RENAL PARENCHYMAL DISEASE IN SINGAPORE
A RENAL BIOPSY STUDY

By Beatrice T. M. Chen, B. S. Ooi and K. K. Tan

SYNOPSIS

Five hundred and forty-seven renal biopsies obtained over a five year period in Medical Unit II, Outram Road General Hospital, Singapore were analysed. The majority of the patients were males between the ages of sixteen and twenty as a result of special referral of young men found to have asymptomatic haematuria and proteinuria prior to compulsory military service. There was no patient selection in the remaining patients.

The clinical syndromes for which renal biopsy was performed were: asymptomatic haematuria (145 patients), the nephrotic syndrome (115), asymptomatic proteinuria (103), young hypertensives (54), systemic lupus erythematosus (47), the acute nephritic syndrome (18), Henoch Schonlein syndrome (16), leptospirosis (14), chronic nephritis (12) and miscellaneous conditions (23).

The relationship between the clinical syndromes and histological lesions was discussed. It was found that the pattern of renal parenchymal lesions as seen in the different clinical syndromes was similar to that reported in the Western literature but different from that found in India, Africa and Turkey.

INTRODUCTION

In 1954, Kark and Muehrcke first introduced the technique of performing renal biopsy in the prone position, using Franklin's modification of Vim Silverman's needle. Since then, it became increasingly evident that renal biopsy is a safe and vital procedure in the investigation of renal disease. Renal biopsy and the different methods of examining the tissue obtained (light microscopy, electron microscopy and immunofluorescence study) are chiefly responsible for the explosive expansion in the knowledge of nephrology in the past twenty years.

Renal histological pattern in the various clinical entities has been fairly consistent in reports from America and Europe (Iverson and Brun, 1951; Parrish and Howe, 1955; Pollak *et al*, 1957; Schriener, 1963; Heptinstall, 1966; Ogg *et al*, 1968; Sharpstone *et al*, 1969; Hamburger, 1969). On the other hand, reports from Africa have shown that the commonest cause of the nephrotic syndrome is Plasmodium infection (Gilles and Hendrick, 1963; Kibukamusoke, 1966; Kibukamusoke *et al*, 1967; Willis, 1968); while in India, renal amyloidosis was found to be an important cause of the nephrotic syndrome (Sarin and Sarin, 1960; Mathur and Srivastava, 1960). In Turkey, renal amyloidosis associating with Mediterranean fever was found in 30 per cent of renal biopsies (Sökmen and Özdemir, 1967).

Since 1967, renal biopsy has been a routine procedure in the investigation of renal disease in Medical Unit II, University of Singapore Department of Medicine, Outram Road General Hospital, Singapore (Chen, 1971). In the ensuing five years, successful renal biopsies were obtained in five hundred and forty-seven patients. We report here an analysis of the results of these biopsies as examined under light microscopy, and attempt to describe the pattern of renal parenchymal lesions in the different clinical syndromes encountered in this country.

PATIENTS AND METHODS

The patients in Medical Unit II were studied. Among other investigations to assess their renal functional status, renal biopsy was performed in each patient. The method of Kark and Muehrcke (1954) with slight modification (Chen, 1971) was used. The tissue obtained was fixed immediately in formalin solution, sectioned at four to five micron and stained with haematoxylin and eosin, periodic-acid Schiff, and silver methenamine methods. Special staining methods were used when indicated.

Medical Unit II, University of Singapore Department of Medicine and Department of Pathology, Outram Road General Hospital.

BEATRICE T. M. CHEN, M.B., F.R.A.C.P., Formerly Senior Registrar in Medicine.

B. S. OOI, M.B., M.R.A.C.P., Formerly Senior Lecturer in Medicine.

K. K. TAN, M.B., B.S., M.R.C.Path., M.R.C.P.A., F.C.A.P., Formerly Senior Pathologist.

Criteria for Diagnosis

The criteria for histological diagnosis according to that of Heptinstall (1966), Ogg *et al* (1968), and White *et al* (1970) had been described previously (Ooi *et al*, 1970; Chen *et al*, 1973). In short, they are as follows:

1. Lipoid nephrosis (minimal change type) in which the glomeruli are normal on light microscopy, with no increase in cellularity or deposition of basement membrane like fibrils in the mesangium. A minority of patients show focal glomerular sclerosis and others, tubular atrophy.
2. Diffuse proliferative glomerulonephritis, with four subtypes:
   (a) Acute exudative type in which the glomerular tufts are swollen with occlusion of capillary loops. There is proliferation of endothelial and mesangial cells as well as invasion by polymorphonuclear leucocytes. The capillary walls are normal.
   (b) Lobular stalk thickening in which there is mesangial proliferation without endothelial swelling or polymorphonuclear exudation. Lobular stalks are thickened owing to deposition of basement membrane like material. Epithelial proliferation and capillary adhesion are inconspicuous.
   (c) Crescent formation in which mesangial proliferation is associated with epithelial proliferation with crescent formation in more than fifty per cent of glomeruli seen, causing partial or rarely, complete obliteration of capsular space.
   (d) Membranoproliferative glomerulonephritis in which there is moderate to severe mesangial proliferation and deposition of basement membrane like material in the mesangium as well as in the basement membrane. These extensive changes produce a lobulated appearance of the glomerular tufts. In silver impregnated sections, the basement membrane appears as two thin black lines giving it a "double contour" appearance while the mesangial deposits are poorly argyrophilic.
3. Focal glomerulonephritis in which there is focal and segmental cellular proliferation as well as necrosis.
4. Membranous glomerulonephritis in which there is diffuse basement membrane thickening. Silver methenamine preparation shows "spiky" projections on the outer aspects of the basement membrane. Cellular proliferation is absent. This has also been variously described as membranous nephropathy (Black *et al*, 1970) and epimembranous nephropathy (White *et al*, 1970).
5. Chronic nephritis in which there is hyalinisation of nearly all glomerular tufts seen, with accompanying tubular, interstitial and vascular changes.
6. Chronic pyelonephritis in which there is extensive infiltration of the interstitium with chronic inflammatory cells, tubular damage and atrophy, "tubular thyroidisation" and varying degree of glomerular damage and periglomerular fibrosis.
7. Acute tubular necrosis in which the glomeruli appear relatively normal while the tubules are dilated and the tubular cells show varying degree of necrosis and regeneration with low basophilic cells and dense nuclei. Pigmented casts are often seen in the lumina.
8. Lupus nephritis in which the glomeruli showed irregular cellular proliferation with underlying necrosis and uneven basement membrane thickening giving the appearance of "wire-looping." Hyaline thrombi and haematoxylin bodies may or may not be present. In some cases, the basement membrane thickening may be diffuse with very little cellular proliferation and underlying necrosis so that it may be difficult to distinguish it from membranous glomerulonephritis.

The clinical diagnosis of the different disease entities was based on the usual criteria. Chronic nephritis was diagnosed when a patient had hypertension with abnormal urinalysis and bilaterally small kidneys on intravenous pyelographic or arteriographic study. Essential hypertension was diagnosed when renal histology was normal or showed hypertensive vascular changes only.

RESULTS AND DISCUSSION

A total of five hundred and forty-seven biopsies were included in this study. Table I shows the clinical data in these patients. There were three hundred and seventy-three males and one hundred and seventy-four females, and the majority of the patients were in the sixteen to twenty-nine age group. One hundred and forty-five patients were investigated because of asymptomatic haematuria, one hundred and fifteen because of the nephrotic syndrome, and one hundred and three because of

TABLE I

CLINICAL DATA IN 547 RENAL BIOPSIES

Sex:	Males	373	Females	174
Age:	10—15			71
	16—19			196
	20—29			131
	30—39			79
	40—49			39
	50—59			27
	Over 60			4
Clinical Diagnosis:				
Asymptomatic haematuria				145
The nephrotic syndrome				115
Asymptomatic proteinuria				103
Hypertension				54
Systemic lupus erythematosus				47
Acute nephritic syndrome				18
Henoch-Schonlein syndrome				16
Leptospirosis				14
Chronic nephritis				12
Miscellaneous				23

TABLE II

145 PATIENTS WITH ASYMPTOMATIC HAEMATURIA

Sex:	Males	110	Females	35
Age:	10—15			9
	16—19			72
	20—29			41
	30—39			11
	40—49			6
	50—59			6
Renal Histology:				
Optically normal				47
Diffuse proliferative glomerulonephritis				47
With lobular stalk thickening			24	
With endothelial proliferation			23	
Focal glomerulonephritis				40
Chronic nephritis				5
Chronic pyelonephritis				2
Malarial nephritis				2
Membranous glomerulonephritis				1
Membranoproliferative glomerulonephritis				1

asymptomatic proteinuria. The other clinical diagnoses and indications for renal biopsy were: young hypertensives (fifty-four patients), systemic lupus erythematosus (forty-seven), the acute nephritic syndrome (eighteen), Henoch-Schonlein syndrome (sixteen), leptospirosis (fourteen), chronic nephritis (twelve) and miscellaneous conditions (twenty-three).

Apart from a group of young adult males who were discovered to have proteinuria and/or haematuria on routine medical examination prior to National Service and were specifically referred to this unit for investigation, there was no bias in patient selection. This group of young men accounted for the large number of males in the sixteen to nineteen age group.

Asymptomatic Haematuria

Of the one hundred and forty-five patients with asymptomatic haematuria (Table II), one hundred and ten were males and the majority of this group of patients was between the ages of sixteen and nineteen.

Forty-seven renal biopsy specimens were normal under light microscopy. Of the remaining ninety-eight patients, forty-seven had diffuse proliferative glomerulonephritis, half of whom had lobular stalk thickening and the other half endothelial proliferation. Forty patients had idiopathic focal glomerulonephritis, and two had severe focal glomerulonephritis consistent with malarial nephritis. They were found to have haematuria after an attack of malaria.

In 1926, Baehr first described the occurrence of frank haematuria in young adults associating with streptococcal infection. In 1960, Ross reported the finding of focal nephritis in nine children with recurrent frank haematuria. Subsequently many reports on recurrent haematuria in children (Bodian *et al*, 1965; Singer *et al*, 1968; Arneil *et al*, 1969; Glasgow *et al*, 1970) and in adults (Ferris *et al*, 1967; Buckholder *et al*, 1969; Rapoport *et al*, 1970; Chen *et al*, 1972) appeared in the literature. Eighty patients in the present study have been the subject of a previous report (Chen *et al*, 1972). In this unselected group of patients reported, it was found that in patients without a documented history of acute nephritis, approximately equal numbers had normal renal histology under light microscopy, focal glomerulonephritis and diffuse proliferative glomerelonephritis. The patients with diffuse glomerulonephritis also showed a female preponderance, had a higher prevalence of frank haematuria, raised sedimentation rate and raised anti-streptolysin O titre.

In the present study, there was a significantly larger number of patients above the age of twenty with abnormal histology as compared with those below twenty ($x^2=10{\cdot}9$, $p<0{\cdot}01$). It is therefore conceivable that subtle changes not seen under light microscopy were present in the younger patients and that with the passage of time, overt histological lesions would eventually appear. On the other hand, the prevalence of focal and diffuse proliferative glomerulonephritis was roughly the same in the below twenty and above twenty age

group. This is in contrast to the findings of Joekes *et al* (1962), Ferris *et al*, (1967) and Buckholder *et al* (1969), who found that focal glomerulonephritis was the commonest histological lesion in children and young adults with recurrent haematuria. The number of patients with abnormal renal histology excreting more than 500 mg. urinary protein daily was also found to be significantly higher when compared with that of patients with normal renal histology ($x^2 = 8{\cdot}9$, p 0·01). Thus in patients with asymptomatic haematuria, the presence of raised sedimentation rate and abnormal quantity of urinary protein excretion indicate underlying renal parenchymal disease. A renal biopsy should therefore be done in such patients and appropriate management instituted.

The Nephrotic Syndrome

One hundred and thirty-one patients in the biopsied series had the nephrotic syndrome and in one hundred and fifteen of them, it was due to primary glomerular disease (Table III).

TABLE III

115 PATIENTS WITH THE NEPHROTIC SYNDROME DUE TO PRIMARY GLOMERULAR DISEASE

Sex:	Males	66	Females	49	
Age:	10—15			36	
	16—19			16	
	20—29			31	
	30—39			12	
	40—49			11	
	50—59			7	
	Over 60			2	
Renal Histology:					
Lipoid nephrosis					45
Diffuse proliferative glomerulonephritis					36
With endothelial proliferation				16	
With lobular stalk thickening				19	
With crescent formation				1	
Focal glomerulonephritis					11
Membranous glomerulonephritis					9
Chronic nephritis					8
Membranoproliferative glomerulonephritis					6

Lipoid nephrosis was found to be the commonest primary glomerular disease causing the nephrotic syndrome, followed by diffuse proliferative glomerulonephritis. The other causes, in order of frequency were: focal glomerulonephritis, chronic nephritis, and membranous glomerulonephritis.

There was a slight male preponderance in this group of patients taken as a whole but if the patients were divided by age into those below the age of fifteen and those above, there was a definite male preponderance in the younger age group (Table IV). Lipoid nephrosis was also observed to become less prevalent as the cause of the nephrotic syndrome with advancing age, while diffuse proliferative glomerulonephritis, focal glomerulonephritis and membranous glomerulonephritis assumed a more important role in the causation of this condition. Our results are in agreement with those reported by Ogg *et al* (1968), Sharpstone *et al* (1969), and White *et al* (1970).

Eleven patients in this series had focal glomerulonephritis with no evidence of systemic lupus erythematosus, Henoch Schonlein purpura and the Goodpasture's syndrome. Although a well recognised cause of recurrent haematuria in the young (Heptinstall and Joekes, 1959; Ross, 1960), "idiopathic" focal glomerulonephritis as a cause of the nephrotic syndrome had not been emphasised in reports from the West.

Asymptomatic Proteinuria

One hundred and three patients were investigated because of asymptomatic proteinuria (Table V). In contrast to the patients with asymptomatic haematuria, nearly seventy-five per cent of the patients in this group had normal renal histology. Sixteen patients had focal glomerulonephritis, ten had diffuse glomerulonephritis and two, chronic nephritis.

In most of the patients in this group, especially those between the ages of sixteen and twenty, orthostatic proteinuria test described previously (Chen *et al*, 1971) was performed. According to

TABLE IV

SEX AND AGE INCIDENCE OF THE NEPHROTIC SYNDROME

Age	Lipoid nephrosis		Other Lesions		Total	
	Male	Female	Male	Female	Male	Female
10—15	12	5	13	6	25	11
Over 16	15	13	26	25	41	38
TOTAL	27	18	39	31	66	49

TABLE V

103 PATIENTS WITH ASYMPTOMATIC PROTEINURIA

Sex:	Males	93	Females	10
Age:	10—15			5
	16—19			82
	20—29			10
	30—39			3
	40—49			3
Renal Histology:				
Optically normal				75
Focal glomerulonephritis				16
Diffuse proliferative glomerulonephritis				10
With endothelial proliferation			6	
With lobular stalk thickening			4	
Chronic nephritis				2

the results of the orthostatic proteinuria test, the patients were divided into two groups: those with positive orthostatic test and normal urinalysis, and those with persistent proteinuria with or without cylindriuria.

Forty-three patients were found to have orthostatic proteinuria alone and they were all under the age of twenty. Renal histology was normal under light microscopy. The prognosis of this condition is believed to be good (Thompson *et al*, 1970). Our findings are in accordance with the findings of Wolman (1945) who found that the incidence of orthostatic proteinuria was highest between the ages of fourteen and eighteen, and was hardly found in subjects above the age of thirty.

Sixty patients had persistent proteinuria of whom thirty-two had normal renal histology. Although slightly more patients under twenty years old had normal renal histology, the difference was of no statistical significance. The results of this study showed a lower prevalence of abnormal renal histology in cases of proteinuria when compared with the studies of Pollak *et al* (1958) and Muth (1965). Pollak's group found only one patient with normal renal histology in their report on nineteen patients aged thirteen to forty-nine. However, cylindriuria and haematuria were found in many of their patients. Muth (1965), on the other hand, showed that in fifty-two patients aged sixteen to thirty-nine with mild intermittent proteinuria of less than 500 mg. per day, thirty-five had abnormal renal histology.

Hypertension

Seventy-six patients in this series had hypertension. However, only fifty-four patients were biopsied because of hypertension alone. These were young hypertensives in whom renal biopsy was performed when all other investigations to elucidate the aetiology showed normal results (Table VI). There were forty-six males and eight females, and the majority of them were aged forty or less. Six patients were between the ages of forty-one and forty-five but they were all found to have hypertension when they were under forty years old. Normal renal histology with or without hypertensive vascular changes was present in thirty-eight patients. Eight patients were found to have proliferative glomerulonephritis, either focal or diffuse; four patients had chronic pyelonephritis; three had chronic nephritis and one membranous glomerulonephritis. Of the remaining twenty-two patients, eight had associating nephrotic syndrome, seven had recurrent haematuria, three had systemic lupus erythematosus and two, the Henoch Schonlein syndrome. The use of renal biopsy in the investigation of young hypertensives has helped to discover more cases of secondary hypertension than if no renal biopsy was performed (Ooi *et al*, 1970).

TABLE VI

54 PATIENTS WITH HYPERTENSION

Sex:	Males	46	Females	8
Age:	10—15			0
	16—19			0
	20—29			12
	30—39			32
	40—45			10
	Over 46			0
Renal Histology:				
Normal				17
Hypertensive vascular chnages only				21
Focal glomerulonephritis				5
Chronic pyelonephritis				4
Chronic nephritis				3
Diffuse proliferative glomerulonephritis				3
Membranous glomerulonephritis				1

If the patients were subdivided into two groups: those above and those below the age of thirty, it was found that the incidence of secondary hypertension was significantly higher in patients below the age of thirty (Table VII). This is in agreement with the findings of Platt (1948) who found seventy-five per cent of cases of secondary hypertension in sixty-four patients, all but one of whom were below the age of thirty-five.

Renovascular hypertension was found to constitute nine per cent of the causes of young hypertensives reported from this unit previously (Ooi

TABLE VII

RELATIONSHIP BETWEEN AGE AND RENAL HISTOLOGY IN HYPERTENSIVES

Age	Normal Histology & Hypertensive Changes	Abnormal Histology	Total
Under 30	6	23	29
Over 30	33	13	46

$x^2 = 15{\cdot}1$ $p < 0{\cdot}01$

et al, 1970). Only two of these patients were subjected to renal biopsy. No glomerular lesion was found in either one of them. Both patients had primary arteritis of the aorta, which has been found to be an important cause of renovascular hypertension in Singapore (Ooi *et al*, 1971).

Systemic Lupus Erythematosus

There were forty-seven patients in this category, and the majority of them were females between the ages of twenty and forty (Table VIII). Only ten patients had normal urinalysis at the time of renal biopsy, and in five of them the renal histology was focal glomerulonephritis. One patient had cylindriuria alone and she had focal glomerulonephritis. The remaining thirty-five patients had proteinuria with or without haematuria. Sixteen of these had the nephrotic syndrome. All but two of the patients with significant proteinuria had abnormal renal histology and neither of them had the nephrotic syndrome. There was a higher prevalence of diminished glomerular filtration rate as evidenced by reduced creatinine clearance and or raised blood urea, in patients with the nephrotic syndrome.

TABLE VIII

47 PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS

Sex:	Males	5 Females	42
Age:	10—15		3
	16—19		6
	20—29		19
	30—39		9
	40—49		7
	50—59		3
	Over 60		0
Renal Histology:			
Normal			7
Focal glomerulonephritis			21
Lupus nephritis			19

The incidence of clinical renal involvement was seventy-eight per cent in this series and this was higher than reports from Western literature (Jesser *et al*, 1953; Harvey *et al*, 1954; Soffer *et al*, 1961; Rothfield *et al*, 1963). If histological involvement were included, the incidence of renal lesions in this series was even higher (eighty-five per cent).

Although severe renal involvement is indicative of poor prognosis and many patients with severe histological damage died of chronic renal failure (Muehrcke *et al*, 1957; Soffer *et al*, 1962; Rothfield *et al*, 1963), the majority of the patients with systemic lupus erythematosus died of infection, usually of the lungs (Harvey *et al*, 1954; Heptinstall, 1966). Among the patients with systemic lupus erythematosus included in this series, five have died but only one of these deaths was renal. The other causes of death were: meningitis, acute pancreatitis, bronchopneumonia and septicaemia with acute tubular necrosis. Many patients improved with steroid therapy (Pollak *et al*, 1965) and some, with cyclophosphamide (Cameron *et al*, 1970).

The Acute Nephritic Syndrome

Eighteen patients were biopsied because of the acute nephritic syndrome with oedema, oliguria, haematuria and hypertension (Table IX). There were equal number of males and females in this small series. This is in sharp contrast to most series reported in which there was a definite male preponderance (Lyttle and Rosenberg, 1929; Ellis *et al*, 1942; Rudebeck, 1946). Twelve of the patients were under fifteen years old. In ten of

TABLE IX

18 PATIENTS WITH THE ACUTE NEPHRITIC SYNDROME

Sex:	Males	9 Females	9
Age:	10—15		12
	16—19		5
	20—29		0
	30—39		0
	40—49		1
	Over 50		0
Renal Histology:			
Normal			2
Diffuse proliferative glomerulonephritis			12
Acute exudative type		10	
With lobular stalk thickening		2	
Focal glomerulonephritis			3
Chronic nephritis			1

these, the renal lesion was that of the acute exudative type most commonly seen after streptococcal infection. A history of fever and sore-throat was obtained in all but one of these children. This child, however, had chronic skin infection of the lower limbs.

It is a well known fact that the acute nephritic syndrome can occur in association with systemic diseases such as systemic lupus erythematosus and the Henoch Schonlein syndrome. However, post-streptococcal glomerulonephritis was found to be the commonest cause of this syndrome in children. This was also borne out by a retrospective study of patients in a paediatric unit in Singapore (Paul, 1963) which showed that beta-haemolytic streptococci was cultured from the throat swabs of nearly thirty per cent of their children with acute nephritis. Thus in Singapore, as in other countries in the temperate climate, post-streptococcal glomerulonephritis is still the commonest cause of the acute nephritic syndrome, especially in the younger age group.

Henoch-Schonlein Syndrome

There were sixteen patients with the Henoch-Schonlein syndrome in this study (Table X). A marked male preponderance was present and all the patients were less than thirty years old. At the time of biopsy, urinary abnormalities were present in all but one patient. Haematuria and proteinuria were present in thirteen patients while the remaining two patients had either isolated proteinuria or haematuria. Abnormal renal histology was present in all biopsies and in the majority of them, the lesion was that of focal glomerulonephritis indistinguishable from that seen in recurrent haematuria, the nephrotic syndrome or systemic lupus erythematosus. Three patients had diffuse proliferative glomerulonephritis involving mainly the mesangium and epithelial crescents were found in one of them.

TABLE X

16 PATIENTS WITH HENOCH-SCHONLEIN SYNDROME

Sex:	Males	14	Females	2
Age:	10—15			5
	16—19			6
	20—29			5
	Over 30			0
Renal Histology:				
Normal				0
Focal glomerulonephritis				13
Diffuse proliferative glomerulonephritis				3

All sixteen patients presented with typical rashes involving mainly the extensor surface of the lower limbs and buttocks. In eight patients, a history of fever with or without sore throat was present two to seventeen days before the first appearance of the rash. Two patients noted the occurrence of frank haematuria after ingestion of salicylates. In seven patients, no preceding history of infection or drug ingestion were obtainable. Alimentary symptoms were found to be more prevalent than joint symptoms (Table XI) and in two patients, the abdominal pain was severe enough to warrant laparotomy. Gastrointestinal bleeding in the form of bloody diarrhoea or melaena was present in five patients. Arthralgia was present in three patients only and was never severe. Two patients presented with the nephrotic syndrome and one patient developed ankle oedema four years after he was first seen. Two patients developed hypertension four and eleven years after diagnosis. The former patient died of chronic renal failure one and a half years later and the latter showed persistence of active renal disease.

TABLE XI

SYMPTOMS AND SIGNS OF 16 PATIENTS WITH HENOCH-SCHONLEIN SYNDROME

Typical rash		16
Alimentary symptoms		14
Abdominal pain	10	
Gastrointestinal bleeding	5	
Frank haematuria		6
Arthralgia		3
The nephrotic syndrome		2

Henoch-Schonlein syndrome is a disease found mainly in childhood and the incidence of urinary abnormalities ranged from four per cent (Oliver and Barnett, 1955) to forty per cent (Wedgewood and Klaus, 1955). Renal involvement was found to be more common in older than in younger children (Burke *et al*, 1960; Allen *et al*, 1960; Meadow *et al*, 1972), although on the whole the prognosis is good (Allen *et al*, 1960).

Renal involvement, when present in adults, is usually more serious than in children (Levitt and Burbank, 1953; McCombs *et al*, 1965; Cream *et al*, 1970; Ballard *et al*, 1970). Ballard *et al* (1970) reported fourteen patients aged twenty-nine to eighty-nine with abnormal urinalysis. All fourteen patients had proteinuria and haematuria, with seven having the nephrotic syndrome. Out of five patients with severe azotaemia, four

died of renal failure. Renal histology was available in seven patients and four of them had diffuse proliferative glomerulonephritis while the remaining three had focal glomerulonephritis. Three of the former died and post-mortem renal histology showed chronic nephritic changes. Cream *et al* (1970) reviewed seventy-seven adult patients presenting with Henoch-Schonlein purpura at an average age of forty-three and found abnormal urinalysis in thirty-eight. Nineteen of these presented with the acute nephritic syndrome and all of them had haematuria and heavy proteinuria. Five of these patients also had transient nephrotic syndrome. Three patients had progressive renal failure and in one of them the renal histology showed severe focal glomerulonephritis.

The patients in our study were not strictly comparable to those reported by Ballard *et al* (1970) and Cream *et al* (1970). Our patients were younger and this probably explains the relatively better outcome in our patients. Apart from one patient who died of chronic renal failure and another who had evidence of persistent active renal disease, all the patients in this series remained well after at least two years follow-up. The nephrotic syndrome, as pointed out by Ballard *et al* (1970), need not be considered ominous, as one of our patients, and four of theirs recovered completely. Both focal and diffuse proliferative glomerulonephritis may be present in patients with the nephrotic syndrome and this is in agreement with the findings of Ballard *et al* (1970). However, it is generally believed that the type of lesion is a good index of prognosis (Ballard *et al*, 1970) and diffuse proliferative glomerulonephritis with crescents is usually associated with a fatal outcome (Levitt *et al*, 1953; Norkin and Weiner, 1960).

Leptospirosis

Leptospirosis is one of the commonest medical causes of acute renal failure in Singapore. Renal biopsy was done in fourteen patients, eight in the acute phase, five at six months to two years after the acute attack, and in one patient, renal biopsy was done both in the acute phase and six months later (Table XII). There was a male preponderance and the patients were mainly young adults between the ages of twenty and forty.

The diagnosis of leptospirosis was based on typical clinical features and a fourfold rise in antibody titre determined by the sensitised erythrocyte lysis test (Chang *et al*, 1957). A good correlation between the degree of renal dysfunction and renal tissue damage had been found (Ooi *et al*, 1972). In cases with only a mild degree of renal insufficiency, renal biopsy done in the acute phase showed normal histology. On the other hand, in patients with very profound reduction of renal function, severe changes in the tubules with desquamation of the epithelium into the lumina was found. Proteinaceous casts, epithelial casts, red cell casts and haem casts were also found. Between these two extremes of a spectrum of histological changes, dilatation and flattening of both the proximal and distal tubules were present.

TABLE XII

14 PATIENTS WITH LEPTOSPIROSIS

Sex:	Males	12	Females	2
Age:	10—15			0
	16—19			1
	20—29			4
	30—39			4
	40—49			0
	50—59			3
	Over 60			2
Renal Histology:				
Acute Phase:				9
Normal		5		
Acute tubular necrosis		4		
At follow-up:				6
All normal except for some interstitial fibrosis				

At follow-up, creatinine clearance returned to normal in all instances and renal histology showed essentially no or very minimal glomerular damage. In our series as well as that reported by Simpson *et al* (1967), a few patients had residual tubular dysfunction as evidenced by a defect in concentrating ability. This is in sharp contrast to renal failure due to other causes in whom a significant proportion were found to have reduced glomerular filtration rates (Finkerstaedt *et al*, 1956; Briggs *et al*, 1967).

Chronic Nephritis

Twelve patients were diagnosed as having chronic nephritis. All of them had mild anaemia, mild proteinuria and bilaterally small kidneys on intravenous pyelography, although their creatinine clearances were either normal or just below normal. Renal histology showed that only three of them had definite features of chronic nephritis. Four patients had normal renal histology of whom one also had hypertensive vascular changes. Four others had diffuse glomerulonephritis in one of whom crescent formation was present. This

patient presented with renal failure thought to be due to chronic nephritis and she died within three months of diagnosis.

Miscellaneous Conditions

Twenty-three patients were biopsied for various reasons: acute renal failure (three), chronic pyelonephritis (three), diabetic nephropathy (three), renovascular hypertension (two), scleroderma (two), toxaemia of pregnancy (two), polyarteritis nodosa (one), nonspecific arthritis (one), unexplained oedema (one) and Hansen's disease with proteinuria (one).

Two of the patients with acute renal failure had acute tubular necrosis while the third had the acute exudative type of diffuse proliferative glomerulonephritis. One of the patients with toxaemia of pregnancy was found to have focal glomerulonephritis, and a typical histology of preeclampsia was found in the other. Apart from the patient with Hansen's disease in whom renal amyloidosis was found, renal histology in the remaining patients was normal.

CONCLUSION

Although Singapore is situated in the tropics, the pattern of renal parenchymal disease as revealed by the present study does not differ significantly from that found in countries in the temperate zone. Until recently, malaria was endemic in Singapore, but unlike Africa, no cases of the nephrotic syndrome associating with malaria were found in the present series. In Turkey, unsuspected renal amyloidosis was found in more than thirty per cent of two hundred renal biopsies done by Sökmen and Özedemir (1967) and in half of these, familial Mediterranean fever was the apparent cause. Some Indian workers (Sarin and Sarin, 1960; Wahi *et al*, 1962) reported a high incidence of renal amyloidosis causing the nephrotic syndrome. In contrast, only one case of renal amyloidosis was found in the present series although tuberculosis and leprosy are still fairly prevalent in Singapore. However, since no systematic study has been carried out, we are unable to state the exact incidence of renal involvement in these patients.

REFERENCES

1. Allen, D.M., Diamond, L. K. and Howell, D.A.: "Anaphylactoid purpura in children (Schonlein-Henoch syndrome). Review with a follow-up of the renal complications." A.M.A. J. Dis. Child, 99, 833-854, 1960.
2. Arneil, G.C., Lam, C.N., McDonald, A.M. and McDonald, M.: "Recurrent haematuria in seventeen children." Brit. Med. J., 2, 233-235, 1969.
3. Baehr. G.: "A benign and curable form of haemorrhagic nephritis." J.A.M.A. 86,1001-1004, 1926.
4. Ballard, H.S., Esinger, R.P. and Gallo, G.: "Renal manifestations of the Henoch-Schonlein syndrome in adults." Amer. J. Med., 49, 328-335, 1970.
5. Black, D.A.K., Rose, G. and Brewer, D.B.: "Controlled trial of prednisone in adult patients with the nephrotic syndrome." Brit. Med. J., 3, 421-426, 1970.
6. Bodian, M., Black, J.A., Kobayashi, N., Lake, B.D. and Shuler, S.E.: "Recurrent haematuria in childhood." Quart. J. Med., 34, 359-382, 1965.
7. Briggs, J.D., Kennedy, A.C., Young, L.N., Luke, R.G. and Gray, M.: "Renal functions after acute tubular necrosis." Brit. Med. J., 3, 513-516, 1967.
8. Buckholder, G.R., Dotin, L.N., Thomason, W.B. and Beach, P.D.: "Unexplained haematuria—how extensive should the evaluation be." J. Amer. Med. Ass., 210, 1729-1733, 1969.
9. Burke, E.C., Mills, S.D. and Stickler, G.B.: "Nephritis associated with anaphylactoid purpura in childhood. Clinical observations and prognosis." Proc. Mayo. Clin., 35, 641-648, 1960.
10. Cameron, J.S., Boutton-Jones, M., Robinson, R. and Ogg, C.: "Treatment of lupus nephritis with cyclophosphamide." Lancet, 2, 846-849, 1970.
11. Chang, R.S., Smith, D.J.W., McComb, D.E., Sharp, C.F. and Ting, J.I.: "The use of erythrocyte sensitising substance in the diagnosis of leptospirosis II. The sensitised erythrocyte lysis test." Amer. J. Trop. Med. Hyg., 6, 101-107, 1957.
12. Chen, B.T.M.: "An analysis of 400 percutaneous renal biopsies." Sing. Med. J., 12, 166-169, 1971.
13. Chen, B.T.M., Ooi, B.S., Lim, C.H. and Khoo O.T.: "Asymptomatic proteinuria and haematuria in young adult males in Singapore." Proc. of 6th Singapore-Malaysia Cong. Med., 6, 60-65, 1971.
14. Chen, B.T.M., Ooi, B.S., Tan, K.K. and Khoo, O.T.: "Causes of recurrent haematuria." Quart. J. Med., 162, 141-148, 1972.
15. Chen, B.T.M., Ooi, B.S., Tan, K.K. and Khoo, O.T.: "Nephrotic syndrome in Singapore." J. Chron. Dis., 26, 237-242, 1973.
16. Cream, J.J., Gumpel, J.M. and Peachey, R.D.G.: "Schonlein Henoch purpura in the adults." Quart. J. Med., 39, 461-484, 1970.
17. Ellis, A.: "Natural history of Bright's disease. Clinical, histological and experimental observations." Lancet, 1, 1-7; 34-36; 72-76, 1942.
18. Ferris, T.F., Gorden, P., Kashgarian, M. and Epstein, F.H.: "Recurrent haematuria and focal nephritis." N. Eng. J. Med., 276, 770-775, 1967.
19. Finkerstaedt, J.T. and Merril, J.P.: "Renal function after recovery from acute renal failure." N. Eng. J. Med., 254, 1023-1026, 1956.
20. Gilles, H.M. and Hendrick, R.G.: "Nephrosis in Nigerian children." Brit. Med. J., 2, 27-31, 1963.
21. Glasgow, E.F., Moncrieff, M.W. and White, R.H.R.: "Symptomless haematuria in childhood." Brit. Med. J., 2, 687-692, 1970.
22. Hamburger, J.: Nephrology. W.B. Saunders, Co., Philadelphia, London and Toronto, 1969.
23. Harvey, A.M., Shulman, L.E., Tumulty, P.A., Conley, C.L. and Schoenrich, E.H.: "Systemic lupus erythematosus. Review of the literature and clinical analysis of 138 cases." Medicine, 33, 291-437, 1954.
24. Heptinstall, R.H.: "Pathology of the Kidney." J. & A. Churchill, Ltd., 1966.
25. Heptinstall, R.H. and Jockes, A.M.: "Focal glomerulonephritis. A study based on renal biopsies." Quart. J. Med., 28, 329-346, 1959.
26. Iverson, P. and Brun, C.: "Aspiration biopsy of the kidney." Acta. Med. Scand., 143, 430-435, 1951.
27. Jesser, R.A., Lamont-Havers, R.W. and Ragan, C.: "Natural history of lupus erythematosus disseminatus." Ann. Intern. Med., 38, 717-731, 1953.

28. Jockes, A.M., Pugh, R.C.B. and Pryor, J.S.: "Recurrent haematuria." Brit. J. Urol., 34, 463-464, 1962.

29. Kark, R.M. and Muehrcke, R.C.: "Biopsy on kidney in prone position." Lancet, 1, 1047-1049, 1954.

30. Kibukamusoke, J.W.: "The nephrotic syndrome in Lagos, Nigeria." West Afr. Med. J., 15, 213-217, 1966.

31. Kibukamusoke, J.W., Hutt, M.S.R. and Wilks, N.E.: "The nephrotic syndrome in Uganda and its association with quartan malaria." Quart. J. Med., 36, 393-408, 1967.

32. Levitt, L.M. and Burbank, B.: "Glomerulonephritis as a complication of the Schonlein Henoch syndrome." N. Eng. J. Med., 248, 530-536, 1953.

33. Lyttle, J.D. and Rosenberg, L.: "The prognosis of acute nephritis in childhood." Amer. J. Dis. Child, 38, 1052-1063, 1929.

34. Mathur, K.S. and Srivastava, S.C.: "Needle biopsy of the kidney. An appraisal of 150 successful biopsies." J. Indian, Med. Ass., 35, 145-150, 1960.

35. McCombs, R.P., Patterson, J.F. and McMahon, H.E.: "Syndromes associated with "allergic" vasculitis." N. Eng. J. Med., 255, 251-261, 1956.

36. Meadow, S.R., Glasgow, E.F., White, R.H.R., Moncrieff, M.W., Cameron, J.S. and Ogg, C.S.: "Schonlein Henoch nephritis." Quart. J. Med., 41,241-258, 1972.

37. Muehrcke, R.C., Kark, R.M., Pirani, C.L. and Pollak, V.E.: "Lupus nephritis, a clinical and pathologic study based on renal biopsies." Medicine, 36, 1-145, 1957.

38. Muth, R.G.: "Asymptomatic mild intermittent proteinuria." Arch. Intern. Med., 115, 569-574, 1965.

39. Norkin, S. and Weiner, J.: "Henoch Schonlein syndrome. Review of pathology and report of two cases." Amer. J. Clin. Path., 33, 55-65, 1960.

40. Ogg, C.S., Cameron, J.S. and White, R.H.R.: "The C'3 component of complement (beta 1c globulin) in patients with heavy proteinuria." Lancet, 2, 78-81, 1968.

41. Oliver, T.K., Jr. and Barnett, H.L.: "The incidence and prognosis of nephritis associated with anaphylactoid (Schonlein Henoch) purpura in children." A.M.A. J. Dis. Child, 90, 544-547, 1955.

42. Ooi, B.S., Chen, B.T.M., Toh, C.C.S. and Khoo, O.T.: "Causes of hypertension in the young." Brit. Med. J., 3, 744-746, 1970.

43. Ooi, B.S., Chen, B.T.M., Yu, S.F., Toh, C.C.S. and Khoo, O.T.: "Primary arteritis of the aorta as a cause of renovascular hypertension in Singapore." Aust. N.Z. J. Med., 2, 132-136, 1971.

44. Ooi, B.S., Chen, B.T.M., Tan, K.K. and Khoo, O.T.: "Human renal leptospirosis." Amer. J. Trop. Med. Hyg., 21, 336-341, 1972.

45. Parrish, A.E. and Howe, J.S.: "Needle biopsy as an aid in diagnosis of renal disease." J. Lab. Clin. Med., 42, 152-157, 1953.

46. Paul, F.M.: "A study of acute nephritis in Singapore children." J. Sing. Paed. Soc., 5, 54-60, 1963.

47. Platt, R.: "Severe hypertension in young persons. A study of 50 cases." Quart. J. Med., 17, 82-93, 1948.

48. Pollak, V.E., Kark, R.M., Pirani, C.L., Soothill, J.F. and Muehrcke, R.C.: "The significance and potential value of renal biopsy in Bright's disease." J. Chron. Dis., 5, 67-86, 1957.

49. Pollak, V.E., Pirani, C.L., Muehrcke, R.C. and Kark, R.M.: "Asymptomatic persistent proteinuria." Guy's Hospital Report, 107, 353-372, 1958.

50. Pollak, V.E., Pirani, C.L. and Kark, R.M.: "Effect of large doses of prednisone on the renal lesions and life span of patients with lupus glomerulonephritis." J. Lab. Clin. Med., 57, 495-511, 1961.

51. Rapoport, A., Davidson, D.A., Devenber, G.A., Ranking, G.N. and McLean, C.R.: "Idiopathic focal proliferative nephritis associated with persistent haematuria and normal renal function." Ann. Intern. Med., 773, 921-928, 1970.

52. Ross, J.H.: "Recurrent focal nephritis." Quart. J. Med., 29, 391-406, 1960.

53. Rothfield, N.F., McCluskey, R.T. and Baldwin, D.S.: "Renal disease in systemic lupus erythematosus." N. Eng. J. Med., 269, 537-544, 1963.

54. Rudebeck, J.: "Clinical and prognostic aspects of acute glomerulonephritis." Acta. Med. Scand., (Suppl 173), 1-184, 1946.

55. Sarin, L.R. and Sarin, J.C.: "Nephrotic syndrome. A clinicopathological study of 50 cases in adults." Ind. J. Med. Sci., 14, 205-213, 1960.

56. Schriener, G.E.: The nephrotic syndrome. "In Diseases of the Kidney." Ed., by M.B., Strauss and L.G. Welt. Little Brown & Co., Boston 1963. Pp. 335-444.

57. Sharpstone, P., Ogg, C.S. and Cameron, J.S.: "Nephrotic syndrome due to primary renal disease in adults I." Brit. Med. J., 2, 533-539, 1969.

58. Simpson, B., Cook, A.T., Diamond, A.H., Brown, M. and Thin, R.N.T.: "Renal function after leptospirosis." Brit. Med. J., 3, 472-473, 1967.

59. Singer, D.B., Hill, L.L., Rosenberg, H.S., Marshall, J. and Swenson, R.: "Recurrent haematuria in childhood." N. Eng. J. Med., 279, 7-12, 1968.

60. Sökmen, C. and Özdemir, A.I.: "The spectrum of renal disease found by renal biopsy in Turkey." Ann. Intern. Med., 67, 603-605, 1967.

61. Soffer, L.J., Southern, A.L., Weiner, H.E. and Wolf, R.L.: "Renal manifestations of systemic lupus erythematosus. A clinical and pathological study of 90 cases." Ann. Intern. Med., 54, 215-228, 1961.

62. Thompson, A.L., Durrett, R.R. and Robinson, R.R.: "Fixed and reproducible orthostatic proteinuria. VI Results of a 10 year follow-up evaluation." Ann. Intern. Med., 73, 235-244, 1970.

63. Wahi, P.N., Wahal, P.K., Mital, V., Kehar, U. and Mathur, K.S.: "Nephrotic syndrome." J. Ind. Med. Ass., 38, 205-217, 1962.

64. Wedgewood, R.J.P. and Klaus, M.H.: "Anaphylactoid purpura (Schonlein Henoch syndrome): a long term follow up study with special reference to renal involvement." Pediatrics, 16, 196-206, 1955.

65. White, R.H.R., Glasgow, E.F. and Mills, R.J.: "Clinicopathological study of nephrotic syndrome in childhood." Lancet, 1, 1353-1359, 1970.

66. Willis, A.J.: "Adult nephrotic syndrome at Ibadan—aetiological considerations." J. Trop. Med. Hyg., 71, 153-157, 1968.

67. Wolman, I.J.: "The incidence, causes and intermittency of proteinuria in young men." Amer. J. Med. Sci., 210, 86-100, 1945.