50%) crescentic	2	0	1
Focal and segmental proliferative	8	1	6
Focal and segmental hyalinosis/sclerosis	21	2	10
Focal sclerosis	4	2	2
Total	47	13	27

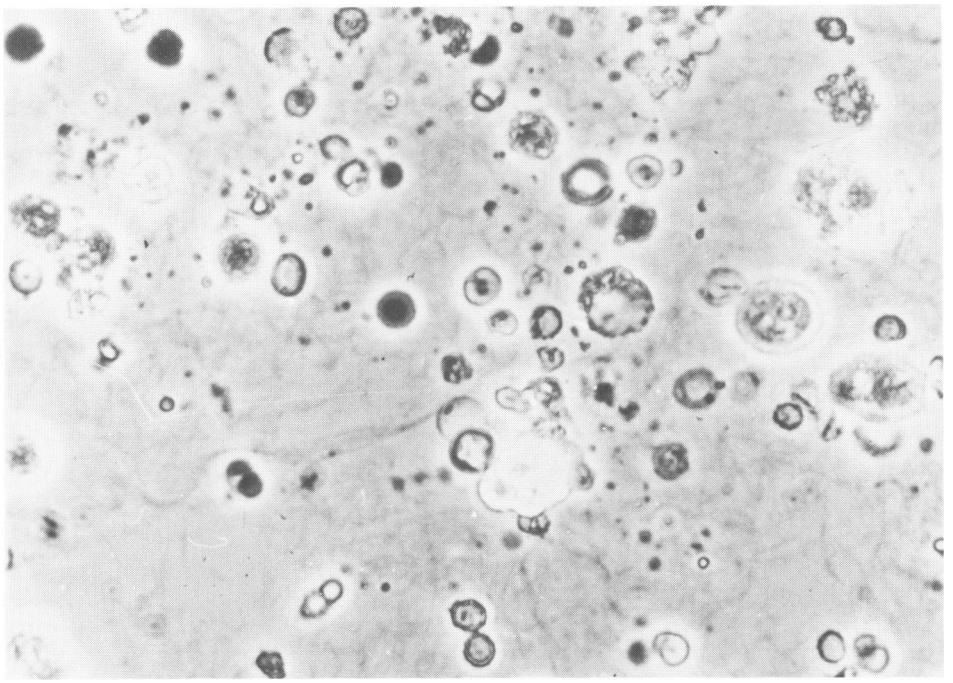

Figure 2 Great variation in size and shape of red blood cells in the urine in a patient with glomerulonephritis. This appearance is typical of glomerulonephritis. In other causes of haematuria such as, renal carcinoma and calculus, red cells are uniform in size and shape.

of patients, justifies making an accurate histological diagnosis.

There is less direct evidence that mesangial IgA nephropathy may be a frequent cause of hypertension in the United Kingdom. The study from St Mary's Hospital showed a strong association between HLA BW35 and microscopic haematuria in a large Hypertension Clinic. There is a clear association between HLA BW35 and mesangial IgA nephropathy (Macdonald *et al.*, 1976; 1980; Noel *et al.*, 1978), and because of this, Mowbray and colleagues (1980) infer that mesangial IgA nephropathy is the cause of microscopic haematuria in patients in their Hypertension Clinic. As in the Singapore Study (Pwee *et al.*, 1978), the study at St Mary's Hospital showed that the presence of microscopic haematuria identified a poor prognostic category. The only patients in their clinic with a raised blood urea were those with microscopic haematuria and presumed mesangial IgA nephropathy. This is in keeping with our own experience, namely that patients with benign hypertension in whom underlying renal disease has been rigorously excluded do show impairment of renal function.

While mesangial IgA nephropathy is probably the lesion most frequently overlooked as a cause of hypertension, 60% of all patients with glomerulonephritis have a raised blood pressure (Kincaid-Smith, 1981). This ranges from 30% in patients with milder forms of glomerulonephritis to 80% in the more severe forms, such as diffuse crescentic glomerulonephritis. It is particularly important to recognise the more active and progressive forms of glomerulonephritis, because it is in such patients that major advances in treatment of glomerulonephritis have occurred (d'Apice & Kincaid-Smith, 1979; Glassock, 1978; Kincaid-Smith, 1979a; 1980b; Kincaid-Smith & d'Apice, 1978).

(b) *Vascular lesions in glomerulonephritis preceding the development of hypertension*

Lesions in arterioles and interlobular arteries which resemble those seen in hypertension are present in 82% of patients with glomerulonephritis before hypertension develops. Between 44% and 93% of biopsies from normotensive patients with glomerulonephritis under the age of 40 years show arterial and arteriolar lesions (Kincaid-Smith, 1975c). These arteriolar and arterial lesions could cause hypertension in glomerulonephritis by causing ischaemia and an increase in renin release (Kincaid-Smith, 1977).

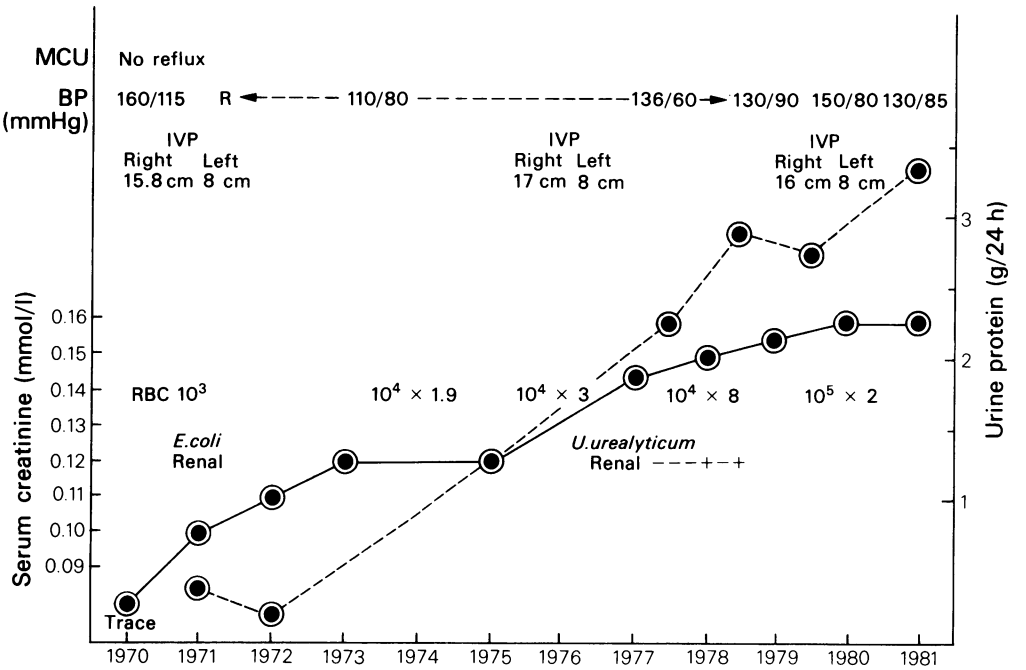

Figure 3 Course in a 27 year old woman with unilateral reflex type scarring in the left kidney. The graph illustrates steady deterioration in renal function (—— serum creatinine), accompanying increasing proteinuria (---- urinary protein). Urinary red cells also increased (RBC = red cells per ml of urine). Over the 11 years included in the graph, hypertension was carefully controlled. Only one *E. coli* infection was documented among monthly MSUs but ureaplasma was detected on several occasions between 1977 and 1979 in needle aspiration specimens from the bladder. Both the *E. coli* and the unreaplasma infections were renal.

(c) *Reflux nephropathy*

Chronic atrophic pyelonephritis, the classic form of scarring which accompanies childhood infection and vesicoureteric reflux (Hodson & Edwards, 1960), is one of the commonest underlying renal lesions in patients with malignant hypertension (Kincaid-Smith *et al.*, 1958).

Reflux nephropathy is probably not quite as frequent in the community as glomeruloneophritis, but it is not a rare disease and appears to be present in between 0.3% and 0.7% of the community, on the basis of radiographs carried out on patients with bacteriuria detected in population screening studies (Kincaid-Smith, 1965; Savage, 1975).

While most coarse parenchymal scars in reflux nephropathy develop during childhood, progression to end stage renal failure is usually due to a glomerular lesion (Kincaid-Smith, 1973a, 1975d, 1979b). Glomerular lesions may develop in an unscarred kidney and may be associated with progressive deterioration in renal function. Such patients usually progress to end stage renal failure over 10–15 years (Figure 3). Proteinuria is the most important prognostic factor in adults with reflux nephropathy (Kincaid-Smith & Becker, 1979).

While most patients with reflux nephropathy and hypertension have clearly demonstrable radiographic scarring, not all do. In a series of adults in whom no previous reflux type scarring have been recognized, biopsies revealed histological lesions suggestive of reflux nephropathy, and subsequent voiding cystograms revealed reflux (Kincaid-Smith, 1979b).

Early recognition of reflux nephropathy in children with hypertension is important because it permits appropriate control of infection and may prevent further scar formation. It is also important to recognize reflux nephropathy in the adult because of the poor prognostic implications of proteinuria in such patients even when scarring is confined to one kidney (Figure 3) (Kincaid-Smith, 1979b).

The role of vascular lesions in causing hypertension in reflex nephropathy remains uncertain. The proposal that vascular lesions, by causing renal ischaemia (Kincaid-Smith, 1955), may cause angiotensin dependent hypertension in reflux nephropathy, has gained some support from recent observations. Savage and colleagues (1978) found an inappropriate

degree of renin elevation in children with reflux nephropathy. Poutasse and colleagues (1978) reported cure of hypertension following removal of segmental scarred areas which were shown to be producing high renin levels in branches of the renal vein. In the experimental model of reflux nephropathy in the pig (Hodson *et al.*, 1975) only those pigs which developed hypertension were shown to have lesions in interlobular and arcuate arteries similar to those described in man in association with hypertension (Kincaid-Smith, 1955; Kincaid-Smith & Hodson, 1979).

(d) *Analgesic nephropathy*

The typical form of renal papillary necrosis which results from excessive use of over the counter analgesics is associated with hypertension in 70% of cases in Australia (Nanra *et al.*, 1978).

European studies have shown a much lower incidence of hypertension of only 36–37% (Bengtsson, 1962; Hultengren, 1961).

A diagnosis of renal papillary necrosis can usually be based on radiographic findings, however necrotic papillae may remain attached, the so-called necrosis *in situ* lesion (Fairley & Kincaid-Smith, 1968), and in such cases the diagnosis may be missed.

Renal biopsy in such cases shows the cortical lesions of obstructive atrophy (Kincaid-Smith, 1967) sometimes called chronic interstitial nephritis (Davson & Langley, 1944; Knutsen *et al.*, 1952; Lindeneg *et al.*, 1959; Schourup, 1957; Spühler & Zollinger, 1953).

In hypertensive patients in whom the lesions of papillary necrosis are not apparent on radiographic studies, deterioration of renal function may be wrongly attributed to so-called 'benign nephrosclerosis' because of failure to recognize renal papilary necrosis (Kincaid-Smith, 1975e).

(e) *Renal artery stenosis*

Many papers which discuss renal hypertension address themselves almost exclusively to the question of renal artery stenosis. In our studies, renal artery stenosis has always been relatively uncommon compared with glomerulonephritis (Table 1). Failure to recognize the group of patients with glomerulonephritis and microscopic haematuria may account for the discrepancy between our study and others (Table 2).

Renal artery stenosis is more frequent in patients with more severe grades of hypertension (Davis *et al.*, 1979). Arteriography has certainly led to detection of renal artery stenosis in a higher percentage of cases, than was recognized in previous autopsy series (Kincaid-Smith *et al.*, 1958). Renal artery stenosis is much more common in whites than in blacks and it may be less frequent in some countries such as the United Kingdom (Swales, 1976). The clearcut association between atheromatous renal artery stenosis and analgesic nephropathy (Table 5), may alter the geographic distribution of renal artery stenosis. There is little doubt about wide variations in the prevalence of analgesic nephropathy in different geographic areas (Kincaid-Smith, 1978a, b).

The renal parenchymal lesions seen in renal artery stenosis, like those in other ischameic lesions, are those of partial infarction or crowding of glomeruli and atrophy of tubules.

Although on the basis of experimental data the kidney distal to a renal artery stenosis should be protected from hypertensive vascular lesions, the vessel lesions in man appear more complex. Quite marked changes including thickening of the vessel wall may be seen in arteries and arterioles distal to a renal artery stenosis (Kincaid-Smith, 1966).

(f) *Scleroderma*

Scleroderma may be associated with a fulminating form of malignant hypertension which was previously regarded as invariably fatal.

Recently various methods of treatment have been successful in arresting the acute renal vascular lesions of scleroderma and stabilizing or even achieving an improvement in renal function (Wasner *et al.*, 1978; Simon *et al.*, 1979; Richmond *et al.*, 1980).

(g) *Hypertension and renal parenchymal lesions in patients with hypertension in pregnancy*

Approximately 40% of patients referred to our department with hypertension and proteinuria as a complication of pregnancy have an underlying glomerulonephritis (Kincaid-Smith & Fairley, 1976). Clearly this represents a selected group of patients.

Table 5 Atheromatous renal artery stenosis in women under 50 years

Age (years)	*229 consecutive arteriograms in women with hypertension*		*37 consecutive arteriograms in women with hypertension and analgesic nephropathy*	
10–49	229	25 (10.9%)	20	8 (40%)

Those with severe pre-eclampsia or proteinuria in early pregnancy tend to be referred.

In patients with pre-eclampsia without any associated glomerulonephritis, well defined glomerular lesions develop during pregnancy and may resolve following pregnancy (Kincaid-Smith, 1973b, 1975b). These lesions may be mistaken for those of glomerulonephritis particularly as immunoglobulins may be deposited in the glomerulus during pregnancy. The name 'pregnancy induced nephropathy' has recently been suggested for these glomerular lesions (Nochy *et al.*, 1980).

Acute vascular lesions may also develop during pregnancy in patients with pregnancy induced hypertension (Kincaid-Smith & Fairley, 1976). In both the glomerular and the vascular lesions associated with pregnancy, there is evidence of participation of coagulation and fibrin deposition (Kincaid-Smith, 1975b).

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