# NEPHROTIC SYNDROME: A CLINICO-PATHOLOGICAL STUDY

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## SYNOPSIS

**Seventy-three patients, with a diagnosis of nephrotic syndrome, were admitted into Tan Tock Seng Hospital over a 5½ year period beginning from 1964. Intrinsic renal disease was found in 59 patients. Renal biopsies were done on 54 patients and serial biopsies were done in approximately half the patients. In 1 patient the biopsy was unsatisfactory. In 5 patients consent for biopsy was refused. There were 22 with "minimal change" lesion, 1 with focal glomerulosclerosis, 6 with membranous nephropathy, 11 with diffuse proliferative glomerulonephritis, 3 with mesangial proliferative glomerulonephritis, 7 with focal glomerulonephritis, 2 with membranoproliferative glomerulonephritis and 1 with chronic glomerulonephritis. Lasting remission with prednisolone therapy was obtained in 5 patients. Persistent proteinuria was found in 29 patients and 25 patients pursued a chronic relapsing course. Cytostatic therapy was exhibited to 25 patients either because of frequent relapses or poor response to prednisolone therapy. It was found to be of value in only one patient with focal glomerulonephritis who showed a histological improvement while on it.**


Nephrotic syndrome is a renal disorder characterised by profuse proteinuria and its accompanying metabolic, nutritional and clinical consequences. There is usually lipiduria, hypoalbuminaemia, hypocholesterolaemia and oedema.

The causes of nephrotic syndrome are legion (Kark *et al*, 1958). These may be broadly divided into two main groups:—

1. Nephrotic syndrome due to intrinsic renal disease and
2. Nephrotic syndrome which occurs during the course of generalised systemic diseases.

By and large nephrotic syndrome due to intrinsic renal disease is much commoner than that which occurs with generalised systemic diseases.

There seems to be no uniformity of nomenclature in the classification of nephrotic syndrome as yet, and different authors use different morphological classifications. We have classified our patients into:— (*1*) "Minimal Change" Lesion; (*2*) Focal Glomerulosclerosis; (*3*) Membranous Nephropathy; (*4*) (a) Diffuse Proliferative Glomerulonephritis, (b) Mesangial Proliferative Glomerulonephritis (L.S.T.), (c) Focal Glomerulonephritis, (d) Membrano-proliferative Glomerulonephritis; (*5*) Chronic Glomerulonephritis, and (*6*) An Indeterminate Group.

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In July 1964 we initiated a prospective study of nephrotic syndrome due to intrinsic renal disease at the Tan Tock Seng Hospital. The study was terminated, after a period of 5½ years, in December 1969. The study was aimed at determining the following:—

1. The renal morphology in the primary form of the nephrotic syndrome.
2. The natural history and prognosis.
3. The correlation between clinical, laboratory and histological findings.
4. The response to corticosteroid and cytostatic therapy.

## MATERIAL AND METHODS

All patients above the age of ten years with a diagnosis of nephrotic syndrome admitted into the Medical Wards at Tan Tock Seng Hospital were taken into the study. Subsequently patients with nephrotic syndrome due to Disseminated Lupus Erythematosus, Diabetes Mellitus, Amyloidosis and other forms of secondary renal disease were excluded.

The investigations done included complete urine analysis, twenty four hour urine protein excretion, blood urea, serum protein, serum cholesterol, serum electrolytes, blood for L.E. cells and A.S.O.T. Most of these investigations were done by standard methods and were repeated during subsequent evaluation of the patient. Other investigations done included a roentgenogram and an intravenous pyelogram.

Renal biopsies were done by modification of the procedure described by Kark and Muehrcke

(1964). Many of the patients had repeat biopsies during the follow-up period.

All the patients were given low-salt high-protein diet. In addition all were prescribed diuretics such as chlorothiazide 0·5 gm. to 1 gm. per day of frusemide 40 mg. to 60 mg. per day. Each patient was treated with prednisolone in the dosage of 30 mg. to 60 mg. per day for four weeks. The dose of steroids was dependent on the age and weight of the patient. If there was a clinical response the dose of the prednisolone was reduced to a maintenance dose after four weeks and then maintained on it for six months. If there was a poor clinical response the dose of prednisolone was reduced but maintained for up to one year before stoppage (Fig. 1).

1. Low salt, high protein diet.
2. Diuretics. Chlorothiazide and Frusemide.
3. Prednisolone 30-60 mg./day.
4. Cytostatics e.g. Cyclophosphamide, Azathioprine (Since 1967).

Fig. 1. Treatment.

Since 1967 cytostatics such as 6-Mercaptopurine at 2·5 mg. per Kg. body weight, azathioprine 200-300 mg. or cyclophosphamide 100-200 mg. per day was added on to the regime of those patients who showed a poor response to steroids. Cytostatics were also exhibited to those who developed frequent relapses or troublesome side effects to prednisolone. In the initial stages of study the higher doses of the cytostatics were used but in the later stages we used a smaller dosage.

## RESULTS

There was a total of 73 patients with the diagnosis of nephrotic syndrome but 14 patients were excluded from the analysis as they were found to be suffering from Diabetes Mellitus, Disseminated Lupus Erythematosus or Amyloidosis (Table I). The remaining 59 patients were made up of 51 Chinese, 6 Malays and 2 Indians. There were 35 males and 24 females (Table II).

Eighty-eight biopsies were done on fifty-three patients. Five patients refused consent for biopsy and in 1 patient the biopsy was unsatisfactory. Twenty-three patients had 2 biopsies and six patients had 3 biopies performed on them.

The duration of observation ranged from 3 months to 5½ years. In one patient the follow-up period was abbreviated to 6 months by death and in only two other patients were the observation periods shorter than one year. There were 5 deaths during the period of study (Table III). The "Indeterminate group" is made up of five patients who refused consent for renal biopsy and one patient in whom the renal biopsy was unsatisfactory.

TABLE I

AETIOLOGY OF 73 CASES OF NEPHROTIC SYNDROME SEEN OVER A 5½ YEAR PERIOD

| | |
|---|---|
| Intrinsic Renal Disease - - - | 59 |
| Diabetes Mellitus - - - - | 9 |
| Disseminated Lupus Erythematosus - | 3 |
| Amyloidosis - - - - | 2 |
| TOTAL NUMBER | 73 |

TABLE II

RACIAL DISTRIBUTION OF THE PATIENTS

| | Males | Females | Total No. |
|---|---|---|---|
| Chinese | 29 | 22 | 51 |
| Malays | 4 | 2 | 6 |
| Indians | 2 | 0 | 2 |

TABLE III

CLINICAL MATERIAL

| | |
|---|---|
| Total number of patients | 59 |
| Indeterminate group | 6 |
| Number of renal biopsies | 88 |
| Duration of observation | 3 months to 5½ years |
| Number of deaths | 5 |

TABLE IV

RENAL MORPHOLOGICAL CLASSIFICATION

| | | |
|---|---|---|
| "Minimal Change" Lesion | 22 | (41%) |
| Focal Glomerulosclerosis | 1 | (2%) |
| Membranous Nephropathy | 6 | (11%) |
| Diffuse Proliferative Glomerulonephritis | 11 | (21%) |
| Mesangial Proliferative Glomerulonephritis | 3 | (6%) |
| Focal Glomerulonephritis | 7 | (13%) |
| Membrano-Proliferative Glomerulonephritis | 2 | (4%) |
| Chronic Glomerulonephritis | 1 | (2%) |
| Indeterminate Group | 6 | (—) |

**"Minimal Change" Group**

There were 22 (41 %) patients in this group in which the renal biopsy appeared normal, or with minimal endothelial and/or mesangial proliferations under light microscopy (Fig. 2). The follow-up period ranged from 1 year to 2 months to 4 years 2 months and there were no deaths. All except one presented with oedema. There was ascites in 7 patients and ascites with hydrothorax in 4 patients. Eleven patients presented with oliguria and there was transient elevation of arterial blood pressure in another 8 patients. Hyponatraemia was present in 17 patients. Hypocholesterolaemia was present in only one patient who was also suffering from schizophrenia and pulmonary tuberculosis. This is the only patient in whom the V.D.R.L. test and Kahn Test were positive. He is also one of two patients who did not receive prednisolone. He received diuretics and parenteral penicillin on which he improved but had one further relapse.

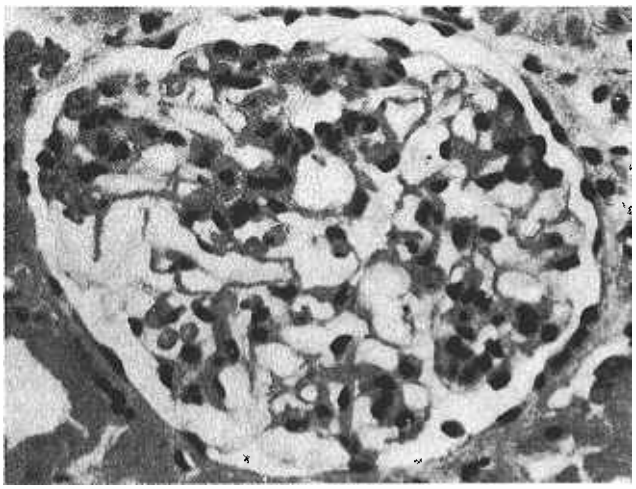

Fig. 2. Minimal Change. There are several areas of crowding of nuclei in the glomerular tuft. The capillaries are patent and the basement membrane is normal. H & E × 500.

There was a lasting remission in 4 patients and this has lasted from 1½ years in 3 patients to 3½ years in one patient. In 12 patients the disease pursued a chronic relapsing course and in 6 others there was persistent proteinuria.

Cytostatics in addition to prednisolone were exhibited to 8 patients with the minimal change lesions because of frequent relapses. When cytostatics were administered the dose of prednisolone was reduced. Four patients were initially given 6-mercaptopurine in the dose of 75-150 mg. per day. It was stopped in one patient after a week because of severe nausea. In another patient it was stopped after 4 months. In two others it was changed to azathioprine after administration of 6-mercaptopurine for 2 months and 9 months respectively. In these two the azathioprine was stopped after a further 4 and 5 months respectively.

None of the patients in this group developed any serious side effects to cytostatic drugs. Two patients on prednisolone developed myopathy characterised by wasting and muscular weakness. One of these two patients had 6 admissions for relapses and was on continuous prednisolone medication. This patient had a cytostatic drug added to her regime in February 1967 and received it for 14 months.

Repeat renal biopsies were performed on 12 patients from periods ranging from 6 months to 3 years after the initial biopsy. Two patients had three biopsies done on them. These biopsies did not reveal any change from the initial biopsy except in one 32 year old patient whose repeat biopsy after 2 years revealed 3 of 15 glomeruli to be hyalinised.

The blood urea of the patients in this group was still normal at the time of review.

**Focal Glomerulosclerosis**

There was only one patient with focal glomerulosclerosis which is characterised by the presence of glomerular sclerosis which is both focal and segmental in distribution (Fig. 3). Some glomeruli may look normal while others may be partly or completely sclerosed.

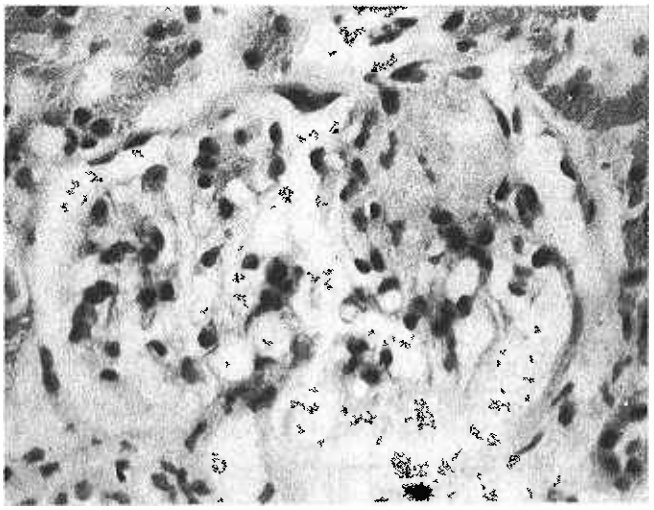

Fig. 3. Focal Glomerulonephritis. This glomerulus is essentially normal except for segmental sclerosis at 1 to 2 o'clock. In this case, out of 15 glomeruli, two are completely sclerosed and this third glomerulus shows early sclerosis. H & E × 500.

The patient is a 21 year old Chinese male who presented in July 1964 with a history of puffy face with a dull lumbar ache for three months and oedema of legs for two months. The urinary excretion of protein was 10 gms. per day. There was microhaematuria with the presence of hyaline and granular casts. The blood urea was 51 mg.% on admission but fell to 21 mg.% on discharge three months later. The serum albumin was 2.4 mg.% and the serum cholesterol 395 mg.% but the ASOT

TABLE V

AGE AND SEX DISTRIBUTION OF THE DIFFERENT RENAL MORPHOLOGICAL TYPES

| Glomerular Morphology | Total No. | Male | Female | Age in Years | Previous Renal Disease |
|---|---|---|---|---|---|
| Minimal Change Lesion | 22 | 12 | 10 | 10-42 (20·6) | 3 |
| Focal Glomerulosclerosis | 1 | 1 | 0 | 21 | 0 |
| Membranous Nephropathy | 6 | 4 | 2 | 16-67 (42·5) | 3 |
| Diffuse Proliferative Glomerulonephritis | 11 | 8 | 3 | 13-51 (24·7) | 2 |
| Mesangial Proliferative Glomerulonephritis | 3 | 3 | 0 | 20-44 (31) | 0 |
| Focal Proliferative Glomerulonephritis | 7 | 4 | 3 | 17-37 (26·1) | 1 |
| Membrano-Proliferative Glomerulonephritis | 2 | 0 | 2 | 30-48 (39) | 1 |
| Chronic Glomerulonephritis | 1 | 0 | 1 | 14 | 1 |
| Indeterminate Group | 6 | 3 | 3 | 11-10 (27·5) | 3 |

was negative. He improved with prednisolone but continued to have persistent proteinuria for which he was admitted in April 1967 for reassessment. He had a proteinuria of 1 to 2 gm. per day at this time but the serum albumin and blood urea were normal. The morphology of a renal biopsy specimen which contained 25 glomeruli was within normal limits. In May 1968, the proteinuria was 1 to 2 gm. per day but the serum albumin and blood urea were still normal. A repeat renal biopsy in May 1968 revealed 6 of 12 glomeruli to be hyalinised. On reviewing the two biopsy specimens, focal areas of glomerulosclerosis were found. The prednisolone has been stopped since May 1969 although he still has proteinuria.

**Membranous Nephropathy**

There is diffuse thickening of the basement membrane in this subgroup and there is usually no increase in cellularity in the glomerulus (Fig. 4). P.A.S. Silver Methanamine staining reveals thickening of the basement membrane with the characteristic "spikes" on the epithelial side of the basement membrane.

There were 4 males and 2 females in this group. One 62 year old male defaulted treatment after four months. A 27 year old male died of fulminant bronchopneumonia after a follow-up period of one year and a 16 year old girl died of renal failure after a follow-up period of 3½ years. The other 3 patients have been followed up for 5 years, 4½ years and 3½ years respectively. Two patients were found to be hypertensive and a third developed hypertension later. Three patients had microhaematuria initially. The other clinical and laboratory features are shown in Tables VI, VII and VIII. The three patients who are still being followed-up have persistent proteinuria but there is no oedema. Repeat renal biopsies were done in two patients and these revealed the presence of hyalinised glomeruli which were not present in the biopsies done a year earlier.

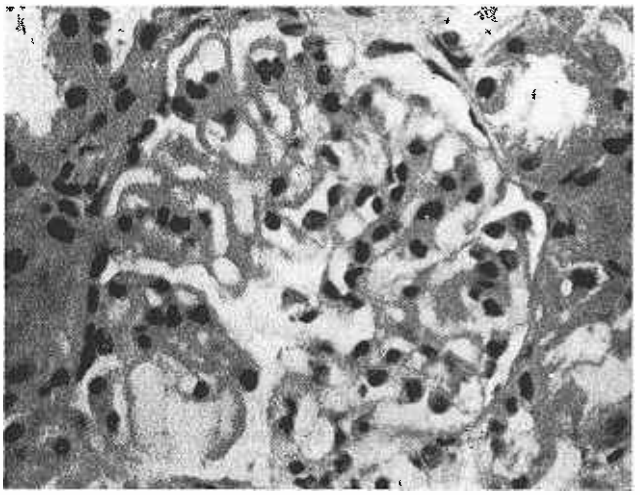

Fig. 4. Membranous Nephropathy. This glomerulus shows uniformly thickened basement membrane. There is no increase in cellularity. P.A.S. × 500.

One patient was treated with diuretics only but the other 5 patients received prednisolone and diuretics. The 27 year old patient who died had azathioprine added to his regime four months before his death. Three other patients had cyclophosphamide added to their regime for 8 months. Now none of the patients are on any specific therapy such as prednisolone or cytostatics.

**Diffuse Proliferative Glomerulonephritis**

This group is characterised by diffuse polymorphonuclear infiltration of the glomerular tufts and mesangial proliferation.

There were 11 patients in this group. The follow-up period was more than 1½ years in all except in 2 patients in whom it was 1 year and 3 months. The longest follow-up period was 5½ years. The clinical and biochemical features are shown in Tables VI, VII and VIII. There was transient hypertension in 2 patients and microhaematuria in 3 patients. One patient had a positive L.E. cell preparation and in another the Antinuclear Factor was positive. The ASOT was determined in 8 patients and in none of them was it elevated.

All the patients were treated with prednisolone and diuretics. This improved their clinical condition but none had a lasting remission. There was persistent proteinuria in 5 patients and 6 patients had frequent admission for relapses. Cytostatics were added to the regime of 5 patients. The cyto-

static was 6-mercaptopurine in one patient, cyclophosphamide in another patient and azathioprine in the remaining 3 patients. The duration of cytostatic therapy ranged from 1 to 1½ years but none of the patients are on it at the time of writing. Only 4 patients are still on prednisolone.

Repeat renal biopsies were performed in 5 of the patients from 1 to 3 years after initial biopsies. There were no significant changes in the renal morphology in 4 patients, but in a 28 year old patient who had 7 relapses, the repeat biopsy showed more hyalinised glomeruli. There were no deaths in this group.

TABLE VI

CLINICAL PRESENTATION OF THE 59 PATIENTS WITH THE NEPHROTIC SYNDROME

| Glomerular Morphology | Total No. | Ascites | Hydro-Thorax | Oliguria | Oedema | Loin Ache | Hypertension (Diastolic >90 mm. Hg.) |
|---|---|---|---|---|---|---|---|
| Minimal Change Lesion | 22 | 7 | 4 | 11 | 21 | 1 | 8 |
| Focal Glomerulosclerosis | 1 | 0 | 0 | 0 | 1 | 1 | 0 |
| Membranous Nephropathy | 6 | 2 | 2 | 2 | 6 | 0 | 2 |
| Diffuse Proliferative Glomerulonephritis | 11 | 6 | 3 | 2 | 10 | 1 | 2 |
| Mesangial Proliferative Glomerulonephritis | 3 | 2 | 2 | 2 | 3 | 1 | 1 |
| Focal Proliferative Glomerulonephritis | 7 | 3 | 1 | 1 | 6 | 1 | 3 |
| Membrano-Proliferative Glomerulonephritis | 2 | 2 | 2 | 2 | 2 | 1 | 1 |
| Chronic Glomerulonephritis | 1 | 0 | 0 | 0 | 1 | 0 | 1 |
| Indeterminate Group | 6 | 2 | 0 | 4 | 6 | 1 | 2 |

TABLE VII

BIOCHEMICAL AND HAEMATOLOGICAL FEATURES OF THE 59 PATIENTS WITH THE NEPHROTIC SYNDROME

| Glomerular Morphology | Total No. | Haematuria >5 ph. pf. | Blood Urea >40 mg.% | Anaemia Hb. <12.5% gm. | Leucocytosis >10,000 | Hyponatraemia <137 Meq./L. | Normal Cholesteral Levels |
|---|---|---|---|---|---|---|---|
| Minimal Change Lesion | 22 | 2 | 3 | 6 | 7 | 17 | 1 |
| Focal Glomerulosclerosis | 1 | 1 | 1 | 0 | 0 | 1 | 0 |
| Membranous Nephropathy | 6 | 3 | 0 | 4 | 3 | 4 | 1 |
| Diffuse Proliferative Glomerulonephritis | 11 | 3 | 5 | 4 | 4 | 9 | 1 |
| Mesangial Proliferative Glomerulonephritis | 3 | 1 | 3 | 0 | 2 | 3 | 0 |
| Focal Proliferative Glomerulonephritis | 7 | 5 | 2 | 4 | 1 | 1 | 3 |
| Membrano-Proliferative Glomerulonephritis | 2 | 2 | 2 | 2 | 0 | 1 | 0 |
| Chronic Glomerulonephritis | 1 | 1 | 0 | 1 | 0 | 0 | 1 |
| Indeterminate Group | 6 | 2 | 2 | 2 | 3 | 2- | 0 |

TABLE VIII

CLINICAL COURSE OF THE 59 PATIENTS WITH THE NEPHROTIC SYNDROME

| Glomerular Morphology | Total No. | Cytostatic Therapy | Lasting Remission | Relapsing Course | Persistent Proteinurin | Deaths |
|---|---|---|---|---|---|---|
| Minimal Change Lesion | 22 | 8 | 4 | 12 | 6 | 0 |
| Focal Glomerulosclerosis | 1 | 0 | 0 | 0 | 1 | 0 |
| Membranous Nephropathy | 6 | 4 | 0 | 0 | 6 | 2 |
| Diffuse Proliferative Glomerulonephritis | 11 | 5 | 0 | 6 | 5 | 0 |
| Mesangial Proliferative Glomerulonephritis | 3 | 3 | 0 | 1 | 2 | 1 |
| Focal Proliferative Glomerulonephritis | 7 | 2 | 0 | 2 | 5 | 1 |
| Membrano-Proliferative Glomerulonephritis | 2 | 2 | 0 | 0 | 2 | 0 |
| Chronic Glomerulonephritis | 1 | 1 | 0 | 0 | 1 | 1 |
| Indeterminate Group | 6 | 0 | 1 | 4 | 1 | 0 |

**Mesangial Proliferative Glomerulonephritis**

In this group there is diffuse proliferation confined to the mesangial or "lobular stalk" region. There is thickening, due to a moderate increase of fibrillar content, which takes up P.A.S. and P.A.S.M. stains well (Fig. 5).

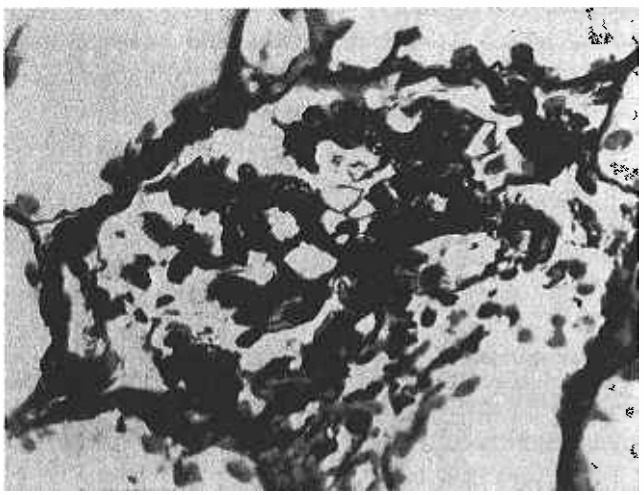

Fig. 5. Mesangial Proliferative Glomerulonephritis. This glomerulus is stained by the periodic acid Schiff silver methanamine method. The central stalk is markedly thickened by Argyrophilic fibres. P.A.S.M. × 500.

There were 3 male patients age 22, 29 and 44 years in this group. The 22 year old patient defaulted after a follow-up period of 2½ years. The 44 year old patient has been followed up for 3 years and he still has proteinuria. The 29 year old patient died in renal failure after being followed up for only 6 months.

The clinical and biochemical features are shown in Tables VI, VII and VIII. The L.E. cell preparations were negative. The ASOT was negative in the 2 patients in whom it was done.

In the case of the patient who died, azathioprine was added to the regime 4 months prior to death. 6-mercaptopurine in the dosage of 200 mg. per day was added to the regime of another patient. This patient developed agranulocytosis but improved when the drug was stopped. Later it was given in the reduced dose of 75 mg. per day for 11 months. Cyclophosphamide in the dose of 100 mg. per day was added to the regime of the 44 year old patient because of persistent proteinuria and frequent exacerbations. This was stopped after 10 months. He has not been on any specific therapy for 21 months and continues to have proteinuria.

**Focal Proliferative Glomerulonephritis**

The renal morphology in the group is characterised by involvement of only some glomeruli, the others being normal. In the affected glomeruli only one or two lobules are involved by proliferation and necrosis. However in severe cases the entire glomerulus is affected. There may be varying number of crescents (Fig. 6). This group cannot be differentiated histologically from cases of Disseminated Lupus Erythematosus, Henoch Schonlein Syndrome, Subacute Bacterial Endocarditis and Good-pasture's Syndrome.

There were 7 patients in this group. The longest follow-up period was 5½ years and the shortest was 1 year in the only patient who died.

There was microhaematuria in 5 patients and hypertension in 3 patients. The hypertension was transient in one and aggravated by prednisolone therapy in 2 patients.

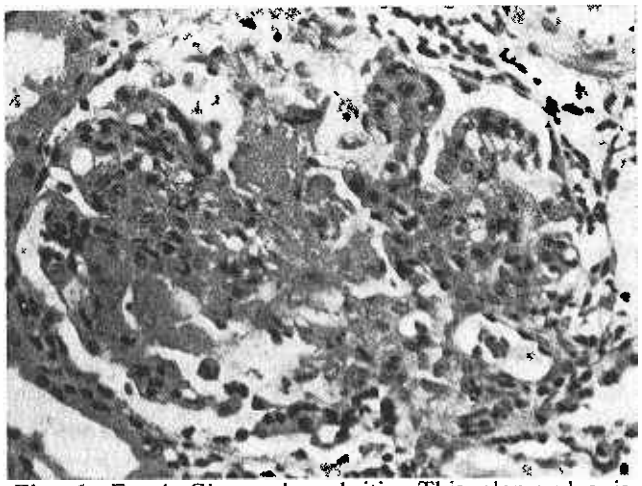

Fig. 6. Focal Glomerulonephritis. This glomerulus is enlarged with hypercellularity at the sides and central necrosis. Some of the necrosis is fibrinoid. H & E × 500.

The blood for L.E. cells was positive initially in a 37 year old patient. This patient developed frank Diabetes Mellitus whenever he was put on steroids and he has had one episode of diabetic ketosis. He has been followed up for 5 years now and has not developed any other evidence for Disseminated Lupus Erythematosus. The prednisolone medication was stopped in July 1967 after which he received cyclophosphamide till October 1967. He still continues to have proteinuria.

The ASOT was positive (625 Todd Units) in a 31 year old patient who died. The blood was also positive for Antinuclear Factor. She was given prednisolone medication only and died of fulminant infection. Azathioprine together with prednisolone was exhibited to a 17 year old Malay girl after the initial renal biopsy. A repeat renal biopsy was performed in this girl 1 year later and this showed absence of crescents that were present initially. All drugs were stopped after the second biopsy. She still continues to have proteinuria although the blood urea and serum proteins are normal. Repeat renal biopsies were done in 4 other patients but these did not show any change in renal morphology when compared with the initial biopsy specimens.

There was no lasting remission in any of the 7 patients, 2 patients followed a relapsing course and in 5 there was persistent proteinuria.

**Membrano-proliferative Glomerulonephritis**

This group is characterised by diffuse mesangial proliferation and capillary wall thickening. The glomerular tufts have lobulated appearance if the mesangial proliferation and sclerosis is marked (Fig. 7).

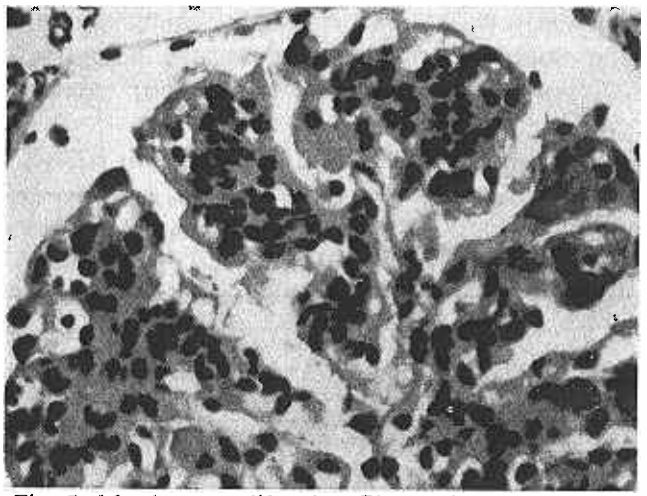

Fig. 7. Membranoproliferative Glomerulonephritis. This glomerular tuft is grossly enlarged. There is a marked increase in endothelial and mesangial cells. Note also the thickened basement membrane. The accentuated lobulation is well shown in the picture. H & E × 500.

There were 2 female patients aged 48 and 30 years. They have been followed up for 4 years and 3 years and 9 months respectively. Both patients presented with generalised anasarca and microhaematuria and the urinary abnormalities are still present. The blood urea in the 48 years old patient has risen from 52 mg.% to 76 mg.% over the years. In the 30 year old patient, whose blood for Antinuclear Factor was positive, the blood urea is normal. However a repeat renal biopsy in the second patient revealed 3 of the 11 glomeruli to be hyalinised and the majority to have pericapsular fibrosis. This patient had 6-mercaptopurine added to her regime for 1 year and cyclophosphamide for another year. Now both have been without any specific therapy for more than 1 year.

**Chronic Glomerulonephritis**

This group is characterised by extensive glomerular sclerosis, interstitial fibrosis, and tubular atrophy (Fig. 8). This is the end result of any form of progressive glomerulopathy.

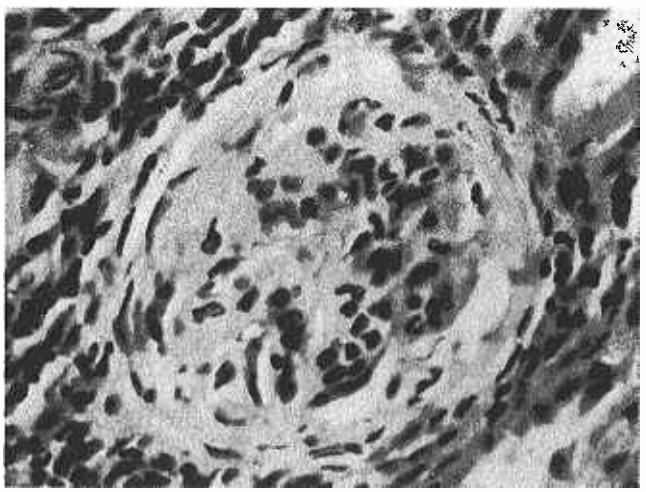

Fig. 8. Chronic Glomerulonephritis. This glomerulus is almost wholly sclerosed, and the degenerating cells are depicted by crowded nuclei. H & E × 500.

The single patient in this group was a 14 year old girl who had been treated by a general practitioner for 2 years. She presented with oedema, hypertension and microhaematuria. The ASOT was 333 Todd Units. She was given prednisolone and guanethidine. Azathioprine was added to the regime 6 months after initial assessment. However, the patient went into renal failure and died in uraemia 1½ years after being first seen in the Tan Tock Seng Hospital.

**Indeterminate Group**

Only 1 patient in this group had a renal biopsy but unfortunately it was not possible to give an opinion on it. The other 5 patients did not have biopsies performed on them as they refused consent for biopsy. In only 1 patient in this group was the follow-up period less than 1½ years but the other 5 defaulted treatment frequently.

## DISCUSSION

Optically normal looking glomeruli were found in 22 (41%) of our adult patients. This is higher than the 18-30% quoted by Robson (1967) and Sharpstone *et al* (1969). However this is the commonest lesion found in children with the nephrotic syndrome and Churg *et al* (1970) found it in 77% of their series. The response to steroid therapy is good and 90% of children have a good initial response and 77% of adults have the same response (Cameron, 1968). There was an initial remission in 10 of our patients but in only 4 was the remission maintained. The other 12 patients pursued a chronic relapsing course and in 6 of these, there was persistent proteinuria. Repeat renal biopsies were done in 12 patients over a three year period and these showed no progression of lesions except in one patient in whose repeat biopsy 3 of 15 glomeruli were found to be hyalinised. This is similar to the 5 year follow-up experience of Pollack *et al* (1968). However McGovern (1964) reported the development of focal glomerular sclerosis in 9 of 39 patients who were initially classified as illustrating the "minimal" lesion and 6 of these 9 died subsequently. There was little tendency for renal function to deteriorate despite frequent relapses and this is similar to the experience of Hardwicke *et al* (1967) and Pollack *et al* (1968). There were no deaths in our series with "minimal" change lesion.

Focal glomerulosclerosis is a previously little recognised entity and patients with this renal lesion have a poor response to steroid therapy (Churg *et al*, 1970). McGovern (1964) believed this to be a slowly progressive disorder. Rich (1957) in an autopsy study of 20 patients drew attention to the fact that the lesion begins in the juxtamedullary glomeruli. Thus a small biopsy specimen of the outer cortical region will miss the lesion and the patient will be classified to be suffering from "minimal change" lesion. The aetiology of both the minimal change and focal glomerulosclerosis is obscure.

Membranous nephropathy is characterised by diffuse thickening of the basement membrane. Biopsy specimens, with proliferative and "minimal change" lesions, which are stained with H & E may give the impression of membranous thickening. But the differentiation can be made with the help of thin sections, special stains (P.A.S. Silver Methanamine) and electromicroscopy (Rastogi *et al*, 1969). Electronmicroscopy will reveal electron dense deposits on the epithelial side of the basement membrane and projections or "splikes" of basement membrane between the deposits (Ehrenreich and Churg, 1968). Serial biopsies have not shown the evolution of "minimal change" or "foot process" lesions into an example of membranous nephropathy (Rosen *et al*, 1964).

All the six patients with membranous nephropathy have persistent proteinuria despite prednisolone therapy and the addition of cytostatics to 4 of the patients. Rastogi *et al* (1969) on the other hand have documented on complete remission with continous corticosteroid therapy in 4 patients. Forland and Spargo (1969) state that corticosteroids rarely provide sustained clinical improvement but they observed remissions or loss of clinical features of the illness in 5 of their 19 patients.

Diffuse proliferative glomerulonephritis may be seen in Post-streptococcal Glomerulonephritis, Disseminated Lupus Erythematosus, Henoch-Schonlein purpura, Polyarteritis Nodosa, Goodpasture's Syndrome and Subacute Bacterial Endocarditis (Leading Article Brit. Med. J., 1970, Cameron, 1970). There was no clinical evidence for any of the above in our 11 patients. However the Antinuclear Factor was positive in one patient in the initial admission. It was negative subsequently and there were no other evidence for Disseminated Lupus Erythematosus. Unlike the report of White and his colleagues (1968), cytostatics were of no value in our patients.

Mesangial proliferations may be seen in subsiding post-streptococcal glomerulonephritis but it may also occur without evidence of previous streptococcal infection (Leading Article Brit. Med. J., 1970). The 3 patients in this group did not have any evidence for previous streptococcal infection. The addition of azathioprine to the prednisolone regime of one patient did not prevent him from dying in renal failure 6 months after being first seen.

There has been scant recognition of focal glomerulonephritis as a distinct morphological entity in most published series of patients with the nephrotic syndrome. It is likely that such cases are being labelled as "minimal change" cases (Heptinstall, 1966). Focal glomerulonephritis may be associated with Henoch-Schonlein Purpura, Disseminated Lupus Erythematosus, Polyarteritis Nodosa, Subacute Bacterial Endocarditis, Goodpasture's Syndrome and in recurrent or isolated haematuria (Heptinstall, 1966). The L.E. cell preparation was positive in 1 of our 7 patients and the Antinuclear Factor was positive in another patient, but none of them had any other evidence for Disseminated Lupus Erythematosus. Azathioprine together with prednisolone was exhibited to one patient when the renal biopsy revealed significant number of crescents. This is the only patient in this series in whom such therapy was of value, as a subsequent biopsy 1 year later showed the absence of crescents. However focal glomerulitis was still present and the patient continues to have proteinuria.

Membranoproliferative glomerulonephritis was reported to cause the nephrotic syndrome from 9-10% of patients (Cameron, 1968; Robson, 1967). However it was found in only 2 of our patients. The capillary thickening which is diffuse is caused by deposition of argyrophilic fibrils between the capillary endothelium and basement membrane. Electron microscopy has revealed the thickening of true basement membrane as well (Cameron *et al*, 1970). A particular feature of the disease is persistently low level of C'3 component or $B_{1C}$ component of the complement (Ogg *et al*, 1968; Cameron, 1970). The prognosis in this group is poor and neither corticosteroids nor cytostatics are of any value. One of our patients has developed uraemia whereas the other has persistent proteinuria and hypoproteinaemia. A repeat biopsy 1 year after the initial one has revealed the progression of the lesions.

The renal biopsy of a single patient revealed such advanced glomerular sclerosis and interstitial nephritis that distinctive morphological features had disappeared, and we had to classify her as suffering from chronic glomerulonephritis. Prednisolone and azathioprine did not prevent her demise in renal failure. However prednisolone and azathioprine therapy has been reported to be of value in such patients (Levitt, 1970).

The value of cytostatic therapy in primary renal disease is still controversial. There are some reports which extol its value (Michael *et al*, 1967; White *et al*, 1968; Moncrieff *et al*, 1969; Levitt, 1970). However these were uncontrolled studies and an international, prospective double-blind controlled trial of azathioprine in children reported that it was of no value and that it should not be given to children with the nephrotic syndrome (Abramowicz *et al*, 1970). In our study cytostatics were of value in only 1 of the 25 patients who received them.

So the mainstay of treatment is still corticosteroid therapy although only one controlled trial has even been attempted. This controlled trial found it to be of value in the "minimal change' group but not in proliferative glomerulonephritis or membranous nephropathy (Black *et al*, 1970).

The commonest complication of steroid therapy was mooning of the face which was seen in all patients at some time. Steroid therapy probably contributed to the deaths of two patients who had fulminant infection.

One patient on 6-mercaptopurine developed pancytopenia which fortunately improved on stopping the drug. Another patient on 6-mercaptopurine developed agranulocytosis which again improved on stopping the drug. A third patient developed severe leucopenia while on cyclophosphamide and this too improved when the drug was stopped. (Table IX). There were no serious complications in those on azathioprine as the dosage used was a small one.

TABLE IX

COMPLICATIONS OF TREATMENT

| | |
|---|---|
| Fulminant Infection | 2 |
| Pancytopenia | 1 |
| Agranulocytosis | 1 |
| Leucopenia | 1 |

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