BY INVITATION

RENAL DISEASE IN SINGAPORE WITH PARTICULAR REFERENCE TO GLOMERULONEPHRITIS IN ADULTS

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SYNOPSIS

Diseases of the genitourinary tract were the 9th major cause of deaths by broad groups of causes in Singapore per 100,000 population; the two major causes of deaths being cardiac/hypertensive disease and neoplasms. There was no change in the cause of deaths between 1972 and 1978, with diseases of the genitourinary system maintaining the 9th position. Glomerulonephritis was the major antecedent disease leading to renal death during this period.

During the period 1972 to 1978, suitable renal biopsies were obtained from 837 patients with glomerulonephritis. Primary idiopathic glomerulonephritis, including IgA nephropathy of Berger, accounted for 72.6% of all cases. Minor glomerular abnormalities, including minimal change lesion with nephrotic syndrome, accounted for 22.7% (190), focal segmental glomerulonephritis for 7.9%, membranous nephropathy for 2.5%, diffuse mesangial proliferation for 4.7%, and IgA nephropathy for 31.3% (262) of patients. Diffuse endocapillary proliferative glomerulonephritis, crescentic and mesangiocapillary glomerulonephritis were less frequent lesions. Of the glomerular diseases secondary to systemic diseases, systemic lupus erythematosus and Henoch Schonlein syndrome were the common diseases, accounting for 15% and 2.7% of cases respectively.

Immune complex glomerulonephritis accounted for most of the human glomerulonephritis, and a second group was negative on immunoflourescene microscopy. Anti-GBM-antibody glomerulonephritis was a rarity, and no case of dense deposit glomerulonephritis was identified. The cause of the most frequent lesion of mesangial IgA nephropathy remains obscure. The immunopathological changes were similar to Henoch Schonlein syndrome which may represent a more severe systemic manifestation of the disease. Glomerulonephritis is the major cause of death, and though dialysis and transplantation are major advances in therapy, the ideal objective should be effective prevention and therapy, which can only occur with an understanding of the aetiology and pathogenesis of glomerulonephritis.

INTRODUCTION

Any study of end-stage renal disease causing death does not take into account disorders like urinary tract infections, renal stones, prostatic diseases and glomerulonephritis which do not lead to renal failure. These conditions cause much suffering and disability to the patients,

and tax the resources of the Medical profession and society. The diseases responsible for end-stage renal failure have drawn the attention of many countries.

Renal diseases consisting of nephritis and nephrotic syndrome rank 12th among the causes of deaths in Japan; the major renal diseases were glomerulonephritis and nephrotic syndrome. Renal lithiasis was of low incidence among the Japanese (1). Glomerulonephritis is the major disease leading to end-stage renal failure in North America, Europe and Australia (2, 3, 4, 5). Data derived from the American Transplant and European Dialysis and Transplant Registries show that glomerulonephritis is the most common antecedent disease requiring dialysis and transplantation, and account for approximately 50% of renal diseases causing renal failure. The examination of kidney tissues from end-stage renal disease has not been able to provide accurate information on the type of glomerulonephritis leading to renal death. The study of glomerulonephritis is better served by examining the tissues taken during the earlier stages of the disease.

The present study was undertaken to determine the causes of renal deaths, and their importance in the morbidity of the population. Another objective was to determine the types of glomerulonephritis seen in adult patients, aged 16 years and over, who had renal biopsies performed. Did the pattern of glomerulonephritis correspond to the findings in other countries, and could the human pathological studies fit into the neat models of immunopathologic renal injury being caused by circulating immune complexes depositing in glomerular and tubulointersititial areas (6, 7), or by anti-glomerular basement membrane (GBM) antibodies reacting with antigens in the glomerular basement membranes (8, 9, 10).

MATERIAL AND METHODS

The major cause of deaths by broad groups of causes in Singapore per 100,000 population was obtained for the periods 1973 to 1977 (11, 12). The study of glomerulonephritis is better served by examining the tissues taken during the earlier stages of the disease, as examination of end-stage kidneys at postmortem has been unsatisfactory. The types of glomerulonephritis were determined by examining the renal biopsies performed in adult patients aged 16 years and over, during the period 1972 to 1978.

All renal biopsy specimens were divided into three pieces, when available, for examination by light, electron and immunofluorescence microscopy.

Light microscopy. Renal biopsy specimens were fixed either in Bouin's solution or in corrosive formol (Mercuric chloride), embedded in paraffin and sections cut at 2 mμ. Serial levels were examined after staining with haematoxylin and eosin (H & E), periodic acid Schiff (PAS), Masson trichrome, and periodic acid silver methenamine (PASM) stains. A minimum number of six glomeruli is needed in the biopsy section to evaluate the specimen properly, otherwise focal lesions will be missed. Sometimes larger number of glomeruli are required for focal lesions. A diffuse lesion can be diagnosed with smaller number of glomeruli.

Electron microscopy. The specimen was fixed in 4% glutaraldehyde, postfixed in 1% Dalton's chrome — osmium fixative and embedded in Araldite. Thin sections cut at 60-90 mμ were stained with uranyl acetate and lead citrate. The sections were examined and photographed in a Hitachi HS-8 electron microscope. In diffuse disease, a minimum of two glomeruli should be examined, but larger numbers are needed in focal glomerulonephritis.

Immunofluorescence microscopy. Renal tissues were snap-frozen in isopentane-liquid nitrogen, or collected in dry ice, and stored at -70°c till immunofluorescence microscopy was done. Cryostat sections were cut at 4 μ, and sections were examined by direct immunofluorescene by a modification of the method by Edgington et al (13). The specimens were tested against rabbit antisera to human IgG, IgA, IgD, IgE, IgM, IgA secretory piece, β 1C-β 1A (C3), C1q, C4, fibrin-fibrinogen and HBs antigen (Hoechst-Behring Laboratories). Details of this procedure have been described (14). The two major immunopathologic processes can be differentiated by immunofluorescence microscopy with anti-GBM antibodies forming linear deposits, and immune complexes granular deposits (10).

The criteria for the diagnosis of glomerulonephritis were based on those set by the World Health Organization Committee on The Histological Classification of Renal Diseases.

RESULTS

Diseases of The Genitourinary tract were the 9th major cause of deaths by broad groups of causes in Singapore per 100,000 population (Table I); the two major causes of deaths being cardiac/hypertensive disease and neoplasms. There was no change in the cause of deaths between 1972 and 1978, with diseases of the genitourinary system maintaining the 9th position (11, 12). Glomerulonephritis was the major antecedent disease leading to renal death in 8.5 to 10.8 per 100,000 population during this period (Table II). Infections of the kidney, calculus and prostatic disease were less important causes. This pattern has not changed.

The types of Glomerulonephritis seen in all adult patients, aged 16 years and over who had renal biopsies performed during the period 1972 to 1978 are shown in Table III. Primary glomerulonephritis accounted for 72.6% of all cases.

Minor Glomerular Abnormalities, including minimal change lesion with the glomeruli appearing normal on light microscopy, accounted for 22.7% (190) of all cases. Minimal change lesion, with obliteration of foot processes on electron microscopy (Figure 1) accounted for 12.9% (108) of all the cases. Immunofluorescence microscopy showed three groups; negative in 89% and 96% of cases with minimal change and minor change lesions respectively. Mesangial specks of IgM and C3 were present in 8.3% and 3.7% of biopsies with minimal change and minor change glomerulonephritis; IgG and C3 in 2.8% of minimal change lesions.

The patients presented with orthostatic proteinuria and recurrent proteinuria (15), microscopic and gross hematuria (14), and nephrotic syndrome. There were no immunoglobulin deposits in orthostatic proteinuria. Nephrotic syndrome was found in 40.5% (77) of the patients, with negative immunofluorescence in 83% (64), IgM and C3 in 13% (10), and IgG and C3 in 4% (3) of the cases.

Table I

DEATHS BY BROAD GROUPS OF CAUSES IN SINGAPORE PER 100,000 POPULATION

	Cause of Death	1973	1975	1977
1.	Heart/Hypertensive Disease	90.0	92.9	105.1
2.	Neoplasms	87.5	94.4	100.8
3.	Respiratory System Disease	79.0	72.5	85.0
4.	Cerebrovascular Disease	51.8	55.3	63.4
5.	Accidental Death	45.5	39.4	39.6
6.	Infective/Parasitic Disease	35.5	28.0	22.7
7.	Diseases of Digestive System	20.7	18.8	16.5
8.	Endocrine/Metabolic Diseases	15.7	16.7	18.6
9.	Diseases of Genitourinary Tract	12.6	13.8	14.0
10.	Immaturity	11.4	6.3	10.7
11.	Congenital Anomalies	8.6	6.5	6.1
12.	Diseases of Nervous System	7.7	5.9	4.8
13.	Diseases of Haemopoietic System	2.8	2.3	2.2
14.	Others & Senility	76.3	54.4	41.6

Deaths are classified according to the Eighth (1965) Revision of the International Statistical Classification of Diseases, Injuries and Causes of Death.

Table II

DEATHS BY DISEASES OF THE GENITOURINARY SYSTEM IN SINGAPORE PER 100,000 POPULATION

	Cause of Death	1973	1975	1977
1.	Acute Nephritis	0.5	0.6	0.6
2.	Other Nephritis and Nephrosis			
	(a) Nephrotic Syndrome	0.4	0.3	0.3
	(b) Chronic Nephritis	7.3	8.6	9.3
	(c) Nephritis, unqualified	0.3	0.5	0.6
		8.5	10.0	10.8
3.	Infections of Kidney	0.8	0.9	0.4
4.	Calculus	0.2	0.3	0.4
5.	Prostatic Disease	0.6	0.4	0.2
6.	Others	2.5	2.2	2.2
		4.1	3.8	3.2

Table III

GLOMERULAR LESIONS IN ADULTS STUDIED BY RENAL BIOPSIES

	Number of Cases	Percentage
Primary Glomerular Lesions		
Minor Changes including Minimal Change Lesions	190 (108)	22.7 (12.9)
Focal/Segmental Lesions	66	7.9
Diffuse Membranous Nephropathy	21	2.5
Diffuse Mesangial Proliferation	39	4.7
Diffuse Endocapillary Proliferation	4	0.5
Diffuse Mesangiocapillary (Type 1) Glomerulonephritis	14	1.7
Crescentic (Extracapillary) Glomerulonephritis	8	0.9
Diffuse Sclerosing Glomerulonephritis	3	0.4
Mesangial IgA Glomerulonephritis	262	31.3
Secondary to Systemic Diseases		
Systemic Lupus Erythematosus	126	15.0
Henoch Schonlein Syndrome	23	2.7
Amyloidosis, Diabetes Mellitus, Thrombotic Microangiopathy etc.	14	1.7
Alport's Syndrome	1	
Unclassified Lesions	66	8.0
Total Number of Cases	837	100.0

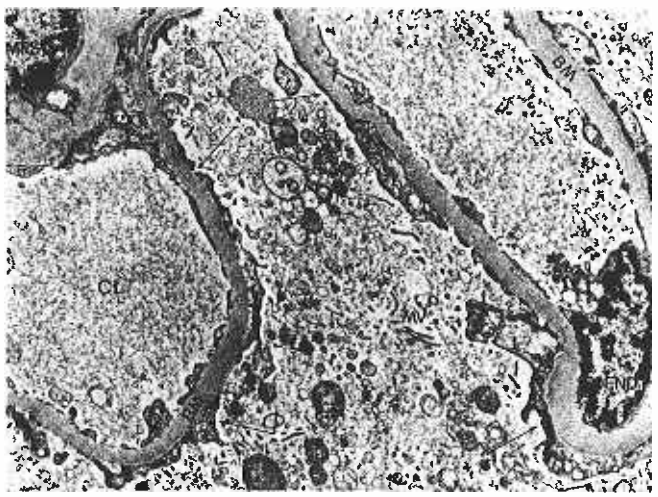

Figure 1. Electron micrograph shows extensive foot process obliteration (arrows), with no change in the basement membrane (BM) of capillary loops. A case of minimal change lesion with nephrotic syndrome. MES = Mesangial cell; END = Endothelial cell; CL = capillary lumen; MV = Microvilli. (Magnification x 12,600).

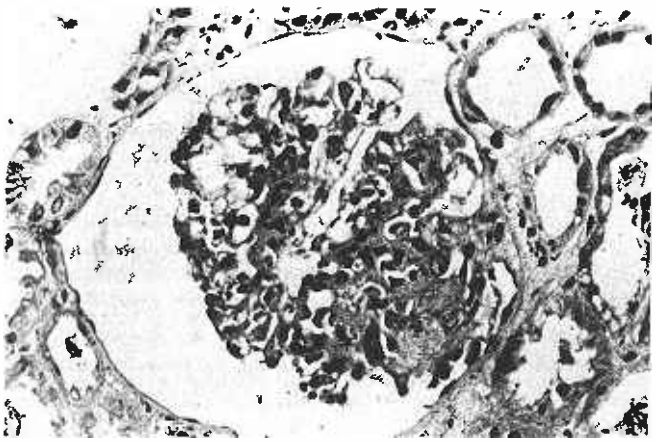

Figure 2. Focal and segmental sclerosing glomerulonephritis with adhesion to Bowman's capsule. (H & E x 350).

Focal and Segmental lesions (with minor changes in the remaining glomeruli) included focal and/or segmental lesions of sclerosis (Figure 2), hyalinosis, capsuloglomerular adhesions, segmental epithelial crescents and global sclerosis. These lesions were found in 7.9% (66) of cases. There was negative immunofluorescence in 72.7% (48), IgM and C3 in 22.7% (15), and IgG, C3 deposits in 4.6% (3) of the biopsies.

The patients presented with recurrent proteinuria, microscopic haematuria, gross haematuria, and the nephrotic syndrome. Nephrotic syndrome was the clinical presentation in 80.3% (53) of the cases with focal segmental lesions. There was negative immunofluorescence in 75.5% (40) of these patients; IgM, IgG and C3 were present as segmental or mesangial specks in the remainder of cases.

Mesangial IgA Nephropathy (IgA glomerulonephritis of Berger) was the most common glomerulonephritis in our biopsy series, accounting for 31.3% (262) of all patients. This high incidence is due partly to the interest in the problem of recurrent proteinuria and haematuria, with renal biopsies being performed in many of them (14, 15), and also to a true high incidence in the local population. Immunoglobulin A was deposited diffusely in the glomerular mesangium in a typical arborized pattern (Figure 3). An IgA — IgG combination was found in approximately 50% of cases. Complement C3 activation was via the alternative pathway. Electron microscopy showed osmiophilic deposits in the mesangium of all cases, with subendothelial — mesangial deposits in some (Figure 4). Light microscopic examination showed variable morphology, with minor change, focal and segmental lesions of sclerosis and hyalinosis, synechiae and crescents, and diffuse mesangial proliferation. Globules of mesangial deposits (Figure 5) can be identified with several techniques, especially PAS, MSB and Masson trichrome stains.

The common clinical presentations were recurrent proteinuria, microscopic and gross haematuria, with or without symptoms, nephrotic syndrome, acute nephritis, and less frequently with hypertension and chronic renal failure.

Figure 3. Immunofluorescence microscopy shows deposition of immunoglobulin A in the mesangium and hilus in a case of IgA glomerulonephritis. (Magnification x 300).

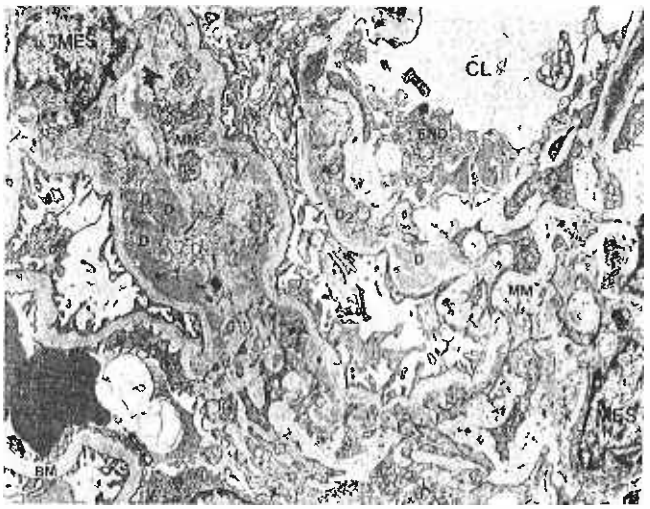

Figure 4. Electron micrograph of glomerulus from a case of mesangial IgA nephropathy. There are heavy osmiophilic deposits (D) in the mesangium, and subendothelium — mesangium (D_2), with increase in mesangial matrix (MM). (Magnification x 8,400).

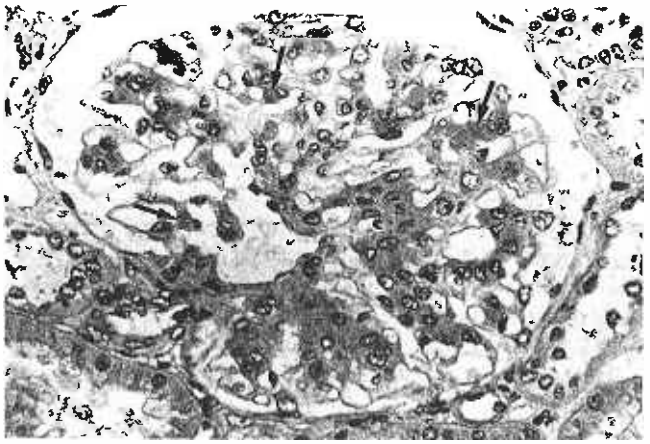

Figure 5. Mesangial IgA glomerulonephritis shows diffuse mesangial proliferation, with globules of deposits (arrows) in the mesangium. (MSB x 500).

Diffuse Mesangial Proliferative Glomerulonephritis was found in 4.7% (39) of cases, with negative immunofluorescence in 84.6% (33) of them; and IgM, IgG and C3 in 15.4% (6). The patients had clinical symptoms of recurrent microscopic and gross haematuria, postacute glomerulonephritis with subsequent persistent microscopic haematuria, proteinuria; and others as nephrotic syndrome or chronic renal failure. In the 10 (25.6%) patients with nephrotic syndrome, immunofluorescence was negative in 9, and in one there were granular deposits of IgG, C3 along the subepithelial peripheral capillary loops.

Diffuse endocapillary proliferative glomerulonephritis with endothelial and mesangial cell hyperplasia, and polymorphonuclear neutrophil infiltration was an uncommon finding, seen in only 0.5% (4) of our biopsy cases.

Crescentic (Extracapillary) glomerulonephritis was an uncommon lesion, observed in only 0.9% (8) of patients. The segmental or circumferential epithelial crescents caused compression of the glomerular tufts (Figure 6). Immunofluorescence was negative in one case; specks of IgM and C3 were found in 4; granular deposits of IgG along the glomerular capillary loops in 2, and strong linear deposition of IgG along the glomerular basement membrane (Figure 7) in one patient. All the patients in this group presented clinically as rapidly progressive glomerulonephritis.

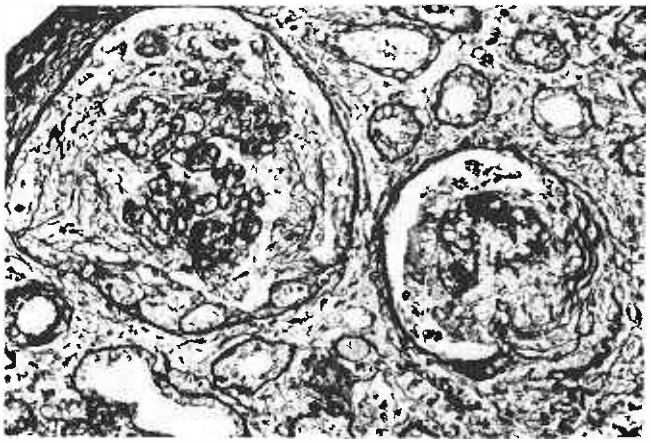

Figure 6. Diffuse crescentic (Extracapillary) glomerulonephritis. The glomeruli show circumferential extracapillary crescents compressing the glomerular tufts. Patient presented with rapidly progressive glomerulonephritis. (PASM x 250).

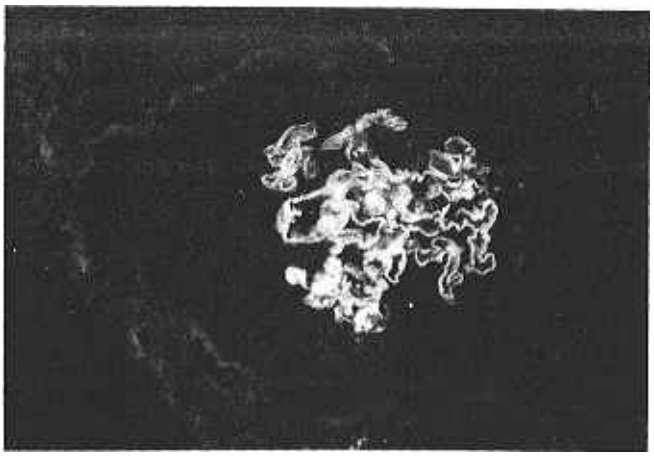

Figure 7. Immunofluorescence microscopy shows diffuse linear deposition of IgG along the glomerular basement membrane, with no deposits in the epithelial crescent Same patient as in Figure 6. (Magnification x 300).

Diffuse Membranous Nephropathy shows a spectrum of changes in the glomeruli ranging from apparently normal to grossly thickened capillary walls. In the majority of cases, silver stains reveal characteristic spikes on the subepithelial basement membrane or capillary wall (Figure 8) (16). Electron microscopy shows the uniform presence of subepithelial dense osmiophilic deposits along the capillary wall (17, 18). These deposits presumed to be immune-complexes contain IgG and complement components (19). Membranous nephropathy was found in 2.5% (21) of cases, and they were subdivided into four groups or stages (18).

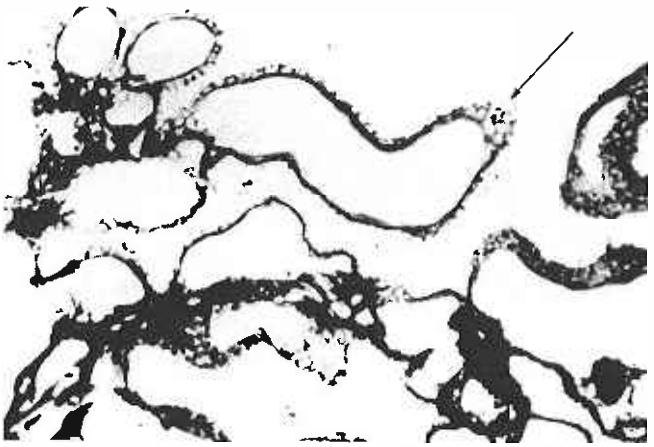

Figure 8. Membranous glomerulonephritis, stage 2, showing the typical spikes on the subepithelial aspect of the basement membrane. Deposits cut tangentially have a mottled appearance (arrow). (PASM x 1,500).

Stage I: There was one patient with minimal change lesion on light microscopy with no capillary wall thickening or spikes. Electron microscopy revealed regular deposits along the subepithelial capillary wall. These deposits contained IgG and C3.

Stage II: There were 15 patients, whose biopsies showed the classical subepithelial spikes (Figure 8), on light microscopy. Electron microscopy revealed osmiophilic deposits on the subepithelial basement membrane, with intervening basement membrane protrusions (Figure 9). Immunofluorescence showed these deposits to contain IgG and C3.

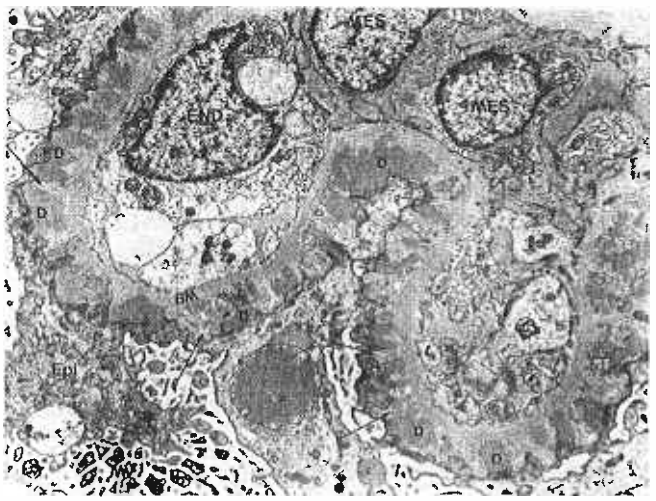

Figure 9. Electron micrograph of glomerulus showing stage 2 membranous nephropathy. The osmiophilic deposits (D) are situated regularly on the subepithelial aspect of the basement membrane (BM). There are basement membrane protrusions (arrows) between the deposits. (Magnification x 12,600).

Stage III: There were 3 cases whose biopsies showed the presence of spikes, with some of the peripheral capillaries having a twisted appearance. Electron dense deposits were found in the subepithelial and intramembranous positions. The deposits contained IgG and C3.

Stage IV: Two patients showed interesting changes in the glomerular capillary loops. There were no deposits on the epithelial side of the basement membrane, and silver

stains showed a twisted and beaded appearance of the peripheral or parietal capillary loops (Figure 10). There were no spikes. Immunofluorescence microscopy performed in one patient showed segmental deposits of IgM and C3 in the peripheral capillary loops. Both patients presented with nephrotic syndrome. The 19 patients with Stage I to III lesions presented clinically with nephrotic syndrome in 17, and with recurrent haematuria proteinuria in 2.

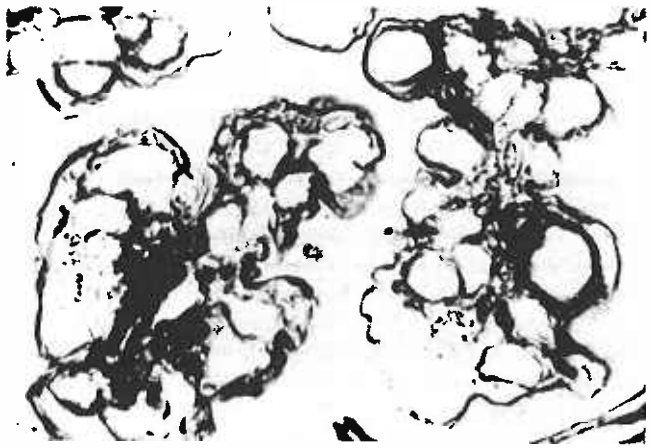

Figure 10. Membranous nephropathy, stage IV, with beaded peripheral capillary loops and absence of spikes. (PASM x 1,500).

Mesangiocapillary glomerulonephritis (Membranoproliferative glomerulonephritis Types 1 and 3).

There are three types due to location of deposits; type 1 with subendothelial deposits between the normal basement membrane and interposition of mesangial matrix; type 3 with interruption or rupture of the lamina densa of the basement membrane by the deposits, and type 2 with dense intramembranous deposits replacing and widening the lamina densa (20, 21, 22, 23, 24). The mesangial ingrowth produced the picture of "split" capillary wall and "tram-track" double outline of the basement membrane (25).

Type 1 mesangiocapillary glomerulonephritis was found in only 1.7% (14) of patients in our series. Eight cases studied by immunofluorescence microscopy showed C3 deposition in all. Immunoglobulin G was present in 5, IgM in 3, IgA in one, and C1q and C4 in 4 cases. They were present as coarsely granular subendothelial deposits, with complement activation by both the classical and alternative pathways, findings similar to other studies (20, 26, 27, 28). The fourteen patients in the present series presented clinically with nephrotic syndrome in 5, gross haematuria in 3, and recurrent microscopic haematuria with proteinuria in 6. There was no case of type 2 dense deposit disease.

GLOMERULAR DISEASES SECONDARY TO SYSTEMIC DISEASES

This group formed 19.4% (163) of all patients in the present series. The major diseases were systemic lupus erythematosus, and the Henoch Schonlein syndrome. Amyloidosis, diabetes mellitus, thrombotic microangiopathy, malaria, etc. were infrequent lesions in our biopsy series. There was only one case of Alport's syndrome. Sixty-six patients with renal biopsies could not be classified due to inadequate tissues or lack of clinical and biochemical information.

The two major secondary glomerular diseases, systemic lupus erythematosus and Henoch Schonlein syndrome shall be discussed briefly as the details have been published (29, 30).

Systemic Lupus Erythematosus (29) was the most common disease in the group, accounting for 15.0% (126) of all cases. The glomerular lesions were classified into five major groups on light microscopy; minor change lesions, including minimal change, focal glomerulonephritis, membranous, diffuse proliferative, and diffuse membranoproliferative patterns. Minor change and focal lesions were invariably associated with normal function. Diffuse proliferative and membranoproliferative lesions showed moderate to severe renal involvement, with nephrotic syndrome. A membranous lesion showed moderate renal involvement and a high incidence of nephrotic syndrome. Heavy subendothelial electron dense deposits in the glomeruli showed worse renal involvement than when the deposits were in the mesangium. Cytoplasmic tubuloreticular, viral-like structures measuring 18 to 20 nm in diameter and 80 to 100 nm in length were found in the majority of biopsies (Figure 11). Immunofluorescence microscopy showed deposition of IgG in the glomeruli of all cases (Figure 12), in association with immunoglobulins IgM, IgA, IgD and IgE in over 80% of the biopsies. C3 activation was via the classical pathway utilising the early complement components C1 and C4. *Henoch Schonlein syndrome* (30) was found to involve the kidneys in both children and adults. The lesion was observed in 2.7% (23) of all cases with renal biopsies performed. The principal glomerular lesion was focal and segmental proliferation. Diffuse mesangial proliferation and minor change lesions were found less frequently. There was mesangial deposition of immunoglobulin A in all the cases, with lesser amounts of IgG and IgM. C3 activation was via the alternative pathway. The osmiophilic deposits were found in the glomerular mesangium. The lesion is a chronic disease of the mesangium, with a worse prognosis with diffuse proliferation and crescent formation.

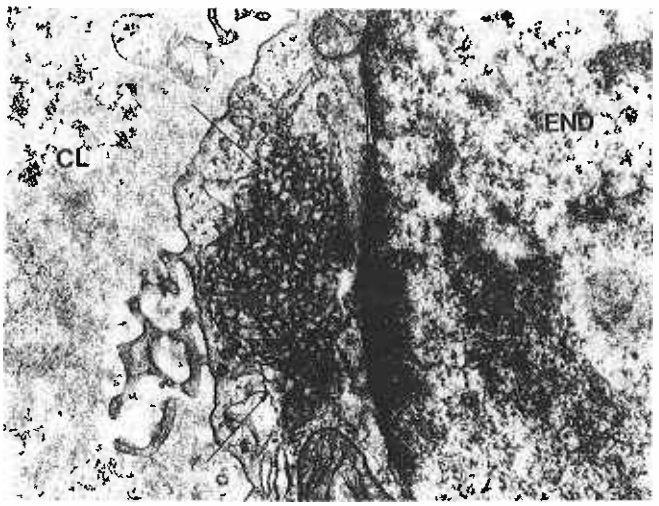

Figure 11. Electron micrograph of glomerulus from a case of systemic lupus erythematosus. Clumps of virus-like, tubuloreticular structures (arrows) are present in the endothelial (END) cytoplasm. (Magnification x 59,400).

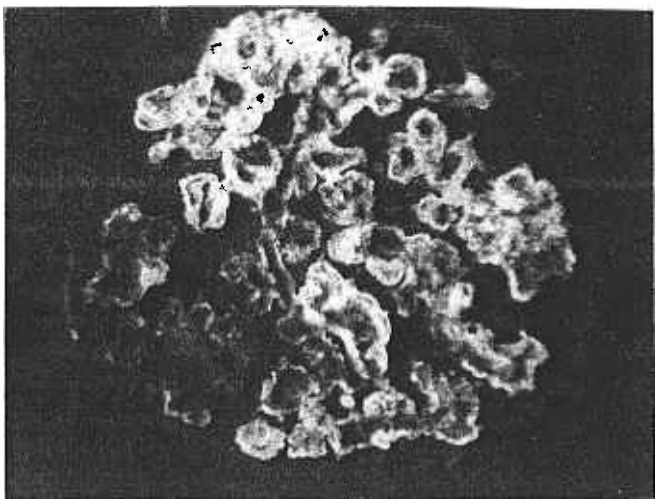

Figure 12 Immunofluorescence microscopy of glomerulus from a case of systemic lupus erythematosus. There is heavy deposition of IgG along the capillary loops in both subendothelial and subepithelial sites. (Magnification x 300).

DISCUSSION

Diseases of the genitourinary tract were the 9th major cause of deaths by broad groups of causes in Singapore per 100,000 population; the two major causes of deaths being cardiac/hypertensive disease and neoplasms. There has been no change in the cause of deaths between 1972 and 1977, with diseases of the genitourinary system maintaining the 9th position (11, 12). Glomerulonephritis is the major cause of renal deaths, and appears to be higher in Singapore than in Japan, North America, Europe and Australia (1, 2, 3, 4, 5).

The pattern of primary or idiopathic glomerulonephritis gives a good indication of the problems faced by workers to prevent the major cause of renal death, and reduce the flow of patients requiring dialysis and transplantation. Minor change glomerulonephritis accounts for 22.7% of all cases, with nephrotic syndrome as a common clinical manifestation. Many papers have shown that the prognosis is better in minimal change lesions with negative immunofluorescence than in minor change with deposits, and focal segmental lesions of sclerosis. The low incidence (0.5%) of diffuse endocapillary proliferative glomerulonephritis is much lower than the 5% to 8% reported from France (31, 32), and not comparable to the high incidence of 37% in Tunisia (33). These marked differences may be due to infrequency of biopsies performed in patients with acute glomerulonephritis in Singapore, or there may be genuine differences in the geographical incidence of this form of non-epidemic glomerulonephritis.

Linear anti-GBM antibody nephritis is a rarity. This characteristic anti-GBM antibody nephritis in the experimental animal is rare in our experience, findings similar to the Australian experience (4) and at variance with the incidence of 5% observed in North America (34). Membranous nephropathy accounted for 2.5% of patients, and they could be subdivided into lesions described as four stages (18). The two patients with lesions similar to stage 4 had peripheral capillaries with a twisted and beaded appearance. These two cases may represent the later stages in the evolution of membranous nephropathy (16, 18, 35), or they may represent a distinct group as postulated by Morel-Maroger (36). Dense deposit glomerulonephritis (Mesangiocapillary glomerulonephritis Type 2) was found in 11% to 19% of biopsies with mesangiocapillary glomerulonephritis by several works (37, 38). Our inability to find a single case of dense deposit glomerulonephritis may be due to the small number of cases, adult patient selection as the lesion is more common in children, or possibly a definite geographical difference.

The most prevalent glomerular lesion in our experience was idiopathic mesangial IgA glomerulonephritis. There was variable glomerular morphology, with the constant finding of diffuse mesangial deposition of IgA, and C3 activation via the alternative pathway. The aetiology was obscure, as conventional methods could not implicate the streptococcus, HBs antigen and parasites. There was a variable clinical presentation, with many patients being found on a routine medical examination to have asymptomatic microscopic haematuria and proteinuria (14, 15). The pathological changes are similar to those seen in the Henoch Schonlein syndrome (30), which may represent part of the spectrum of the disease with systemic manifestations. Lupus nephritis was the most common glomerular disease secondary to systemic diseases. The diagnosis can be entertained when the biopsy shows a variable glomerular pattern with the presence of haematoxylin bodies, a "full house" of immunoglobulins with C3 activation via the classical pathway, and the presence of large numbers of virus-like tubuloreticular structures seen on electron microscopy (29).

The neat experimental models of anti-GBM antibody glomerulonephritis and immune complex glomerulonephritis do not seem to explain all the human problems of nephritis. From our experience, so-called immune complex glomerulonephritis accounts for most of the human glomerular diseases, and a second group is negative with immunofluorescence studies. Anti-GBM antibody glomerulonephritis is a rarity. Due to the eradication of malaria, malarial nephropathy is uncommon, unlike the experience in parts of Africa and elsewhere (39). The inability to find dense deposit disease and the observation of two cases with membranous nephropathy with parietal beaded changes may be significant, but the cases are too few to draw any conclusions. Glomerulonephritis is the major cause of renal deaths, and though dialysis and transplantation are major advances in therapy, the ideal objective should be effective prevention and therapy. It may be possible that studies based on geographical and epidemiological patterns may help to solve the urgent probelm of glomerulonephritis.

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