NEPHROTIC SYNDROME IN AFRICAN AND INDIAN CHILDREN IN SOUTH AFRICA

BY

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"To connect accurate and faithful observations after death with symptoms displayed during life, must be in some degree to forward the objects of our noble arts, and the more extensive the observation, and the more close the connection which can be traced, the more likely we are to discover the real analogy and dependence which exists both between functional and organic disease, and between those, and the external symptoms which are alone submitted to our investigations during life".

(Richard Bright 10th August, 1827).

DECLARATION

This thesis is the candidates own original work.

Selected results from this thesis have been published in scientific journals. Research workers who were closely associated in these studies are co-authors in these publications.

1. Adhikari M., Coovadia H.M., Chrystal V. Absence of "True" Minimal Change Nephrotic Syndrome in African children in South Africa. To be published in the Journal of Tropical Medicine and Hygiene 1982.

2. Adhikari M., Coovadia H.M., Chrystal V. Extra-membranous Nephropathy - submitted for publication.

3. Adhikari M., Coovadia H.M., Chrystal V. Diffuse Mesangial Proliferative Glomerulonephritis - submitted for publication.

4. Dilima M.G., Adhikari M., Coovadia H.M. (1981). Rapidly Progressive Glomerulonephritis in Black Children. A Report of 4 cases. South African Medical Journal, 60, 829 - 832.

5. Coovadia H.M., Adhikari M., Morel-Maroger L. (1979). Clinicopathological Features of the Nephrotic Syndrome in South African Children. Quarterly Journal of Medicine, 48, 79 - 91.

6. Adhikari M., Coovadia H.M., Greig H.B.S., Christensen S. (1978). Procoagulant Activity in Children with the Nephrotic Syndrome and Post-streptococcal Glomerulonephritis. Nephron 22, 301 - 305.

7. Hallett A.F., Adhikari M., Cooper R., Coovadia H.M. (1977). Poststreptococcal Glomerulonephritis in African Children. Transactions of the Royal Society of Tropical Medicine and Hygiene, 71, 241 - 246.

8. Adhikari M, Coovadia H.M., Loening W.E.K. (1976). The Nephrotic Syndrome in Children. South African Medical Journal, 1, 39 - 43.

THE NEPHROTIC SYNDROME IN AFRICAN AND INDIAN CHILDREN IN SOUTH AFRICA

ABBREVIATIONS AND SYMBOLS

NS	=	Nephrotic Syndrome
MCNS/MIN	=	Minimal Change Nephrotic Syndrome
EM/MEM	=	Extramembranous Nephropathy
DMP/MES	=	Diffuse Mesnagial Proliferative
DP	=	Diffuse Proliferative
DE/EXUD	=	Diffuse Exudative
Endo	=	Diffuse Endocapillary
MPGN/MEM-PR	=	Membranoproliferative Glomerulonephritis
FPGN/FP	=	Focal Proliferative Glomerulonephritis
FGS	=	Focal Glomerulosclerosis
TEM/TE	=	Tropical Extramembranous Nephropathy
TN	=	Tropical Nephropathy
UNC	=	Unclassified Glomerulonephritis
GBM	=	Glomerular Basement Membrane
GN	=	Glomerulonephritis
AN	=	Acute Nephritis
RPGN	=	Rapidly Progressive Glomerulonephritis
APSGN	=	Acute Poststreptococcal Glomerulonephritis
SLE	=	Systemic Lupus Erythematosis
HSP	=	Henoch Schönlein Purpura
HBsAg	=	Australia Antigen (surface)
GFR	=	Glomerular Filtration Rate
IF	=	Immunofluorescence
ASOT	=	Antistreptolysin O Titre
HPT	=	Hypertension
Haem	=	Haematuria

Rem	=	Remission
Rel	=	Relapse
PP	=	Persistent Proteinuria
ME	=	Multiple Episodes
M	=	Males
F	=	Females
S	=	Steroids
E	=	Cyclophosphamide
C	=	Chlorambricil
+	=	Response to therapy/presence of clinical feature
-	=	No response to therapy/absence of clinical feature
$\pm$	=	Equivocal response to therapy
N/G	=	Not given
X	=	African
O	=	Indian

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SUMMARY

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1. Introduction

There are comprehensive accounts of the nephrotic syndrome in childhood in temperate countries. Many of the important features of this disease have been known for close on to two decades. The causal link between malaria and nephrosis in tropical Africa has also been recognised and documented for a similar length of time. Very little was known of the nephrotic syndrome in the sub-tropical zones of Africa where malaria is not endemic. Anecdotal evidence in South Africa suggested that African children with this disease appeared to have steroid-resistant nephrosis and a more protracted clinical course than expected from prevailing accounts in the literature and that Indian South African children generally responded to steroids.

This thesis is the result of detailed investigations in to this disease in African and Indian children in Durban, South Africa.

2. Preliminary Study

A preliminary study was undertaken in which 53 (12 African and 41 Indian) children with the nephrotic syndrome defined by clinical and biochemical criteria

were studied. Renal biopsies were not available on these patients. The results revealed that two thirds of the African children were over 5 years of age and 50% were males. Of the Indian children 50% were under 5 years of age and 50% were males.

Nine African children were treated with steroids and 8 did not respond whereas 31 of the 39 Indian children treated clearly responded to steroid therapy. In addition 5 Indian patients were treated with cyclophosphamide and 3 responded.

On follow-up 7 of the African children had persistent proteinuria, 2 experienced remissions and 3 were lost to follow-up. All the Indian patients experienced remissions.

The differences between the 2 groups of nephrotic patients were quite striking and therefore a more detailed prospective study of this problem was undertaken.

3. Prospective Study of Primary Nephrotic Syndrome

One hundred and seventy children of whom 104 were African and 66 Indian with primary nephrotic syndrome were studied. In both racial groups the male sex dominated, Indian children tended to present

at a younger age group whereas African children presented at two peak ages, 5 years and between 5 - 10 years.

3.1 Histological Differences

The histological types found on light microscopic examination of renal tissue were distinctly different between the African and the Indian children. The majority (85.6%) of the African children had 'obvious' glomerular lesions, the commonest being extramembranous nephropathy (29.8%). Although the proliferative group was the single largest group (40%) none of the subgroups exceeded the extramembranous type in their number. Minimal change accounted for only 14.4% of the African children with nephrotic syndrome.

The majority of Indian children (72.7%) had minimal change on light microscopy, 9.1% focal glomerulosclerosis and 12.1% had proliferative changes.

3.2 Immunofluorescence

Immunofluorescent studies also indicated differences between the two groups of patients. Generally, heavier deposits of immunoglobulins

and complement components were identified on renal biopsy specimens of African children. This occurred even in MCNS where most African children had heavy IgG, light IgM, IgA and complement components whereas only a few of the Indian children had light IgM deposits. Similar differences were observed in diffuse mesangial proliferative glomerulonephritis and focal glomerulosclerosis where the numbers of patients were comparable.

3.3 Presenting Features

Clinical features at presentation in the two groups were different, as expected from the nature of the histological findings in each group. In the African children (all histological groups) haematuria occurred in 35.5%, hypertension 16.3% and renal failure in 2.9%.

The clinical features in the Indian children were not too different from MCNS elsewhere. Haematuria occurred in a small percentage (3%) of MCNS but was more frequent (10.7%) in other groups. Hypertension and renal failure occurred infrequently in histological categories other than MCNS where they did not occur at all.

3.4 Course and Outcome

In view of the above it was not unexpected to find that the clinical course and outcome in the two groups were quite dissimilar. African patients in certain of the histological groups fared reasonably well, but none of the groups had the excellent prognosis of Indian MCNS.

3.4.1 Minimal Change

One third of the African MCNS patients remitted and this was unrelated to steroids. The remainder who were followed for a reasonable duration of time remained proteinuric. None developed signs of serious renal impairment (azotaemia, hypertension). Indian MCNS experienced an excellent prognosis with 97.8% achieving remission and 81.6% being steroid sensitive. One third of these patients had a single episode of nephrosis while frequent relapses occurred in 28.2%.

3.4.2 Extramembranous Nephropathy

Patients with extramembranous nephropathy, the largest group in the African patients, experienced hypertension more often (20%)

and remission less often (30%) than do children in temperate climates. The clinical presentation, course and outcome in the majority of these patients were similar to adults with extramembranous nephropathy.

3.4.3 Proliferative Glomerulonephritis

The patients in the proliferative group had a variable outcome depending on the subgroup to which they belonged.

In diffuse mesangial proliferation, African patients had a higher incidence of hypertension and fewer remissions and fared less well than Indian patients. The diffuse endocapillary glomerulonephritis, membranoproliferative and focal proliferative nephritis groups of patients suffered severe disease with a failure to remit and progression to death. In the diffuse exudative group, remissions occurred or proteinuria persisted but severe relapse and death did not occur. The worst prognosis was in the focal proliferative group with the highest incidence of persistent relapse.

3.4.4 Focal Glomerular Sclerosis

Focal glomerular sclerosis was an unusual

histological diagnosis in the African child (3.9%) with a poorer prognosis (persistent proteinuria or death) when compared to Indian children in whom one third remitted and the rest had persistent proteinuria.

3.4.5 Tropical Nephropathies

It is difficult to comment on the course of the tropical nephropathy (not related to malaria) and tropical extramembranous groups as the numbers are small. However, in tropical extramembranous, none remitted (all African children) and in tropical nephropathy one Indian child remitted but one of 2 African children died and the other had persistent proteinuria.

3.5 Response to Therapy

Perhaps the most important practical aspect of the nephrotic syndrome in the African child was the response to steroid therapy. Thirty-two African children were given steroid therapy. Thirty (93.7%) did not respond. Five children deteriorated or died during steroid therapy. Very few patients (4) were given cyclophosphamide and none responded.

Generally intravenous albumen, diuretics and a high protein dietwere not very effective in those patients with severe, clinical disease but were of benefit in milder disease.

Indian children taken as a whole, responded well to steroid therapy. Seventy-eight percent of the whole group responded to steroids and 21.4% developed cushingoid features. Of the 19 Indian children (all MCNS) treated with cyclophosphamide 63.2% responded of whom about a quarter got toxic side effects (alopecia, darkened nails and leucopenia). Chlorambucil therapy in 4 children (all MCNS) was successful in all.

3.6 Complications

Serious infections (septicaemia, peritonitis, urinary tract infection, meningitis, arthritis, osteitis, measles, chicken pox) occurred in 8.7% of the African patients. Eighteen percent had less severe infections.

Just over a quarter of the Indian children suffered severe infections. The majority of these patients were MCNS and about 50% were on steroids or cyclophosphamide at the

time of their infection.

Renal biopsy complications were minor, these being abdominal pain and tenderness or transient haematuria. A few patients developed renal haematomas which were detected or monitored by ultrasonography. The single serious complication was the development of a renal abscess at the biopsy site requiring partial nephrectomy.

3.7 Mortality

The overall mortality was 5.8%. Seven of the 10 deaths were African children in the Proliferative Group and 3 of the 10 deaths were Indian children.

4. Secondary Nephrotic Syndrome

The secondary nephrotics formed an interesting group of patients. Of the 22 patients classified as secondary nephrotics 11 (50%) were related to streptococcal infection either as rapidly progressive glomerulonephritis or transient NS following APSGN. HB_SAg was detected in the blood of 8.6% of the African patients. However the HB_SAg carrier rate in this age group is 7.4%. The incidence in these

patients probably reflects the high incidence in this population group. Collagen vascular disease occurred in 2 patients, both Indian.

5. Conclusions and Recommendations

The results of this study demonstrates the strikingly different incidences of the various histological categories in the two race groups studied with a less favourable prognosis and fewer remission rates being achieved in African children. Indian children had more serious infections more often than African children. Steroid and immunosuppressive agents were of no value and probably hazardous in the African child. Some patients deteriorated on these drugs. Indian children who had an excellent response to these drugs were however at significant risk of developing serious infections.

Why African children in Durban develop obvious glomerular lesions has not been established. Known or possible aetiological agents such as malaria, schistosomiasis, streptococcal infections and collagen diseases have been excluded.

The answer to the above question may in fact lie in genetic predisposition, host factors and environmental influences, either singly or in combination, predisposing to the development of obvious

glomerular lesions. These require more intensive investigation and judging from the yield of similar studies in other areas of the world expectations have to be guarded.

1. INTRODUCTION

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1.1 Historical Review

The nephrotic syndrome is a well recognised clinical entity known to have varying histological patterns, the incidence of which differs in adults and children.

'Nephrosis' was a term first used by Friedrich Müller and referred to the degenerative lesions of the kidney which chiefly involve the tubules (Müller 1905). Volhard & Fahr (1914) emphasised the distinction between "nephrosis" and "nephritis".

Conversely Ellis (1942) regarded the nephrotic syndrome as a form of nephritis and called it type II nephritis. The nephrotic syndrome in children is now recognised as a primary renal disease affecting the entire nephron, the characteristic lesion occurring on the glomerular basement membrane.

"White clouds in the urine" had been noticed by Hippocrates (Garrison 1960). Probably the earliest account of chronic nephritis was noted by the Italian surgeon William de Saliceto of the 13th Century who pointed out the association of dropsy, scanty urine and hardened kidneys (Garrison 1960). Some 500 years later Frederik Dekkers and Domenico

Cotugno (Major 1939) noted albuminuria without recognising the possible significance of their finding. In the early 19th Century William Charles Wells and John Blackall (Major 1939) established the correlation between dropsy and albuminous urine. Morgagni described the clinical and postmortem findings in renal disease (Castiglione 1947).

However, it was Richard Bright's brilliant clinical and pathological observations in the 19th Century that associated diseased kidneys with dropsy and albuminuria. Bright's disease then entered the category of renal disease states and the term was used to describe a heterogeneous group of conditions outlined by Volhard and Fahr (1914) characterised by nonsuppurative inflammatory, degenerative or sclerotic changes in the kidneys.

It then became obvious that a particular clinical syndrome varied greatly pathologically and that a pathological entity presented with a number of clinical expressions. The terms "nephritis" then used was limited to those cases in which inflammatory changes predominated, "nephrosis" to those associated with degenerative tubular changes and "nephrotic-nephritis" to a subacute phase following acute nephritis (Ellis 1942). Samuel Wilks in 1853 suggested that several renal diseases might

give rise to the nephrotic syndrome and renal failure.

Early in the 20th Century attempts were made to categorise the pathologic features of the nephrotic syndrome. Two broad groups of diseases were recognised; in one, glomerular lesions predominated, associated commonly with left ventricular hypertrophy, nitrogen retention and uraemia (Schmidt 1906, Widal et al 1912); the other was nephrosis, in which tubular lesions were predominant (Müller 1905, Volhard and Fahr 1914). The term "nephrosis" was used with 2 very different connotations - one was a descriptive histopathologic term for renal disease without an inflammatory component and the second was to describe the clinical picture caused by heavy urinary protein losses.

Addis considered that all cases of glomerulonephritis started with an acute stage which in some cases was inapparent. Those who survived the acute attack entered the latent stage in which the urinary sediment was abnormal, with or without significant proteinuria. Some patients recovered completely whereas other patients after a period of years developed renal failure, hypertension and death. A certain proportion of these passed into a degenerative phase with the clinical features of

the nephrotic syndrome. The prognosis for those in the degenerative stage was poor with 52% dying within 3 years and only 3% surviving as long as 12 years (Heptinstall, 1966). (Figure 1).

Longcope and Ellis had very similar views. Longcope noted that nephritis could present as type A or B. In type A the initial attack followed Streptococcal infections. Some patients died while the majority passed into a quiescent stage with persisting urinary changes which might take up to 2 years to resolve.

In type B the onset was insiduous with no preceding infection and with features of the nephrotic syndrome. During the course of their disease these patients experienced episodes of hypertension oedema, haematuria and varying degrees of proteinuria. Death frequently occurred in a state of hypertension and renal failure. (Figure 2).

Ellis called his two groups types 1 and 2 (figure 3) which resembled Longcopes' Types A and B. Type 1 was acute in onset with haematuria, proteinuria, some oedema and transient hypertension, preceded in the majority by an infection of the throat. 60% occurred in the first 2 decades of life. The general trend was towards recovery and this occurred in 82%

FIGURE 1

ADDIS' THEORY (1949)

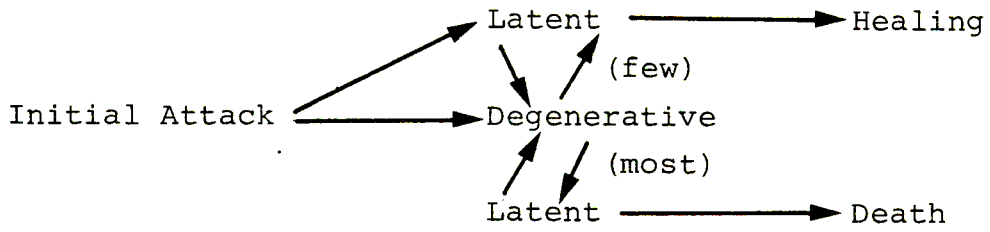
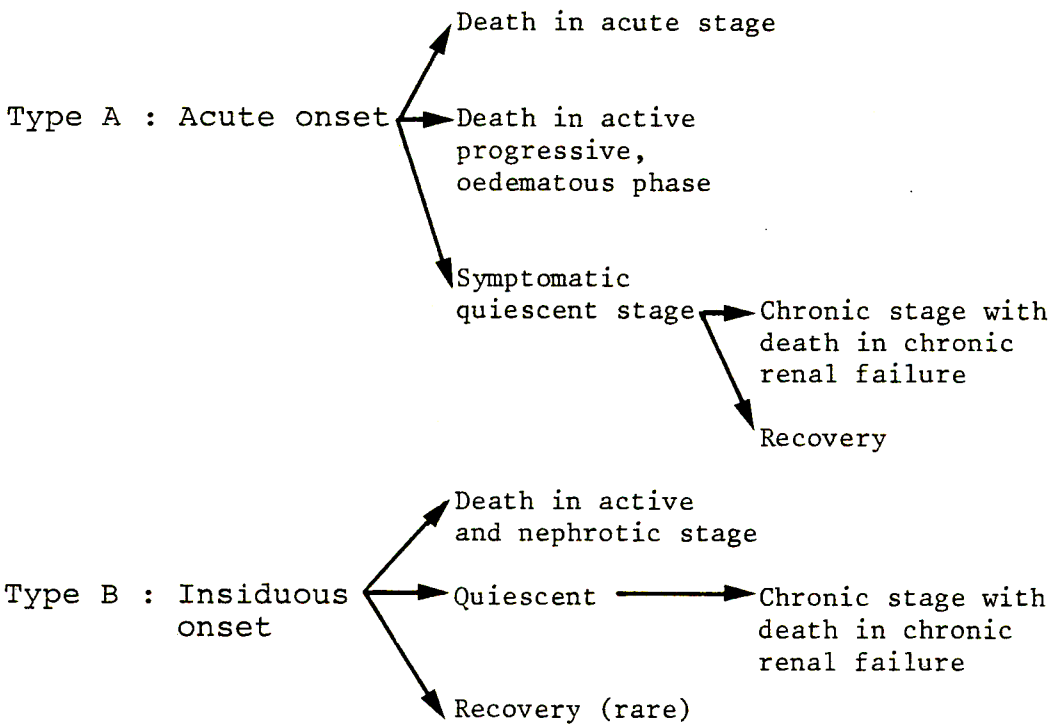


FIGURE 2

LONGCOPE'S THEORY (1936, 1937)



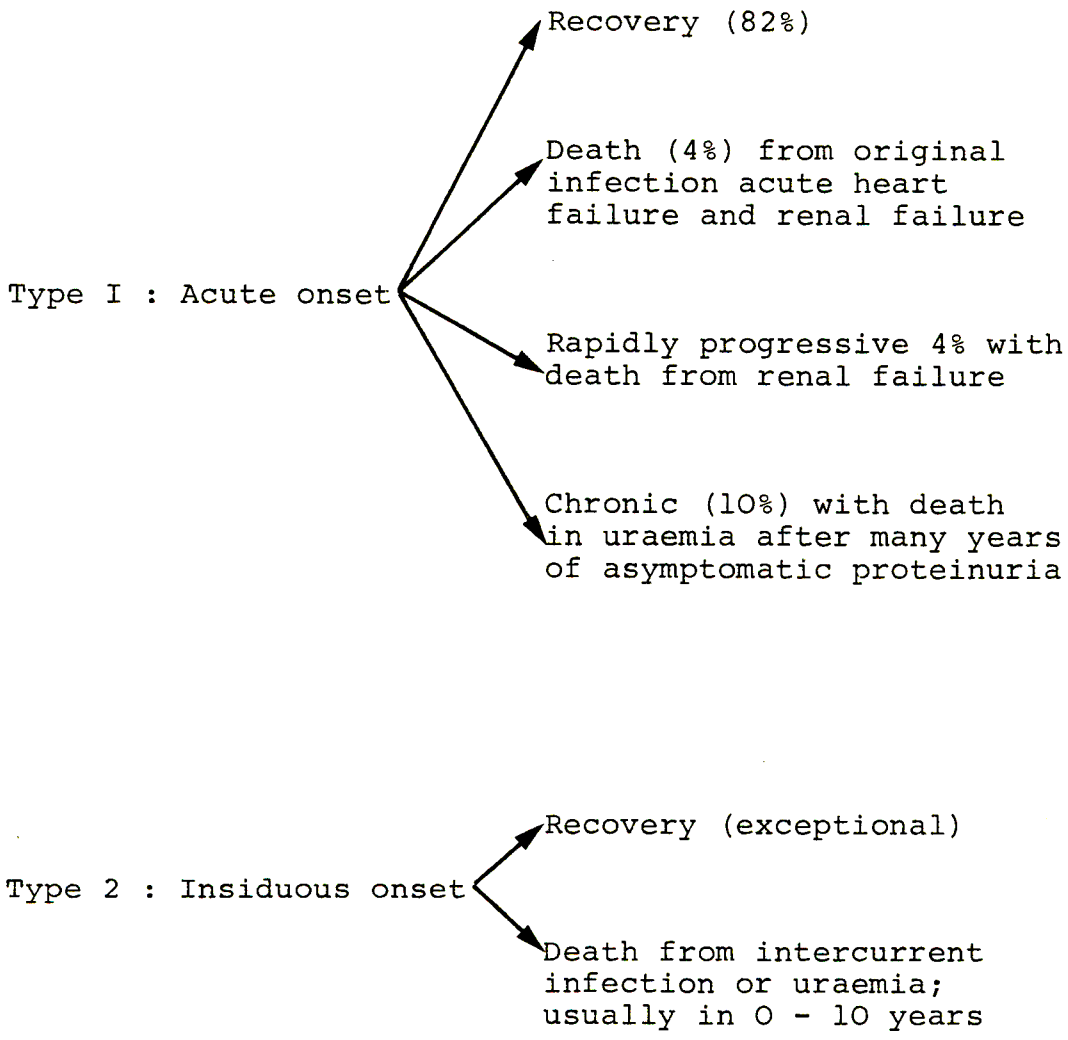
within 2 weeks of the attack. A small percentage (4%) died in the acute attack from infection, uraemia and heart failure. A further 4% showed persistent signs with deterioration of renal function and death within weeks or months. This was the rapidly progressive form similar to Volhard's (1918) subacute form and the progressive oedematous form of Longcope.

The type 2 had an insiduous onset with severe persistent oedema and severe proteinuria. There was a wider age distribution and a previous history of infection in fewer than 5%. The clinical course was generally fatal from infection, hypertension or renal failure over a period of months or years. Most died within 5 years. Similarities between the various concepts were quite striking but a conflict arose as to whether the two were aetiologically different diseases or clinical variants of a single theme. The concepts of Volhard and Addis favoured the latter. The type B of Longcope and type 2 of Ellis were considered by both these workers to be the result of subclinical acute attacks.

Many patients with chronic nephritis did not give a history of an antecedent attack of glomerulonephritis. It followed that chronic nephritis arose de novo or followed an inapparent acute attack.

FIGURE 3

ELLIS' THEORY (1942)



At that time it was accepted that most cases of chronic nephritis were the end result of an acute post streptococcal glomerulonephritis.

The insiduous onset type B of Longcope and type 2 of Ellis were obviously the nephrotic syndrome in current terminology. The nephrotic syndrome now is a term of clinical convenience used to describe a clinical state of multiple origin and varying histology. It is clear today that the condition represents a stage in a variety of disorders in which increased permeability of the glomerular basement membrane causes heavy proteinuria resulting in hypoproteinaemia, excessive retention of salt and water, along with other metabolic disturbances. The same diseases may exist in less severe or subclinical forms for months or years before oedema develops or the patient is aware of any illness with or without haematuria.

1.2 Histological Classification

In King Edward Hospital, Durban, the commonest form of glomerular disease is acute poststreptococcal glomerulonephritis followed by the nephrotic syndrome. In other parts of the world where this disease in no longer prevalent the nephrotic syndrome is the most important form of glomerular disease.

The nephrotic syndrome with or without haematuria is one of the clinical expressions of glomerular disease. It is also the commonest presentation of glomerulopathy. In Habib's (1974a) series of 1368 paediatric cases of glomerular disease, 875 had nephrotic syndrome. The other clinical presentations of glomerular disease may be asymptomatic haematuria, asymptomatic proteinuria, proteinuria and haematuria (Habib 1974 (a)) and acute nephritic syndrome (Morel-Maroger 1976).

The nephrotic syndrome is associated with a number of different histological changes in renal tissue (Habib 1974d). The problem is complicated by the fact that histology does not relate directly to aetiology. The same histological pattern may be due to different causes. However, certain types are not seen in systemic disease e.g. infantile mesangial sclerosis or focal glomerular sclerosis. Conversely a nephropathy accompanying a particular disease process may show various types of histological lesions - the classic example being systemic lupus erythematosus (Ginzler et al 1980, Churg et al 1970, Habib 1970).

In recent years the understanding of glomerular lesions has vastly improved and this has been due to the advances in the study of kidney tissue obtained by

biopsy. The greatest value of renal biopsy has been in the nephrotic syndrome (Muehrcke and Pirani 1975), this being the only way of making an exact morphological evaluation of renal tissue. Besides light microscopy, electron and fluorescence microscopy have aided in diagnosis of glomerular disease.

It is possible to classify glomerular lesions in a number of ways - clinically, aetiologically, pathogenetically and morphologically. As discussed above, a number of clinical variations are possible and it is often not possible to detect the aetiological agent. Furthermore, although considerable evidence is available indicating an immunopathological background for certain types of glomerular disease, this is not often useful for classification or management. Although a large number of histological patterns have been recognised, the most important basic fact is that each histological group corresponds roughly to a particular clinical pattern with a particular course (Habib 1970). The correlation extends from being exact for some to imprecise for others. From the practical point of view however it is the only way presently in which prognosis can be assessed in the individual patient and may be independent of aetiological factors and symptomatology (Habib 1974d).

1.2.1 Classifications

A number of classifications have developed since renal biopsies became standard practice. Heptinstall (1966) reviewed the aetiology and pathological changes of the nephrotic syndrome. He included paediatric cases and his own experience. The following tables were taken from his book (Heptinstall 1966). Table I and Table II.

Churg et al (1970) re-examined the histological features of a number of paediatric patients studied prospectively by members of the International Study of Kidney Diseases in Children (Abramowicz et al 1970). They also examined the relative frequences of the histological groups and the clinical course. Table III from Churg et al (1970) gives their findings. Table IV is Habib's classification.

Generally excluded from the category of primary nephrotic syndrome is nephrosis secondary to systemic diseases or other obvious causes e.g. systemic lupus erythematosus, anaphyloctoid purpura, renal vein thrombosis, diabetes mellitus, amyloidosis (Habib & Kleinknecht 1971, Rance et al 1976).

All the classifications discussed are firstly divided into 2 broad groups of specific or secondary nephrotic syndrome and non-specific, idiopathic or primary nephrotic syndrome.

TABLE I

HEPTINSTALL'S HISTOLOGICAL DIAGNOSIS OF NEPHROTIC SYNDROME AT BIOPSY

(1966)

Diagnosis	Number
Glomerulonephritis	
Proliferative	9
Idiopathic membranous	13
Membrane thickening and proliferative	3
Lobular	
Subacute	
Chronic	3
Focal	9
Type 2	
Lipoid nephrosis	17
"minimal change" etc.	3*
Increased renal vein pressure	4
Diabetes mellitus	2
Amyloidosis	2
Systemic lupus erythematosus	
Nephrosclerosis	3
Other	2
Total	70

*Tubular dilatation in addition to lipoid nephrosis.

TABLE II

HISTOLOGICAL DIAGNOSIS OF NEPHROTIC SYNDROME AT BIOPSY IN RELATION TO SEX AND AGE (HEPTINSTALL 1966)

Diagnosis	No of Patients	Male	Female	Age (yr.)
Glomerulonephritis				
Proliferative (diffuse)	9	7	2	7, 12, 23, 35, 35, 42, 44, 50, 75
Idiopathic membranous	13	12	1	15, 19, 22, 25, 30, 31, 33, 37, 41, 44, 51, 66, 68.
Combined membrane thickening and proliferative	3	1	2	29, 43, 21.
Chronic	3	2	1	3, 23, 54.
Focal	9	8	1	9, 19, 42, 44, 50, 55, 55, 61, 68.
Lipoid nephrosis ("minimal change" or "no change" with light microscope)	17	9	8	2, 2, 3, 5, 9, 12, 14, 16, 19, 19, 26, 27, 37, 38, 46, 51, 53.
Same but with conspicuous tubular dilatation	3	2	1	3, 5, 21.
Renal vein thrombosis	4	3	1	55, 56, 56, 60.
Diabetes mellitus	2	1	1	28, 35.
Amyloidosis	2	2	0	38, 60.
Miscellaneous				
Kidneys with arteriosclerosis and arteriolosclerosis only	3	1	2	53, 69, 81.
Mercurial diuretic	1	1	0	71.
Nephrocalcinosis	1	1	0	7.
Total	70	50	20	

Source: Heptinstall, R.H., and Joekes, A.M. Unpublished data, 1960.

TABLE III

(CHURG & HABIB) 1970

Glomerular Changes	
Minimal changes	98
Focal sclerotic lesions	12
Proliferative glomerulonephritis	
Mesangial	4
with crescents	4
Membranoproliferative	6
Membranous nephropathy	2
Chronic glomerulonephritis	1
TOTAL	127

TABLE IV

CLASSIFICATION OF GLOMERULAR NEPHROPATHY (1368 CASES)
(HABIB 1974)

I	GLOMERULAR NEPHROPATHIES ASSOCIATED WITH MINIMAL GLOMERULAR LESIONS (586 cases)	
	Pure idiopathic nephrotic syndrome	317
	Idiopathic nephrotic syndrome with hematuria	110
	Idiopathic "proteinuria hematuria" syndrome	82
	Isolated proteinuria	55
	Isolated hematuria	22
II	GLOMERULAR NEPHROPATHIES ASSOCIATED WITH SPECIFIC GLOMERULAR LESIONS (142 cases)	
	Thrombotic microangiopathy	110
	Amyloidosis	9
	Diabetic glomerulosclerosis	2
	Malarial "membranous" glomerulonephritis	21
	Lupus nephritis (with hematoxylin bodies)	0
III	GLOMERULAR NEPHROPATHIES ASSOCIATED WITH NONSPECIFIC GLOMERULAR LESIONS (607 cases)	
	A. Diffuse glomerular lesions	
	1. Nonproliferative	
	Extramembranous glomerulonephritis	50
	"Membranous" glomerulonephritis	10
	Infantile mesangial sclerosis	10
	2. Proliferative	
	Pure endocapillary glomerulonephritis	86
	Endocapillary and extracapillary glomerulonephritis (with focal crescents)	121
	Endocapillary and extracapillary glomerulonephritis (with diffuse crescents)	27
	Membranoproliferative and lobular glomerulonephritis	106
	B. Focal glomerular lesions	
	1. Segmental and focal glomerulonephritis	99
	2. Focal glomerular sclerosis	
	Segmental hyalinization	74
	Global fibrosis	24
IV	UNCLASSIFIED GLOMERULAR LESIONS (33 cases)	
	Alport's syndrome	6
	Focal "membranoproliferative" glomerulonephritis	4
	Extramembranous glomerulonephritis with mesangial proliferation	4
	Lesions too advanced for classification	19

The primary group is then divided into

1) the minimal change group (normal glomeruli).
2) the membranous group (thickened GBM with spikes).
3) the proliferative group with a number of subgroups based on the type of cellular proliferation with or without BM thickening. With time the clinical presentation and natural history is being more clearly defined for each subgroup.
4) focal glomerulosclerosis which appears to be more defined histologically and clinically.
5) other histological categories that cannot be classified into any of the above and occur in the experience of different investigations e.g. malarial nephropathy (Hendricks et al 1972) focal membranoproliferative nephritis (Habib 1974a).

1.2.2 Definitions of Histological Groups

The definitions used in this study are based on the classification by Lilian Morel-Maroger, who was a co-investigator in this project. (See Histopathological Analysis of Glomerular Disease Advanced Medicine 1976). Table V.

I No obvious lesions

Minimal Change

All the glomeruli appeared normal on light microscopy

TABLE V

CLASSIFICATION OF GLOMERULAR DISEASE - MOREL MAROGER 1976

I Idiopathic Glomerular Disease

1. Nephrotic syndrome with minimal changes.
2. Membranous glomerulonephropathy.
3. Membranoproliferative glomerulonephritis with
   (i) subendothelial deposits.
   (ii) dense deposits.
4. Focal hyalinosis or Focal Glomerular Sclerosis.
5. Focal Proliferative Glomerulonephritis.
6. Focal Glomerulonephritis with Mesangial IgA.
7. Other Primary Proliferative Focal Glomerulonephritis.
8. Diffuse extra capillary or crescentic glomerulonephritis.

II Glomerular Diseases Associated with Infections and Parasitic Disease

1. Diffuse Proliferative Glomerulonephritis (Acute Glomerulonephritis mainly Post Streptococcal).
2. Glomerulonephritis in Subacute Bacterial Endocarditis and Shunt Nephritis.
3. Quartan Malarial Nephropathy and Tropical Nephropathies (Schistosomiasis, Kala-azar, filariasis).

III Glomerular Lesions in Systemic Diseases

1. Systemic Lesions Erythematosus (SLE).
2. Diffuse Glomerulonephritis.
3. Focal Glomerulonephritis.
4. Extramembranous Glomerulonephritis of SLE.
5. Minimal Changes in SLE.
6. Henoch-Schonlein Syndrome.
7. Goodpastures Syndrome.
8. Polyarteritis nodosa.
9. Thrombotic Microangiopathy.
10. Dysproteinaemias.
11. Amyloidosis.
12. Diabetes.

with at most fusion of epithelial foot processers on electron microscopy.

II Obvious Glomerular Lesions

1. Extramembranous

The glomerular basement membrane is thickened with spikes arising from the GBM. Deposits which are separated by the spiky projections arising from the GBM are located on the epithelial aspect of the GBM beneath the foot processes. The spikes are detected using the silver stain. Cellular proliferation is absent.

2. Proliferative

a) Mesangial Proliferative (see Waldherr et al 1978).

By light microscopy there was generalised diffuse mesangial - cell hyperplasia. The basement membrane, tubules and interstitium were normal.

b) Membranoproliferative

The following features on light microscopy were accepted for this diagnosis.

(i) Diffuse mesangial proliferation.

(ii) Increase in mesangial matrix.

(iii) Diffuse irregular thickening of the walls

of the glomerular capillaries some showing distinct double contours.

(iv) Extra capillary proliferation with epithelial crescents.

c) Diffuse Proliferative

The criteria for the subgroups of this category were:

1) Diffuse Exudative (see Turner 1978)

Diffuse endocapillary proliferation polymorph infiltration with or without epithelial proliferation and crescent formation in 50% of the glomeruli. The GBM is normal with sub-epithelial "lumps" being visible.

2) Diffuse Extracapillary or Crescentic Glomerulonephritis

There is cellular proliferation of the cells of Bowman's capsule in more than half the glomeruli. These crescents later become fibrous obliterating the urinary space. Mesangial and endothelial proliferation may be present with various capillary wall abnormalities: tram tracks, subendothelial deposits, dense deposits. Immunofluorescence demonstrates fibrinogen in the crescents. IgG may be present on the capillary wall.

3) Diffuse Endocapillary

Diffuse proliferation of endocapillary cells with accentuation of lobules and normal GBM.

d) Focal Proliferative Glomerulonephritis

Focal and segmental endothelial or mesangial cell proliferation. Glomerular sclerosis might be present in fewer than half the glomeruli.

3. Focal Glomerular Sclerosis (see also Habib and Gubler 1975)

Focal and segmental shrinkage of glomerular tufts usually in the juxtamedullary glomeruli with adhesions to Bowmans capsule. Fibrinoid deposits and fatty vacuoles on the endothelial side of the glomerular basement membrane. Diffuse mesangial hypercellularity may be present. Tubular atrophy and interstitial fibrosis with the presence of foam cells in the interstitium are almost always present.

4. Tropical Extramembranous

Marked extramembranous thickening with spike formation and conspicuous cellular proliferation on light microscopy. On electron microscopy the basement membrane had both extramembranous and intramembranous deposits with no lacunae, splitting and intrusion

into the capillary lumena. Cellular proliferation is due to mesangial and endothelial cells.

5. Tropical Nephropathy (see also Hendrickse et al 1972).

The histological findings in these patients were as follows: capillary wall thickening and segmental glomerular sclerosis which may lead to progressive glomerular damage and secondary tubular atrophy. Cellular proliferation is inconspicuous and absent. The basement membrane has a characteristic splitting or flaking of the glomerular capillary walls and intrusion of basement membrane-like material into the lumen seen on silver stains.

Initially only occasional capillary loops may be affected with increasing involvement diffuse capillary wall thickening occurs. The sclerosing process spreads to involve the mesangium producing segmental lesions which lead to total obliteration of the tuft.

Since the broad categories of minimal, membranous and proliferative were designated, morhpological classification has progressed considerably with regular modification as evolution of disease processes are clarified. However problems still exist despite the best of efforts to remove prejudice. For example in quantitating histological change,

interpretation is still highly subjective. How important is mesangial prominence in minimal change nephrotic syndrome? When does the prominence become proliferative? How important are the focal glomerular changes with minimal change nephrotic syndrome. At which point is the disease no longer minimal change but focal glomerulosclerosis. These questions cannot be answered with objectivity.

Furthermore, there may be agreement with the histological classifications, but outcome for the patient may be quite different. An example is membranoproliferative glomerulonephritis where 2 subtypes have been recognised - type I characterised by endothelial deposits and type II with dense intramembranous deposits (Habib & Kleinknecht 1971, Davis et al 1978). Some reports indicate that the clinical course, rate of progression to renal insufficiency, complement levels and presence of nephrotic syndrome vary between the two types (Cameron et al 1973, Habib et al 1973b) whereas other observers find these two clinically indistinguisable (Davis et al 1978, Antoine and Faye 1972).

One of the major difficulties in this study has been the interpretation of the histology of renal biopsies. For uniformity, biopsies were sent to Dr. Morel-Maroger (Paris). More recently the Department of

Pathology has been able to offer a great deal more assistance with interpretation of histology, immunofluorescence and electron microscopy. We have had to accept certain technical differences e.g. sections for light microscopy could not be thinner than 4 um.

The purpose of any classification is to provide a guide for the clinician. As noted in Tropical Africa (Hendrickse et al 1972) and South Africa (Coovadia et al 1979), the incidence of the various histological categories in the African child with nephrotic syndrome is very different. In the majority of cases the idiopathic nephrotic syndrome is not minimal change but demonstrates obvious glomerular lesions. Systemic diseases are very uncommon. Infections and parasitic diseases therefore assume a more important role. In Tropical Africa the importance of Malaria as the cause of the nephrotic syndrome in the African child has been shown (Hendrickse et al 1972, Kibukomusoke et al 1967). Whilst in South Africa, no parasite or infection has been implicated.

1.3 Pathogenesis

1.3.1 Historical Review of Pathogenesis

The first good demonstration of kidney disease induced by immunological mechanisms was demonstrated

by Lindemann (1900 a). He injected kidney homogenates from rabbits into the peritoneum of guinea pigs. He then obtained serum from the guinea pigs and injected the rabbits, inducing proteinuria, uraemia and death 3-5 days after the injection. Lindemann suggested that specific substances formed in the guinea pig serum and that these substances resulted in damage to the rabbit kidneys.

During the last decade of the 19th Century, heterologous serum was used as a therapeutic agent in infectious diseases. For example serum was administered for the neutralisation of diphtheria toxin (von Behring and Kitasato 1890, von Behring 1892). The side effects of this therapy were urticarial rashes, joint pain, enlargement of lymph nodes, fever and occasionally proteinuria. Rarely, there was an anaphylactic reaction. This syndrome was termed "serum sickness" by Clemen von Pirquet. The first monograph on serum sickness was published by Francioni (1904).

Von Pirquet (1911) suggested that in serum sickness the combination of antibodies with the foreign protein may lead to a "new toxic agent" capable of causing tissue injury. Thus the concept of immune complexes was formulated in theory.

The kidney pathology in serum sickness was noted by Longcope (1913). He injected animals repeatedly with foreign proteins, following which these animals developed proteinuria, had renal interstitial mononuclear cell infiltrates and marked changes in the glomeruli - crescent formation, proliferation of endothelial cells, fibrosis and glomerular sclerosis. This was explained by Loncope as being due to increased toxicity of the proteins repeatedly injected. This was similar to the explanation given for Arthus phenomenon. "Arthuslike" lesions were demonstrated in the kidneys of rabbits sensitised to horse serum or egg albumen and then injected with the specific antigens directly into the kidney.

It was thought that the changes which occurred in the kidney were the result in some way of micro organisms. Negative results were obtained by most workers when injecting bacteria in animals. Two groups of workers obtained results which could not be reproduced. One group (Bell et al 1925) induced glomerulonephritis in monkeys by repeated intravenous injections of streptococci. A second group of workers (Duval & Hibbard 1926, 1927) sensitised rabbits to streptococci, then injected streptococci into the peritoneal cavity, or incubated streptococci in vitro with specific antiserum and injected these

intravenously. The glomerulonephritis that these workers produced were probably the result of immune complex formation. Before immune complexes were understood to play a role in the development of glomerulonephritis toxic substances were shown to cause lesions in the kidneys. Lindemann (1900 b) showed that serum from a dog treated with potassium trichromate could induce proteinuria when injected into a normal dog. Many toxic agents have been implicated in the triggering of autoimmune phenomena. Recently, inhalation of hydrocarbons has been associated with Goodpastures disease. New Zealand mice and their hybrids may develop immune complex nephritis resembling human lupus nephritis. The role of viruses (Oldstone & Dixon 1971) in kidney diseases may add to the understanding of the aetiology of nephropathies. Mice persistently infected with lactic dehydrogenase virus were shown to have a mild glomerulonephritis with granular deposits of IgG,C_3 and viral antigen in the glomeruli and it was thought that the renal lesion resulted from the trapping of virus antibody complexes in the glomeruli.

Masugi (1934) and his group studied the histopathology of nephrotoxic serum nephritis and immune complex glomerulonephritis. In their study of immune complex nephritis they found varying results in

rabbits in that chronic serum sickness could not be produced by repeated injections with egg albumen but could result following intraperitoneal injection of rat organ homogenates and intravenous administration of horse serum. He stressed that the reaction to protein injections differed among individual rabbits.

Radio-labelled antigens and antibodies became available in the 1950's. It was then demonstrated that the acute lesions of serum sickness developed during the phase of immune elimination of the antigen (Germuth 1953). Germuth proposed that the serum sickness pathology was induced by immune complexes formed in the circulation.

Two models of autoimmune diseases, the autoimmune antiglomerular basement membrane nephritis in sheep (Steblay 1962) and autoimmune complex nephritis in rats (Heymann et al 1959) established the link between experimental models and human disease of the kidneys.

The induction of tissue injury by immune mechanisms was studied from the early 1900's. Complement, white cells and coagulation were studied. Low complement levels were noted in rabbits injected with foreign antigens (Moreschi - cited in von Pirquet 1911). A similar result was obtained on patients with serum

serum sickness (Francioni 1908). Francioni (1904) had previously suggested that antibodies and white cells were important in serum sicknes. Marked neutropenia in the active phase of serum sickness was noted by (Bienenfeld, 1907) and abnormal phagocytic function in serum sickness was noted by Menabouni. Decreased coagulation time (Biedl and Kraus 1909) (cited in Francioni 1908) and the presence of fibrin (Vaubel 1932) in animals with glomerulonephritis suggested coagulation factors played a role in the pathogenesis of immune complex disease. This was later confirmed in animals (Vassalli and McCluskey 1964a) and in humans (Kincaid-Smith 1972).

The role of cell mediated immunity was only established in 1976 when the first experimental model for the inducation of lesions characteristic of delayed hypersensitivity was described (van Zwieten et al 1977). It was found that a cellular response occurred when lymph node cells and not serum was injected into the kidney of guinea pigs.

Developments in the technique of renal biopsy and improved immunohistological techniques lead to the classification of clinicopathological syndromes. These aspects will be discussed later.

OUTLINE OF APPROACH TO PATHOGENESIS

INTRODUCTION

I Immune Complex Glomerulonephritis

(i) Experimental

1) Acute

2) Chronic

(ii) Factors involved in Determining Renal Involvement in Immune Complex Nephritis

1) Size and Structure

2) Reticuloendothelial System

3) Glomerular C_3b & C_4b Receptors

4) Local Formation

5) Factors Determining Tissue Injury

(iii) Immune Complex Nephritis in Man

II Anti GBM Nephritis

(i) Experimental

(ii) Human

III Mediators of Glomerular Injury

IV Immunity and Pathogenesis of Nephritis

1.3 Pathogenesis of Glomerular Lesions

General

It is important from the clinical point of view to approach renal disease from the standpoint of primary site of injury or disturbed physiology.

Site of damage may be the glomerulus, proximal or distal tubule, interstitial tissue or vasculature. As there, obviously, is a close relationship between these sites, injury of one component may result in altered structure or function in other parts.

This as previously discussed, although in understanding glomerular disease, a knowledge of clinical presentation, laboratory results, histopathologic changes, natural history and treatment is essential. It is equally important to try to identify aetiology and pathogenesis.

Furthermore, glomerulonephritis is the commonest cause of chronic renal failure and it is therefore extremely important to understand the basic mechanism of glomerular injury in order to prevent serious renal disease. The following is a summary of some aspects of glomerular injury.

In order to appreciate the pathogenesis of glomerular lesions one has to consider certain aspects of

experimental nephritis.

1.3.3 Immune Complex Glomerulonephritis

I This is the most common form of glomerular injury.

(i) Experimental Immune Complex Nephritis

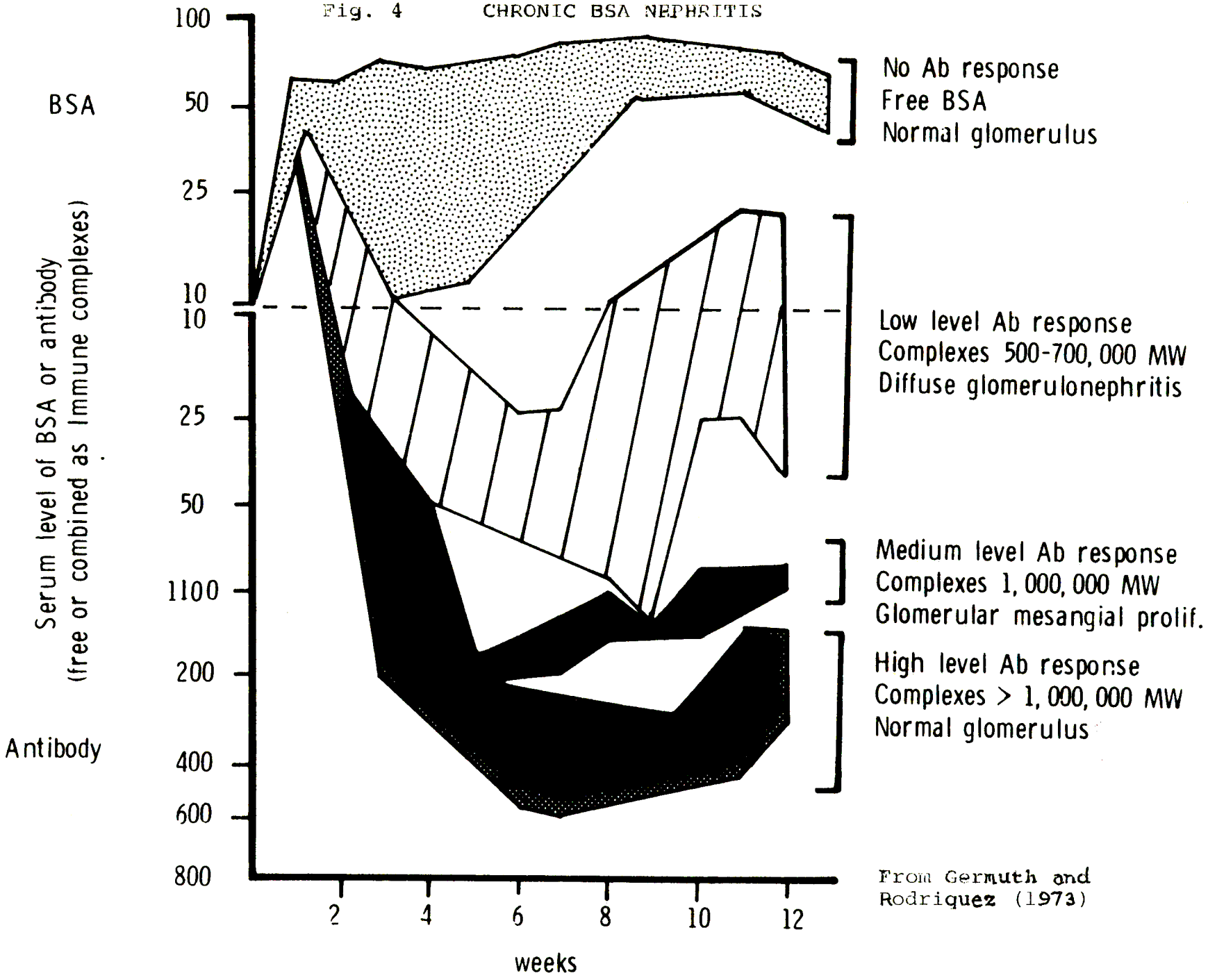
1. Acute Immune Complex Nephritis

This is most easily induced in the rabbit. A single large injection of foreign serum protein (usually bovine serum albumen - BSA) resulted in "Acute serum sickness" manifested as transient vasculitis, arthritis and glomerulonephritis. Manifestations lasted as long as the soluble complexes of antigen and antibody occur with antigen excess in the circulation (Germuth 1953, Dixon et al 1958). This is an acute self-limiting illness and recovery occurs when all circulating antigen is eliminated. Histological changes in the glomeruli were swelling and proliferation of endothelial, mesangial cells and hypertrophy of epithelial cells. Immuno-fluorescence shows discrete granular deposits of antigen (BSA) antibody (rabbit IgG) and complement on the GBM.

2. Chronic Immune Complex Nephritis (see figure 4)

Repeated injections of smaller doses of BSA can

Fig. 4 CHRONIC BSA NEPHRITIS



From Germuth and Rodriquez (1973)

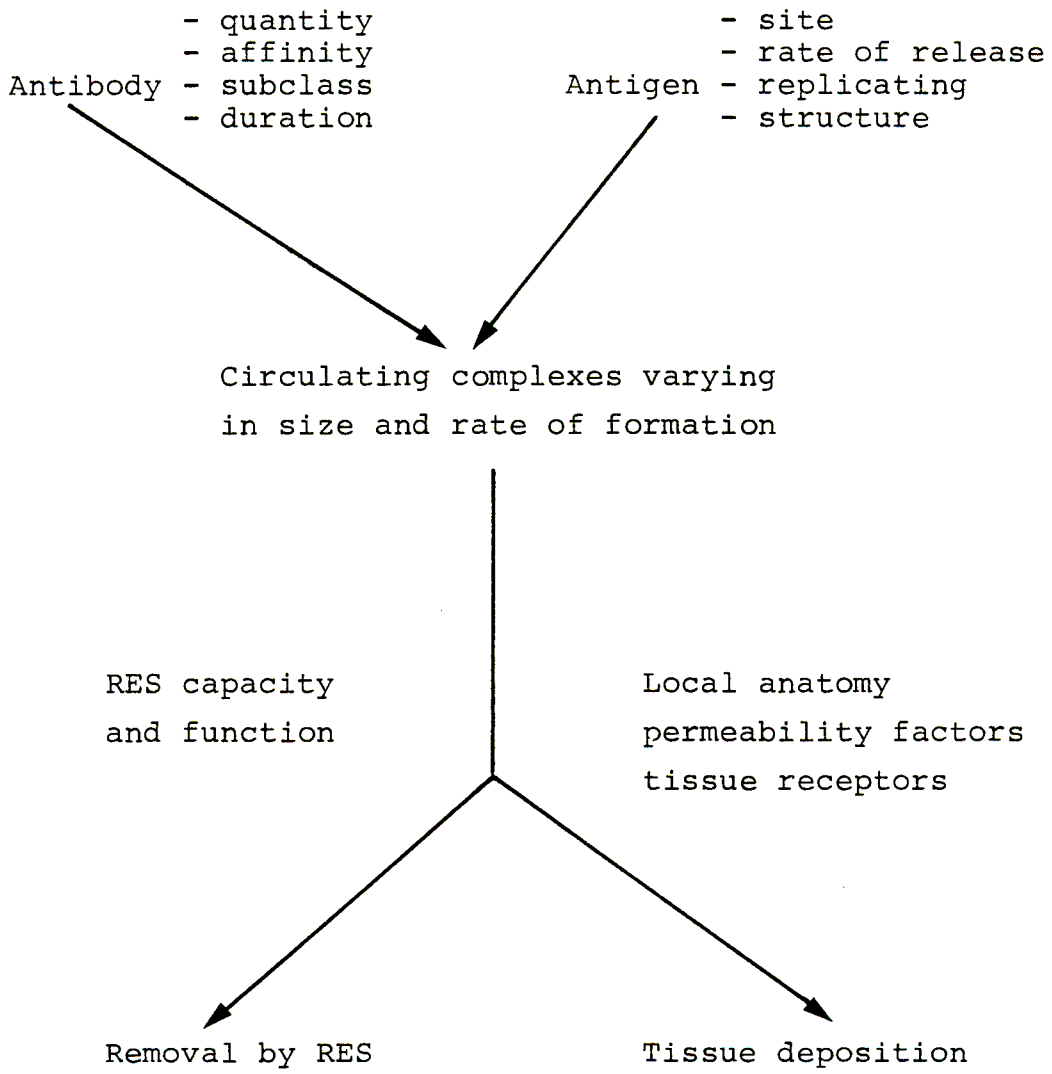
give rise to subacute or chronic glomerulonephritis. Histologically a wide variety of changes occurred varying from isolated mesangial cell proliferation, membranous changes together with proliferation or fulminating necrotising crescentic glomerulonephritis. In some animals interstitial nephritis with tubular damage infiltration of the interstitium with mononuclear cells and polymorphs may occur.

Immunofluorescent studies show granular, coarse, confluent deposits of immunoglobulin, antigen and complement, on the GBM or the mesangium (only in mesangial proliferative nephritis) unlike the fine discrete deposits of acute disease. The occurrence of chronic nephritis was recognised as being related to the antibody response of the animal (Dixon et al 1961). Those animals (rabbits) that produced anitbodies in amounts barely sufficient to neutralise the injected antigen developed subacute or chronic glomerulonephritis. Whereas those who developed large amounts of antibody developed an acute, self-limiting glomerulonephritis.

II Factors determining renal involvement by circulating Immune Complexes (see figure 5)

FIGURE 5

SUMMARY OF FACTOR AFFECTING IMMUNE COMPLEX FORMATION AND REMOVAL FROM CIRCULATION



From Sissons 1976

1. Size and Structure

Important factors responsible for the rate of removal of the complexes and their nephrotoxicity are the size, structure and the proportions of antigen and antibody of the complexes.

The complex size is affected by the nature of the antigen, the subclass of antibody and it's affinity and the binding of complement.

The extent of the "lattice" structure formed by the antigen (Ag) and antibody (Ab) determines the rate of removal of the complexes (Mannik et al 1974). Complexes formed in antibody excess with a lattice Ag_2 Ab_2 and larger than 19S in size are rapidly taken up by the reticulo-endothelial system (RES), and deposited in the mesangium with mesangial cell proliferation. Small and intermediate size complexes with a lattice of Ag_2 Ab_2 or less formed at equivalence or antigen excess, and 11-19S in size tend to persist longer in the circulation. They tend to localise in the GBM and result in diffuse proliferative or membranous nephritis.

Diffuse glomerulonephritis is brought about by complexes found in moderate antigen excess and

these are typically localised in a subepithelial position. The smallest complexes formed in gross antigen excess do not cause glomerular damage. Complexes formed in moderate antibody excess localise in the glomerular mesangium and on the endothelial aspect of the GBM. These complexes give rise to less severe focal glomerular disease (Germuth & Rodriguez 1973). Animals making a high level of antibody tend not to develop nephritis as large complexes are formed and the antigen rapidly cleared. Those with very low antibody response show nephritis (Figure 4).

2. Renticuloendothelial System (RES)

In the kidney the mesangial cell is regarded as part of the RES. The RES is obviously important in the rate of removal of immune complexes from the circulation. In animals with chronic immune complexes, decreased clearance of complexes and macromolecules has been shown (Wilson & Dixon 1971, Mannik et al 1974).

Increased RES clearance capacity was present in patients with proliferative, membranous, mesangial IgA and active Henoch-Schönlein nephritides.

These patients demonstrated increased RES phagocytosis. (Drivas et al 1976).

3. Glomerular C_3b and C_4b Receptors

A cellular receptor for C_3b has been demonstrated within the human glomerulus (Gelfand et al 1975). This receptor is sited on the epithelial cells of the glomerulus and there is an inverse correlation between the amount of C_3 detectable on immunofluorescence and the number of demonstrable receptors. It may be possible that this receptor plays a role in localising the immune complexes in the subepithelial site.

The glomeruli of the human kidney have also been shown to possess receptors for C_4b (Matre and Tonder 1980). These receptors are present on all glomeruli and can also be found in the foetal kidney.

Both these receptors probably play a role in the binding of complement containing immune complexes onto the GBM in glomerulonephritis.

Fc gamma receptors for IgG could not be demonstrated on human glomeruli (Matre et al 1980). From the available evidence it appears that the antigen C_3b, or C_4b have to be deposited on the

GBM before the remaining components of the immune complexes are attached to the GBM.

4. Local Formation of Immune Complexes in the Kidney

Ag - Ab reactions can take place locally in the glomerulus. The deposited immune complexes are in equilibrium with Ag and Ab in the Circulation (Wilson and Dixon 1971) and can fix further antibody and complement after deposition. Massive amounts of infected antigen can accelerate the removal of complexes from the glomeruli probably by altering antigen - antibody ratios (Valdes et al 1969, Wilson & Dixon 1971). The progression of the renal disease is stopped and the glomerular pattern of immune deposits is altered. Eventually fluorescent deposits disappear and glomerular lesions heal with improved renal function (Valdes et al 1969).

An experimental model has been described in which antigen previously localised in mesangial cells reacted with subsequently injected antibody to produce glomerular damage (Mauer et al 1973).

In the rat, antigen (ferritin) was bound to the glomerular basement membrane. (Batsford et al 1980).

This was followed by an injection of the antibody (antiferritin). Glomerulonephritis with significant proteinuria was induced. Histology revealed GBM spike formation with hypercellularity. Immunofluorescence showed fine granular deposition of antigen, antibody and C_3 along the glomerular capillaries. Electron microscopy demonstrated fused foot processes and subepithelial deposits (containing ferritin). This neat experiment demonstrated the role of in situ antigens in the pathogenesis of immune complex nephritis.

Therefore the antigenic load, quality and quantity of antibody, size and structure of complex and RES function determine the rate of deposition, removal and production of immune complexes.

5. Factors Determining Tissue Injury

Although there was definite evidence of tissue injury in serum sickness due to the deposition of circulating antigen-antibody complexes, it was noted that it was not always possible to reproduce consistently the same lesions. Some workers (McCluskey et al 1960, Benacerraf et al 1960) were able to produce glomerular and vascular lesions in mice and rats following an

injection of immune complexes in antigen excess whereas others (Fish et al 1966, Cochrane and Koffler 1973) were unable to reproduce similar results in mice or rabbits. Fish et al (1966) stated that it was not only the elimination of the antigen and the formation of antigen antibody complexes that were important factors in the pathogenesis of serum sickness. Additional parameters such as kinetics of antibody production, the specific nature of the complexes formed, glomerular localisation of macromolecules and the individual vulnerability of difficient animals to tissue injury by immune complexes had to be considered. An explanation for the failure to produce tissue injury was given by Henson and Cochrane (1971) who showed that in order to produce tissue injury in rabbits 2 requirements had to be met.

a) Complexes greater in size than 19S must circulate.

b) Increased capillary permeability is necessary to allow localisation. Any factor affecting an increased permeability will facilitate complex deposition e.g. turbulent blood flow at bifurcations of vessels. Immune complexes

when localised cause increased permeability and allow further localisation of complexes.

In rabbits vasoactive amines (Cochrane & Koffler 1973) are released from platelets, facilitating localisation of complexes. As human platelets contain much less vasoactive substances the relevance of this mechanism is not clear.

III Immune Complex Nephritis in Man

The study of large numbers of human renal biopsy material has demonstrated deposits of immunoglobulin and complement in the glomerulus. This has been taken as evidence of immune complex disease, this mechanism accounting for the majority of human nephritides (McCluskey 1971, Berger et al 1971). The antigen resulting in nephritis has been identified in a minority of conditions. More often straightforward immunofluorescent techniques will not reveal the antigen and the antigen and antibody have had to be eluted from renal tissue. Resolution of nephritis after elimination of a suspected antigen and detection of circulating immune complexes are indirect evidence of immune complex disease.

The antigen is more often identified when the nephritis is part of a systemic disease for example Hepatitis B viraemia, the exeptions being acute post streptococcal nephritis and quartan malarial nephrotic syndrome.

Table VI gives a list of nephritides in which the antigen has been proven or is strongly suspected (from Sissons 1976).

Most patients with nephritis do not have evidence of systemic disease. A blind search for antigens is almost impossible and quite impractical. The finding of circulating immune complex lead to the conclusion that these complexes are the cause of the nephritis. Cryoglobulins are often taken as an index of circulating immune complexes and their prevalence in human nephritis has been demonstrated (Adam et al 1973, Druet et al 1973, McIntosh et al 1975). Cryoglobulins are generally detected in patients with nephritis of known aetiology e.g. SLE and rarely in idiopathic nephritis, usually proliferative rather than membranous (Adam et al 1973).

The difficulty in demonstrating immune complexes in idiopathic nephritis may be due to the fact

TABLE VI

ANTIGENS IMPLICATED IN THE PATHOGENESIS OF HUMAN IMMUNE COMPLEX GLOMERULONEPHRITIS

Infectious agents	
Streptococci	Post-streptococcal nephritis/SBE
Staphylococci	'Shunt' nephritis/SBE
M.leprae	Leprosy
T.pallidum	Syphilis
Pl.malaria (Pl.falciparum)	Quartan malaria
Schistosoma	Schistosomiasis
Hepatitis B antigen	Hepatitis B antigenaemia
Measles antigen	SSPE
EB virus	Burkitt lymphoma
Oncorna virus antigen	Lymphoma/leukaemia
Endogenous	
Nuclear antigens	SLE
Thyroglobulin	Autoimmune thyroiditis
Renal tubular antigens	Membranous GN
	Sickle cell disease
	Renal carcinoma
IgG	'Mixed cryoglobulinaemia'
Carcinoembryonic antigen	Colonic carcinoma
Drugs	
Penicillamine and others	

Antigen/antibody system not specifically identified.

Other infections, neoplasia, Guillain-Barrè syndrome, sarcoidosis.

that the complex load is small. The presence of immune complexes in proliferative nephritis correlates with activity on renal biopsy. The cryoglobulins associated with nephritis contain IgG and IgM, but the antigen is rarely demonstrated. However, it has not been shown that these represent the complexes causing damage.

A wide gap therefore exists between suspected mechanisms and proven pathogenetic mechanisms in human nephritis.

1.3.4 Anti GBM Nephritis

(i) Experimental (Unanue & Dixon 1967).

The injection of heterologous antibody to glomerular basement membrane causes glomerulonephritis and immunofluorescence demonstrates. The antibody fixed in a characteristic linear pattern along the GBM.

Two phases of injury are produced:

a) The heterologous phase

The heterologous phase is characterised by proteinuria lasting 24 - 48 hours and is the direct result of the fixation of the antibody on the GBM. Early on morphological changes are inconspicuous. When a complement-fixing antibody is used polymorphs infiltrate within 2 - 3 hours of the antibody administration.

The only other early change is the deposition of poorly defined electron-dense material on the capillary side of the GBM within 6 - 12 hours following injection.

b) The autologous phase

The autologous phase develops 5 - 8 days later, manifesting clinically as renal failure in 10 - 20 days. This phase is the result of the production of host antibody to the administered antibody. Severe nephritis develops with endothelial and epithelial cell proliferation, and fresh subendothelial deposition which is dense and abundant occurs for up to 4 weeks after injection.

(ii) Human Anti-GBM Nephritis

Anti-GBM antibody is of prime pathogenetic importance. As has been shown in primates (Lerner, Glassock and Dixon 1967), antibody to GBM can be eluted from the diseased kidney. The eluted antibody will induce nephritis in the normal recipient monkeys and the anti-GBM antibody can be demonstrated in the circulation after bilateral nephrectomy.

Patients with anti-GBM antibody induced nephritis (Good-pasture's Syndrome) usually have rapidly

progressive crescentic nephritis, and the majority have associated intra-alveolar lung haemorrhage.

The association of lung and kidney disease in Goodpastures syndrome is likely to be based on the antigenic similarity of the glomerular and lung basement membranes. In sheep an autoimmune nephritis (Steblay 1962) can be induced by immunisation with lung basement membrane (Rudofsky and Steblay 1965). The cause of pulmonary haemorrhage in Goodpasture's syndrome is uncertain. In some patients, antibody is fixed on lung basement membrane. In rats, large doses of nephrotoxic antibody have been shown to cause haemorrhagic pheumonitis (Willoughby and Dixon 1970). This does not necessarily establish that the lung disease is the result of such an antibody. Under some circumstances, pulmonary damage might result in the formation of antibody reacting with both lung and glomerular basement membranes. This is supported by reports of Goodpasture's syndrome following exposure to hydrocarbonsolvents (Beirne & Brennan 1972). It is postulated that in this situation chemical damage of the lung had resulted in the release of basement membrane antigens with an antibody response and basement membrane damage ensuing in the kidneys and the lungs.

Autoimmune nephritis was produced in rabbits by Lerner & Dixon (1968). A proportion of these rabbits (about 15%) developed a predominantly tubular lesion with linear deposition of antibody on the tubular basement membrane (TBM). Similarly some 60 - 70% of patients with anti-GBM glomerulonephritis produce antibody to TBM with linear deposits of IgG occuring on the TBM. Globulin eluted from human kidneys containing anti-GBM antibodies reacted in vitro in 9 of 10 instances with the GBM, TBM and Bowman's capsule (Lerner et al 1967).

Rarely, nephritides associated with deposits along the TBM (McPhaul & Dixon 1970) have been observed in other situations in man, for example, in allotransplanted kidneys, (Klassen et al 1973), following immune complex nephritis in a patient with post streptococcal nephritis, (Morel-Maroger et al 1974), in a patient with Fanconi's syndrome (Levy 1974) and in patients with acute renal failure associated with methicillin sensitivity (Baldwin et al 1968, Border et al 1974).

More recently antibodies to renal tubular antigen could not be demonstrated in the serum or the eluates of renal tissue of some patients with membranous glomerulonephritis (Collins et al 1981).

The role of renal tubular antigen, if any, in glomerulonephritis is not clear. The available evidence is conflicting. It may be that the causative agents in the various forms of glomerulonephritis may be responsible for the presence or absence of renal tubular antibodies.

1.3.5 The Mediators of Glomerular Injury (Figure 6).

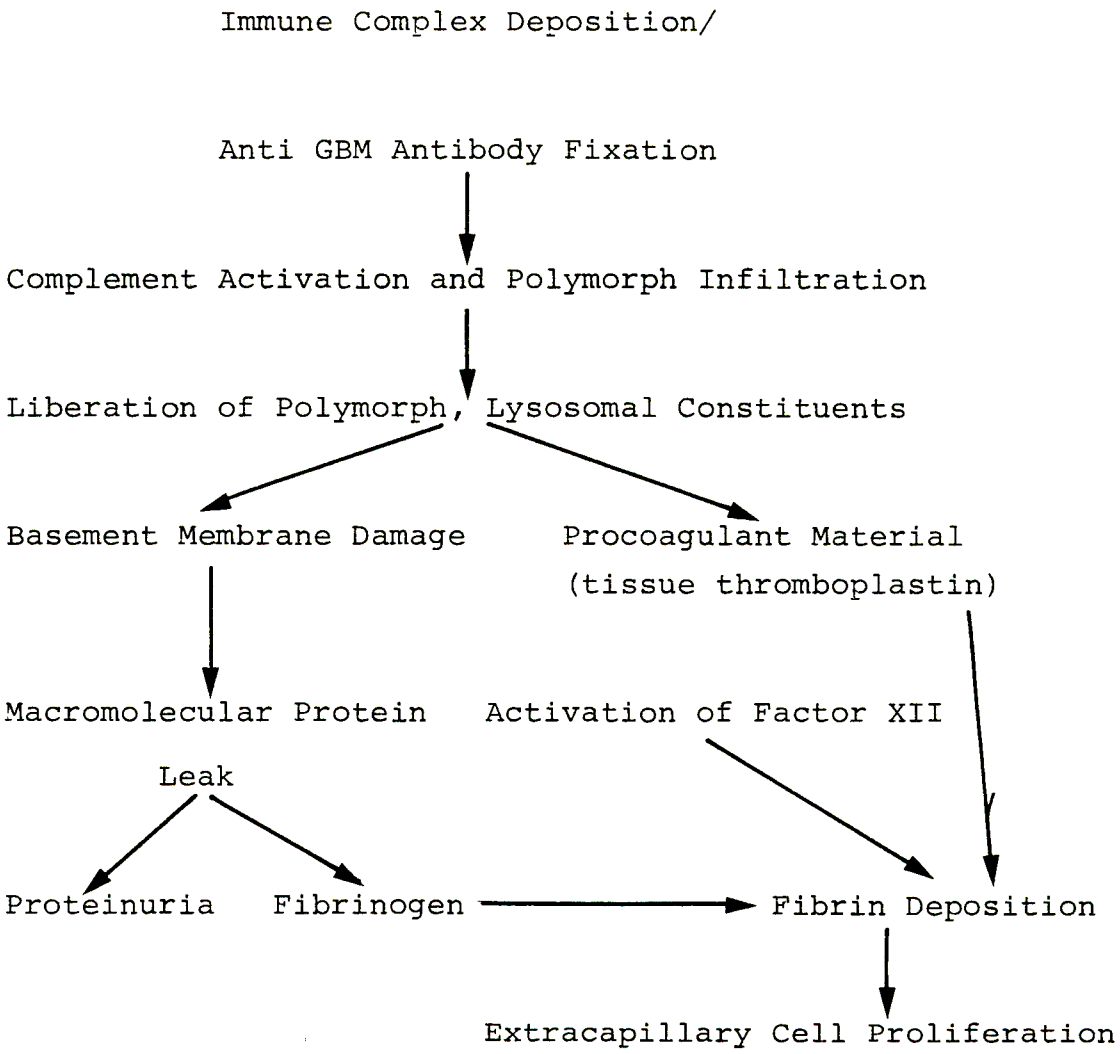
The deposition of immune complexes or the fixation of anti-GBM antibody may result in sufficient damage to cause proteinuria. It appears that these events alone will not produce progressive glomerular damage, but that other factors that participate in the inflammatory response such as complement, the coagulation system and polymorphonuclear leucocytes may also contribute to renal damage. (Sissons 1976).

(i) Complement

This is the best understood mediator of allergic tissue injury. The early complement components are also important in the defence against infection. Activation of the full classical or alternate pathway is required for cell damage. The major immunopathological effects of complement activation depend on C_3b which causes immune adherence of

FIGURE 6

SUMMARY OF FACTORS INVOLVED IN THE MEDIATION OF GLOMERULAR DAMAGE



From Sissons 1976

polymorphs and platelets at the site of complement fixation. C_3b is also responsible for opsonisation. The smaller breakdown fragments of C_3 and C_5, namely C_3a and C_5a, have anaphylotoxic properties. In addition, B lymphocytes have receptors for the large fragment of C_3 and C_3b. These facts have suggested that complement may have a role in the cellular interactions involved in antibody formation (Peters & Williams 1975).

Tissue damage from complement generally appears to have no requirement for the late complement components, since C_6 deficient rabbits are not protected from the damaging effects of antibodies to GBM. (Rother et al 1966).

Complement is not always required to induce tissue injury. Approximately 20 - 25% of patients with Goodpasture's syndrome have no detectable C_3 deposited in the glomeruli (Wilson and Dixon 1973, Sissons et al 1974). Complement independent injury has also been demonstrated in sheep (Henson 1971) using the $\gamma 2$ fraction of anti-GBM antibody.

In most patients with membranous and proliferative nephritis C_3 is detected by immunofluorescence. Classically reduced plasma levels of C_3 are found in poststreptococcal glomerulonephritis, the

nephritis of systemic lupus erythematosus and in subacute infective endocarditis. Persistently low plasma levels of complement may be found in membrano proliferative glomerulonephritis.

(ii) Coagulation Factors

a) Fibrin deposition is a feature in more severe grades of proliferative nephritis in association with crescent formation and is the stimulus to proliferation.

b) Factor VIII antigen is not detectable by immunofluorescence in crescents but is present in the intraglomerular fibrin deposits suggesting that fibrin deposition occurs as a result of activation of extrinsic and intrinsic limbs of coagulation system (Hoyer et al 1972).

In rabbits with anti-GBM nephritis anticoagulants such as heparin or dicoumarol markedly decrease crescent formation and protection of function is provided (Vassalli and McCluskey 1964b).

Hence this supports the suggestion that fibrin stimulates proliferation. The exact mechanisms of fibrin deposition are not understood.

c) Platelets

In man, platelets and polymorphs may release

procoagulant substances. (Peters & Williams 1975). In addition, tissue injury resulting in exposure of the GBM to plasma might lead to direct activation of the coagulation system.

(iii) Polymorphs

Polymorphs are frequently seen in active proliferative nephritis, but migrate in and out of the tuft. Their absence therefore, does not mean that they were not involved in the tissue injury at some earlier stage.

1.3.6 Immunity and the Pathogenesis of Nephritis

The association of immune complex disease and nephritis suggests that the development of these diseases can be related to a failure of defence mechanisms. Overt infection is not apparent but the immune deficiency results in pasistence of organisms and predisposes to immune complex disease.

(i) Complement Deficiency

As mentioned previously early complement components are important in the defence against infection. The failure of synthesis and deficiency of C_3 activator are both associated with recurrent, life - threatening infections. Hypocomplementaemia is associated with mesangiocapillary glomerulonephritis (MCGN). This

TABLE VII

COMPLEMENT COMPONENT DEFICIENCIES AND GLOMERULAR LESIONS

Complement Component Deficiency	Glomerular Lesion	Reference
C1r	Chronic glomerulonephritis	Pickering et al 1970
C4	Diffuse proliferative nephritis	Jackson et al 1976
C2	Membranoproliferative glomerulonephritis	Holland et al 1972a
C1 Inhibitor	Glomerulonephritis (? type)	Peters & Lachman 1979

is not simply due to the immune complex process in the kidney, because hypocomplementaemia persists after bilateral nephrectomy. Low complement, partial lipodystrophy (PLD) (Peters et al 1973, Peters and Williams 1974) and MCGN may occur in the same patient, the PLD preceding the nephritis. It is thought that the low complement precedes the nephritis (Peters and Williams 1976) and there is probably a group of apparently healthy individuals with the same complement deficiency. A possible explanation for the relationship between MCGN and hypocomplementaemia is the increased susceptibility to infection leading to immune complex nephritis. Deficiencies of other complement components may be associated with renal diseases. Table VII lists the complement component deficiency and the glomerular lesions.

(ii) Deficient Antibody Response

Certain strains of mice tend to produce antibody of low affinity when immunised with antigens such as human albumen (Soothill and Steward 1971). These antigen-antibody complexes are poorly eliminated and would set the environment for the development of immune complex disease (Alpers et al 1972).

(iii) Deficient Cell Mediated Immunity

Deficient T cell function as a result of infection, malnutrition or immunosuppressive drugs would allow persistence of infections. There are T lymphocyte suppressor cells which modulate and control antibody synthesis (Barthold et al 1974). Failure of suppressor function could lead to overactivity of antibody forming cells and hyperglobulinaemia.

Given above are some possible explanations for the development of immune complex disease. However, what is really required is finer detailed studies of immune mechanisms in nephritis in order to isolate the crucial defect in immunity which may be subtle and not detectable by present relatively crude methods.

HLA typing may be important as genetic markers of susceptibility or resistance to disease in the nephrotic syndrome. A recent study (Alfiler et al 1980) showed that the incidence of HLA - DRw7 was significently greater in steroid responsive nephrotic than controls.

The most intriguing glomerulonephropathy is that of minimal change. In this category are three types of histological change accepted as part of the diagnosis.

1) fusion of foot processes only a feature of all glomeruli that lose protein (Churg et al 1962, Spiro 1959).

2) focal glomerular sclerosis of juxtamedullary glomeruli initially but which can progress.

3) mesangial proliferation.

The significance of these changes is not understood although circulating immune complexes have been demonstrated in minimal change disease, (Levinsky et al 1978) immunoglobulin and complement are not usually demonstrated and in the focal-sclerosis or mesangial-proliferative variations IgM, IgG and C_3 may be found (Folli et al 1958).

In spite of these very slender immunological factors steroids and cyclophosphamide alter the course of the severe proteinuria and induce remission. Cyclophosphamide has been shown to alter the ultra-structural fusion of foot processes to normal ultrastructure (Rathi et al 1979). There may be several possible explanations for this effect of cyclophosphamide. There is evidence of T cell dysfunction in MCNS. (Shalhoub 1974, Moorthy et al 1976). Altered cell mediated immunity to kidney - derived antigens using the leucocyte -

migration - inhibition test was demonstrated in one study (Mallick et al 1972). Further support for disturbance in cell mediated immunity came from the demonstration of greater lymphotoxicity of lymphocytes from those with minimal change than either proliferative nephritis or controls (Eyres et al 1976). Inhibition of lymphocyte blastogenesis by plasma of patients with minimal change has also been shown (Moorthy et al 1976). Lymphocytes cultured from patients with nephrotic syndrome release a lymphokine factor which results in an inflammatory response and enhances vascular permeability so affecting GBM permeability (Larque et al 1975).

Cyclophosphamide appears to be capable of controlling all these aspects effectively; it has powerful anti-inflammatory, immunosuppressive and lympholytic action. It therefore may inhibit the immunological reaction or suppress the release of mediators of inflammation (Moncrief et al 1969).

A very important aspect of the use of cyclophosphamide in MCNS was the effect observed on suppressor T cell function (Taube et al 1981). Patients treated with cyclophosphamide and who had not relapsed had significantly less suppressor T cell function than controls or patients not treated with

cyclophosphamide. Those not treated with cyclophosphamide had suppressor T cells not very different from normals. This implies that either suppressor T cell disturbance is important in the pathogenesis of MCNS or it is an effect of cyclophosphamide therapy. Factors determining improvement or progression of nephritis remain unsolved. Why do some patients with APSGN develop progressive renal disease? What induces spontaneous remissions, in for example, membranous nephropathy? Antimalarials do not result in remission in patients with quartan malarial nephrotic syndrome but control of infection in bacterial endocarditis and syphilis results in clinical improvement and remission.

1.4 Renal Biopsy

1.4.1 Introduction

In the early 1950's renal biopsy was reported as a safe and relatively simple clinical procedure. (Perez 1950, Iversen and Brun 1951). The first report of the use in nephrotic children was in 1957 (Galán & Masó). The safety and value in both clinical and research purposes has been firmly established. (Dodge et al 1962). The safety

of the procedure depends on careful selection of patients, pre and post-biopsy care and skill and experience on the part of the doctor (Muehrcke & Pirani 1975). It is a technique not to be recommended for general use (Dodge et al 1962).

Examination of renal tissue is the only certain way of making an exact morphological evaluation of diffuse renal disease in life. The information obtained is then correlated with the clinical and laboratory findings leading to a better understanding of the natural history and pathological progression of disease. Insight into the prognosis is gained along with an improvement in management of renal diseases. Renal biopsies therefore, play a major role in the diagnosis, management and prognosis of renal disease.

The histological classification and definitions used in this study have been discussed on page 24.

1.4.2 Immunofluorescence

The use of immunofluorescence (IF) has resulted in considerable expansion of our understanding of human glomerular diseases. Generally a diagnosis of immune-complex disease is inferred by immunofluorescent studies of kidney tissue (Berger et al 1971, McCluskey 1971, Michael et al 1971, Morel-

Maroger et al 1972). Immunofluorescence depends on the use of fluorochrome labelled antibodies for detecting immunoglobulins, complement, fibrinogen and specific antigens (e.g. Plasmodium malarial) within the renal biopsy specimen. Experimental studies indicate that about 5 ug of diffuse linear IgG or 0.25 ug of discrete granular antigen /g of renal tissue can be detected by the immunofluorescence technique (Wilson and Dixon 1974). The same technique can be used to detect cell types such as T cells in the cellular infiltrates seen in rejecting renal allografts. It is possible to generalise with regard to the quantities and pattern of deposition of immunoglobulin classes, complement and fibrinogen on the GBM or in the mesangium of the more frequently observed histological forms of glomerulonephritis (see table VIII).

Besides providing evidence of immunologic mechanisms the finding of fibrin suggests that coagulation is involved in the pathogenesis of glomerular disease. Correlation of histology and immunofluorescence is useful as it provides a guide to prognosis and evaluation of therapy. In certain conditions the IF findings are highly characteristic if not entirely pathognomonic (McCluskey, 1971). The technique is

TABLE VIII

GENERALISATIONS REGARDING IMMUNOFLUORESCENCE FINDINGS IN PRESUMED IMMUNE COMPLEX AND MINIMAL CHANGE FORMS OF GLOMERULONEPHRITIS (GN)

Morphologic classification	Immunofluorescence findings
Proliferative GN Diffuse proliferative GN, including PSGN.	IgG, C3 with variable amounts of IgA and IgM in diffuse granular deposits. FRA variable, IgA and Clq unusually abundant in SLE. In PSGN, C3 is prominent, sometimes without Ig.
Diffuse proliferative GN with crescent formation.	As above, with prominent FRA in areas of crescents.
Focal proliferative GN	IgG and often striking IgA or IgM and C3 along segments of GBM and/or in the mesangium. FRA prominent in Henoch-Schönlein purpura.
Membranous GN	Prominent IgG, C3 with variable amounts of IgA, IgM in a diffuse granular pattern outlining the GBM. FRA variable. IgA, Clq prominent in SLE.
Membranoproliferative GN	Granular deposits of IgG, variable IgM, IgA in two-thirds with heavy C3 in the GBM of expanded glomerular capillary loops. FRA variable.
Focal sclerosing GN	IgG, IgM, C3 may be present in granular deposits in areas of sclerosis.
Chronic GN	IgG, IgA, IgM variably present in remnants of GBM and mesangium. C3 often present even in absence of Ig. FRA variable.
Minimal change GN	Negative immunofluorescence findings.

Abbreviations: FRA = fibrinogen-related antigens
SLE = systemic lupus erythematosus
PSGN = poststreptococcal glomerulonephritis

not essential but an important supporting investigation, particularly if electron microscopy is not available. For example, the difference between MCNS and early membranous nephropathy may not be easily distinguishable on light microscopy. Membranous nephropathy will demonstrate granular deposits of IgG whereas in MCNS there will be no deposits as a general rule. The major importance of differentiating between these 2 diagnoses is from the point of view of management. MCNS is sensitive to steroids, while membranous nephropathy is not. Other diseases which have consistent patterns on immunofluorescence are IgA glomerulonephritis, (Berger 1969) mesangial proliferation with mainly IgM deposition, focal glomerular sclerosis (IgM, C_3) (Morel-Maroger et al 1972) and fibrinogen in rapidly progressive glomerulonephritis with epithelial crescents (Morel-Maroger et al 1972).

More recently interest in immune processes which may result in injury to tubular and interstitial structures has developed (McCluskey and Klaasen 1973). This may be associated with anti-GBM disease (Lerner et al 1967) or as a primary disease (McCluskey and Klaasen 1973). Tubular damage and interstitial inflammation or fibrosis

may be associated with glomerular lesions. However, there are cases of unexplained, tubulointerstitial disease without glomerular disease which are often diagnosed as chronic pyelonephritis. Evidence for bacterial infection is often lacking (McCluskey & Klaasen 1973). It is thought that some of these lesions may be immunologically mediated.

In about 75% of patients with SLE their biopsies demonstrate granular deposits of immunoglobulin and complement in the TBM, peritubular capillaries and/or interstitium (Wilson and Dixon 1973). In experimental serum sickness antigen antibody and complement have been detected in similar sites suggesting immune complex disease.

The technique of immunofluorescence was established in 1974 at Natal University Medical School and almost all renal biopsies since that time have been examined by this technique.

1.4.3 Electron Microscopy

As discussed previously, the safety of percutaneous renal biopsy has provided a means of classifying renal disease, improving our understanding of underlying disease processes, elucidating the natural history of kidney disease and providing a guide to management. The histopathological

features on biopsy remain the single most important criterion for classification. Electron microscopy (EM) provides for more precise evaluation of histo-patholotical change that is not possible by light microscopy alone. Initially there was some doubt as to the value of electron microscopy as a routine procedure. In one study (Muehrcke et al 1969) it was thought that ultrastructural evaluation assisted in only 6% of cases studied. Electron microscopy was not regarded as important in the confirmation of the histological diagnosis.

However, in 1957 Farquhar described the usefulness of EM in children. In children with familial nephrosis the clinical, histological and EM features were examined. Although there was marked variation on clinical presentation and differing histological changes EM examination clarified the basic pathological changes.

Later another study demonstrated that routine electron microscopy proved to be of greatest value in the differential diagnosis of the nephrotic syndrome (Tighe and Jones, 1970). Four of the 12 patients diagnosed as membranous on EM were diagnosed as minimal change on LM. These children had failed to respond to steroids. Whereas only 1 of the 9 children diagnosed as minimal change on EM failed

to respond to steroids and had less selective proteinuria. Another study (Seigel et al 1973) found that the additional information obtained by ultrastructural studies was of value in nearly 50% of cases examined by light and electron microscopy. These workers also pointed out as it is not possible to predict in which patients electron microscopic examination of renal tissue would be of most benefit, it should be used as a routine procedure. The risk of examining inadequate and unrepresentative samples of the biopsy is greater than with light microscopy. However, the greater precision obtained by EM in the classification of renal disease and the fine structural changes observed in repeat biopsies outweigh this disadvantage.

The question of cost and time involved could be partly overcome by centralising, such a service having well trained personnel and strict criteria for the procedure.

There is no question as to the role electron microscopy has to play in glomerular disease. It has, along with improvements in histological techniques and immunofluorescence, contributed to histopathological classification, pathogenesis of disease processes and changes following therapy.

Electron microscopy is therefore a vital part of the study of renal tissue.

In certain histological categories of nephrotic syndrome classical changes are observed on ultra-structural examination of renal tissue. A brief description of these changes in relevant histological groups are given below: (Spargo & Seymour 1979).

Electron Microscopic Changes in the Nephrotic Syndrome

Minimal Change

Foot process obliteration, coalescence of epithelial cytoplasm over basement membrane. No cellular proliferation except mild mesangial excess.

Focal Glomerular Sclerosis

Folding, collapse, coalescence of capillary loops, masses of acellular and convoluted basement membrane results. Masses of granular deposits may be seen in these segments (correspond to hyalinosis on LM and presence of IgM C_3 on IF (Jenis et al 1974) obliteration of foot process, focal degeneration of epithelial cells (Grishman and Churg 1975).

Membranous Nephropathy

Discrete deposits between membrane and epithelial cell. Epithelial foot processes obliterated.

Spikes of new membrane are formed between the deposits. Larger spikes fuse over the surface of the deposits incorporating them into the greatly thickened membrane. The membrane then appears moth-eaten. Progressive sclerosis decreasing vascularity occurs producing an avascular mass of wrinkled and thickened basement membrane. (Ehrenreich and Churg 1968).

Rapidly Progressive Glomerulonephritis

The fibrin identified on immunofluorescence appears between large, active cells which often contain dense lyzosomes and ingested fibrin. Crescentic cells have been thought to originate from parietal epithelium but apparent continuity between both parietal and visceral epithelium and the crescents can often be seen. Breaks can be demonstrated in the glomerular basement membrane (Stejskal et al 1973) and probably provide the source of entry for the white cells and fibrin. Granular deposits may or may not be seen depending on the cause of the nephritis.

Mesangiocapillary Glomerulonephritis

This is essentially a morphological diagnosis (West 1976). On light microscopy there is mesangial

proliferation and sclerosis associated with thickening of the capillary walls. This thickening may be clearly divided into 2 groups (Habib et al 1973b). The first group is the "double contour" easily recognised on L.M. The thickening is due to the interpositions of mesangial cytoplasm and matrix between endothelium and basement membrane. The "double contour" is the result of staining of both the original membrane and the interposed material. This group is always associated with subendothelial deposits. In the second group the capillary wall is thickened by abnormal dense material within the basement membrane. Mesangial interposition is not always present. The nature of this dense material is thought to be a modification of membrane structure rather than extraneous deposits (Galle and Mahieu 1975). Other less well defined patterns may be observed on EM such as subepithelial humps and crescents in both forms.

OBJECTIVES AND PILOT STUDY

2.1 Objectives of Study

Clinicians in the late 1960's and early 1970's who looked after children with the nephrotic syndrome in Durban observed that the African child did not appear to respond to steroids. This was quite

unlike the experience of steroid-sensitive nephrotic syndrome in Caucasian children. Little was known about the nephrotic syndrome in Indian South African children. The most interesting aspect of childhood nephrotic syndrome in Africa at that time was the association of malaria with this disease in Uganda (Kibukamusoke et al 1967). There was little documented evidence of the features of nephrotic syndrome in childhood in Africa outside of the tropical and malarial infested zones. It therefore became necessary to establish the histological picture, treatment responses and natural history of the nephrotic syndrome among African and Indian children in South Africa.

Accordingly I have undertaken to investigate as fully as possible, within the constraints of the facilities available, African and Indian children admitted to the Department of Paediatrics and Child Health with the nephrotic syndrome. In particular I have recorded clinical details, made an attempt to determine aetiology, performed renal biopsies and tried to follow-up patients after discharge.

2.2 Pilot Study

Nonbiopsied Nephrotics

A total of 53 patients were diagnosed as nephrotic

syndrome clinically and biochemically. Renal biopsies could not be obtained on these patients.

a) Race, Number, Age, Sex

Race	N	Peak Age	M
African -	12	>5 (66.6%)	6
Indian -	41	≤5 (48.8%)	22

b) Follow-up Duration

African patients 1 to 20 months

Indian patients 5 to 144 months

c) Therapy

(i) Steroid Therapy

	Number Treated	Response		
		+	-	±
African	9	1 (11.1%)	8	0
Indian	39	31 (79.4%)	1	7

+ = good response

- = no response

± = equivocal response

(ii) Cyclophosphamide

5 Indian patients: 3 frequent relapsers, 1 with severe steroid toxicity and 1 steroid insensitive patient were given cyclophosphamide. 4 patients responded

d) Outcome

(i) African

7 persistent proteinuria

1 remission with steroids

1 spontaneous remission (failed steroid therapy)

3 lost to follow-up

(ii) Indian

single episodes	in 13 patients
two episodes	in 13 patients
multiple (infrequent episodes	in 4 patients
frequent relapses	in 3 patients

The patient who did not respond to steroids and cyclophosphamide remitted spontaneously.

Those patients (7) described as having a doubtful response to steroids fluctuated between remission and persistent proteinuria.

Conclusion

This study of unbiopsied children with nephrotic syndrome confirms the general findings described for biopsied patients. The majority of African children treated did not respond to steroids whereas the majority of Indian children responded to steroids.

Most of the African children remained proteinuric while the majority of Indian children achieved remissions. Those Indian children who were frequent relapsers responded well to cyclophosphamide therapy.

3. PATIENTS AND METHODS

Between 1966 and 1980, 243 children with the nephrotic syndrome attended King Edward VIII Hospital, Durban. One hundred and seventy had renal biopsies performed. The majority of these patients were admitted directly to the hospital from the out-patient department. Others were referred for biopsy from peripheral hospitals.

1. Diagnostic Criteria

The diagnostic criteria for the nephrotic syndrome were:

1. Oedema
2. Hypoalbuminaemia (<30 gms/L)
3. Heavy proteinuria (2 gm/m^2/24 hrs or >3 gm/L on repeated random samples) (Drummond 1979)
4. Additional criteria: hyperlipidaemia and raised alpha 2 globulin.

2. Investigations

Investigations were undertaken to confirm the biochemical profile of nephrotic syndrome and to exclude possible secondary causes of the disease. The following investigations were undertaken in all patients on admission and later when indicated.

urinalysis and culture - 24 hour urinary protein excretion
stools for microscopy and culture - urea and electrolytes
serum protein electrophresis - serum cholesterol
full blood count including - a smear for malarial parasites
complement components - antistreptolysin "O" titre
chest x-ray - excretory urogram
renal biopsy

Excretory urograms are done routinely to demonstrate two functioning kidneys and to exclude any congenital anomalies prior to performing a renal biopsy.

Many patients had the following investigations undertaken as well: Wasserman reaction, selectivity of proteinuria either as selective excretion of IgG and transferrin expressed as a ratio (Cameron & Blandford, 1966) or IgG/albumin clearance percentage (Barratt & McCaulay 1972). Glomerular filtration rate (Cr (51) EDTA), antinuclear factor, LE cells, hepatitis B surface antigen, bilharzia complement fixation test.

3. Methods

1. IgG and Transferrin

Serum and urine levels of IgG, and transferrin were determined by radial immuno-diffusion (Behringwerke).

2. Complement

Haemolytic complement was assayed by the method of Mayer (1964) using sheep red blood cells stored at $4^{o}C$ and rabbit haemolytic serum. Complement components C_3, C_4 were estimated in plasma by radial immuno-diffusion (Mancini et al 1965).

3. Selectivity of Proteinuria

Selectivity of proteinuria was determined by the method of Cameron and Blandford (1966). The selective excretion of albumin and transferrin is expressed as a ratio. Selective proteinuria is the slight clearance of proteins of high molecular weight but increased clearance of protein of low molecular weight. In non-selective proteinuria the clearance of high molecular weight approaches that of low molecular weight proteins. Selective proteinuria is a ratio <0.2 and non-selective proteinuria a ratio >0.2.

The ratio is of the two clearances and is calculated as follows:

$$\frac{u}{P}\ \text{IgG} \times \frac{P}{u}\ \text{Transferrin}$$

u - urine P - plasma

Actual volumes of urine are not necessary.

4. Glomerular Filtration Rate (GFR)

The GFR is determined by the single injection Chromium (^{51}Cr)-EDTA technique (Chantler et al 1969). This method depends upon the clearance rate of the injected substance and does not depend on complete urine collection which is always difficult and often impossible in children. The blood samples are collected 2 hours apart commencing 1 hour after the intravenous injection. The difference in the radio-activity counts between the samples enables the determination of the fractional clearance rate.

The actual GFR in children is calculated by 2 methods; firstly a simple weight ratio or secondly the surface area.

5. Renal Biopsy

Technique of Renal Biopsy

There are two difficulties associated with renal biopsy.

a) Locating the kidney
b) Obtaining an adequate representative sample from a narrow cortex.

Initially we localised the kidney by using a grid overlying an excretory urogram. The lower outer pole of the left kidney usually was marked. More recently ultrasonogram localised the outer lower pole and the depth of the kidney from the surface of the patient's back.

In addition landmarks used were the lumbar vertebral spinous processes, the iliac crest, twelfth rib, the guadratus lumborum and the spinal extensor muscles.

A complete aseptic technique with gowns, masks and gloves was used to obtain biopsy material. The skin was disinfected using chlorhexidine in alcohol and savlon. A 6 inch long 16 gauge needle was first used to locate the kidney depth after local anaesthetic was infiltrated or the general anaesthetic had been induced. The patient inspired or was held in inspiration by the anaesthetist while the exploring needle

was advanced through the soft tissues of the back till resistance of the renal capsule was encountered. The patient was requested to breathe in and out. The kidney depth was recognised when the needle oscillated with respiration. The needle was then withdrawn and the depth of the kidney noted on the needle at the skin surface. This distance was marked on the biopsy needle. The biopsy needle used was the modified Vim Silverman disposable needle, the Tru-cut biopsy needle (Kaplan et al 1970). Any difficulty encountered while localising the kidney was overcome by using direct fluoroscopy. The biopsy material was removed by sterile forceps and cut on dental wax into 3 sections for:

a) light microscopy and placed in Bouin's solution
b) electron microscopy in 4% glutaraldehyde
c) immunofluorescence on a glass slide in a petri dish and snap frozen within 15-30 mins in liquid nitrogen.

If necessary a second biopsy specimen was obtained.

The biopsy area was cleaned and covered with collodion and a pressure dressing applied.

The patient was kept in bed for 24 hours after the procedure. The blood pressure and pulse monitored, the urine checked for haematuria, and the abdomen observed for tenderness, guarding or a mass.

Indications for Biopsy

All African patients with nephrotic syndrome were biopsied. All Indian children with nephrotic syndrome were biopsied in the early part of the study until it became clear that the majority had minimal change and were steroid sensitive. Indian patients presenting with pure nephrotic syndrome or nephrotic syndrome and haematuria were thereafter not biopsied until the effects of course of steroids and/or cyclophosphamide could be assessed. Failure to respond to specific drug therapy, persistent haematuria, uraemia and the development of hypertension were regarded as indications for biopsy in Indian children.

Informed consent was obtained from all parents. Biopsies were performed if the urea was under 10 m.mol/L, the blood pressure was controlled or normal, bleeding and clotting times within normal values. Excretory urograms were performed on all patients to exclude congenital

anomalies in particular the solitary kidney and to examine the size and morphology of the kidneys.

The procedure was explained to the older child and deep breathing with holding of the breath at the height of inspiration encouraged. The patient was placed prone with a firm pillow under the abdomen to fix the kidney against the back tissue. Initially local anaesthetic (10 - 20 mls 1% lignocaine) was injected in the area chosen for biopsy. Pethidine 1 mg/kg i.m. was given half hour before the procedure because many patients were very apprehensive and unco-operative. More recently general anaesthesia was found to be more satisfactory. Muscle relaxants were not used (White 1963).

Handling of Biopsy Tissue

Interpretation of light microscopic findings proved initially to be a great problem. The specimens were therefore sent to Dr. Lillian Morel-Maroger in Paris. Currently the Department of Pathology, under a new head, has been able to provide a reasonably good service with regard to interpretation of renal biopsies.

Light microscopy sections 3-4 u thick were stained with haematoxylin and eosin, silver methanamine, Masson's trichrome and Periodic Acid Schiff. Tissue for immunofluorescence study was snap frozen in liquid nitrogen and sectioned at 4 u. Sections were incubated with commercially obtained FITC (Hoechst) antiserum to complement (C3) and fibrin/fibrinogen and FITC (Burroughs Wellcome) antiserum to IgG, IgM, IgA and IgE for 30 minutes at room temperature. Sections were screened in a Leitz Ortholux microscope employing an HBO 200 lamp with a BG 38 primary filter and K530 barrier filter.

Immunofluorescent techniques have been available for the past 5 years only. Interpretation of immunofluorescent findings has been limited to the findings on the GBM and not much attention has been paid to tubular and vascular immunofluorescence. This is to be done.

Specimens for electron microscopy were fixed in cold 4% gluteraldehyde in 0,2 m cacodylate buffer (pH 7,2) for 6 hours at 4^{o}C. The tissue was then washed 3 times in cacodylate buffer followed by a Palade's buffer, dehydrated through graded alcohols and placed in araldyte epoxy resin overnight. The next day the tissue

was placed in the oven at 50°C for two hours then embedded in B.E.E.M. capsules. The tissue was stained with 2% uronyl acetate for 4 minutes and 2% lead citrate for 4 minutes. Sections were read on a J.E.O.L. 1005 electron microscope.

Facilities for this service became available only very recently.

6. Definitions

The following definitions for the clinical outcome of the nephrotic syndrome were used: 'relapse' was defined as the presence of the three diagnostic features of the nephrotic syndrome; 'remission' was the absence of all criteria while not on any specific drug therapy and 'persistent proteinuria' was the loss of oedema with proteinuria >1 gm/1/24 hours. 'Frequent relapsers' were those patients who experienced 3 or more relapses in 1 year or 2 such episodes in 6 months (Abramowicz et al 1970).

Drugs

7. The following drugs were used where indicated.

1) Diuretics

(i) Chlorothiazide 20 mgs/day in 2 doses

(ii) Cyclopenthiazide 1-2 tabs daily

(iii) Furosemide 1 mg/kg/dose intravenously

(iv) Spironolactone 2 mg/kg/day in 3 or 4 doses

(v) Hydrochlorothiazide (25 mgs) and Triamterene (50 mgs) 1 or 2 tablets daily.

2. Immunosuppressive Agents

(i) Prednisone 2 mgs/kg/day for 4 weeks, the dosage was then gradually reduced over a further 8 weeks and discontinued.

(ii) Cyclophosphamide 3 mgs/kg/day for 8 weeks. The blood count was monitored weekly in these patients.

(iii) Chlorambucil 0,1-0,2 mg/kg/day for 8 weeks. This drug was given after a steroid-induced remission. The blood count was monitored weekly in these patients.

3) Antihypertensive Agents

(i) Reserpine 0.1-0,5 mgs/day as a single daily dose.

(ii) Hydrallazine 7.5 mgs/m^2/4 times a day.

(iii) Alphamethyldopa 10-60 mgs/kg/day/4 times a day.

(iv) Propranalol 1 mg/kg/day/3 times a day.

(v) Diazoxide 5-20 mgs/kg/day.

4) Antibiotics

The choice obviously depended on the nature of the suspected infection.

(i) For suspected gram positive infections (in particular pneumococcal):-

Soluble Penicillin -1/4-1/2 m units 6 hourly intramuscularly or intravenously was commenced till confirmatory laboratory reports were available.

(ii) For suspected gram negative infections: Gentamycin 5 mgs/kg/day in 3 divided doses.

(iii) While awaiting the results of culture and sensitivity in urinary tract infections (UTI): Nitrofurantoin 5-10 mgs/kg/day in 3 to 4 doses. The acute infection was treated for 10-14 days. Repeat cultures of urine were obtained between 48-72 hours following the commencement of therapy and once therapy was completed. A few more samples were checked over the next 6 months.

Recurrent UTI or those associated with urinary tract anomalies were treated prophylactically for 6 months on low dosage Nitrofurantoin 1-2 mgs/kg/day.

(iv) For tuberculosis the following oral drugs were used: Isoniazid 20 mgs/kg/24 hours as a single daily dose; Ethionamide 10-20 mgs/kg/23 hours in 2-3 divided dose; Ethambutol 20 mgs/kg/24 hours as a single daily dose.

8. Management of Patients on Admission

All patients were assessed clinically by myself.

1. The following clinical parameters were monitored:

a) Weight - daily to assess oedema loss or gain measured.

b) If the blood pressure was elevated it was monitored 4 - 6 hourly till normotensive.

c) Renal function was assessed regularly by measuring the:

(i) blood urea and electrolytes, serum creatinine

(ii) daily urine output, examination for the presence of proteinuria and haematuria.

2. A high protein diet 3 - 4 gms/kg/day was generally recommended unless the patient was severely uraemic.

3. Salt restriction (40-80 mg) was recommended only in exceptional cases when there was a great deal of difficulty experienced in controlling the oedema.

4. Infections, in particular urinary tract, pneumococcal and tuberculosis were actively anticipated and vigorously treated when confirmed.

9. Follow-up Period

Once the patient's symptoms were controlled in the Paediatric wards they were discharged and given a letter to attend the Paediatric Renal Clinic. The African patients were generally discharged on diuretics and the Indian patients on Steroids.

The patients attended the Renal Clinic approximately at monthly intervals until remission was achieved or their symptoms (e.g. oedema) were well controlled. The visits were then requested at 3 monthly or 6 monthly intervals. Those children who achieved remission and appeared

to maintain their clinical condition were then requested to attend during the school holidays at yearly intervals.

Attempts were made to keep careful records of adresses and when a patient was noted not to have attended the clinic for some time, a letter was sent to the parents requesting a visit to the clinic. These patients did not pay for the hospital visit and their travel fare was compensated.

Unfortunately many African patients live in rural areas and addresses are inaccurate (e.g. local store, school or headman). Most of these patients could not be called to the clinic. The distance from hospital, poor transport facilities and cost of transport compounded the difficulties for the African child.

Those patients who were referred from other hospitals were sent back with request to be seen at 3-6 montly intervals. Similar difficulties were encountered with repeat visits if these patients lived outside of urban limits.

10. Records

A set of forms for keeping both inpatient and outpatient data was drawn up.

For the initial presentation and investigations a form detailing relevant information (Form 1) was completed.

The data obtained at visits during the period of observation were recorded on a sheet (Form 2) indicating serial changes in the clinical condition, biochemical parameters, tests of renal function and treatment. Generally one sheet served for one year of observation.

Height and weight were recorded on the standard Harvard centile charts (Forms 3 and 4).

All the forms were placed in a large envelope with the patient's name, inpatient number and a clinic number. The names were recorded in a book in alphabetical order and the relevant clinic number recorded as a cross reference. Any patient attending the clinic would then have his or her name listed alphabetically together with the clinic number which referred to the envelope containing all relevant clinical and laboratory investigations.

Form 1

NEPHRITIS - NEPHROTIC SYNDROME STUDY

IP No. Age Sex Race Admission Date
OP No. Discharged Date

Name

Address

A. CLINICAL PRESENTATION

URTI	Hypoalbuminaemia	Onset
Skin Lesions	Oedema	Haematuria
HPT	Albuminuria	Allergies
Relevant Family/Past History		

B. CLINICAL CLASSIFICATION

1. Nephritis	2. Nephrotic	3. Mixed
4. Acute Renal Failure	5. Chronic renal Failure	6. Other

C. INVESTIGATIONS

Throat Swab	CRP	Electrolytes
Skin Swab X 3	FBC (Malaria)	Cholesterol / Lipids
Streptococcal ABS		
Complement Compoments		
Protein Electrophoresis		
Urea	Creatinine	WR, ANF, LE CELLS
Serum Osmolarity		Australia Antigen
Serum FDP		Bilharzia CFT
CXR		Selectivity of Proteinuria
GFR		Factor VIII
Urine: 24 hr Protein Excretion		Excretory Urogram
FDP		
Routine		

D. RENAL BIOPSY

E. IMMUNOFLUORESCENCE

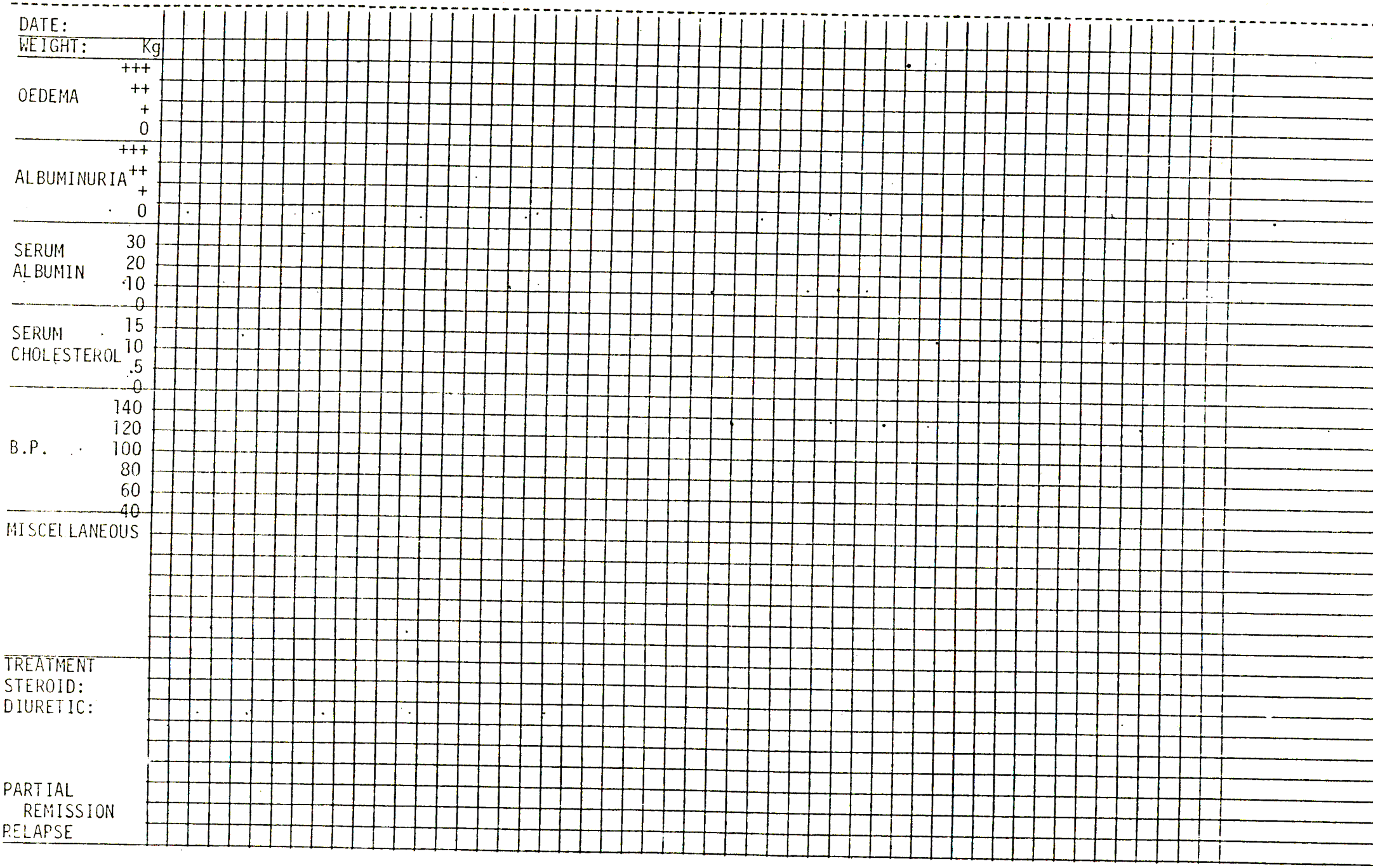
F. ELECTRON MICROSCOPY

G. MISCELLANEOUS

H. TREATMENT ON DISCHARGE

Form 2.

NAME O.P. I.P. DIAGNOSIS CLINIC NO.



Form 3

NAME
NAAM _____

DATE OF BIRTH
GEBOORTEDATUM _____

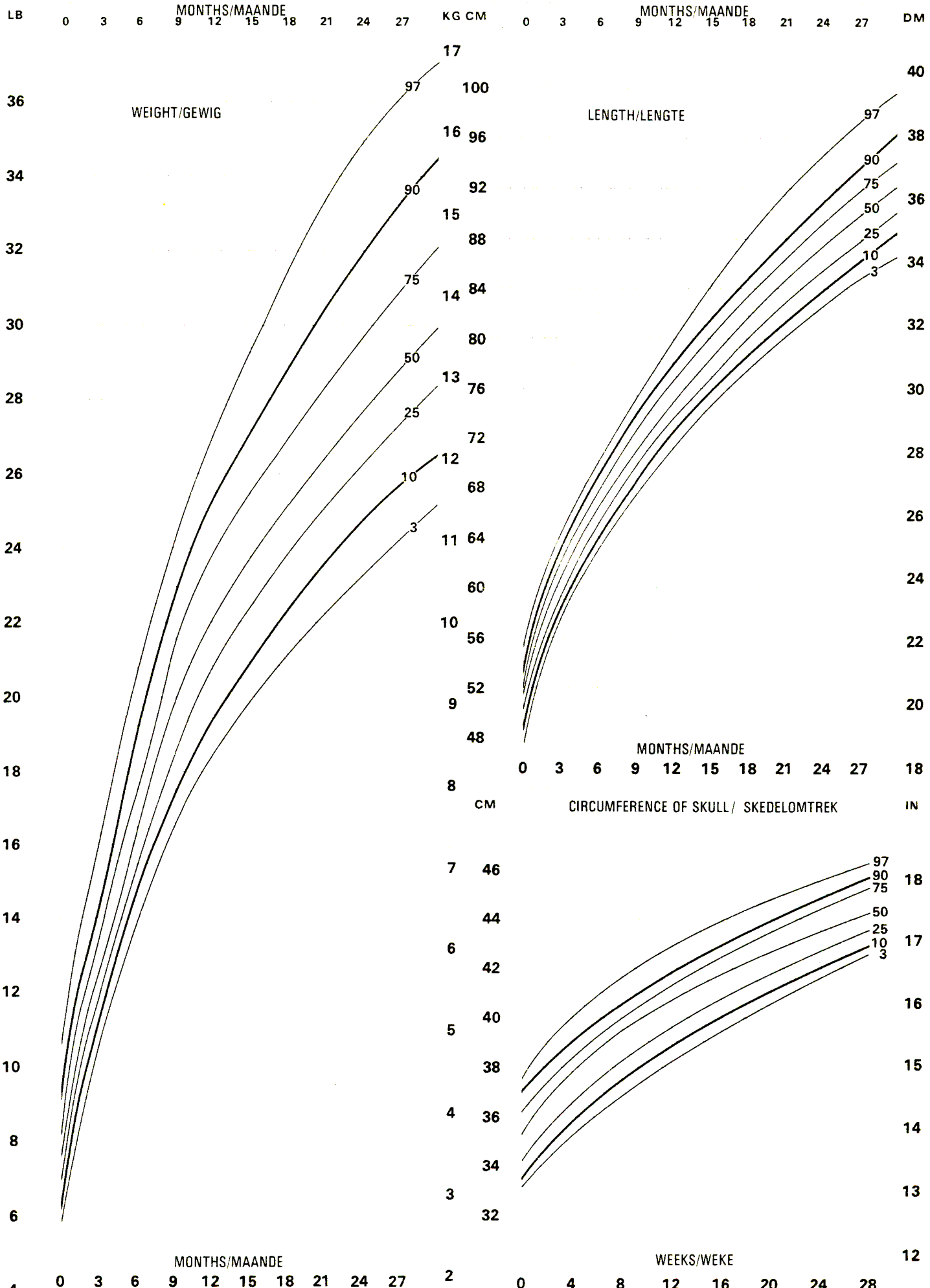
HOSP. NO. _____

TPH 221

HOSPITAL
HOSPITAAL _____

GROWTH CHART/ GROEIKAART

BABY BOYS/ BABASEUNS



NAME
NAAM _____

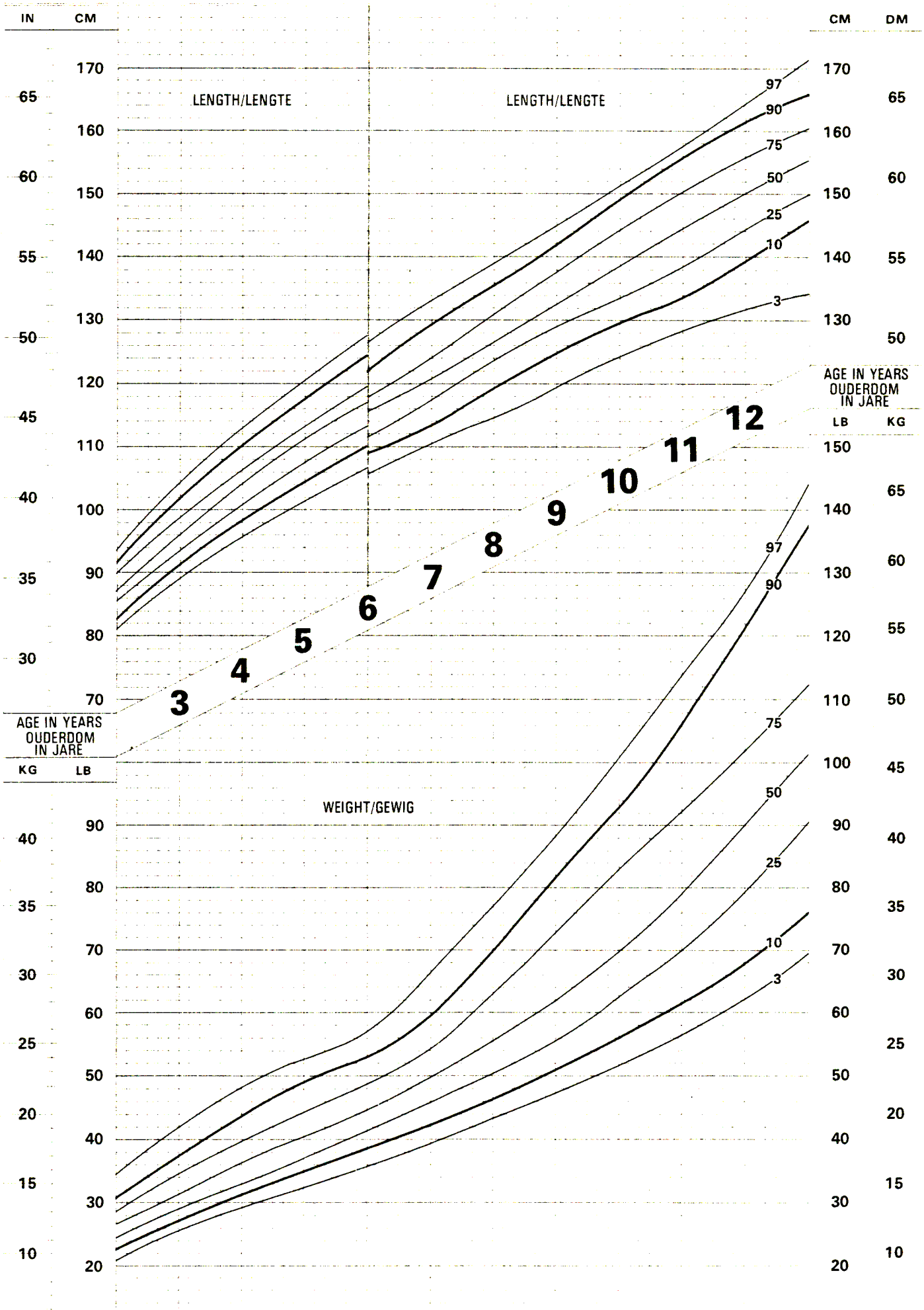
DATE OF BIRTH
GEBOORTEDATUM _____

HOSP. NO. _____

TPH 224

HOSPITAL
HOSPITAAL _____

GROWTH CHART/ GROEIKAART
GIRLS/ DOGTERS



4. PRIMARY NEPHROTIC SYNDROME

Overall results of African and Indian patients studied.

4.1 Race, Age, Sex

A total of 170 nephrotic children were studied, 104 were African and 66 were Indian. Seventy African (67%) and 42 (63.6%) Indians were males. The age distribution is shown in figure 7. The maximum age of incidence for the Indian children was 4 years (52.0% presented at 5 years of age or less) whereas African children were grouped around two peaks, one at 5 years and another between the ages of 8 and 10 years.

4.2 Incidence, Histology, Immunofluorescence

The incidence of the nephrotic syndrome was 0.17% of the total paediatric admissions during the period of study. Ninety-nine (85.6%) of the African children had obvious glomerular lesions (see table IX) in contrast to the majority, (48) (72.7%) of Indian children who had minimal change on light microscopy. The commonest lesion in the African child was extramembranous nephropathy while next in frequency were the subgroups of proliferative nephritis.

The immunofluorescent findings in each histological group are shown in Table X. A comparison between Indians and Africans shows that in general heavier deposits were detected in African children.

FIG. 7: AGE DISTRIBUTION OF NEPHROTIC CHILDREN

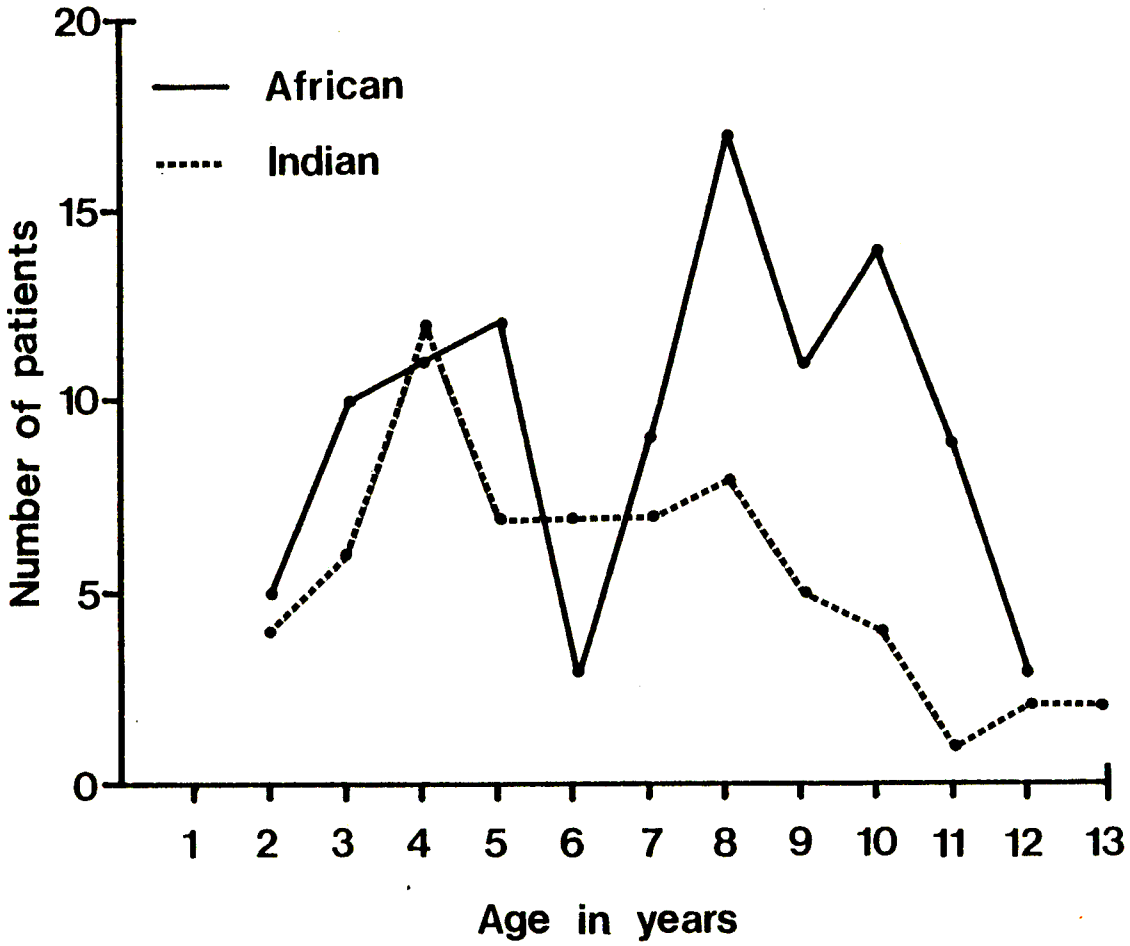


TABLE IX

HISTOLOGICAL CATEGORIES OF NEPHROTIC SYNDROME IN AFRICAN AND INDIAN CHILDREN IN SOUTH AFRICA

	AFRICAN		INDIAN	
	N	%	N	%
NO OBVIOUS LESIONS				
Minimal Change	15	14.4	48	72.7
OBVIOUS GLOMERULAR LESIONS				
1. Extramembranous	31	29.8	2	3.1
2. Proliferative	42	40.4	8	12.1
a) Mesangial	7	6.7	4	6.2
b) Exudative	9	38.7	1	1.5
c) Endocapillary	7	6.7	0	
d) Membranoproliferative	9	8.7	2	3.1
e) Focal	10	9.6	1	1.5
3. Focal Glomerulosclerosis	4	3.9	6	9.1
4. Tropical Extramembranous	6	5.8	0	
5. Tropical Nephropathy	2	1.9	1	1.5
6. Unclassified	4	3.8	1	1.5
	104	100.0	66	100.0

TABLE X

IMMUNOFLUORESCENT DEPOSITS IN EACH HISTOLOGICAL GROUP

HISTOLOGICAL GROUP		N	IgG	IgM	IgA	CC
NO OBVIOUS LESIONS						
Minimal Change	I	13		+		
(8 African, 23 Indians	A	5	+++	+	+	+
no deposits) others not investigated						
OBVIOUS GLOMERULAR LESIONS						
1. Extramembranous	I	0				
	A	21	+++	+++	+	+
2. Proliferative						
Mesangial	I	3	+	+	-	+
	A	5	++	++	-	++
Exudative	I	0	-	-	-	-
	A	7	+++	+++	+	+++
Endocapillary	I	0	-	-	-	-
	A	5	+++	++	++	+++
Membranoproliferative	I	0	-	-	-	-
	A	4	++	++	++	++
Focal	I	1	-	+		
	A	9	++	++	++	++
3. Focal Glomerulosclerosis	I	4	-	+	-	+
	A	3	-	++	++	+
4. Tropical Extramembranous	I	0	-	-	-	-
	A	6	+++	++	+	+++
5. Tropical Nephropathy	I	1	+	-	-	+
	A	2	++	++	-	++
6. Unclassified	I	0	-	-	-	-
	A	1	-	-	-	+++

\+ Light deposits
++ Moderate deposits
+++ Heavy deposits
CC Complement components (C_3 C_4 C_{1g})

I = Indian
A = African

4.3 Clinical Features at Presentation

The clinical features of the African children are presented in table XI and those of the Indian children in table XII.

(1) African Children - clinical features at presentation:

Age - 51.9% of all the African children presented over the age of 8 years. (Fig. 7)

Sex - Males either dominated or were equal in numbers to the females in all histological groups.

Haematuria
- occurred in nearly all the histological groups
- an overall incidence of 35.5%

Hypertension
- occurred in nearly all the histological groups
- an overall incidence of 16.3%

Renal failure
- an uncommon feature at presentation
- an overall incidence of 2.9%

(2) Indian Children - clinical features at presentation:

Age - 52% MCNS presented at 5 years of age or

TABLE XI

SOME CLINICAL FEATURES AT PRESENTATION IN AFRICAN CHILDREN WITH NEPHROTIC SYNDROME

HISTOLOGICAL GROUP	PEAK AGE-YRS	SEX	HPT %	HAEM %	R.F. %
Minimal Change	>5	M>F	0	27	0
Extramembranous	>5	M>F	20	47	0
Proliferative:					
Mesangial	<5	M=F	50	28.5	0
Exudative	>5	M=F	22.2	44.4	0
Endocapillary	>5	M=F	28.6	28.6	0
Membranoproliferative	<5	M>F	10	33	10
Focal	>5	M=F	20	40	0
Focal Glomerusclerosis	>5	M>F	25	0	0
Tropical Extramembranous	>5	M>F	0	0	0

TABLE XII

SOME CLINICAL FEATURES AT PRESENTATION IN INDIAN CHILDREN WITH NEPHROTIC SYNDROME

HISTOLOGICAL GROUP	N	Ages Yrs	Sex	HPT	Haem	R.F.
Minimal Change	48	Peak at 5	M>F	0	2	0
Extramembranous	2	2, 5½	M	0	1	0
Proliferative						
Mesangial	4	Mean 7.5	M<F	0	0	0
Exudative, Endocapillary	1	13	M	0	0	0
Membranoproliferative	2	2½, 8	M=F	0	0	0
Focal	1	10	F	0	0	0
Focal Glomerulosclerosis	6	Mean 5.9	M=F	1	3	1
Tropical Nephropathy	1	6	M	1	0	0
Unclassified	1	7	M	0	1	0

younger 27% of the other histological groups presented at this age. (Fig. 7).

Sex - Males dominated in MCNS

Equal sex distribution in other groups.

Haematuria - 2 (3%) in MCNS

7 (10.7%) in other groups

Hypertension - 2 (3.0%) in other histological groups

Renal failure - 1 (1.5%) in other histological groups.

4.4 Outcome

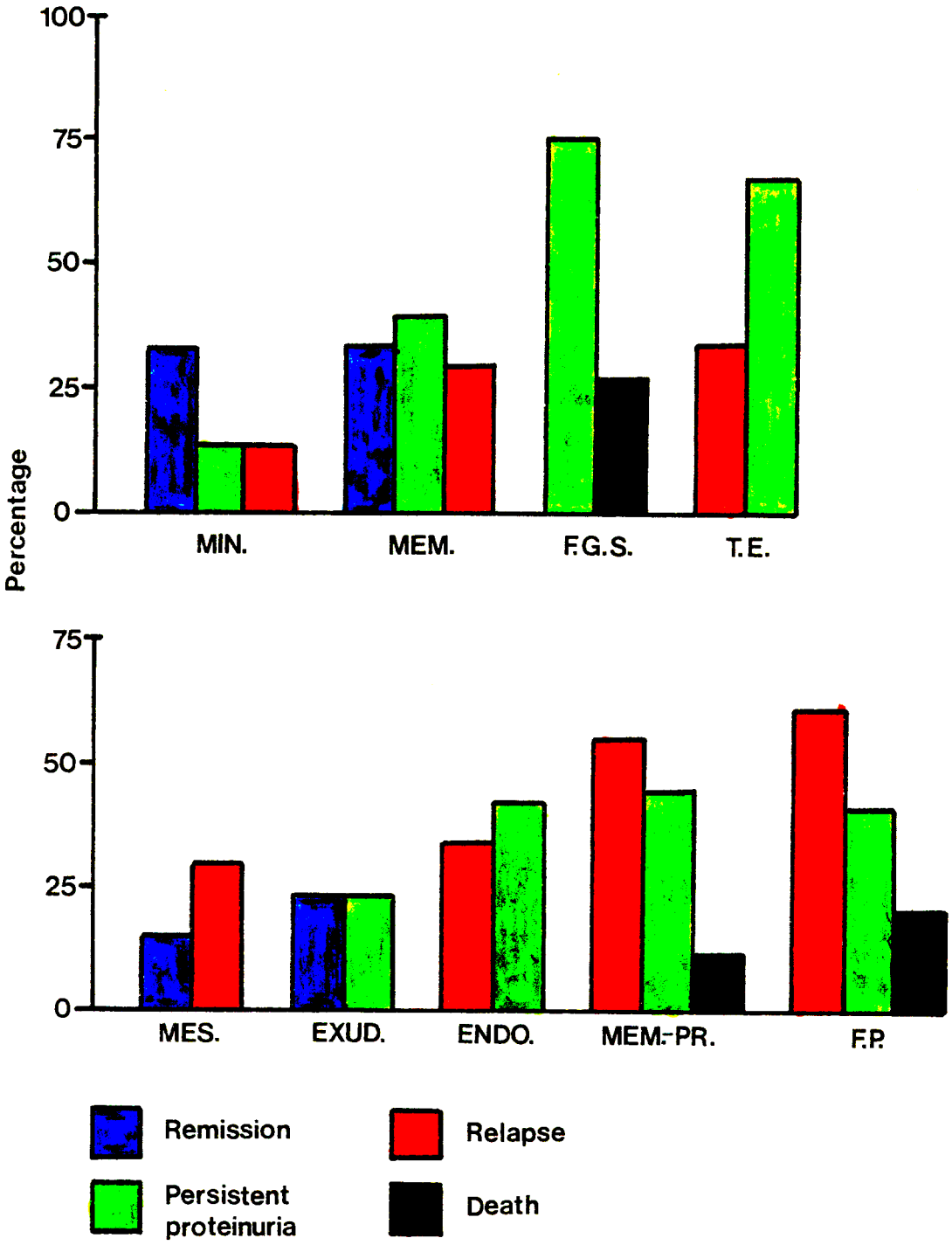
(i) African

The clinical course and outcome of patients over a period of observation, varying from 6 months to 10 years is presented in figure 8 It can be seen that the prognosis was fair among children with minimal change, membranous, mesangial proliferative and exudative proliferative. Remissions occurred in some of the children in these groups. Twenty percent of the minimal change group experienced remissions and multiple relapses.

The overall prognosis in the other groups was less favourable, the majority either remaining

Figure 8

CLINICAL COURSE IN AFRICAN CHILDREN WITH NEPHROTIC SYNDROME



proteinuric or in relapse, and a few patients dying.

Since writing these results one patient has died in the endocapillary group.

(ii) Indian

The clinical course of Indian children with MCNS is shown in figure 9 and that in the other histological categories is shown in figure 10. Although the numbers are small it can be seen that in each histological category (except the unclassified group) some patients did achieve remission.

4.5 Associated Infections and Other Complications

Infections regarded as serious were septicaemia, peritonitis, urinary tract infection, meningitis, arthritis, osteitis, measles and chickenpox.

(i) African (Table XIII)

Nine (8.7%) patients had serious infections. Nineteen (18.2%) had less severe infections. Parasitic infestations of the bowel occurred in the majority of patients. Two patients had cirrhosis of the liver (cryptogenic), one of whom died in combined hepatic and renal failure. Another patient had neurofibromatosis and a fourth was an asthmatic. (Table XIV).

FIG.9: CLINICAL COURSE AND STEROID RESPONSE IN INDIAN CHILDREN WITH MCNS.

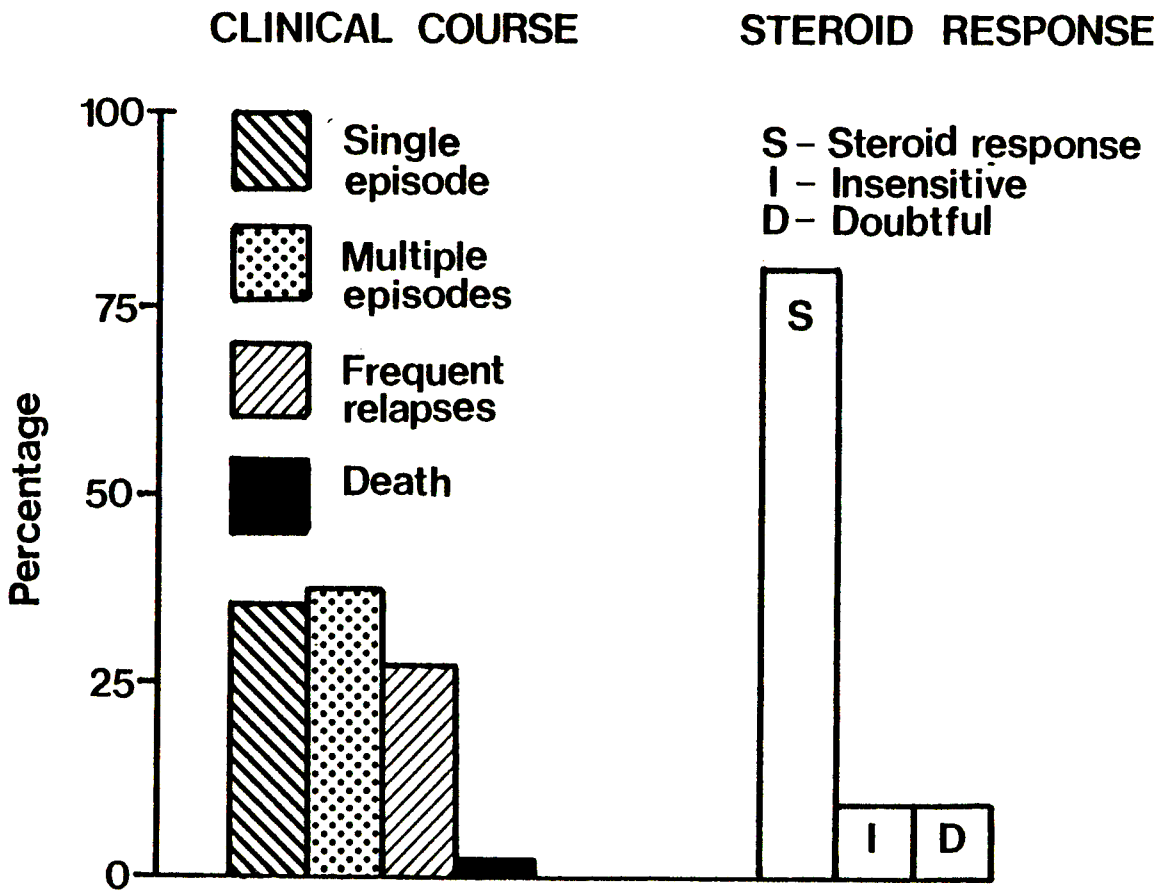


FIG.10: CLINICAL COURSE IN INDIAN PATIENTS OTHER THAN MCNS

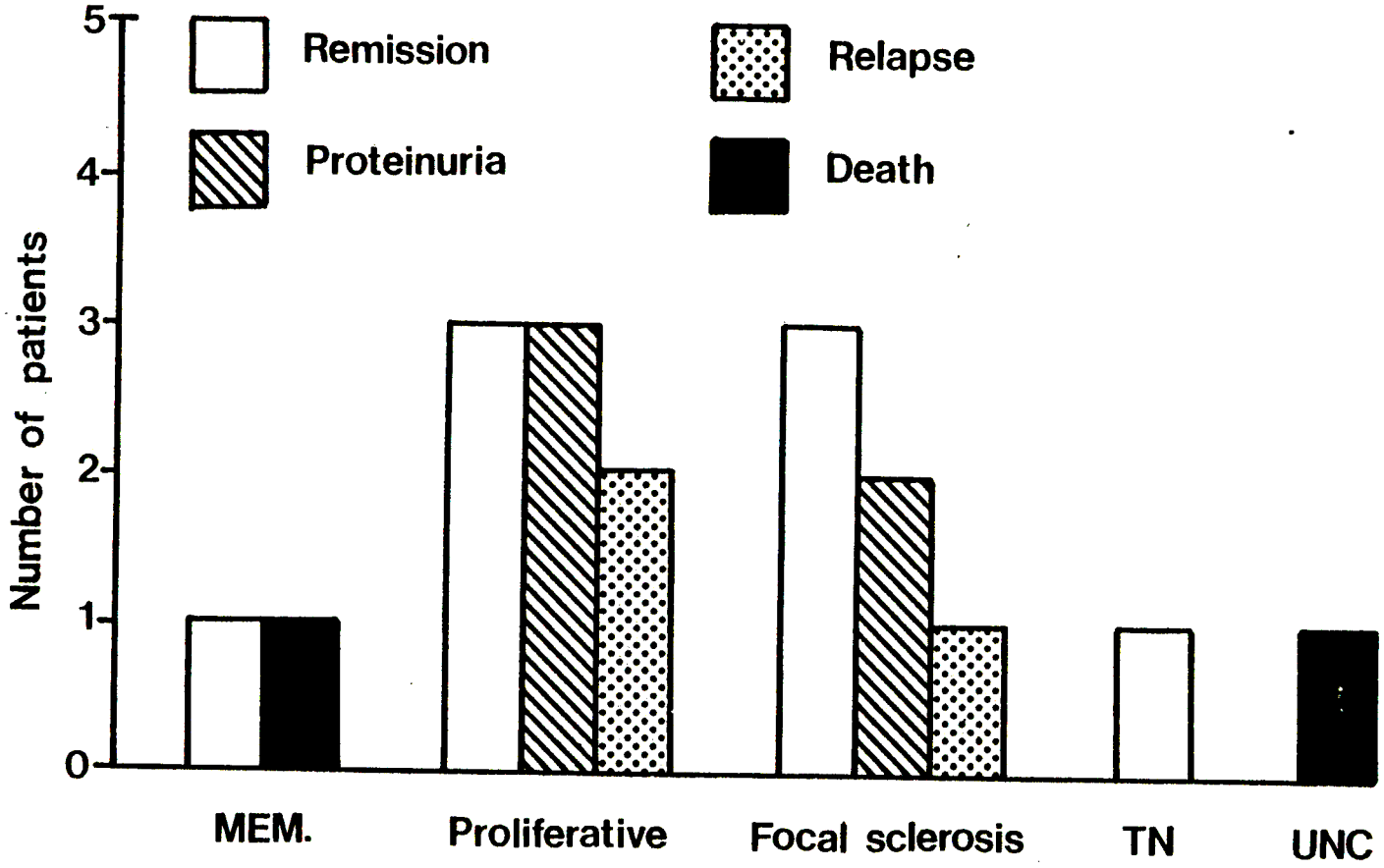


TABLE XIII

ASSOCIATED INFECTIONS IN AFRICAN NEPHROTICS

INFECTION	AFRICAN NEPHROTICS		
	N	Histology	Comment
Septicaemia	1	MPGN	E.Coli (terminally)
	1	FPGN	Klebsiella pneumoniae
	1	TEM	Klebsiella pneumoniae plus Salmonella
	1	FGS	E.Coli (None of the patients were on treatment)
Peritonitis	1	EM	E.Coli plus pneumococcal
	1	FPGN	Klebsiella pneumoniae
Urinary Tract Infection	4	EM	
(E.Coli plus Klebsiella pneumoniae)	1	DE	
	1	FGS	
Tuberculosis	1	EM	Pulmonary calcified hilar glands
	1	MPGN	Lymphadenitis of pelvis and groin
	1	FPGN	Pulmonary tuberculosis
	1	MPGN	Pulmonary tuberculosis
	1	MPGN	Heaf grade IV and hilar glands
	1	DE	Pulmonary tuberculosis
Abscesses	1	Endo	Skin abscesses
Cellulitis	1	EM	Foot
Measles	1	EM	In relapse (not on S)

TABLE XIII

(continued)

INFECTION	AFRICAN NEPHROTICS		
	N	Histology	Comment
Chickenpox	1	EM	In relapse
Hepatic bilharzia	1	EM	
	1	DE	
Herpes simplex	1	MPGN	Terminally associated with gram negative septicaemia
S.haematobium	1	FPGN	
	1	EM	
S.mansoni	1	FPGN	
S.typhimurium enteritis	1	EM	
Shigella dysentry	1	EM	
HB_SAg	1	MPGN	
	1	DMP	
	3	EM	All carriers
	1	Endo	
	1	DE	
	1	DE	Acute hepatitis carrier 3½ years
	1	TN	Died in renal failure
Syphilis	1	EM	Wasserman positive
	2	MCNS	Wasserman positive

TABLE XIV

ASSOCIATED DISEASES IN AFRICAN NEPHROTICS

AFRICAN NEPHROTICS

	N	Histology	Comment
Cirrhosis	1	MPGN	Died in hepatic and renal failure
	1	Endo	Portal hypertension, severe ascites
Asthmatic	1	FPGN	
Neurofibromatosis	1	Endo	Associated short stature

(ii) Indian (Table XV)

Altogether 25 (37.8%) patients had associated infections. Twenty-two (45.8%) patients with MCNS had infective complications. Seventeen (25.7%) had serious infections including 1 child with meningitis resulting in death. 12 patients were on steroids or cyclophosphamide at the time of their infection.

4.6 Anomalies

3 patients (2 African and 1 Indian) had associated anomalies of the urinary tract. These were an ectopic right kidney and a duplex right ureter in the African children and gross vesicoureteric reflux associated with pyelonephritis in the Indian child.

4.7 Treatment and Drug Complications

See Table XVI for treatment response.

(i) African

A Steroids

32 African children were treated.

30 (93.75%) did not respond. 2 children (1 MCNS, 1 EM) responded.

3 children (1 TN, 1 FGS, 1 FPGN) deteriorated,

2 (TN, FGS) died during steroid therapy.

B Cyclophosphamide

4 children were treated (2 MCNS, 1 MPGN, 1 FGS).

TABLE XV

INFECTION	INDIAN NEPHROTICS		
	N	Histology	Comment
Septicaemia	2	MCNS	1 Haemophilus influenza, not on S. 1 E.Coli (on S)
Meningitis	1	MCNS	Meningitis both on S organisms not known
	1	EM	
Peritonitis	1	MCNS	
Urinary Tract Infection	1	MPGN	Klebsiella pneumoniae
	1	TN	Pyelonephritis, vesico ureteric reflux - nephrectomy
	5	MCNS	(2 E.Coli, 3 Klebsiella pneumoniae)
	1	UNC	Klebsiella pneumoniae
Osteitis	1	MPGN	
Pumonary tuberculosis	2	MCNS	
Arthritis	1	MCNS	Septic on E
Abscesses	1	MCNS	Pneumococcal pelvic abscess on S. Later Klebsiella pneumoniae buttock abscess in remission.
URTI	1	MPGN	Recurrent infections
	6	MCNS	2 associated diarrhoea 1 associated amoebic dysentery.

TABLE XV

(continued)

INFECTION	INDIAN NEPHROTICS		
	N	Histology	Comment
Measles	4	MCNS	2 on S - 1 single episode, 1 relapsed subsequently; 1 on E.
	1	FGS	Not on treatment
Chickenpox	5	MCNS	2 on steroids (1 haemorrhagic) 1 remitted permanently 1 relapsed frequently 1 was not on steroids remitted (single episode) 2 others relapsed subsequently (frequent relapses).
Herpes Zoster	1	MCNS	On E
Oral moniliasis	1	MCNS	Associated with S therapy and gross S toxicity

TABLE XVI

DRUG THERAPY RESPONSE IN AFRICAN AND INDIAN CHILDREN WITH NEPHROTIC SYNDROME

Histological Group		Steroids N	+	−	±	Cyclophosphamide N	+	−	±
Minimal Change	A	6	1	5		2	0	2	
	I	44	36	5	3	17	12	3	2
Extramembranous	A	9	1	8		-			
	I	1		1		-			
Proliferative	A	1		1					
Mesangial	I	3	2	1					
Diffuse proliferative	A	4		4					
	I	-							
Membranoproliferative	A	3		3		1		1	
	I	2	1	1		1		1	
Focal proliferative	A	3		3					
	I	-							
Focal Sclerosis	A	3		3					
	I	4	1	3		1		1	
Tropical Nephropathy	A	1							
	I	1	1						
Unclassified	A	2		2					
	I	1		1					

+ = response

− = no response

± = equivocal

None responded.

No serious side effects were noted.

(ii) Indian

A Steroids

56 children were treated (44MCNS, 1 EM, 3 MP, 2 MPGN, 4 FGS, 1 TN, 1 UCL).

41 (73.2%) responded to steroids, 3 other children had a doubtful response. Therefore the maximum steroid response may be regarded as 78.6%.

12 (21.4%) did not respond to steroids.

The majority developed cushingoid features which were excessive in 12 patients. In 3 of these patients (all MCNS) there was such gross steroid toxicity that cessation of prednisone was necessary and cyclophosphamide given instead.

B Cyclyphosphamide

19 children were treated.

12 (63.2%) responded.

5 (26.3%) experienced toxic effects namely alopecia, darkened nails, leucopenia.

C Chlorambucil

4 children (all MCNS) were given this form of treatment with good results in all.

4.8 Complications of Renal Biopsy

The majority of patients appeared to have none or only minor problems following biopsy. Complications following renal biopsy have been mainly haemorrhagic in nature (Dodge et al 1962, White 1963). The minor problems were haematomas that could be detected by ultrasonogram.

1. Abdominal pain and tenderness.
2. Haematuria - transient.
3. Transient hypertension - this might have been the result of removal of the pillow and release of pressure from the inferior vena cava. (Muercke and Pirani 1975).
4. Renal abscess at biopsy site - one patient developed pain, tenderness and a high fever following the biopsy, the urine culture was positive and the patient required surgery for drainage of the abscess and partial nephrectomy.
5. Haematomas.

4.9 (i) Mortality

The overall mortality was 5.8%. The 10 patients who died are discussed under the relevant histological categories.

(i) African

Seven (6.7%) deaths occurred in this group - 4

in the proliferative group (2 FP, 1 MPGN, 1 endocapillary), 1 TN, 1 FGS and 1 with end stage renal disease.

(ii) Indian

Three (4.5%) deaths occurred - 1 MCNS, 1 membranous, and 1 end stage disease.

Table XVII compares the African and Indian children studied. Differences are noted with regard to the age of presentation, histological categories immunofluorescent deposits, response to therapy and ultimate outcome.

The details of each histological category will be discussed in the following pages.

TABLE XVII

FEATURES OF THE NEPHROTIC SYNDROME IN SOUTH AFRICAN CHILDREN

	AFRICAN	INDIAN
Incidence	0.17%	Very few Indian children are admitted to the King Edward VIII Hospital. A large number of the nephrotic patients are referred. An incidence over this study period would therefore be falsely high.
Peak Age	2 peaks 5 yrs, 8 - 11 yrs	Pre-school (4 yrs)
Sex Incidence	M > F	M > F
Aetiology	Unknown in majority	Unknown in majority
Dominant Histological Groups	Obvious glomerular lesions (85.6%) (Proliferative, membranous) Minimal change (14.4%)	Minimal change (72.7%)
Immunofluorescence	Deposits in majority - usually moderate - heavy (including minimal change)	No deposits in majority
Response to Therapy - Steroids and Cyclophosphamide	No response	Majority steroid sensitive (81.6%)
Frequent relapses	-	28.3%
Prognosis	Related to histological group	Excellent

5. HISTOLOGICAL CATEGORIES

5.1 INDIAN MINIMAL CHANGE NEPHROTIC SYNDROME

5.1.1 Summary

Indian children with MCNS have an excellent prognosis. The majority 81.6% are steroid sensitive and 97.8% achieve remission. A few more than one third (34.8%) experience single remissions, a similar number (37.0%) experience multiple episodes and fewer than one third (28.2%) have frequent relapses,

5.1.2 Incidence, Age, Sex

Forty-eight (72.7%) of the 66 Indian children were minimal change on light microscopy. The age distribution is shown in figure 11. Twenty-three patients (about 50%) presented at or under 5 years of age. 35 (72.9%) were males.

5.1.3 Clinical Details

(i) Initial Presentation

All had the clinical features of the nephrotic syndrome. Haematuria occurred in 2 patients (4.2%)

Hypertension)
) - did not occur in any patient.
Renal failure)

(ii) Follow-up (See figure 9)

46 patients were observed for longer than 3 months. Only 5 of these were seen for a period of less than 6 months. (The following results are calculated from the 46 patients followed-up).

16 (34.8%) experienced single episodes

17 (37%) experienced more than 1 episode (but these relapses occurred infrequently).

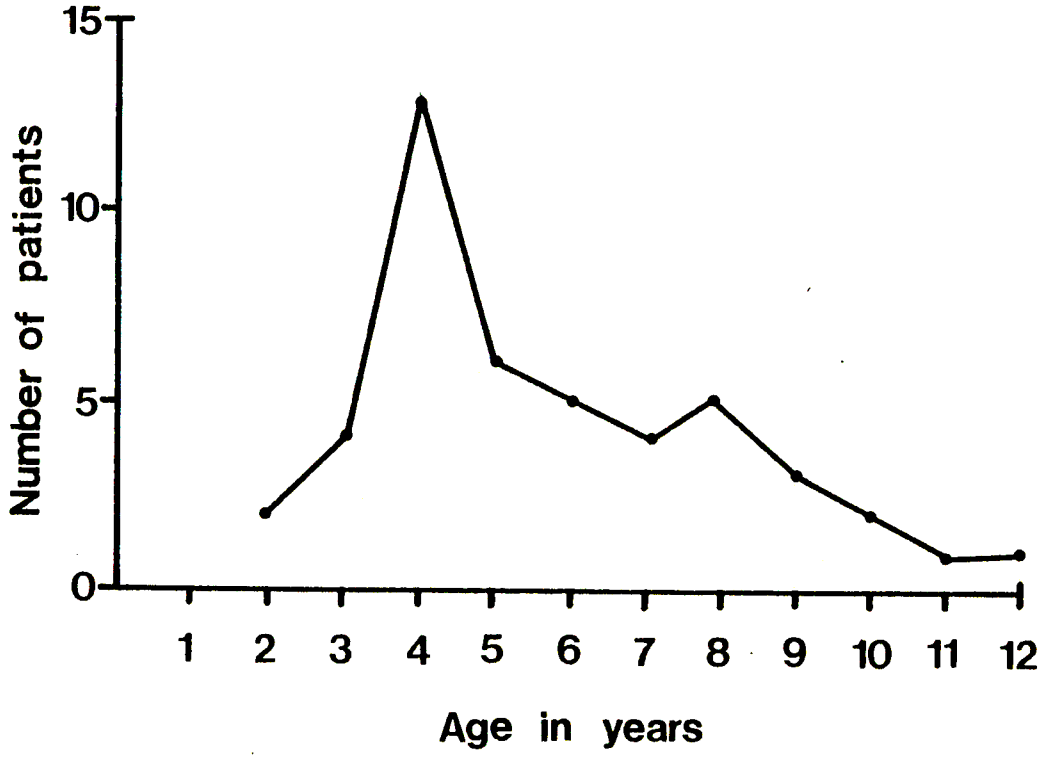
10 had 2 episodes

2 had 3 episodes

5 had more than 4 episodes

(1 died)

FIG. 11: AGE DISTRIBUTION IN INDIAN MCNS



13 (28.2%) relapsed frequently.

A single patient had not achieved remission since the onset of her disease. One child died while on steroids from purulent meningitis. No organism was isolated from the CSF in this patient.

5.1.4 Investigations

All had biochemical features of nephrotic syndrome.
All had normal renal function on presentation.
Urine : haematuria in 2 patients.

E. coli 10^5 orgs/ml cultured in 1 patient.
Blood culture was positive for E.coli in the same patient with UTI.
Other investigations were non-contributory.

5.1.5 Immunofluorescent Findings in Indian MCNS (Table XVIII)

N	No deposits	IgM	IgM, IgG, IgA (+)
35	23	12*	1

The IgM deposits were in the mesangium or on the glomerular basement membrane. *In one patient the initial biopsy had no deposits but a repeat biopsy had some IgM deposits.

5.1.6 Electron Microscopy

This was performed on 6 patients. Five biopsies

demonstrated fusion of the foot processes and in one biopsy there were normal glomeruli.

5.1.7 Selectivity of Proteinuria

Selective excretion of IgG and transferrin expressed as a ratio was determined in 7 patients. All had selective proteinuria (i.e. a ratio <0.2).

5.1.8 Response to Treatment

(i) General - Diuretics (Thiazides, Spironolactone, Triamterene) were used singly or in combination. All patients except one with UTI and E.coli septicaemia responded to diuretic therapy. This patient showed clinical improvement once the infection had been controlled with antibiotics. A high protein diet was generally given to all the patients.

(ii) Steroid Therapy (See figure 12)

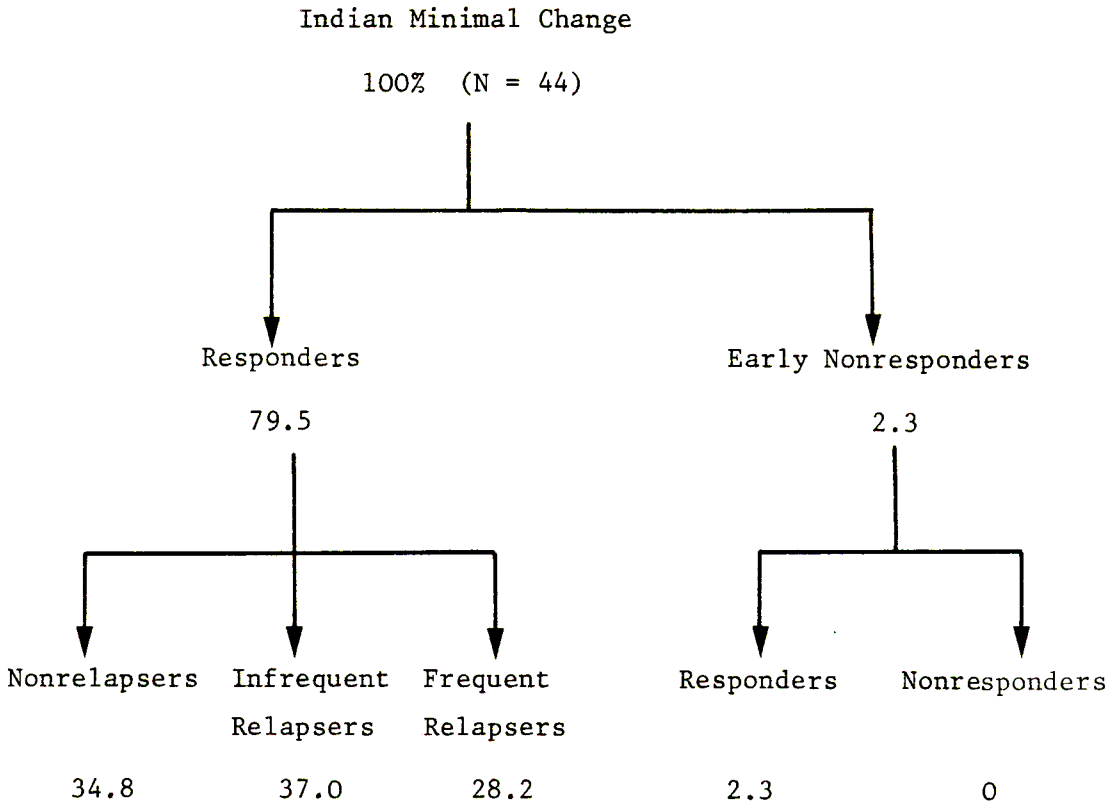
44 patients were treated.

Single episodes (15) - 10 responded
- 4 did not respond
- 1 doubtful response

Two episodes (10) - 9 responded (1 with UTI and septicaemia did not respond at first.

FIGURE 12

STEROID RESPONSE IN TREATED MCNS



- 1 uncertain

Three episodes (2) - 2 steroid sensitive

Multiple (4) - 3 steroid sensitive

- 1 steroid insensitive

Frequent relapses (13) - 12 steroid sensitive

- 1 doubtful response

Overall 36 patients (81.8%) steroid sensitive

5 patients (11.4%) steroid insensitive

3 patients (6.8%) doubtful.

NOTE: 1 patient with multiple episodes and steroid insensitivity had 2 renal biopsies. The first biopsy had no deposits while the second biopsy had weak IgM deposits.

(iii) Cyclophosphamide

17 patients were treated.

Frequent relapses (12) - 9 responded. All experienced decreased rates of relapses with prolonged remissions.

- 2 did not respond

- 1 doubtful response

Single episodes (3) - 2 responded (both steroid resistant)

- 1 did not respond (initially steroid resistant, subsequently responded to steroid).

Steroid toxicity (2) - 1 responded

- 1 doubtful

Overall 12 patients (70.5%) responded to cyclophosphamide.

(iv) Chlorambucil

4 patients with frequent relapses were treated, all 4 responded.

3 were steroid and cyclophosphamide sensitive.

1 was steroid sensitive with a doubtful cyclophosphamide response.

Transient neutropenia occurred in one child.

5.1.9 Associated Infections (Table XIX)

22 (45.8%) patients had infective complications. Serious infections occurred in 17 (35.4%) patients.

5.1.10 Comparison of Patients without IgM Deposits and with IgM Deposits (Table XX)

Two groups of patients, one without IgM deposits and the other with IgM deposits are compared in Table XX. No significant differences were detected between these 2 groups. The numbers in each group are too small to comment upon the differences.

TABLE XIX

ASSOCIATED INFECTIONS IN INDIAN MCNS

INFECTIONS	N	COMMENT
Septicaemia	2	H. influenza, E coli (on no treatment)
Meningitis	1	No organism (on S)
Peritonitis	1	Not on S
Urinary Tract Infection	5	2 E. coli, 3 K. pneumoniae
Pulmonary tuberculosis	2	
Arthritis	1	S viridans on E
Abscesses	1	Pneumococcal pelvic abscess on S. K. pneumoniae buttock abscess off treatment.
Upper respiratory tract infections	6	2 associated with diarrhoea 1 associated with amoebic dysentery
Measles	4	2 on S (single episodes) 1 on E 1 relapsed subsequently.
Chickenpox	5	2 on S (1 haemorrhagic) - (1 single episode, 1 relapsed frequently). 1 not on S, 2 frequent relapses.
Herpes zoster	1	On E
Moniliasis (oral)	1	On S with gross S toxicity

TABLE XX

COMPARISON OF MCNS WITHOUT IGM DEPOSITS AND MCNS WITH DEPOSITS

	MCNS - NO DEPOSITS		MCNS - IGM DEPOSITS	
N	23		13	
Age				
<5 yrs of age	±	50%	±	50%
Sex				
Males		60%		76%
Urine findings				
Haematuria	1		1	
Relapses				
Single episodes	7	30.4%	2	15.3%
Two episodes	5	21.7%	3	23.0%
Three episodes	1	4.3%	1	7.6%
Multiple	3*		1	
Frequent relapses	5	21%	4	30.7%
Infections	9	39%	7	53.8%
Therapeutic response				
Steroid sensitive	16	69.5%	9	69.2%
Steroid insensitive	3		0	
Steroid doubtful	3*		1	
Cyclophosphamide sensitive	4	17.3%	4	30.7%
Cyclophosphamide insensitive	2		1	
Cyclophosphamide doubtful	2		1	

* 1 initially no deposits, repeat biopsy IgM deposits.

5.1.11 Discussion

Minimal change nephrotic syndrome (MCNS) is the commonest form of the nephrotic syndrome in childhood (White et al 1970). The prognosis is excellent (Habib 1974 a) and steroid therapy results in diuresis with clearing of the proteinuria (International Study of Kidney Disease 1974, Rubin 1975a).

The majority (72.7%) of Indian children with nephrotic syndrome in South Africa had minimal change on light microscopy. In contrast African children with nephrotic syndrome were diagnosed as minimal change in only 14.4%. Indian nephrotics behaved like nephrotic children elsewhere (White et al 1970, Habib 1974 a). The clinical presentation, course, response to steroid therapy and prognosis were similar. The Indian children with nephrotic syndrome therefore served as good parallels for the African children with the disease.

The peak age of incidence was 4 years, the percentage of children presenting at 5 years or younger was 50%. These are lower figures than generally reported (Report of ISKDC 1981). Males dominated and features suggestive of possible poor prognosis such as hypertension and renal failure were not present in any of the patients. A small number (3%) had haematuria.

Eighty-one percent were shown to have a definite response to steroid therapy. If the patients with a doubtful response were included the percentage rose to 88.8%. Seventy-eight to 93% is a generally accepted overall steroid response in MCNS (ISKDC 1981, White et al 1970, Grupe 1979).

Cyclophosphamide was given to patients who experienced severe steroid toxicity, frequent relapses and to those patients who failed to respond to steroids. The majority of patients, including those who were steroid insensitive, responded. Those with frequent relapses experienced a decreased rate of relapses with prolonged periods of remission following cyclophosphamide therapy.

Steroid insensitive MCNS and frequently relapsing MCNS have been shown to respond to cyclophosphamide therapy in exactly the same manner as these patients did (ISKDC Study 1974). All except one patient had achieved remission.

Selectivity of protein excretion, although performed on a few patients, demonstrated selective proteinuria in all. All these patients were steroid sensitive (Grupe 1979).

Chlorambucil (Grupe et al 1976) was used with good effect in 4 patients who relapsed frequently all

of whom had previously had cyclophosphamide therapy.

The toxic effects of the above drugs was reversible in all the patients who suffered side effects.

Associated infections, serious and minor, occurred in a significant number of patients. Infections are known to complicate the course of the paediatric patient with nephrotic syndrome and may result in death. Interestingly these infections may occur in relapse while on treatment with steroids or cyclophosphamide or in remission (Anderson et al 1979). Many of the patients experiencing infections in this series were in different stages of their disease. The pathogenesis of infections in the nephrotic syndrome is not well understood. Some immunological aspects have been demonstrated to be defective (Anderson et al 1979) and may play a role in the higher incidence of associated infections.

In this study 13 patients were noted to have light IgM deposits in the mesangium or on the glomerular basement membrane. There was no associated mesangial cell increase as in the study on page Comparing the clinical features, outcome, drug responses to therapy and overall prognosis there was no significant differences between the group

which had deposits and the group with no deposits. Infections appeared to occur more frequently in those with IgM deposits. This similarity in minimal change with and without IgM is like the findings by Vilches et al (1980).

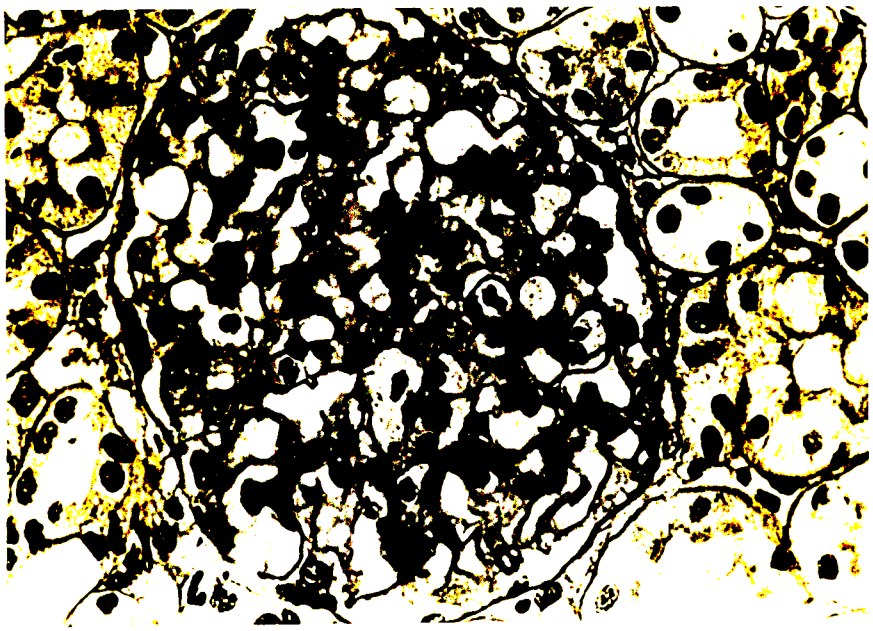
The suggestion that the IgM deposits were the result of a nonspecific immune response (Cavallo and Johnson, 1981) appears feasible if one postulates that patients who experience infections more frequently demonstrate weak IgM deposits in the glomeruli.

Indian children with the nephrotic syndrome in South Africa have the "typical" MCNS with an excellent prognosis. Chemotherapy is valuable in the treatment of these children. Care is required in the monitoring of these patients on these drugs. Toxic effects and associated infections occurred commonly.

INDIAN MINIMAL CHANGE NEPHROTIC SYNDROME

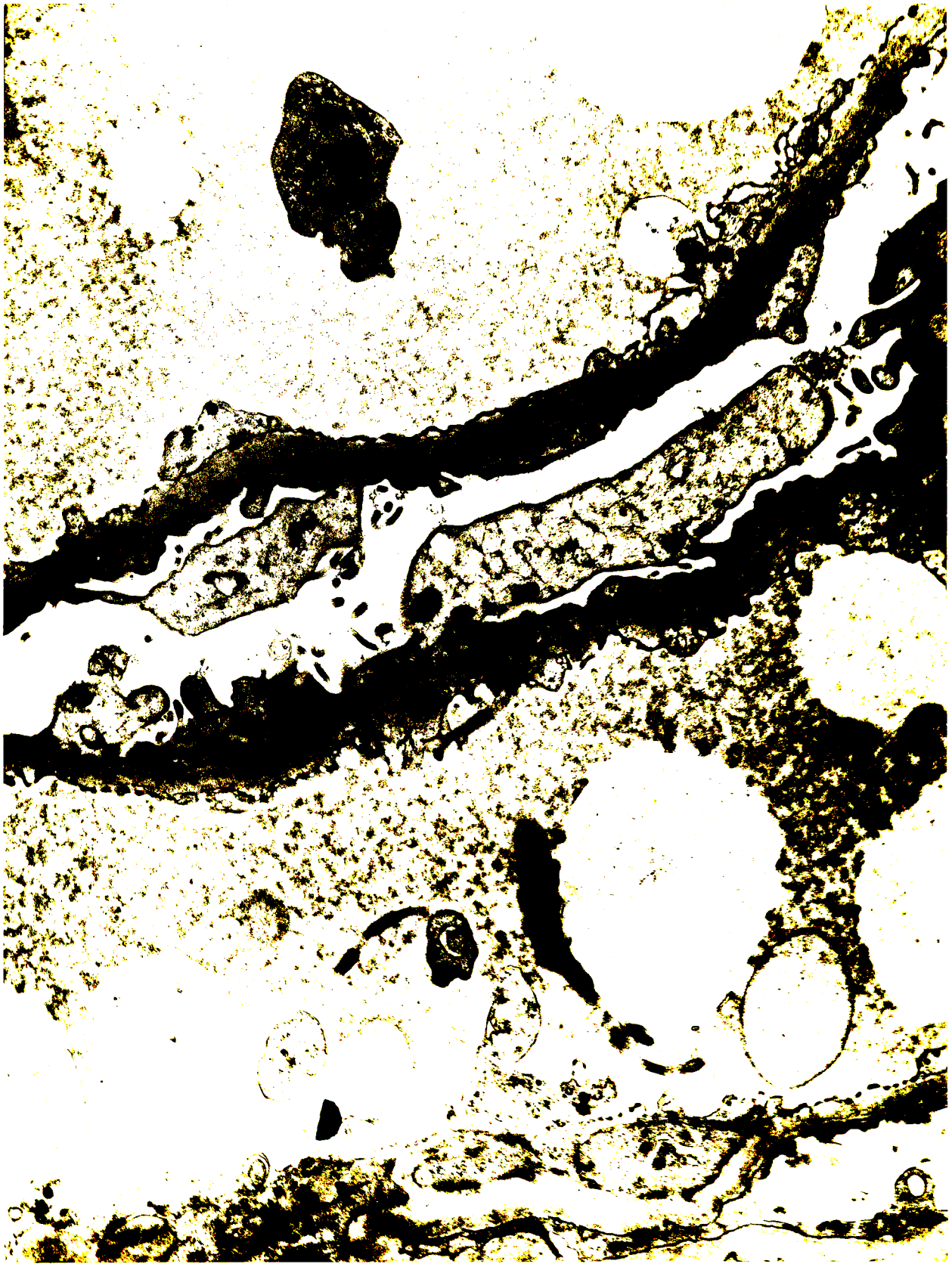
MINIMAL CHANGE NEPHROTIC SYNDROME

(Magnification x 640)



Electronmicrograph (x 10,500)

MCNS - FUSION OF FOOT PROCESSES



5.2 AFRICAN MINIMAL CHANGE NEPHROTIC SYNDROME

5.2.1 Summary

This diagnosis made on 14.4% of biopsies from African nephrotics. The age of presentation is older, one third have immune deposits on the GBM. The prognosis is fair, one third remit spontaneously. There was no response to steroid therapy.

5.2.2 Incidence, Age and Sex

Fifteen (14.4%) of the Africans were minimal change.

The peak age incidence (Fig. 13) of MCNS in the African children was 7-8 years (8 patients). Five (33%) patients presented at or below the age of 5 years. Ten (66%) of the children were males.

5.2.3 Clinical Details

(i) Initial Presentation

All the patients presented with oedema, massive proteinuria and hypoalbuminaemia. None of them had hypertension or azotaemia:

Hypertension - none

Haematuria - 4 African patients, 3 settled later

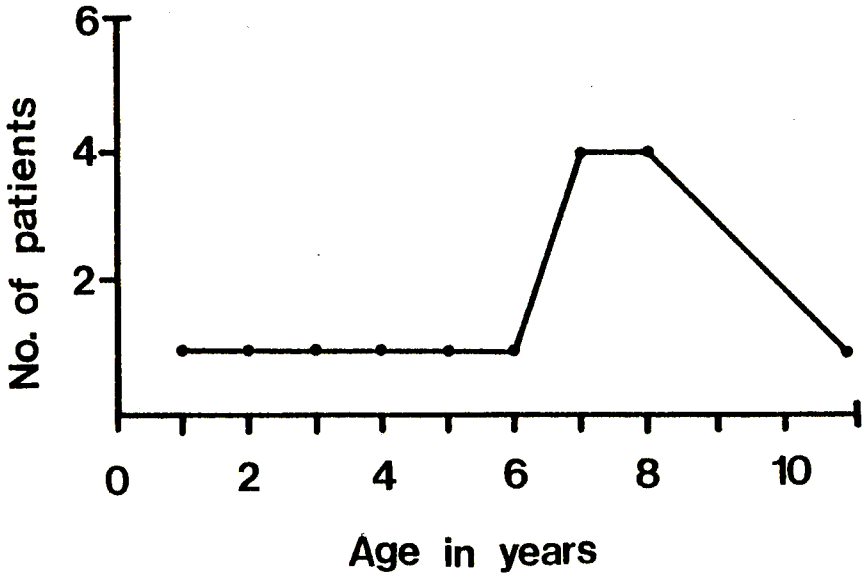
Renal failure - none

(ii) Follow-up

Twelve patients were followed up for more than 6 months, while 3 were seen only at initial presentation.

Single episode: 9 - 5 remitted 1 - 30 months after onset.

FIG. 13: AGE DISTRIBUTION IN AFRICAN MCNS



	- 2 persistent proteinuria)	4-48 months duration
	- 2 persistent relapse)	
Multiple episodes 3	- remission varied from 2-15 months	
	- relapse varied from 2-28 months	
Frequent relapses	- did not occur	

Serious renal impairment (azotaemia, hypertension - did not occur.

5.2.4 Investigations

The nephrotic syndrome was confirmed biochemically in all the patients. Renal function was normal in all patients studied. Urine examination in all revealed proteinuria >2 gms/m^2/24 hours and nothing else of note.

Urine examination :	5 leucocytes/HPF in majority
	5 red cells/HPF in 8
	negative cultures in all

Schistosomal infestation: negative in stool and urine.

Wasserman reaction positive (1/8 and 1/32 dilutions) and fluorescent treponema antibody absorption test (IgM) in 2 patients.

All other investigations under patients and methods were negative.

5.2.5 Immunoflourescent Findings (See Table XXI)

In 8 of 13 patients no immune deposits were demonstrated. One patient had slight deposits of IgM, 2 patients had IgM + IgA, and 2 others had course granular or heavy deposits of IgG + Clq.

5.2.6 Electron Microscopy

Electron microscopic examination was performed in 3 patients; fusion of the epithelial foot processes was the only abnormality detected in all 3.

5.2.7 Immunofluorescent Deposits and Outcome

(See Table XXI)

The presence or absence of immune deposits did not influence the outcome in individual patients.

5.2.8 Selectivity of Proteinuria (See Table XXI)

Elective excretion of albumen and transferrin expressed as a ratio was determined in 8 patients.

Selective proteinuria (i.e. ratio <0.2)

- 6 patients - 4 remitted

Non-selective proteinuria (i.e. ratio >0.2)

- 2 patients - 1 remitted

Selective proteinuria did not indicate a more favourable clinical outcome in children.

5.2.9 Response to Treatment

(i) General - Diuretics (Thiazides, Spironolactone, Triamterene) were used either singly or in combination. All patients improved on diuretics except for one African patient who subsequently was given cyclophosphamide. A high protein diet was generally recommended or given.

(ii) Steroid - Immunosuppressive Therapy - The response of patients to steroids, cyclophosphamide is shown in the Tables XXI and XXII.

1 (11 year old male) responded in 1 month.

5 - failed to respond to the 3 month course.
- all remitted spontaneously 11-36 months later.
- 2 relapsed subsequently for 3 and 4 months remitting again.

2 - treated with steroid and cyclophosphamide did not respond.

2 patients with positive Wasserman reactions were treated with penicillin and did not receive steroids.

TABLE XXI

IMMUNOFLUORESCENCE, SELECTIVITY OF PROTEINURIA, OUTCOME AND RESPONSE TO THERAPY IN AFRICAN MCNS

	Immunofluorescence Deposits					Selectivity of Proteinuria				
		Negative		Positive			Selective		Non-selective	
African	N 13	8		5		N 8	6		2	
		Outcome					Response to Therapy			
		Remission	No Remission	Remission	No Remission		S Response	No Response	Response	E No Response
African	N 10	3	4	2	1	N 8	4	2	1	1

TABLE XXII

STEROID AND IMMUNOSUPPRESSIVE DRUG THERAPY IN AFRICAN MCNS

		RESPONSE	
	N	+	-
Steroids only	6	1	5
Steroids and Cyclophosphamide	2	0	2

+ = Response obtained

- = No response

N = Number

5.2.10 Complications of Treatment

No complications were encountered in the patients on steroids or cyclophosphamide.

5.2.11 Discussion

This study of 15 African patients initially diagnosed as MCNS on light microscopy has demonstrated that although the histology appears identical to the universally recognised form of childhood MCNS some of the other correlates were dissimilar. The description of this disease from other parts of Africa, (Hendrickse et al 1972; Kibukamusoke, Hutt & Wilks 1967) would appear to support some of these findings. There are only a few (8) patients with MCNS in West (Hendrickse et al 1972) and East Africa (Kibukamusoke, Hutt & Wilks 1967) who more closely resemble typical MCNS. It is evident therefore that the complete syndrome of minimal change nephrosis is so infrequent as to justify its exclusion from the routine differential diagnosis of childhood African nephrotic syndrome except where facilities for renal biopsy, appropriate therapy and follow-up are available. Accordingly in the absence of such facilities, as obtains in many centres in Africa, therapy for nephrotic syndrome should exclude steroids and cyclophosphamide.

Whereas two-thirds of MCNS at first presentation are under the age of 5 years (Habib et al 1974; Heyman et al 1972; Sudash et al 1974 Heyman 1974) the peak age incidence in this study was 7 - 8 years (53%). In the two studies of malarial nephrotic syndrome (Hendrickse et al 1972; Kibukamusoke et al 1967) the 'minimal change group' of West Africa presented under 5 years and the 'nil lesion' in Uganda under two years of age. None of the prognostic features of poor outcome (e.g. hypertension, sustained haematuria, azotaemia) were detected at onset of the disease.

Neither steroids nor cyclophosphamide, which are effective in the vast majority of MCNS, were of similar benefit to the African children in this study. The one patient who appeared to respond may have in fact had a spontaneous remission. The response to drug therapy is strikingly different from that reported by Hendrickse (1972) and Kibukamusoke (1967). In both these studies patients with minimal or 'nil' lesions responded to steroids. The spontaneous remission rate (33%) noted in the African patients documented here is surprisingly very similar to that experienced in 'true' MCNS before the advent of antibiotics and corticosteroids (Cameron 1979).

The clinical course in African children with MCNS tended towards remission and a favourable outcome. During the period of follow-up none of these patients developed any ominous signs of renal insufficiency or failure. Therefore, on balance, an absence of obvious glomerular lesions in African children with nephrosis would indicate a good prognosis for the short term. Long term follow-up is needed to clarify the natural history of the disease.

Two aspects in African children which were similar to 'true' MCNS were male dominance (White et al 1970; Heyman et al 1972) (69%) and clinical presentation.

The majority of patients with 'true' MCNS have no immune deposits on immunofluorescent examination, very few may have slight deposits. In QMNS (Hendrickse et al 1972) all 5 of the minimal change group had well defined immunofluorescent deposits on the glomerular basement membrane (GBM) whereas in these South African children 60% had no deposits. The two African patients with coarse granular or heavy deposits of IgG and C1q were Wasserman positive. These patients had been treated with penicillin and when seen at follow-up had gone into remission 1 - 4 months after presentation.

Falls et al (1965) has demonstrated a similar improvement in the nephrotic syndrome caused by secondary syphilis following treatment with penicillin. He demonstrated improvement on light and electron microscopy of renal tissue. Both these children were under 5 years of age and appear therefore to be examples of endemic syphilis (Le Roux & van Buuren 1978). Yuceoglu et al (1966) reported minimal changes on light microscopy in a 10 week old baby with congenital syphilis. Absence of immune deposits did not favour a better outcome in individual patients. Some patients remained in relapse with persistent proteinuria and only one remitted spontaneously.

Electron microscopic examination of renal tissue in 3 patients confirmed the findings expected in MCNS. This would suggest that the light microscope definition of minimal change was fairly accurate and obvious glomerular lesions had not been missed.

Selectivity of proteinuria has been reported to be helpful by some workers in identifying steroid responsive patients (White et al 1970; Heyman et al 1972; White 1971). However the proportion of MCNS demonstrating highly selective proteinuria varies from 53% to

75%, (White et al 1970; Cameron & Blandford 1966; White 1971). One third of patients with non-selective proteinuria also respond to steroids (Cameron & Blandford 1966). Selectivity of proteinuria proved to be of no assistance among the African patients reported here in detecting those who might remit or respond to steroids. Six of the patients had selective proteinuria but the outcome was variable. This is in contrast to QMNS in which one third of the children with highly selective proteinuria responded to corticosteroids (Adeniyi et al 1976). The lack of response to steroids indicated that although the histology was minimal change on light microscopy, this may in fact have been a precursor to the evolution of more obvious glomerular lesions, a progression noted by other workers (Ginzler et al 1980; Hayslett et al 1973; Habib et al 1974). This interpretation would be supported by the findings of minimal change on histology in two of our patients with syphilis who had deposits of IgG and complement on the GBM and in whom obvious lesions were expected.

It is necessary to emphasize that in the African children with MCNS the older age at presentation and lack of a predictable response to steroids

or cyclophosphamide clearly distinguishes them from 'true' MCNS. The other features of the disease, discussed above, are less obviously different. In comparison to minimal change from tropical zones the children from South Africa differ in respect of age at onset, immunofluorescent findings, selectivity of proteinuria and response to steroids.

There is suggestive evidence that increased urbanisation and adoption of Western life-styles by Africans has been associated with the appearance of diseases characteristic of more affluent societies. (Seftel et al 1970). It may be similarly argued that the incidence of 'true' MCNS may rise among Africans with accelerating social change. However, this seems less likely as 'true' MCNS does not appear to be a disease clearly related to socio-economic conditions as it occurs equally frequently in both rich and poor nations.

5.3 EXTRAMEMBRANOUS NEPHROPATHY

5.3.1 Summary

This study has described the features of 31 African and 2 Indian children of membranous nephropathy which is the most frequent histological category among Black children with nephrotic syndrome. The male sex dominate and there were 2 peak age groups (4 - 5 years and 8 - 11 years) in the African children. The incidence and clinical outcome in these patients were similar to adults with membranous nephropathy. Hypertension occurred more frequently (20%) and spontaneous remission less often (30%) than in children with membranous nephropathy elsewhere. The lower remission rate and persistence of proteinuria during the course of the disease were similar to the disease seen in adults. Renal failure was not encountered in any patient. Steroids were of no value in the treatment of these children. Five patients (16.2%) experienced associated infections. HB_SAg was described in 3 other patients (9.7%) giving an incidence no higher than in the general population.

5.3.2 Incidence, Race, Age, Sex

31 (29.8%) of the Africans and 2 (3.0%) of the Indians demonstrated the histological features of membranous nephropathy. Twenty (64.5%) African children were over 5 years of age at presentation (see figure 14). One Indian child was 2 years and the other 5½ years of age at presentation. 25 (80.6%) of the African children and 1 Indian child were males.

5.3.3 Clinical Details (see Table XXIII)

(i) Initial Presentation

All the patients presented with massive oedema, proteinuria and hypoalbuminaemia.

Hypertension : 2 African children (6.5%)
Haematuria : 14 African children (45.2%)
Renal failure : None

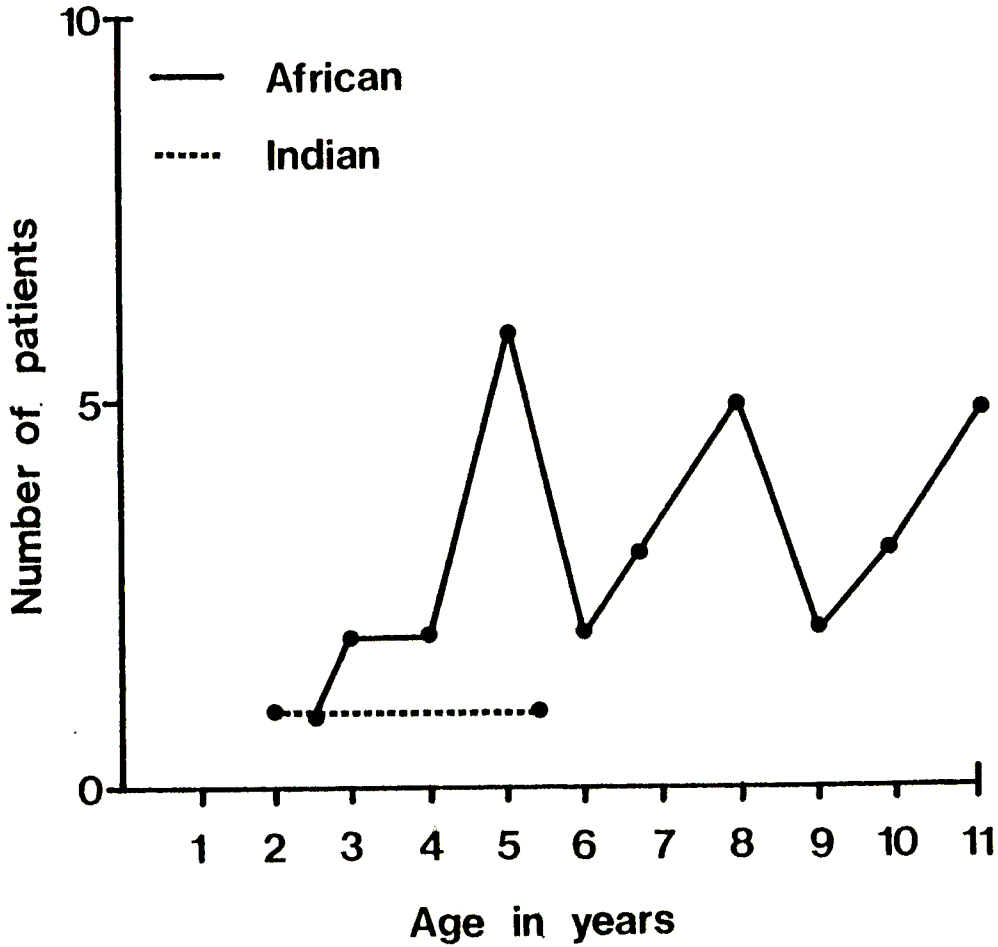
None of the above occurred in Indian children.

(ii) Follow-up

1. African

Six children were seen only at initial presentation.
Twenty-five were followed-up for 3 months or more.

FIG. 14: AGE DISTRIBUTION OF PATIENTS WITH EXTRA-MEMBRANOUS NEPHROPATHY.



- single episode of nephrosis - 8 children (33.3%).

  Spontaneous remission occurred 3-11 months after the onset of their nephrosis.

- persistent proteinuria - 9 children (37.5%)
- persistent relapse - 7 children (29.2%)

) for 3 - 60 months from onset of their disease

One patient - multiple episodes of nephrosis. The duration of the relapses were 5-15 months and remissions varied from 5-20 months.

Hypertension - 4 patients. One patient remitted (for 4½ years) but remained hypertensive. A second patient is nephrotic 5 years after the onset of his illness.

Overall incidence of hypertension (2 at initial presentation and 4 on follow-up) was 20%.

2. Indian

Single episode of nephrosis - 1 child. Episode lasted 3 months and the child has been in remission since then for 7 years.

Two episodes - 1 child. Three months

following the first episode of steroid sensitive nephrotic syndrome the patient relapsed. Steroid therapy was commenced and 4 days later the patient died.

5.3.4 Investigations

All the patients had low serum albumin, raised cholesterol and heavy proteinuria during their periods of relapse. All had a normal blood urea, serum sodium, potassium and chloride and intravenous pyelogram.

Urine examination : 14 patients - 5 leucocytes/HPF
>5 red cells /HPF.
: 3 patients - positive cultures. (E. coli, K. pneumoniae).

Wasserman was positive (2 dilutions) in one patient.

HB_sAg was detected in 3 patients (liver function tests were normal).

5.3.5 Electron Microscopy

Electron microscopy was performed in 3 African patients. One biopsy showed focal fusion of foot processes only, the other 2 demonstrated thickened glomerular basement with deposits.

5.3.6 Immunofluorescence

Twenty African patients were investigated for immunofluorescent deposits.

N	IgG	IgM	IgA	C_3
13	+++	+++		+++
3	+++	+++	+++	+++
2	+++			+++
1		+++		
1	0	0	0	0

Immunofluorescent studies were not performed on either of the 2 Indian patients.

5.3.7 Selectivity of Proteinuria

Performed in 3 patients - 2 selective proteinuria
- 1 non-selective proteinuria

5.3.8 Response to Treatment

(i) General - Diuretics (Thiazides, Spironolactone, Triamterene) were used singly or in combination. Most patients improved on diuretics except for the 7

TABLE XXIII

CLINICAL DETAILS IN EXTRAMEMBRANOUS NEPHROPATHY

	N	<5 yrs	M	HPT	HAEM	REM	REL	PP	ME
African	31	11	25	6	14	8	7	9	1
Indian	2	1	1	0	0	1	0	0	0

HPT - hypertension

HAEM - haematuria

REM - remission

Rel - relapse

PP - persistent proteinuria

ME - multiple episodes

TABLE XXIV

TREATMENT RESPONSE IN EXTRAMEMBRANOUS NEPHROPATHY

	N	Steroid Response		Cyclophosphamide	
		+	-	+	-
African	9	1	8	0	1
Indian	1	1	0	0	0

TABLE XXV

ASSOCIATED INFECTIONS IN EXTRAMEMBRANOUS NEPHROPATHY

Infection	Number of Patients
Urinary tract infection	3
Pulmonary tuberculosis	1
Pneumonia	1
Wasserman positive, hepatosplenomegaly	1
Heaf positive	
HB_sAg	3

African patients who remained in relapse.
A high protein diet was generally recommended.

(ii) Steroid-Immunosuppressive Therapy

(Table XXIV)

1. African

Steroid

9 treated

1 responded

8 no response - 2 remitted 6 months after steroid therapy was stopped.

Cyclophosphamide

1 treated (failed steroid therapy) - no response.

2. Indian

1 Indian child responded to steroids during the first episode of nephrosis; he died in relapse with meningitis 4 days after commencing steroids for his 2nd episode of nephrosis. An autopsy was not performed. The second child was not given steroids and remitted spontaneously.

(iii) Complications of Therapy

None of the patients given steroids became

cushingoid. The patient treated with cyclophosphamide developed transient neutropenia.

5.3.9 Associated Infections (Table XXV)

Three patients had evidence of acute urinary tract infection. 1 patient had pulmonary tuberculosis. 1 patient had pneumonia. 1 had hepatosplenomegaly, a positive Heaf reaction and a positive Wasserman test. His liver biopsy suggested bilharziasis. 3 patients had positive HB_sAg in their blood.

5.3.10 Discussion

This study of 33 children (31 African and 2 Indian) with membranous nephropathy has extended and amplified the description of this histological category among Black children in South Africa. (Coovadia et al 1979). This report has demonstrated a higher incidence of hypertension and a poorer outcome in this group than in similarly affected children elsewhere. (Habib et al 1973, Cameron 1979). Membranous nephropathy was originally described as a specific and not uncommon lesion among adult nephrotics (Ehrenreicht and Churg 1968 and Forland and Spargo 1969) but regarded as a rare diagnosis in children, (Churg et al 1970, White et al 1970,

Cameron 1979). Studies of childhood nephrotic syndrome give an incidence of 1 - 10% (Habib et al 1973). The 29.8% incidence of membranous glomerulonephropathy among South African children with nephrotic syndrome reported here is considerably higher than the 10% incidence in Habib's series which is the largest paediatric series of membranous nephropathy.

Obvious glomerular lesions are in general more common in African children with nephrotic syndrome in South Africa (Coovadia et al 1979) than in children on other continents who mainly have minimal change. Membranous nephropathy accounts for most of these glomerular lesions.

The majority of the African children in this report were males (83.3%) which endorses the findings in adult (Pollak et al 1968) and other paediatric series (Habib 1974a). Pierides (1977) for example, found that males accounted for 66% of adults with membranous nephropathy. Paediatric patients (Habib 1974a) like adults (Gluck et al 1973) may present at any age with membranous nephropathy. In this study the ages of the African children at presentation ranged from 2½ years to 11 years. However, as previously noted, there appear to be 2 peak age groups at which African children with nephrotic syndrome present, one between 4 to 5 years and the other between

8 - 11 years. The incidence of hypertension (6.5%) at initial presentation in these children was similar to that noted by Habib (3 of 50 patients). However 4 patients developed hypertension during their period of follow-up and therefore the overall incidence rose to 24%. In adult series hypertension occurs in about 25%. (Noel et al 1979) to nearly 50% (Pierides et al 1977, Gluck et al 1973) of patients. One patient lost the signs and symptoms of the nephrotic syndrome but has remained hypertensive for many years since admission. This progression in membranous nephropathy has been recorded by Noel et al (1979) who had 5 patients remaining hypertensive in spite of being in nephrotic remission. Haematuria which occurred in 45% of the patients studied was less frequent than that detected by Habib et al (1973a), almost all of whose patients had significant red cells in the urine. In adult series (Gluck et al 1973, Noel et al 1979, Cameron 1979) haematuria was noted to be a common though not invariable finding, occurring in 40 to 50% of cases. Haematuria as seen in our patients did not occur in the absence of proteinuria.

Renal failure did not occur on admission nor develop subsequently in any of the children reported here.

Ten percent of children with membranous nephropathy have been reported in other series to go onto develop chronic renal failure. The incidence of renal failure in adults on the other hand is nearly twice that in children. Noel et al 1979, Gluck et al 1973). It has been noted that half the number of children with membranous nephropathy go into remission (Habib et al 1973a). Therefore the 30% remission rate in African children is much less than would be expected from studies in Europe.

Nearly 70% of the patients had continuing proteinuria or nephrotic syndrome without evidence of a decrease in renal function. The lower remission rate with persistence of proteinuria and nephrosis is similar to the experience in adults. (Noel et al 1979, Pierides et al 1977, Black et al 1970).

There is no good evidence that steroids, Azathioprine (MRC working party 1971) or cyclophosphamide (Donadio et al 1974) influence the outcome in children with membranous nephropathy. In most series a significant number of such patients remit spontaneously (Pierides et al 1977, Gluck et al 1973). Furthermore steroids have little place in the management of nephrotic syndrome of any histological category (including

minimal change) in African children (Adhikari et al 1976). This view was endorsed in the current study in which only one of 9 African patients given steroids appeared to respond. In membranous nephropathy the immunofluorescent deposits on the basement membrane are mainly IgG and C_3 (Cameron 1979, Gluck et al 1973). Light deposits of IgM and IgA may also be detected. All except one of our patients studied had IgG + C_3. IgM was detected in most patients and IgM alone was found in one patient.

Electron microscopy was performed in only 3 patients so that little comment is possible except that 2 of these patients demonstrated changes compatible with the diagnosis of membranous nephropathy. Similarly, selectivity of proteinuria was investigated in only 3 patients and therefore the possible value of this test cannot be assessed. Generally however, selectivity is said to be intermediate in membranous nephropathy, but as there are many exceptions it is not valuable in the diagnosis of this histological category of the nephrotic syndrome.

Infections associated with nephrotic syndrome are frequent and can be life threatening. Acute urinary tract infection occurred in 3 patients. Clinical improvement in their nephrotic syndrome

occurred once the urinary tract infection had been controlled by appropriate antibiotics. One patient had multiple clinical problems which included hepatosplenic schistosomiasis, a strongly positive Heaf reaction and a positive Wasserman. He was treated with soluble penicillin for 10 days, but was lost to follow-up. Three patients were carriers of HB_sAg. One of these patients was lost to follow-up and 2 have been seen for 4-5 years. Both of these latter have remained nephrotic. Hepatitis B virus infection has been shown to be associated with membranous nephropathy, (Takekoshi et al 1979, Kleinknecht et al 1979, Slusarczyk et al 1980) and the majority of cases reported have been children. HB_sAg has been identified in both serum and kidney tissue of patients with glomerulonephritis (Nagy et al 1979). The Hg_sAg carrier rate in the children described here with membranous nephropathy was about 10%. This is not unexpected as the incidence of Hg_sAg among adult African blood donors is about 7.4% and among 5 - 10 year old children 20% (Vos et al 1980). It is therefore unlikely that HB_sAg was casually related to the renal diseases. Repeat biopsies were performed in 3 patients who were followed-up for 5 years. The initial biopsy in one of these patients demonstrated very little change on light microscopy

while repeat biopsy showed definite thickening of the glomerular basement membrane with spike formation. Immunofluorescence revealed diffuse granular deposits of IgG, IgM + C_3. Both biopsies in the second patient (who was one of the HB_sAg carriers), revealed thickened glomerular basement membranes, with spike formation. The lesions appeared to have remained static. There were heavy deposits of IgG + C_3 with light deposits of IgM + IgA. The third patient who had hypertension, unremitting nephrosis and pyelonephritis, showed progression from mild basement membrane thickening on the first biopsy to very thickened glomerular basement membranes with large spikes and some obsolescent glomeruli in the second biopsy. Heavy IgG, C_3 and IgM were present on immunofluorescence. All 3 biopsies had evidence of interstitial fibrosis and round cell infiltration.

The information available on these patients is inadequate to indicate a consistent aetiological agent in the pathogenesis of this disease.

Schistosomiasis, HB_sAg and positive tests for syphilis and tuberculosis were found in some patients but nor more often than would be expected for the general population.

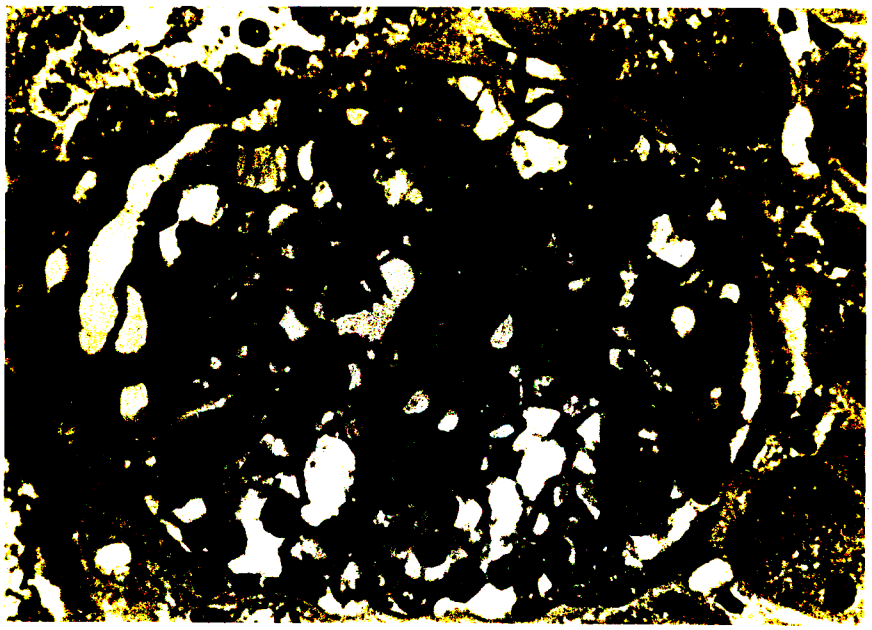
The African children described here resemble adults rather than children from the developed world with this disease in frequency of histological category, hypertension, haematuria, persistent proteinuria and lower remission rates. It is evident from this study that membranous nephropathy in the African child is less benign than in children elsewhere (Habib et al 1973, Pierides et al 1977, West 1973a).

It appears from our experience in Durban, South Africa that certain illnesses among African children when compared to standard descriptions tend to resemble adult rather than the childhood forms of the disease. For example the incidence of the different histopathological categories in the African nephrotic children is similar to the adult. This is also seen in leukaemia. The frequency of myeloblastic is equal to or commoner than lymphoblastic leukaemia (Kusman et al 1975, Naidoo et al 1980 - personal communication). Higher serum immunoglobulin levels are detected in African children as compared to whites. This suggests a more rapid maturation of factors determining the profile of serious ill health in the African child.

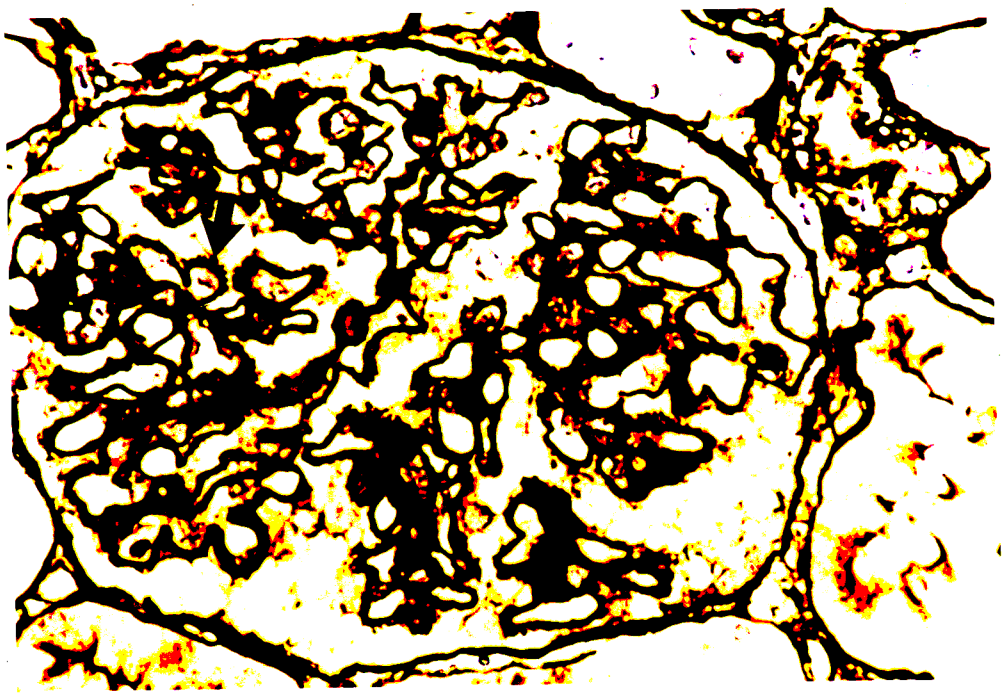
EXTRAMEMBRANOUS NEPHROTIC SYNDROME (In Remission)

Susceptibility to severe infection shown by scar of pelvic abscess.

EXTRAMEMBRANOUS NEPHROPATHY



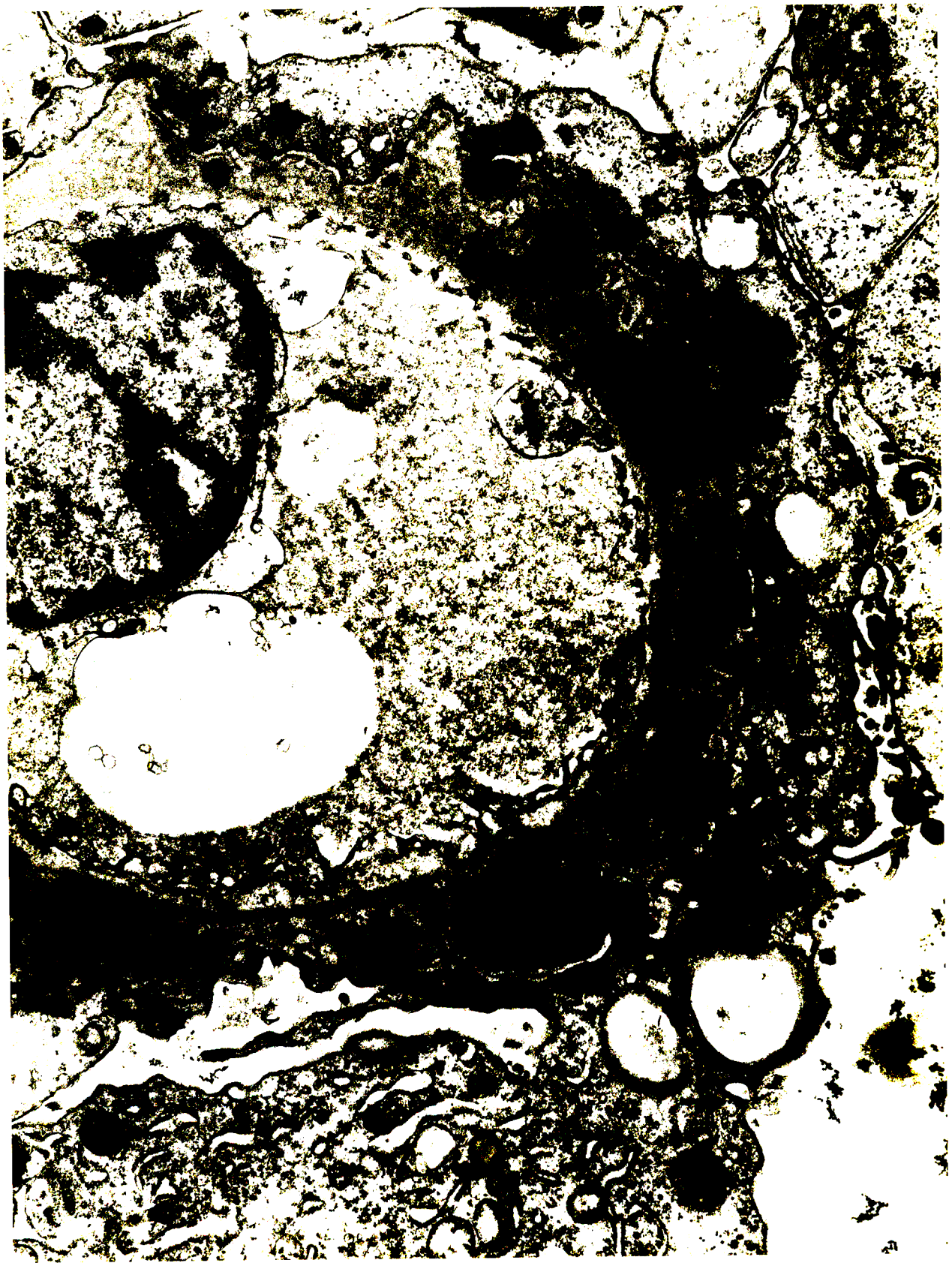
Arrow indicates thickened GBM. (Magnification x 640)



Arrow indicates subepithelial deposits ("spikes")
(Silver Methanamine Stain, Magnification x 640)

Electronmicrograph (x 17,500)

MEMBRANOUS NEPHROPATHY. SUBEPITHELIAL AND INTRAMEMBRANOUS DEPOSITS



5.4 PROLIFERATIVE GLOMERULONEPHRITIS

5.4.1 Diffuse Mesangial Proliferative

5.4.2 Summary DMP

This diagnosis was made in 7 African and 4 Indian children. Four African patients had hypertension and 3, (2 African and 1 Indian) haematuria. One African child remitted spontaneously, 2 Indian children had steroid-induced remissions. The overall prognosis was worse in the African children.

5.4.3 Incidence, Age and Sex

One hundred and four patients were African and 66 were Indian. Seven of the 104 African patients and 4 of the 66 Indian patients demonstrated DMP on histology. Four of the African patients presented under 5 years of age and three between 8 - 10 years. One Indian child was under 5 years at presentation while the remaining three children were between 8 - 10 years. Three each of the African and Indian children were females.

5.4.4 Clinical Details (Table XXVI)

(i) Initial Presentation

Hypertension - 4 African patients only

Haematuria - 2 African - transient

- 1 Indian - microscopic

Renal failure - None

(ii) Follow-up (Table XXVII)

1. African

Three African patients were followed-up for longer than six months while 4 were seen only at initial presentation.

Relapse - 1 patient for 6 months

Remission - 1 patient after a 1 month relapse (had pulmonary tuberculosis).

TABLE XXVI

CLINICAL PRESENTATION IN DIFFUSE MESANGIAL PROLIFERATION

	N	<5 yrs	M	HPT	Haem	Renal Failure
AFRICAN	7	4	4	4	2	0
INDIAN	4	1	1	0	1	0

HPT = hypertension

Haem = haematuria

TABLE XXVII

FOLLOW-UP IN DIFFUSE MESANGIAL PROLIFERATION

FOLLOW-UP FOR MORE THAN 6 MONTHS

	Number	Single episode with remission	Persistent relapse/Proteinuria
AFRICAN	3	1	2
INDIAN	4	2	2

- 1 patient remitted after 8 months. Relapsed subsequently after 9 months remission. This patient developed hypertension after 3 years and developed a strongly positive tuberculin test with no other evidence of tuberculosis.

2. Indian

All 4 followed-up for longer than 6 months

Remission - 2 steroid induced within 1 month of commencing treatment.

Persistent proteinuria - 1 (no S)

Relapse - remission - 1 boy developed hypertension and haematuria 15 months after the onset of his disease. Steroid insensitive. He relapses frequently and remits spontaneously.

5.4.5 Investigations

Biochemistry was compatible with nephrotic syndrome in all the patients.

Urine - E. coli 10^5 organisms/ml cultured in 1 Indian patient.

All other investigations were normal.

TABLE XXVIII

IMMUNOFLUORESCENT STUDIES IN DIFFUSE MESANGIAL PROLIFERATION

	Number	IgM	IgM, C3	IgM, IgG, C3	IgG, C3
AFRICAN	5	1	1	1	2
INDIAN	3	1	1	1	-

TABLE XXIX

STEROID RESPONSE IN DIFFUSE MESANGIAL PROLIFERATION

		Treated		Untreated
	N	+	-	
AFRICAN	7	0	1	6
INDIAN	4	2	1	1

+ = response

- = no response

5.4.6 Histology (Waldherr et al 1978)

The features for the diagnosis of this category on light microscopy was generalised diffuse mesangial cell hyperplasia. The basement membrane, tubules and interstitium were normal.

5.4.7 Electron Microscopy

Electron microscopy was performed on biopsies of 2 African and 1 Indian patient. One African patient and the Indian patient had an increase in the mesangial cells with mesangial deposits. The other African patient had increased mesangial cells with deposits in the glomerular basement membrane.

5.4.8 Immunofluorescent Studies

Results are given in Table XXVIII

5.4.9 Discussion

This report describes 7 African and 4 Indian children with nephrotic syndrome whose renal biopsies demonstrated diffuse mesangial cell proliferation (DMP) on light microscopy.

The small number of patients with DMP does not allow us to come to any firm conclusion as to

whether this is a distinct entity. The variability in renal problems implies that in fact there is no clear correlation between histological change and clinical disease. This discordance in African children resembles that described in children from developed countries.

Pure mesangial proliferative glomerulonephritis was initially described during the healing phase of acute poststreptococcal glomerulonephritis (APSGN). Dodge et al 1968, 1972, Jennings & Earle 1961, Levy et al 1972). With improved diagnostic techniques for evaluation of renal biopsy material, mesangial proliferation has been associated with minimal change, focal and segmental sclerosis and/or hyalinosis (Cameron 1979, Waldherr et al 1978, Murphy et al 1979) and considered a possible entity in its own right (Bhasin et al 1978, Cohen et al 1978).

APSGN is the commonest renal problem in the paediatric wards in King Edward VIII Hospital and would obviously be the most important condition to exclude in the patients reported here. None of the patients described had any clinical or serological evidence of APSGN.

It is believed by some (Roy et al 1973, Prasad et

al 1977) that DMP is a variation of minimal change nephrotic syndrome (MCNS). The patients described were examined for this possible association. MCNS is an unusual diagnosis occurring in only 13% of African nephrotics (Coovadia et al 1979).
The sex and age distribution, the number of patients with hypertension and the amount of immunoglobulin deposits in the mesangial and capillary walls is against the diagnosis of MCNS in the African nephrotics described here. The Indian children presented clinically much like MCNS, and two of the children responded promptly to steroids. However, the age of these patients and significant deposition of immunoglobulins in the mesangium made a diagnosis of MCNS less likely.

Focal and segmental sclerosis and/or hyalinosis was not found in any of the 11 patients. It is possible that these changes may be present on repeat biopsies of those children who remain in relapse (Habib & Kleinknecht 1971, Waldherr et al 1978). Therefore this diagnosis cannot be excluded.

(Waldherr et al 1978) divided their patients into 2 groups. One group of pure mesangial proliferation in which most of the children were under 5 years of age, were males and were less severely affected. A second group with superimposed

lesions of focal and segmental sclerosis and/or hyalinosis in which fewer than half of the patients were under 5 years of age, the sex distribution was almost equal and were more severely affected.

It would appear that the clinical course of the African patients was more like the second group and the Indian like the first.

Amongst the African patients studied, the sex distribution was almost equal and 4 were under 5 years of age. Among the Indian patients females predominated and only one child was under 5 years of age. The age and sex distribution of these patients were in no way different from the other series in which DMP was encountered (Waldherr et al 1978).

Despite the presence of hypertension in 4 of these patients none had evidence of renal failure. This accords with the findings of other studies dealing with DMP in which renal failure is not a feature (Murphy et al 1978, Hayslett et al 1973, Habib & Kleinknecht 1971). It would appear that renal failure occurs when DMP is associated with focal sclerosis (Habib & Kleinknecht 1971, Waldherr et al 1978). Hypertension is a variable finding in DMP and occurs in 25 - 45% (Cohen et al 1978, Bhasin et al 1978 respectively) and was present in nearly 50%

of the children studied; hypertension would be the most important prognostic factor in this group of patients.

There was an unpredictable response to steroids in these children with 2 of 4 benefiting from the drug. This is in keeping with the experience of other workers who have found steroid responsiveness to be variable (Murphy et al 1978, Churg et al 1970).

It is difficult to comment on the clinical course in the patients described because of the small number and poor follow-up, particularly in the African group. It seems that the Indian children with DMP and nephrotic syndrome may have less severe disease and a better prognosis than the African children. Many of the African children presented with hypertension and haematuria and only one patient remitted.

DMP is frequently associated with immunoglobulin and/or complement deposits (Cohen et al 1978, Bhasin et al 1978, Waldherr et al 1978) in the mesangium although a group of patients with DMP and the absence of deposits has been described (Murphy et al 1978). It is not clear whether the last mentioned is a separate group within the category of DMP but patients appear to be similar to those patients with deposits.

Proteinuria is said to be moderately or poorly selective in DMP (Waldherr et al 1978). Three of the patients described here who demonstrated highly selective proteinuria developed hypertension and one of these was steroid resistant. Selectivity of proteinuria therefore appeared to be of little value in predicting outcome in these children.

Studies in children have generally shown the prognosis of DMP to be good although less so than MCNS. The proportion of patients with this disease who on long term follow-up develop signs of renal impairment is small and in one large series approximated 20% (Waldherr et al 1978). Some children appear to respond to steroids, others remit spontaneously while a few have haematuria, hypertension or renal failure. The outcome in the children reported here was relatively poor. Three of seven children followed for longer than 6 months showed either hypertension and/or the presence of nephrosis.

When a clinico-pathological diagnosis of MCNS is made the presence of FGS carries with it a poorer prognosis. Habib et al 1971 and Schoeneman et al 1978 suggest that DMP may also have a similar negative effect on outcome.

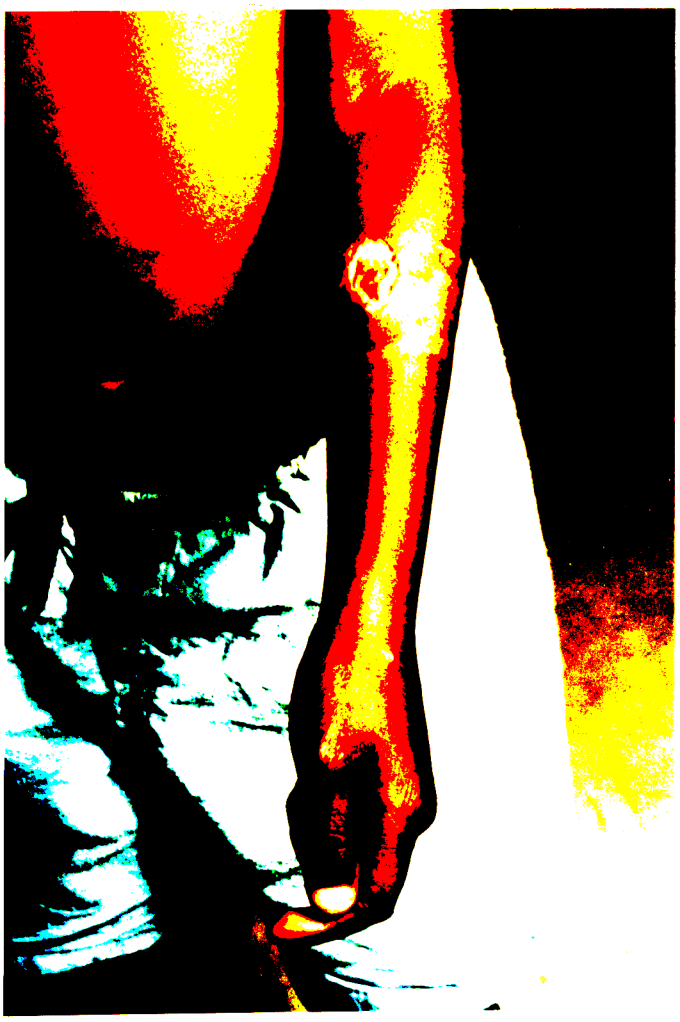
The lack of consistency in the various clinico-pathological features of mesangial proliferative glomerulonephritis is paralleled by a failure to construct a unifying hypothesis on the immuno-pathogenesis of this disease. The mesangial cell is the renal component of the reticulo-endothelial system but also has distinct functions separable from those of the other members of this system (Mauer et al 1976). It is involved, therefore, in the continuous uptake and clearance of circulating antigens (Michael et al 1967). Experimental data has, in general terms, shown that proliferation of mesangial cells occurs when an excessive quantity of antigen-antibody complexes are cleared from the blood (Germuth 1973) or when an antigen enters the mesangium and subsequently combines with circulating antibody (Mauer et al 1973). It is known that particular characteristics of the antigen (Germuth & Rodriquez 1973) or the host (Devey & Steward 1980), modulate immune responses and thereby determine the pattern of renal injury. Medium-sized complexes (Germuth 1953) and high antibody affinity (Devey & Steward 1980) are important in the pathogenesis of renal damage with dominant mesangial cell involvement. Mesangial proliferation occurs with a variety of immunopathological diseases (Berger et al

1969; Meadow 1979) and can be one of a number of histological expressions of a single disease (Ginzler 1980). Infections and malnutrition both of which affect macrophage function (Trautwein 1975; Coovadia and Soothill 1976) are common in the communities from which the subjects for this report were studied. However, none of the patients had overt protein-calorie-malnutrition and we were unable to detect an infectious agent which could be implicated in these children's disease. This is not surprising as in other syndromes where mesangial proliferation can be marked, the antigen is equally obscure (Berger et al 1969; Meadow 1979).

NEPHROTIC SYNDROME : DIFFUSE MESANGIAL PROLIFERATIVE

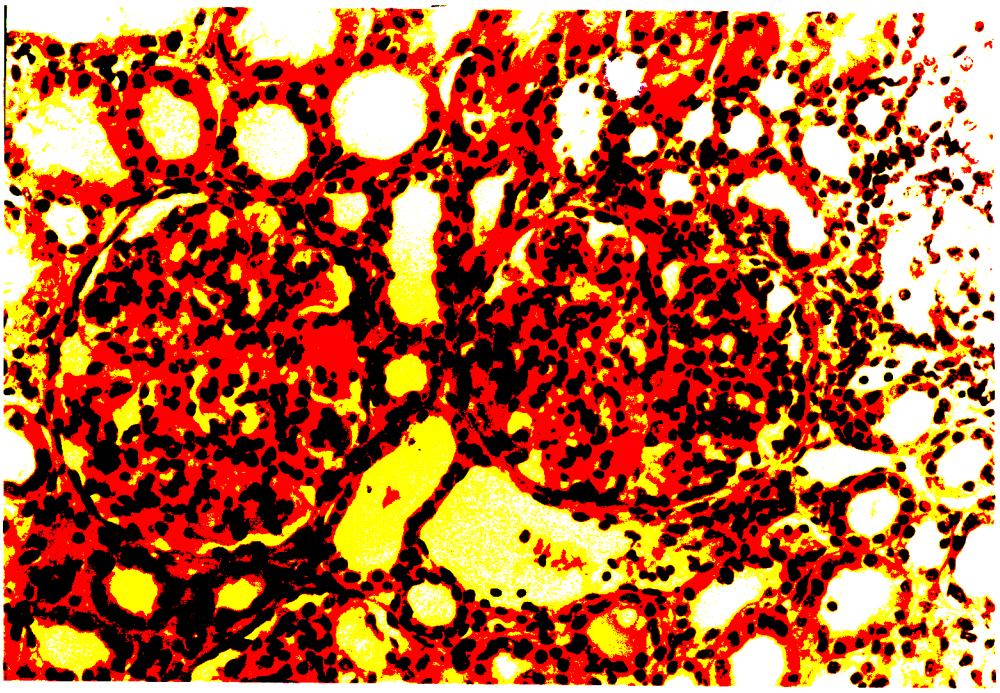
Susceptibility to Infection

GRADE IV POSITIVE HEAF



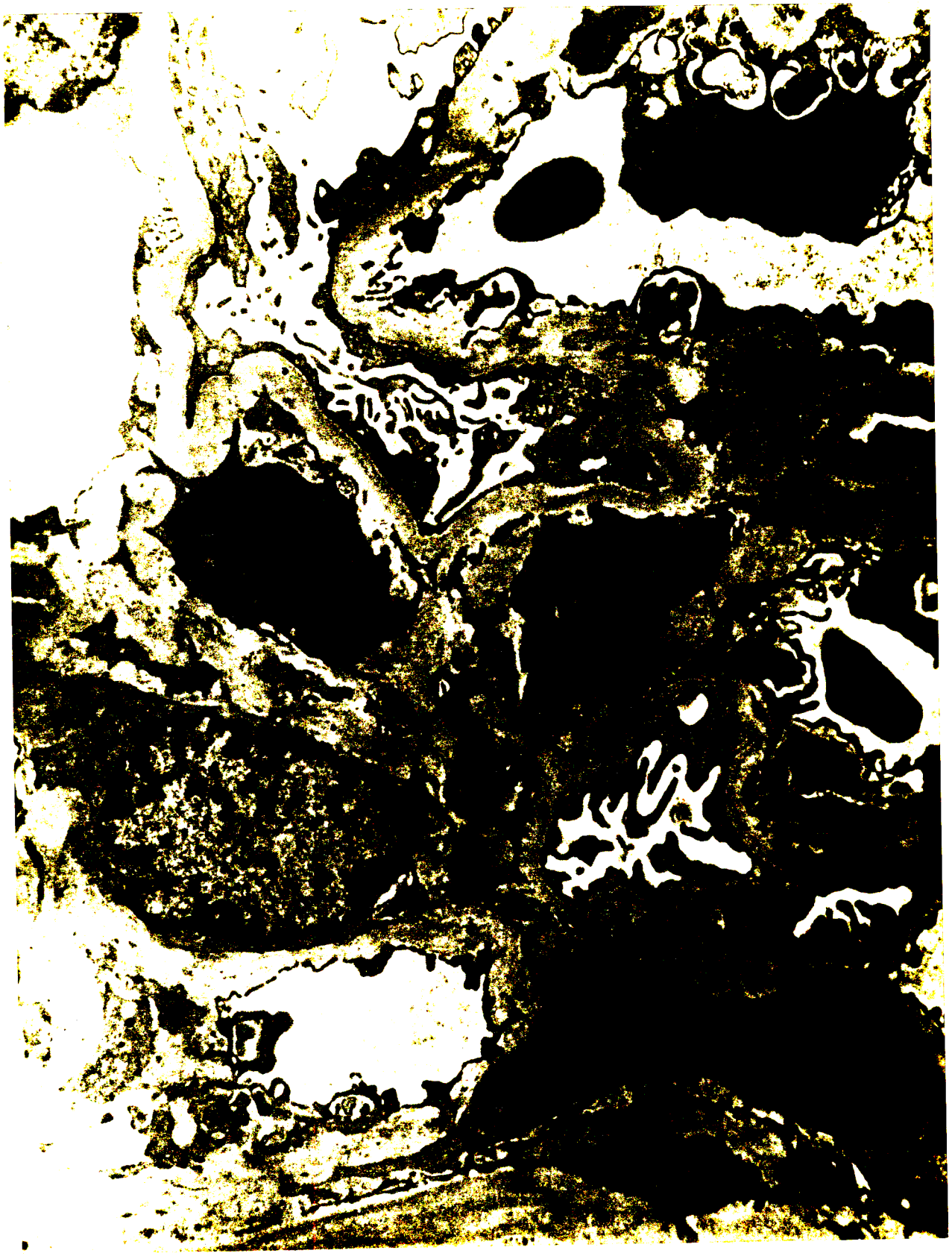
MESANGIAL PROLIFERATIVE GLOMERULONEPHRITIS

(Haematoxylin and Eosin Stain, Magnification x 250)



Electronmicrograph (x 10,000)

DIFFUSE MESANGIAL PROLIFERATION
MESANGIAL DEPOSITS



5.5 DIFFUSE PROLIFERATIVE GLOMERULONEPHRITIS

5.5.1 Summary

Diffuse Proliferative Glomerulonephritis

The majority of the children were over 5 years of age. 12% presented acutely, about one third had hypertension and/or haematuria, none had renal failure. The prognosis in the group with endocapillary proliferation was worse (death, relapse or proteinuria) whereas those children with exudative changes faired better either remitting or remaining proteinuric.

5.5.2 Incidence

Ten nephrotics were diffuse exudative and 7 pure diffuse endocapillary proliferation. Sixteen of the patients were African and 1 was Indian.

Age, Sex

The age range of this group was 3 - 13 years. Fourteen of the patients were over 5 years of age. The number of males (9) and females (8) was almost equal.

5.5.3 Clinical Presentation

(i) All the patients had the clinical features of the nephrotic syndrome. Two patients (both diffuse exudative) presented acutely with oedema, proteinuria and haematuria.

Hypertension - 4 patients - 2 exudative
- 2 endocapillary - 1 experienced transient hypertension and one was lost to follow-up.

Haematuria - 6 patients - 4 exudative
- 2 endocapillary

Renal failure - no patients

(ii) Follow-up

1. Diffuse Exudative

5 were seen at initial presentation only.

4 (4 Africans and 1 Indian) were observed for 2 - 42 months.

Remissions - 2 patients remitted after 6 and 9 months.

Persistent Proteinuria - 3 (including the Indian patient) remained proteinuric for 3 - 23 months.

The patient who remitted after 6 months was 1 of the 2 patients who presented acutely. He had a low C_3 and raised ASOT.

2. Diffuse Endocapillary

2 were observed for 1 month only.

5 were observed for 7 - 96 months.

Relapse - 2

Persistent proteinuria - 3

5.5.4 Investigations

Biochemistry was compatible with nephrotic syndrome in all the patients.

Urine : E. coli in 2 patients (diffuse exudative)

S. haematobium in 1 patient (diffuse exudative)

Stool : S. mansoni in 1 patient (diffuse exudative)

Blood : HB_sAg in 3 patients (2 diffuse exudative, 1 endocapillary).

Liver enzymes were mildly elevated in 1 patient with cirrhosis and portal hypertension. Before death these enzyme levels increased with a falling prothrombin index.

5.5.5 Histology

The sub-groups of diffuse proliferative were as follows.

(1) Diffuse exudative

Diffuse endocapillary proliferation, polymorph infiltration with or without epithelial proliferation and crescent formation in <50% glomeruli. Normal GBM and subepithelial "lumps" may be visible.

(2) Diffuse endocapillary

Diffuse proliferation of mesangial endocapillary cells with accentuation of lobules and normal glomerular basement membrane.

5.5.6 Immunofluorescence

The biopsies of 12 of these 17 patients were examined

for immunofluorescent deposits.

(1) Diffuse Exudative (7 patients)

5 patients had IgM + C_3, 1 IgG + C_3 and 1 IgG only.

(2) Pure Endocapillary (5 patients)

Three patients had the three immunoglobulins (IgG, IgM, IgA) and complement components (Clq, C_3, C_4). (A repeat biopsy in one of these demonstrated heavier deposits of the same nature). 1 had slight C_3 deposition and 1 no deposits.

5.5.7 Selectivity of Proteinuria

Selectivity excretion of albumen and transferrin, expressed as a ratio, was determined in 4 patients with pure endocapillary porliferation. All 4 had selective proteinuria (ratio <0.2). 2 of these patients had severe histological changes and one died.

5.5.8 Response to Treatment

(1) General

Diuretics (Thiazides, Spironolactone, Triamterene) were used either singly or

in combination. All the patients improved on these drugs except for the patient with cirrhosis whose ascites and oedema were partly due to liver disease. A high protein diet was generally given except in the patient with liver disease where a normal diet was given.

(ii) Steroid Therapy

Four patients (2 exudative, 2 endocapillary) were given steroids. None responded to a 3 month course of steroids.

5.5.9 Associated Clinical Problems

Three patients were HB_sAg positive, one of whom had a history of an attack of acute hepatitis and remained HB_sAg positive for 3½ years.

One patient had an acute E. coli urinary tract infection. Two patients had pulmonary tuberculosis, one of whom had hepatic bilharziasis and the other cirrhosis with portal hypertension. The latter died in liver and renal failure with associated Staphylococcus aureus septicaemia. At autopsy pyaemic abscesses were present in the liver and the lungs. One patient had neurofibromatosis with

delayed menarche and with short stature. Full endocrine investigation revealed no abnormality.

5.5.10 Discussion

The diffuse proliferative histological category is to some extent difficult to define. Usually this category is subdivided into exudative, endocapillary/mesangial and membranoproliferative subtypes. The exudative group is the classical post-streptococcal category but it is recognised that some patients in this histological group do not have any evidence of streptococcal infection and do not follow the natural history of this disease (Habib 1974a, Habib & Kleinknecht 1971; Turner 1978). Epithelial cell proliferation may occur and if more than 80% of the glomeruli have crescent formation this group is called rapidly progressive glomerulonephritis (Habib 1974a). The patients follow a rapid and severe downhill course.

The endocapillary/mesangial proliferative group is less well understood. It may be regarded as resolving post-streptococcal nephritis. The diagnosis depends on the clinical features and immunofluorescent findings. More recently a

group of pure mesangial cell proliferation with mesangial cell deposition has been described. A group of patients with these features have been described on page 138.

There is left a group of patients who appear to have the same cellular proliferation but have deposits on glomerular basement membrane. These have been included as part of this study.

The clinical details of age and sex presentation do not appear to be clearly defined in the literature. In this study the majority of children were over 5 years of age, a general trend in the African nephrotic child (Coovadia et al 1979). The male and female incidence was almost equal. The two patients who presented more acutely in the exudative group were interesting; both eventually remitted but had proteinuria rather than haematuria as the predominant feature during their illness suggesting that they were not post-streptococcal nephritis. The one had a low C_3 and raised ASOT but the other did not. One can only assume that they were post infectious nephrotics. Five of the 9 patients were not observed at all. The natural history of the exudative group is accordingly not clear.

The endocapillary group appear to have had a poorer outcome. Two patients had persistent relapse and one of these died in hepatic and renal failure. Both of these had selective proteinuria and yet had significant numbers of sclerosed glomeruli on histology.

None of 4 patients treated with steroids responded to therapy. The immunofluorescent findings were striking. In the exudative group most had IgM and C_3 instead of IgG and C_3

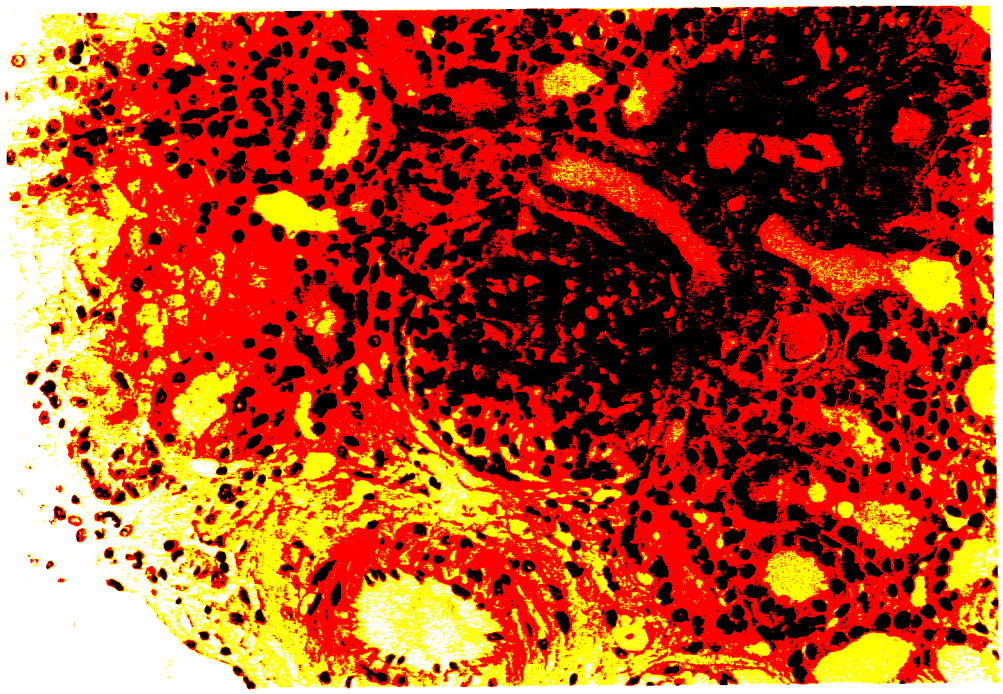
The endocapillary group was obviously different in immunofluorescent deposits from pure mesangial proliferation in which IgM is the main mesangial deposit. Most patients had all 3 immunoglobulins with complement components on the glomerular basement membrane.

The numbers of patients are not sufficient to arrive at any definite conclusions with regard to prognosis and natural history. It would appear on the available evidence that comparing the two groups, the exudative group had the better prognosis; endocapillary proliferative nephrotics experienced no remissions and remained in relapse or proteinuric.

ACUTE EXUDATIVE PROLIFERATIVE GLOMERULONEPHRITIS

Arrow indicates polymorphonuclear leucocyte.

(Haematoxylin and Eosin Stain, Magnification x 250)



5.6 MEMBRANOPROLIFERATIVE GLOMERULONEPHRITIS

5.6.1 Summary MPGN

Half of these children were over 5 years of age and males predominated. The complement levels were normal in all the patients and the incidence of poor prognostic features was lower. However the patients remained in relapse or proteinuric.
One child died.

5.6.2 Incidence, Age, Sex

Nine (8.7%) African and two (3.1%) Indian children had features of membranoproliferative glomerulonephritis on light microscopy. Four of the African children were over 5 years of age, the youngest was 2 years old. The Indian children were 2½ years and 8 years of age. Seven of the African and one of the Indian children were males.

5.6.3 Clinical Details (Table XXX)

(i) Initial Presentation

All the patients had the clinical features of the nephrotic syndrome.

Hypertension	:	1 patient
Haematuria	:	3 patients
Uraemia	:	2 patients (1 Indian, 1 African)

None of the children had histories of preceding upper respiratory tract infection.

(ii) Follow-up (Table XXX)

1. African

Duration 1 - 12 months.

Persistent relapse - 5

TABLE XXX

CLINICAL FEATURES AND OUTCOME IN MPGN

Patients	Age yrs	Sex	HPT	Haematuria	Renal failure	Duration of follow-up months	S E Treatment	Associated Problems	Outcome
African									
M.M.	5	M	–	+	–	3	N/G	–	Persistent proteinuria
K.M.	8	F	–	–	–	1	S–	–	Persistent relapse
B.M.	11	M	+	–	–	2	N/G	–	Persistent proteinuria
Z.N.	4	F	–	++	+	8	S+ & E–	–	Persistent relapse
M.K.	4	M	–	+	–	5	N/G		Persistent relapse
D.B.	2	M	–	–	–	3	S–	–	Persistent proteinuria
Z.M.	9	M	–	–	–	1	N/G	–	Persistent proteinuria
S.M.	4	M	–	–	–	6	N/G	Tuberculous Lymphadenitis	Persistent relapse
A.S.	10	M	–	–	–	12	N/G	E. coli Septicaemia Oral herpes	Persistent relapse. Died.
Indian									
R.J.	$2\frac{1}{2}$	M	–	–	–	60	S– & E–	Broncho-pneumonia	Remission
D.N.	8	F	–	–	+	48	S–		Severe relapse persistent proteinuria

Persistent proteinuria - 4

Remission - 0

Death - 1 (i.e. 1 of 5 in relapse).

One patient developed pelvic tuberculous lymphadenitis. In addition he had an ectopic right kidney. A second patient was noted to have a hard liver clinically with post necrotic scarring demonstrated on liver biopsy. This patient had severe persistent oedema and ascites which was probably of hepatic origin and extremely difficult to control. He died in hepatic failure 1 year after presenting with the nephrotic syndrome. Terminally the blood urea was markedly elevated and he developed an E. coli septicaemia and oral herpes.

2. Indian

Duration 4 - 5 years

Remission - 1

Persistent relapse - 1 (with frequent infection and signs of renal impairment).

The female child was admitted in severe relapse 7 times during her period of 4 years of observation. Her course was a

stormy one with frequent infections. She developed pneumonia, E. coli urinary tract infection, chronic osteitis, cellulitis and severe bilateral conjunctivitis. When last seen she was proteinuric with a rising blood urea.

5.6.4 Investigations

The nephrotic syndrome was confirmed biochemically in all the patients studied.

Blood - C_3, C_4, CH_{50} were normal in all the patients
- 1 patient HB_sAg positive
- 1 patient who died terminally, had decreased levels of complement components.

Terminally the patient who died in hepatic and renal failure had decreased levels of complement components.

5.6.5 Light Microscopy

The following features on light microscopy were accepted for this diagnosis.

(i) diffuse mesangial proliferation

(ii) increase in mesangial matrix

(iii) diffuse irregular thickening of the walls of the glomerular capillaries some showing

distinct double contours.

(iv) extra capillary proliferation with epithelial crescents.

(Sections were not thin enough to assess the different degrees of thickening of the glomerular basement membrane).

All the patients had the features given above (i), (ii), (iii). One patient had marked increase in mesangial matrix giving a lobular appearance. One hypertensive patient and another who subsequently died, had more than 50% and 45% crescents respectively. The patient who experienced a number of bacterial infections had marked interstitial infiltration and tubular atrophy suggestive of pyelonephritis.

5.6.6 Immunofluorescence

This investigation was performed on 4 African patients. All four demonstrated granular IgG, IgM, IgA and complement on the glomerular basement membrane.

5.6.7 Electron Microscopy

Electron microscopy was not performed in any of these patients.

5.6.8 Selectivity of Proteinuria

This was performed in 3 patients. Two African patients had highly selective proteinuria. Both these patients had haematuria and one died in hepatic and renal failure.

The patient who suffered a number of bacterial infections had moderately selective proteinuria.

5.6.9 Response to Treatment

(i) General

1. Diuretics (Thiazides, Spironolactone, Triamterene).

   These were used either singly or in combination. Generally most patients responded to these drugs and their oedema was reduced from severe to mild. The exception was the patient who died in liver and renal failure. At times it was necessary to administer 4% albumen (10 - 20 mls/kg) slowly followed by intravenous furosemide 1 - 2 mgs/kg/dose.

2. The one hypertensive patient was controlled with methyldopa and hydrallazine.

3. A high protein diet was generally given.

(ii) Steroid - Immunosuppressive Therapy (Table XXX)

Prednisone was given to 3 African and 2 Indian patients. All the patients with the exception of the one Indian child failed to respond. The Indian child had a partial response in hospital, had proteinuria on later visits and was in remission when last seen.

Cyclophosphamide was given to 1 African and 1 Indian patient. Neither responded.

Complications directly related to the above therapy did not occur in any of these patients.

5.6.10 Discussion

This group of patients with membranoproliferative glomerulonephritis studied appear to have a number of features different from the classical descriptions of the subendothelial deposit form of disease (Habib 1974a, Jenis and Lowenthal 1978). The differences are the lower incidence of poor outcome

and normal complement levels in this study. Complement levels are variable in the subendothelial deposit disease. The proportion of this histological category is similar to that described in other studies in this age group in which it varies from 5% to 13% (Churg et al 1970, Habib and Kleinknecht 1971). The majority of the patients reported here were males whereas females tend to predominate among children in temperate countries (Habib and Kleinknecht 1971, Habib 1974a, West 1973b).

An unusual feature of this group was that 50% of the children were under 5 years of age at presentation. Very few studies have patients presenting with membranoproliferative glomerulonephritis at this young age (Cameron et al 1970, West 1973b, Herdman et al 1970). The youngest in this group studied was 2 years old, the youngest in West's series was just under 2 years (West 1973b). Habib, from her clinical experience went as far as to state that this disease never occurred under 2 years of age (Habib 1974a).

Haematuria, poor renal function and hypertension were inconspicuous in the clinical presentation and course of most of these patients. Haematuria is said to occur almost invariably (Habib 1975).

Hypertension and renal failure occur in about a third of the patients (Habib & Kleinknecht 1971, Habib 1974a).

Two important features for poor prognosis, namely hypertension (Habib et al 1973b, Barbiano di Belgiojoso 1977) and renal failure (Habib et al 1973) occurred in only 10% of the patients studied. However during the course of the disease 50% of the patients had persistent or severe intermittent nephrotic syndrome. This feature indicates a grave outcome (Habib et al 1973b, Barbianodi Belgiojoso et al 1977, Jenis and Lowenthal 1978). The outcome is worse in patients with the presence of crescents on histology (Barbianodi Belgiojoso et al 1977). Two of those with severe nephrosis had about 50% crescents. One of these patients had hypertension and the other developed hepatic and renal failure. Tubular interstitial changes parallel the severity of glomerular damage. The patient who had frequent bacterial infections possibly reflects this feature. In spite of there being only one poor clinical prognostic feature of persistent nephrotic syndrome the patients appeared not to do worse, one child remitted spontaneously as may occur in children. (Habib et al 1973b).

The response to steroid and immunosuppressive therapy was quite unimpressive as has been shown by many others (Habib et al 1973b, 1974a, West 1973b, Churg 1970, Holland et al 1972b). The majority of patients studied were African and therefore the lack of response to these drugs was not at all unexpected (Coovadia et al 1979). In one study, a favourable response occurred in some patients on treatment but the ultimate outcome was unaltered by use of these drugs (Holland et al 1972).

The immunofluorescent findings were consistent with the subendothelial deposit disease in which IgG, IgM, Clq, C_4 and C_3 may be present on the GBM. In dense deposit disease C_3 is the characteristic deposits on immunofluorescent studies. Selectivity of proteinuria was not of any help in predicting outcome.

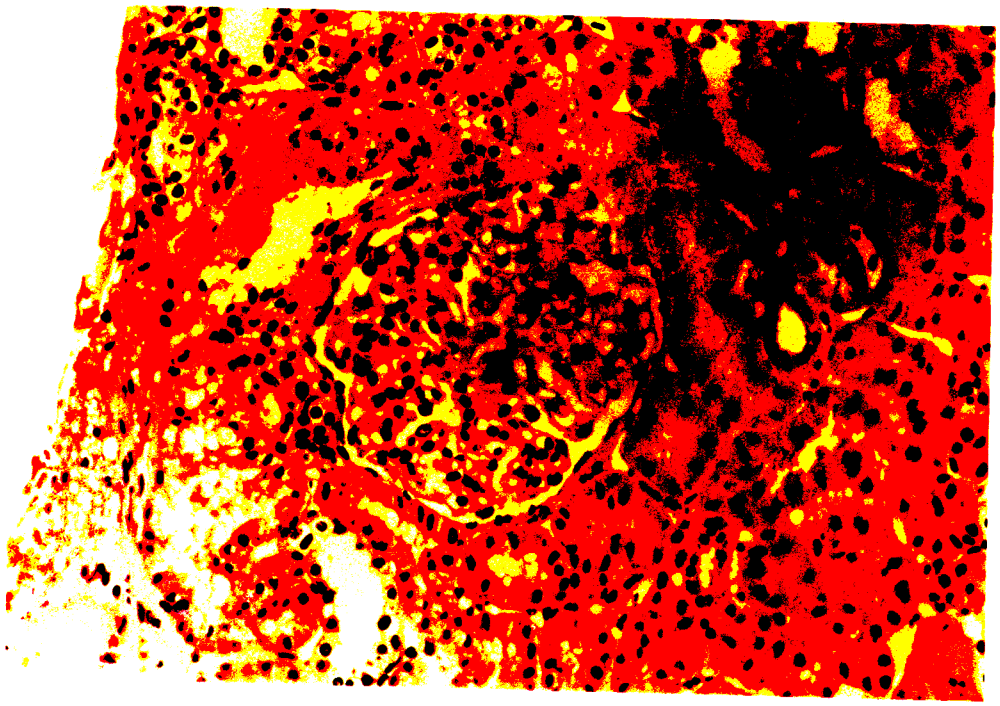
One of the most interesting and unusual aspects of this group of patients was the normal levels of C_3. In almost all studies of membranoproliferative glomerulonephritis C_3 and other complement components have been shown to be reduced (West et al 1965, Gotoff et al 1965, West 1973b, Habib et al 1973b, Barbiano di Belgiojoso et al 1977). Generally persistent hypocomplemtaemia is associated with dense

deposit disease (Peters and Lachmann 1979). It has been said that normal complement levels occur in 12 - 16% of patients with membranoproliferative nephritis and that in these patients low levels may never occur (Cameron et al 1970, Andres et al 1975). One study (Davis et al 1978) comparing the two morphological forms of the disease in children found that there was no correlation between the C_3 levels and the morphological diagnosis. The normal complement levels, different clinical presentation and course suggest that although the histological features may be similar, this disease process is not similar to that described elsewhere. A similar situation has been described with regard to African children with MCNS.

The very low C_3 level found just before death in the patient with hepatic and renal failure may have been due in part to severe liver failure. Low C_3 levels have been found to be an important prognostic factor in liver disease (Mackenjee et al 1981a). More recently serum complement levels have been found not to be of prognostic value in membranoproliferative disease (Barbiano di Belgiojosi 1977).

MEMBRANOPROLIFERATIVE GLOMERULONEPHRITIS

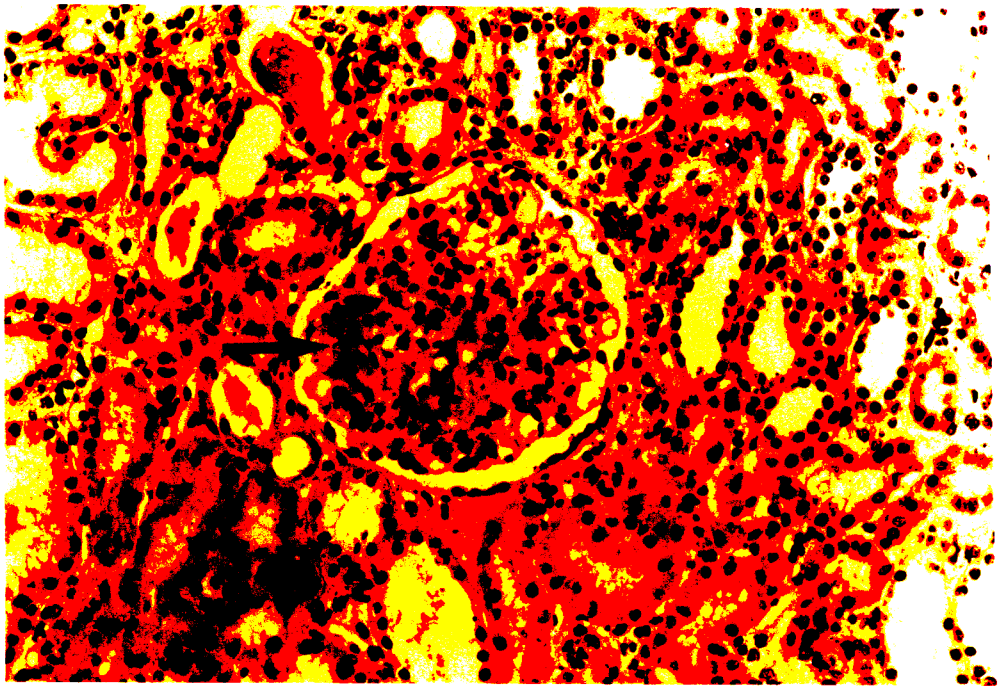
(Haematoxylin and Eosin, Magnification x 250)



FOCAL PROLIFERATIVE GLOMERULONEPHRITIS

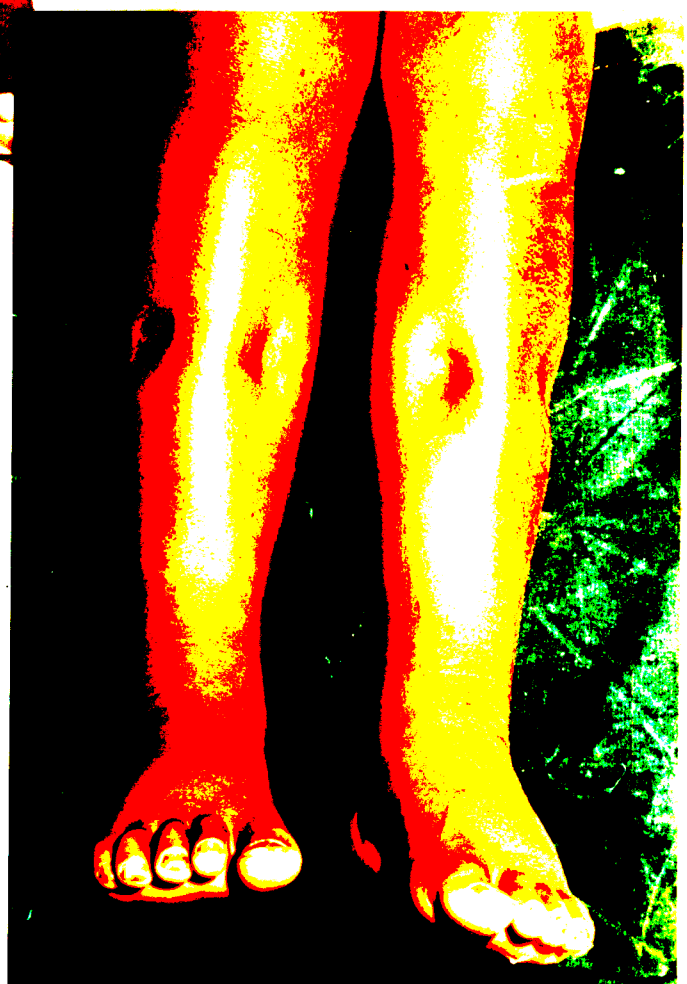
Arrow indicates segmental proliferation.

(Haematoxylin and Eosin Stain, Magnification x 250)



NEPHROTIC SYNDROME - Focal Proliferative Glomerulonephritis

GROSS OEDEMA



5.7 FOCAL PROLIFERATIVE GLOMERULONEPHRITIS

5.7.1 Summary FPGN

This histological diagnosis carried the worst prognosis. Sixty percent were older than 5 years and the sex incidence was equal. Fewer than half the patients had hypertension and haematuria. The majority remained in relapse, a fifth had persistent proteinuria and a fifth died.

5.7.2 Incidence, Age, Sex

Ten (9.6%) of the Africans and 1 (1.5%) of the Indians demonstrated the histological features of focal segmental proliferation on light microscopy.

Six of the African and the Indian child were over 5 years of age at presentation. Five of the Africans and the Indian were females.

5.7.3 Clinical Details

(i) Initial Presentation

All except 1 Indian child presented with the nephrotic syndrome; the Indian child presented as acute nephritis (A N) with hypertension, haematuria, albuminuria and oedema, all of which persisted for 6 weeks. None had an upper respiratory tract infection.

Hypertension - 2 patients, 1 transient and 1 persistent

Haematuria - 4 patients. Settled in 3. Patient with persistent haematuria also had hypertension.

Raised urea - 1 patient who presented as acute nephritis and settled in a few weeks.

Follow-up

1. African

Duration 4 months to 108 months.

2 seen at initial presentation only.

Persistent relapse - 5 patients

Persistent proteinuria - 3 patients. One patient who had proteinuria for 84 months and whose renal function was normal did not attend follow-up for 3 years and presented in May 1981 with acute on chronic renal failure. She is being considered for renal transplantation at the present time.

Remissions - 0

Deaths - 2 (both in persistent relapse).

One patient had right upper lobe pneumonia with shrinkage although the diagnosis of tuberculosis was not proven she was treated as such. She spent the major part of her 9 months of severe illness in hospital.

The other patient first suffered a Klebsiella urinary tract infection which was successfully treated then suffered a peritonitis which settled on treatment with penicillin. A

pneumococcal infection could not be proven on this patient. His course was a fulminating one over 4 months.

2. Indian

The Indian patient remitted spontaneously 1 month after the onset of her disease and has been well since.

5.7.4 Investigations

Biochemistry confirmed the nephrotic syndrome in all.

Urine : Haematuria 4 patients
: Positive culture for K. pneumoniae
: S. haematobium in 1
Stool : S. mansoni

Raised blood urea : 1 patient terminally
Low C_3 level : 1 patient who presented as AN (ASOT was negative)

5.7.5 Light Microscopy

The histological criteria for this diagnosis on light microscopy were focal and segmental endothelial or mesangial cell proliferation, with or without glomerular sclerosis involving capillary loops in fewer than half the glomeruli. All the

patients had mild to significant focal segmental increase in cells; the basement membranes appeared normal in all. The patient who died 4 months after the onset of his disease demonstrated a significant progression in his renal lesion from mild focal mesangial cell proliferation to marked cellular increase, an increase in mesangial cells; one glomerulus had a crescent, one was sclerosed and there was mild focal interstitial fibrosis. The Indian patient who presented with acute nephritis had in addition to focal proliferation, one glomerulus with focal adhesions and one with sclerosis. Associated mild interstitial fibrosis and tubular atrophy was present.

5.7.6 Immunofluorescence

Ten of 11 patients had this investigation performed. Two patients had no deposits, 3 igM only (1 Indian), 2 IgM + C_3, 1 C_3 only, 2 IgM, IgA, IgG and complement components. All the deposits were focal in nature and on the glomerular basement membrane.

5.7.7 Electron Microscopy

This was performed on 2 patients. Both revealed focal increase in mesangial cells, focal glomerular basement membrane deposits and focal fusion of the

foot processes.

5.7.8 Response to Treatment

(i) General

Diuretics, (Thiazides, Spironolactone, Triamterene) were used singly or in combination. In 8 patients the oedema was difficult to control and intravenous 4% albumen followed by intravenous Furosemide was given usually with some success. Three patients who eventually lost their oedema did so spontaneously. A high protein diet was generally given. Anti-hypertensives used were methyldopa and hydrallazine in recommended dosages.

(ii) Steroid Therapy

Three patients were given a full course of Prednisone, but did not respond. One patient deteriorated while on therapy i.e. developed a rising blood pressure and worsening oedema.

5.7.9 Complications of Renal Biopsy

One child had a subcapsular haematoma which was

palpable clinically and demonstrated on ultrasonogram. This resolved spontaneously in a few weeks.

5.7.10 Congenital Anomalies

One patient had a duplex ureter on the right side demonstrated by excretory urography.

5.7.11 Discussion

Focal proliferative glomerulonephritis is an unusual cause of nephrotic syndrome in children. (Habib et al 1974, Cameron 1979). In a report for the International study of Kidney Disease in Children this histological category was not encountered (Churg et al 1970). Patients with focal nephritis may present with haematuria, proteinuria and an acute nephritic episode or nephrotic syndrome. Fifty percent of focal proliferative glomerulonephritis may be associated with systemic disease (Habib 1974) and primary focal proliferative nephritis may follow pharyngitis (Habib 1974, West et al 1968). In the original description of this form of glomerulonephritis (West et al 1968) it was stated that the clinical presentation was similar to acute post streptococcal glomerulonephritis associated with nephrotic syndrome. Since then clinical

syndromes varying from Bergers disease (Berger et al 1969) to nephrotic syndrome have led to clinical and pathological confusion. Many clinical patterns are in fact associated with the histology of focal proliferative glomerulonephritis. The commonest secondary causes of this histological group are Henoch Schönlein purpura, systemic lupus erythematosus, bacterial endocarditis and polyarteritis nodosa (Habib 1970, Whitworth et al 1978, Cameron 1979). None of the patients in this study had any evidence of these diseases. Streptococcal infection likewise was not associated with any of these patients.

In the literature studied sex and age incidences are not discussed. More emphasis is placed on clinical features and findings on histology. One paper (Glasgow et al 1970) discusses symptomless haematuria occurring more frequently in males.

The initial presentation in all the patients was that of the nephrotic syndrome. About 25% had haematuria and hypertension both of which were transient except in one patient who lost the oedema and proteinuria but remained hypertensive with haematuria.

One of the patients presented as an acute nephritic

episode. More striking clinically was the severity of the nephrotic syndrome in 5 patients, 2 of whom subsequently died. They presented grave problems in management of their severe oedema which eventually settled spontaneously in three patients.

The histology in the majority of the patients was focal segmental proliferation. One of the patients who died demonstrated a marked progression from mild focal proliferation on the first biopsy to more extensive glomerular involvement with fibrosis and sclerosis on postmortem biopsy. Severe histologic lesions may be associated with severe nephrotic syndrome (West et al 1968). This association of focal proliferation and focal glomerulosclerosis is well known (Whitworth et al 1978) and there may be difficulty in classifying an individual biopsy. Focal proliferative glomerulonephritis is therefore not regarded by some as a distinct entity (Habib 1975).

Generally the outcome in these patients is regarded as benign (Habib et al 1974, Rubin 1975b) although it is recognised that some patients may experience a stormy clinical course (Rubin 1975b, Cameron 1979). The clinical course in the 11 patients studied does not appear to be as good as expected from the

literature; persistent nephrotic syndrome and severe proteinuria occurred in 8 patients, 2 of whom died. The Indian patient had a short illness and remitted. Once again the African patients had a less benign course than would be expected from experience elsewhere.

Immunofluorescent findings in this study were similar to that found in other studies (Rubin 1975, Whitworth et al 1978). The expected variation occurred with no deposits in some (Whitworth et al 1978), IgM with or without C_3 in the majority and only 2 having all three immunoglobins and complement components in a focal distribution on the glomerular basement membrane.

Electron microscopy confirmed the histological diagnosis in 3 patients. Electron microscopy may be required in certain instances to clarify the histological diagnosis (Rubin 1975b).

Steroid therapy may be helpful in this condition (West 1968) in particular when the nephrotic syndrome develops (Rubin 1975b). However, the 3 patients treated did not respond and in fact one patient deteriorated with worsening oedema and hypertension. Steroids are therefore dangerous in FPGN.

About one third of the patients had associated infections. These are not uncommon in our patients in particular in association with the nephrotic syndrome (Coovadia et al 1979).

Very few patients have had serious complications following renal biopsy. One patient experienced a renal haematoma which settled spontaneously.

Focal proliferation in the African nephrotic child appears to have a bad prognosis. The severity of the disease is not necessarily reflected histologically. Once again repeat renal biopsies in these patients would be of great value in trying to clarify the natural history of this disease in the African child.

5.8 FOCAL GLOMERULOSCLEROSIS

5.8.1 Summary FGS

This was an unusual diagnosis in the African child. The children were over 5 years, males dominated and most of this small group remained proteinuric, 1 died. Indian children appeared to have a better prognosis. One third remitted, the remaining patients had persistent proteinuria.

5.8.2 Incidence, Age, Sex

Four African children and 6 Indian children had focal glomerular sclerosis on biopsy. An overall incidence of 5.9%. Three of the African and two Indian children were males. The ages of the African children ranged from 2½ years to 10 years, (2½. 9, 10, 10) and the Indian children 1½ to 8 years (1½, 7, 7, 8, 8 years).

5.8.3 Clinical Details (Table XXXI)

(i) Initial Presentation

(a) African

All the patients had the clinical features of the nephrotic syndrome.

Hypertension - 1 patient, controlled and lost to follow-up after 3 weeks hospitalisation.

Haematuria - none

Renal failure - none

One patient had an E. coli septicaemia on admission.

(b) Indian

Hypertension - none

Haematuria - four

TABLE XXXI

CLINICAL FEATURES, IMMUNOFLUORESCENCE, STEROID RESPONSE AND OUTCOME IN FGS

Patients	Age	Sex	HPT	Haematuria	Immunofluorescence	Steroid Response	Associated Problems	Outcome
African								
ZB	2½	M	-	Nil	-	-	-	Persistent proteinuria
NB	9	M		Nil	IgM, IgG, C_3	-	E. coli septicaemia Urinary tract infection	Died
MH	10	F	Present	Nil	Weak IgM, C_3	-	5 cm. hepar.	Persistent proteinuria
MS	10	M	Present	Nil	Focal IgM	N/G	-	Lost to follow-up
Indian								
KK	1½	M	-	-	Mesangial IgM + C_3	+	Measles	Two episodes of nephrotic syndrome
FS	7	F	-	Present	No deposits	-	-	Persistent proteinuria
MM	7	M	-	Present	Focal IgM + C_3	N/G	Klebsiella pneumoniae Septicaemia + urinary tract infection. Acute renal failure	Remission after 4 months
KR	8	F	-	Present	Focal IgM	-	Upper respiratory tract infection	Persistent proteinuria
RS	8	F	-	Present	-	N/G	-	Persistent proteinuria
LP	4	M	-	-	No deposits	N/G	-	Persistent proteinuria or relapse for 12 months. (No response to Cyclophosphamide

+ = good response : - = no response : N/G = not given

Renal failure - 1 patient presented acutely with severe oedema, oliguria, uraemia and pyrexia. Both blood and urine cultures revealed Klebsiella pneumoniae. He was dialysed and recovered rapidly.

(ii) Follow-up (Table XXXI).

(a) African

The period of observation ranged from 4 months to 2 years.

Persistent proteinuria - 3 patients. One of these patients developed hypertension and haematuria 6 months after the onset of the nephrotic syndrome. Following control of the high blood pressure by drug therapy the haematuria settled as well.

(b) Indian

The period of observation was 12 months to 10 years.

Remission - 2 patients - 1 patient had 2 steroid sensitive episodes of nephrotic syndrome; the other who

presented acutely remitted spontaneously after 4 months.

Persistent proteinuria - 4 patients.
One boy followed for 10 years fluctuated between proteinuria and relapse. The diagnosis of FGS was made on his 3rd renal biopsy, the first 2 were diagnosed as MCNS but he failed to respond to steroids, cyclophosphamide and chlorambucil.

5.5.4 Investigations

Investigations confirmed the nephrotic syndrome biochemically and excluded all known causes of secondary nephrotic syndrome. Excretory urography was normal in all patients except for the expected increase in renal size in some patients.

5.5.5 Light Microscopy

The features on light microscopy were similar to those adopted by Habib and Gubler 1975. The salient features being involvement of juxtamedullary glomeruli in which there is localised hyaline deposition in the absence of hypercellularity.

The hyaline material is PAS positive and an increase in PAS positive mesangial fibrillar material also occurs. The capillary lumina are obliterated, the loops stick together and adhere to Bowman's capsule. The rest of the tuft and glomeruli appear normal. Diffuse mesangial hypercellularity may be present. Tubular atrophy and interstitial fibrosis with the presence of foam cells in the interstitium are almost always present.

All our patients had the above histological changes in varying degrees. Only 2 patients had focal glomerular damages with minimal tubulo-interstitial changes.

5.5.6 Immunofluorescence (Table XXXI)

Three of the African patients who were investigated showed slight granular to heavy IgM + C_3 deposits on the GBM. The patient with heavy deposits had some IgG as well. This patient died. Five of the Indian patients were investigated. No deposits were detected in 2. 2 had focal IgM + C_3, and one had predominantly mesangial IgM + C_3.

5.5.7 Electron Microscopy

Obtained in only 2 patients. Both showed fusion

of foot processes. Adhesions of the affected tufts were confirmed.

5.5.8 Selectivity of Proteinuria

This test was performed on four Indian patients. Four had non-selective proteinuria and 1 selective proteinuria.

5.5.9 Associated Infections

2 patients, 1 African and 1 Indian had severe sepsis with Gram negative septicaemia (E. coli and Klebsiella pneumoniae respectively) with urinary tract infections. The African boy died and the Indian boy had acute renal failure but subsequently recovered.

5.5.10 Response to Drug Therapy - Steroids and Cyclophosphamide (Table XXXI)

Three of the African patients did not respond to steroids. 1 was given cyclophosphamide without response. Four Indian patients were treated with steroids. One responded to steroids in 2 separate relapses. Three others were steroid-resistant. Their oedema was controlled with the aid of diuretics but they continued having proteinuria.

One boy was given cyclophosphamide and Chlorambucil with no response to either drug.

Antihypertensives

Both hypertensive patients were controlled fairly easily using Methyldopa and Reserpine.

5.5.11 Discussion

This study of a few patients with focal glomerulosclerosis has demonstrated that although the incidence is lower than described elsewhere (Habib and Kleinknecht 1971, White et al 1970) the clinical spectrum and outcome are not too different to that described in other centres (Habib and Gubler 1975). The incidence is perhaps higher amongst Indian children but the figures are possibly too small to make a definite statement concerning the incidence. The African children experienced a poorer outcome as compared to the Indian children.

It has been stated that this category occurs most frequently in children under 5 years. In this group of patients only one child in each of the 2 race groups was under 5 years of age at presentation. This follows the general pattern of African children with nephrotic syndrome who present at a later age group. All the patients presented as severe

nephrotics, except the patient who in addition presented with acute renal failure.

Fifty percent of the children experienced significant infections. Two patients (1 Indian and 1 African) had gram negative septicaemia and urinary tract infections. Death occurred in the African child. This susceptibility to sepsis has been noted by others (Newman et al 1976, Habib and Gubler 1975). Haematuria occurred in Indian patients only. Thirty-eight percent of all the patients had haematuria and persistent hypertension was present in 25% (both African). Both these clinical features occurred less commonly than in other studies in which haematuria was found in 50 - 68% of patients (Newman et al 1976, Habib and Gubler 1975), and hypertension in 40 - 75% (White et al 1970, Jenis et al 1974).

During the period of observation the African patients fared less well as compared to the Indian nephrotics. They developed hypertension. Two of the Indian patients remitted, one in response to steroids and the other spontaneously, having presented as a seriously ill child with acute renal failure and gram negative septicaemia.

The 3 other Indian patients failed to remit on

steroids but the nephrotic syndrome improved, and they now have persistent proteinuria. The majority of patients with focal sclerosis do not respond to steroids (Habib and Gubler 1975). The Indian child who fluctuated between relapse and proteinuria and was observed for 10 years demonstrated the late histological diagnosis that may occur in this form of glomerulonephritis (Habib 1974). The initial biopsies were diagnosed as MCNS on L.M. and there were no deposits on immunofluorescent deposits. The third biopsy demonstrated the focal glomerular and tubulo-interstitial changes. Retrospectively there were mild tubulo-interstitial changes on the second biopsy.

The immunofluorescent findings were quite consistent with the usual description of focal glomerulosclerosis (Jenis and Lowenthal 1976, Newman et al 1976, Habib and Gubler 1975). Of interest was one patient with predominantly mesangial deposits who on light microscopy also demonstrated mesangial proliferation along with glomeruli showing focal glomerulosclerosis. Mesangial proliferation was noted to occur in focal glomerulosclerosis by Habib & Gubler (1975).

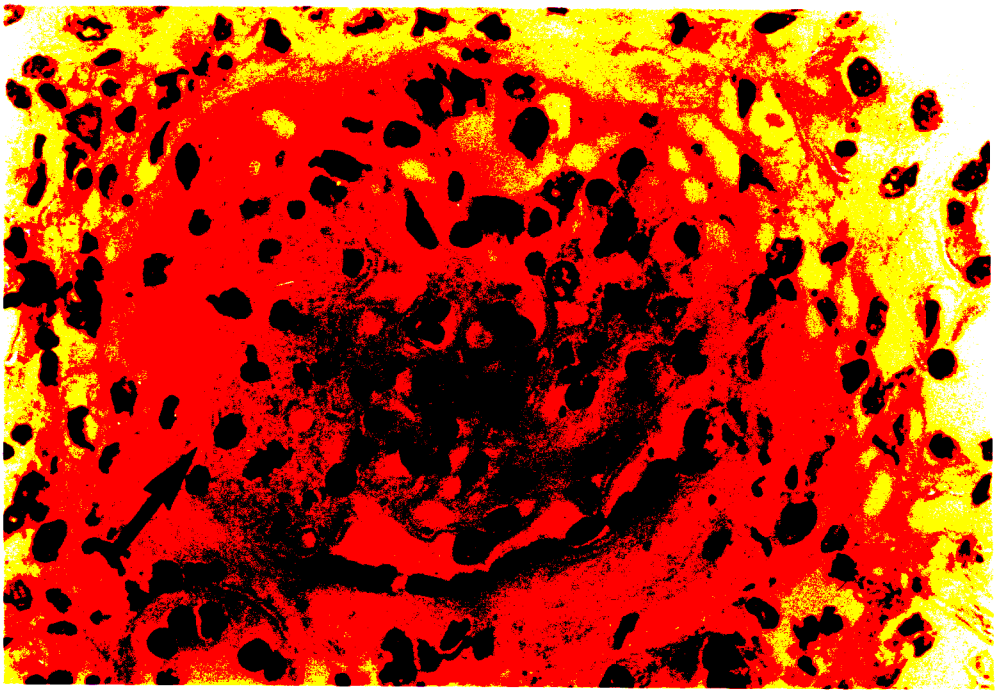
The histology was typical in all but one patient

(1½ years) who had very immature glomeruli along with focal glomerulosclerosis. The electron microscopic examination done on 2 patients confirmed findings of sclerosis.

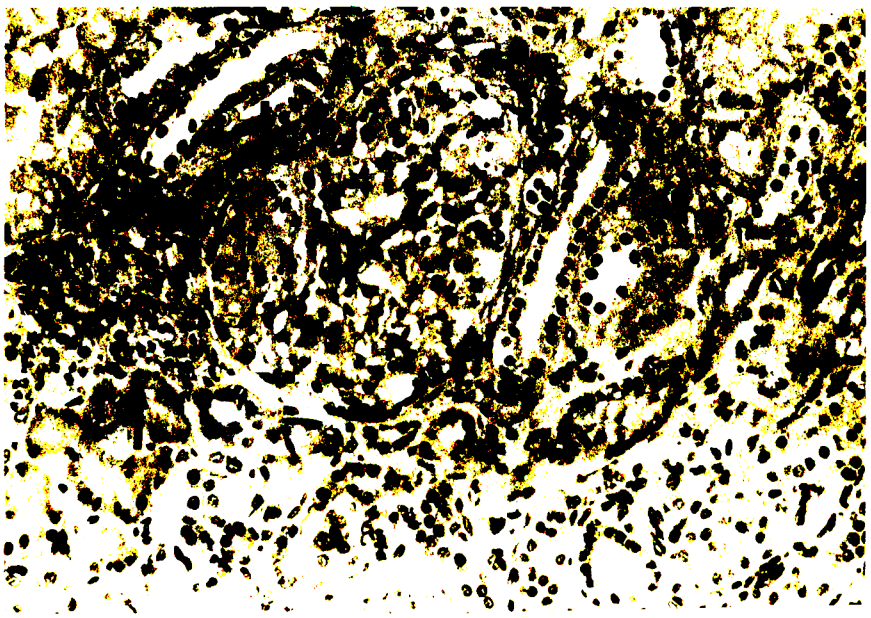
The Indian patients demonstrated the typical poor selectivity of proteinuria which is commonly associated with focal glomerulosclerosis (Cameron 1979, Habib & Kleinknecht 1971, White et al 1970).

This well defined histological category in which the natural history of the disease has to some extent been explained and which may occur in allografted kidneys (Raij et al 1972) is a fascinating one with regard to pathogenesis and origins of the glomerular lesions. Firstly as described by Rich (1957), the juxta-medullary glomeruli are predominantly involved. This may be related to redistribution of blood volume in the kidney (Hollenberg et al 1970) and therefore be the result of some form of vascular injury. The injured segments of the tuft have IgM and C_3 suggesting that these are deposited secondarily onto established lesions. (Saint Hillier et al 1975).

FOCAL GLOMERULOSCLEROSIS



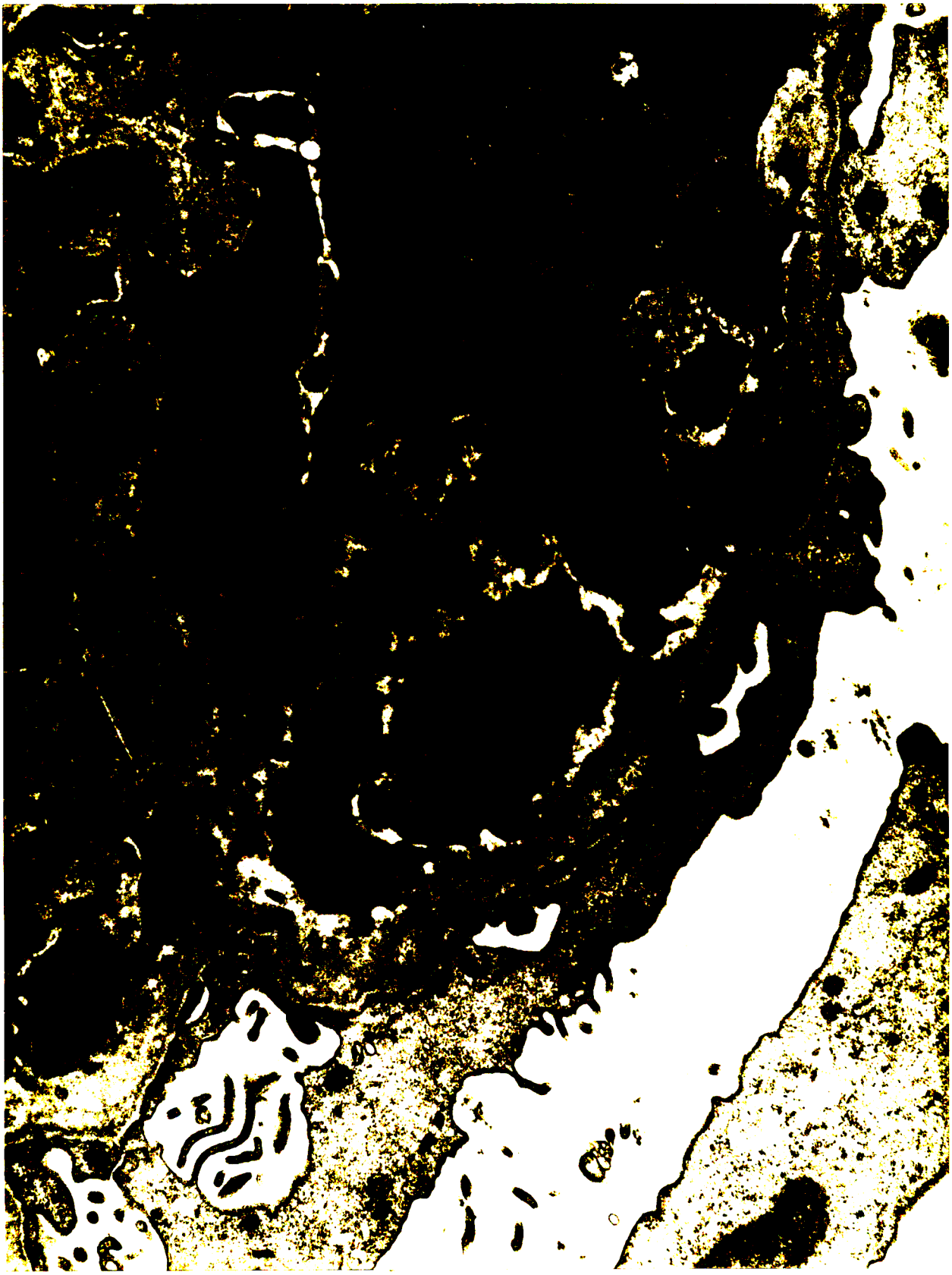
Arrow indicates sclerosed segment of glomerulus
(Haematoxylin and Eosin Stain, Magnification x 640)



Arrows indicate sclerosed segment of glomerulus
and focal interstitial fibrosis and inflammation.
(Magnification x 250).

Electronmicrograph (x 18,000)

FOCAL GLOMERULOSCLEROSIS. SCLEROSED SEGMENT OF GLOMERULUS



5.9 TROPICAL EXTRAMEMBRANOUS NEPHROPATHY

5.9.1 Summary

A few patients were diagnosed as tropical extra-membranous nephropathy. These were all African males with a wide age range. There were no poor prognostic features, none remitted, two thirds had persistent proteinuria and the rest remained nephrotic.

5.9.2 Incidence, Age, Sex, Race

Six (5.7%) children, all African of a total of 104 biopsied nephrotics had features of tropical extramembranous on histology.

All were males and their ages ranged from 4 to 9 years (4, 5, 6, 7, 8, 9 years).

5.9.3 Clinical Presentation

(i) Initial presentation

Hypertension - none

Haematuria - 1 patient

Renal failure - none

(ii) Follow-up (Table XXXII)

Three children were observed for 3 months or less.

Persistent proteinuria - all 3.

Three others observed for a period of 6 months to 5 years.

Persistent proteinuria in 2 patients

Relapse - in 1 patient

Remission - 0

5.9.4 Investigations

Biochemical investigations confirmed the nephrotic

TABLE XXXII

COMPLEMENT LEVELS, IMMUNOFLUORESCENCE AND OUTCOME IN TROPICAL EXTRAMEMBRANOUS NEPHROPATHY

NAME	AGE (yrs)	C_3% Mgs	IMMUNOFLUORESCENCE IgG	C_3	C_{1q}	C_4	Others	FOLLOW-UP PERIOD (months)	OUTCOME PR	PP
S.B.	9	-	+++	+++	+++	+++	IgM+	48	48	-
R.M.	5	74	++	++	-	-	-	3	1	2
G.M.	8	54	-	-	-	-	-	60	60	-
M.N.	6	100	+++	+	+	+	IgM+	2	1	1
M.X.	7	86	++	+	+	-	-	3	1	2
A.M.	4	86	++	++	++	++	IgM+ IgA+	6	1	5

syndrome in these 6 patients. The complement levels were normal in 5 patients tested and investigations for secondary causes of the nephrotic syndrome were negative.

5.9.5 Light Microscopy

The histological changes in these patients showed marked glomerular basement membrane thickening with spike formation and conspicuous cellular proliferation of endothelial and mesangial cells.

5.9.6 Immunofluorescence (Table XXXII)

Immunofluorescence studies were obtained in 6 patients. Three patients had heavy deposits of IgG and complement components C_{1q}, C_3 and C_4, (one of these had IgM deposits as well). 1 had IgG and C_3, 1 had IgG, IgA, IgM, C_{1q}, C_3 and C_4 and in one no deposits were detected.

5.9.7 Response to Treatment

(i) General

Diuretics (Thiazides, Spironolactone, Triamterene) were used singly or in combination. Five patients responded but the 6th patient remained oedematous throughout his period of illness.

(ii) Steroid Therapy

None of the patients were given steroids.

5.9.8 Discussion

"Tropical Extramembranous" nephropathy was described in 1975 by Morel-Maroger et al 1975. In a study in Senegal 4 children demonstrated an unusual form of glomerulonephritis. The biospies demonstrated extramembranous glomerulopathy with the typical spike formation but in addition significant cellular proliferation was noted. On ultra-microscopic studies the cells involved were shown to be mesangial and endothelial. Two children had haematuria, none had hypertension or renal failure. An aetiological agent could not be established nor was the natural history of this group elucidated. The odd feature in these 4 patients was the low complement. This combination of extramembranous nephropathy and hypocomplementemia was previously reported in patients with systemic lupus erythematosus (Gewurz et al 1968).

In the present study one child had haematuria, none had hypocomplementaemia and no aetiological agent could be found. Immunofluorescent findings were similar to the Senegalese study.

The natural history seemed to suggest persistent on-going insult to the kidney. Those observed for longer than 6 months remained in relapse or had significant proteinuria; these children had suffered significant renal disease.

This histological group is one not described in nephrotic children in temperate climates (Churg et al 1970), White et al 1970). The poor prognosis makes the search for aetiological agents or therapeutic means of decreasing glomerular injury of critical importance.

5.10 TROPICAL NEPHROPATHY

5.10.1 Summary

Three children (2 African and 1 Indian) were classified as tropical nephropathy. One of the African children died and one remained proteinuric. The Indian child remitted.

5.10.2 Incidence, Age, Sex, Race

Three patients of the 170 nephrotics who were biopsied were classified as tropical nephropathy Two children (1 male - 1 female) were African and 1 child (male) Indian.

The African children were aged 3 and 10 years, the Indian boy was 6 years of age.

5.10.3 Clinical Presentation

(i) Initial

Hypertension - 2 (1 African, 1 Indian). Settled by 3 weeks.

Haematuria) 1 African child. Gross
Renal failure) oedema was present with progressive renal failure and death within 14 days of admission.

(ii) Follow-up

Persistent proteinuria - 1 African child observed for 2 years.

Remission - Steroid induced in 1 Indian child observed for 4 years.

Following biopsy, the Indian boy developed

a left renal subcapsular abscess which required partial nephrectomy. One year later an excretory urogram which by error had not been performed on the first admission was performed for repeated attacks of urinary infection revealed a right pyelonephritic kidney with gross vesicoureteric reflux and calyceal dilation necessitating a right nephrectomy.

5.10.4 Investigations

The biochemical investigations confirmed the nephrotic syndrome in these patients. The African patient who died and the Indian patient had elevated factor VIII levels of 255 mgs% and 175 mgs% respectively. The patient who died was a carrier of HB_sAg.

The serum complement C_3 levels were normal in all cases tested (5 patients).

5.10.5 Light Microscopy

The histological findings in these three patients were as follows: capillary wall thickening and segmental glomerular sclerosis. Cellular proliferation was inconspicuous or absent. The

basement membrane had a characteristic splitting or flaking of the glomerular capillary walls and intrusion of basement membrane-like material into the lumen seen on silver stains.

5.10.6 Immunofluorescence

Diffuse granular deposits of IgG and C_3 were detected in 2 patients and fine granular segmental deposits of IgM and C_{1q} in the third patient.

5.10.7 Response to Treatment

(i) General

Diuretics (Thiazides, Spironolactone, Triamterene) were used singly or in combination. Two patients, both hypertensive responded well in that they lost their oedema and their blood pressures gradually decreased to within normal limits. Specific antihypertensive drugs were therefore not required in these 2 patients. The third patient had severe progressive oedema uncontrolled by diuretics till death.

(ii) Steroid Therapy

Two patients were given steroids; the Indian boy remitted and remained in remission, the African child with

severe nephrotic syndrome had no clinical improvement but rather with deterioration. He died within a fortnight of admission.

5.10.8 Discussion

Tropical nephropathy is the term used to describe the characteristic histological changes associated with quartan malarial nephropathy. (Hendrickse et al 1972, White 1973b, Morel-Maroger et al 1975). Similar histological changes were noted in nephrotic children in the Ivory Coast (de Paillerets et al 1972). In Senegal the nephrotic syndrome is common and quartan malaria is an unusual disease (Morel-Maroger et al 1975). However, the characteristic light microscopy changes associated with malarial nephropathy (Hendrickse et al 1972, White 1973b) were found in 16 of 24 children investigated (Morel-Maroger et al 1975).

Morphologically the changes which are slight to diffuse may be termed focal, segmental and diffuse mesangio-capillary sclerosis as suggested by White (1973b). However, these changes are arbitrarily termed "quartan malarial nephropathy".

This histological category is not only interesting

with regard to malaria but the fact that it may occur in its absence among children in tropical and subtropical environments. It is an unusual form not described in nephrotic children in temperate climates (Churg et al 1970, White et al 1970).

The features in these children which were different from quartan malarial nephropathy were the lack of diffuse immunoglobulin on immunofluorescent studies and an absence of areas of lacunar basement membrane resorption (Hendrickse et al 1972, White 1973b).

In this study the 3 patients histologically and on immunofluorescent studies resemble the Nigerian children except that they did not have quartan malaria. Ultramicroscopic studies were not available therefore no comment on the areas of lacunae formation in the basement membrane is possible. In Senegal no obvious aetiological agent was implicated.

The outcome of the Senegalese children is not known. In quartan malarial nephropathy the outcome depended on two factors firstly, the grade of histological change and secondly the degree of selectivity of proteinuria. Grade I and those

with highly selective proteinuria fared best.

As more cases are studied it may be possible in the future to clarify the natural history of the disease in situations where malaria is not endemic.

In malarial nephropathy the outcome is often poor (Hendrickse 1976). The outcome in this study is not easy to comment upon because of the few patients available. It is interesting that the Indian child did well, responded to steroids but suffered other complications. The African children fared less well suffering significant disease; one died and the other has persistent proteinuria.

TABLE XXXIII

CLINICAL PRESENTATION AND OUCOME IN TROPICAL NEPHROPATHY

NAME	RACE	AGE	SEX	HPT	HAEM	RF	IMMUNOFLUORESCENCE				FOLLOW-UP PERIOD (months)	OUTCOME	ASSOCIATED PROBLEMS
							IgG	IgM	C_3	C_{1q}			
E.D.	A	3	F	-	+	+	+++	-	++	++	0.5	Died	HB_sAg Pos
N.G.	A	10	M	+	-	-	-	+	-	+	26	Persistent proteinuria	Nil
K.N.	I	6	M	+	-	-	++	-	++	-	60	Steroid Induced Remission	1. Subcapsular abscess partial nephrectomy. 2. Right pyelonephritis Kidney with gross reflux - right nephrectomy.

5.11 UNCLASSIFIED GLOMERULAR LESIONS

5.11.1 Summary

This represented a small group with end stage renal disease. The outcome was uniformly poor with patients dying or remaining in severe relapse.

5.11.2 Incidence

Five of a total of 170 biopsied nephrotics presented with lesions which could not be classified according to the histological groups described.

Race

Four of these children were African and one Indian.

Age and Sex

Their ages ranged from 4 - 12 years. (4, 5, 7, 7 and 12 years). Two were males.

5.11.3 Clinical Presentation

(i) Initial

Hypertension - 3 patients (2 African, 1 Indian).
Haematuria - 3 patients
Renal failure - None

The Indian was hypertensive, severely nephrotic and had been seen by a general practitioner for 2 years prior to referral.

Follow-up

The duration of observation was 2 to 9 months. One patients was seen initially only.

Relapse (severe) - 5 patients

Death - 2 patients (1 African, 1 Indian)

(ii) Both patients remained hypertensive, the African child had haematuria and both died in renal failure.

The Indian boy had severe recurrent anaemia for 2 months before his death.

5.11.4 Investigations

The biochemical investigations confirmed the nephrotic syndrome in all 5 of the patients. One patient had a persistently low C_3 during the course of her illnes. The Indian boy who died had a Klebsiella pneumoniae urinary tract infection and a GFR, of 16 mls/min. Two of the other patients had GFR's of 16 and 45 mls/min.

5.11.5 Light Microscopy

The 4 African patients had obvious glomerular lesions which were too far advanced to be classified into a definite histological category.

The Indian child had hypercellular glomeruli with adhesions and many glomeruli were completely fibrosed. Some glomeruli had periglomerular

fibrosis and marked interstitial inflammatory reaction with marked tubular atrophy was present. It was thought that some of these changes were due to chronic pyelonephritis.

5.11.6 Immunofluorescence

This was performed on 1 patient who had marked C_3 deposits on the glomerular basement membrane (this patient also had very low plasma C_3 levels).

5.11.7 Response to Treatment

(i) General

Diuretics (Thiazides, Spironolactone, Triamterene) were used singly or in combination. In this group of patients oedema was difficult to control.

Antihypertensives, Serpasil and Methyldopa were used in the 3 hypertensive patients. The hypertension was difficult to control in all 3.

A high protein diet was generally given.

(ii) Steroid Therapy

Three patients (1 Indian) were given steroids but none responded.

5.11.8 Associated Problems

The Indian patient had recurrent episodes of urinary tract infection due to Klebsiella pneumoniae.

5.11.9 Discussion

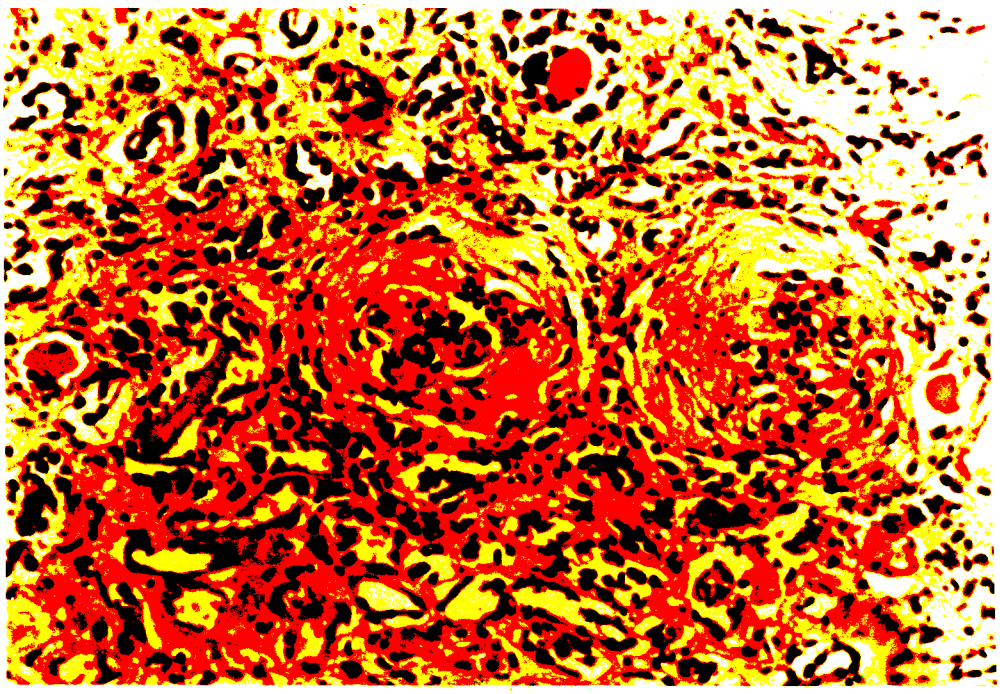
Four of the five patients demonstrated histological changes of end-stage glomerulonephritis. Of these the patient of interest is the child with persistently low C_3 who was hypertensive and had haematuria. This patient remained in relapse for the course of the illness and could initially have been a rapidly progressive or membranoproliferative glomerulonephritis. Unfortunately neither electron microscopy nor immunofluorescence, either of which might have assisted in the diagnosis, were available.

The most interesting of this group of patients is the Indian boy who presented as a steroid-resistent nephrotic with hypertension and recurrent urinary tract infection. His clinical course was a relentless downhill one with unresponsive hypertension, nephrotic syndrome and urinary tract infection. The histological findings in this boy were perhaps the most difficult of all to interpret. There appeared to be glomerular, tubular and

interstitial change which could have all been associated with chronic pyelonephritis.

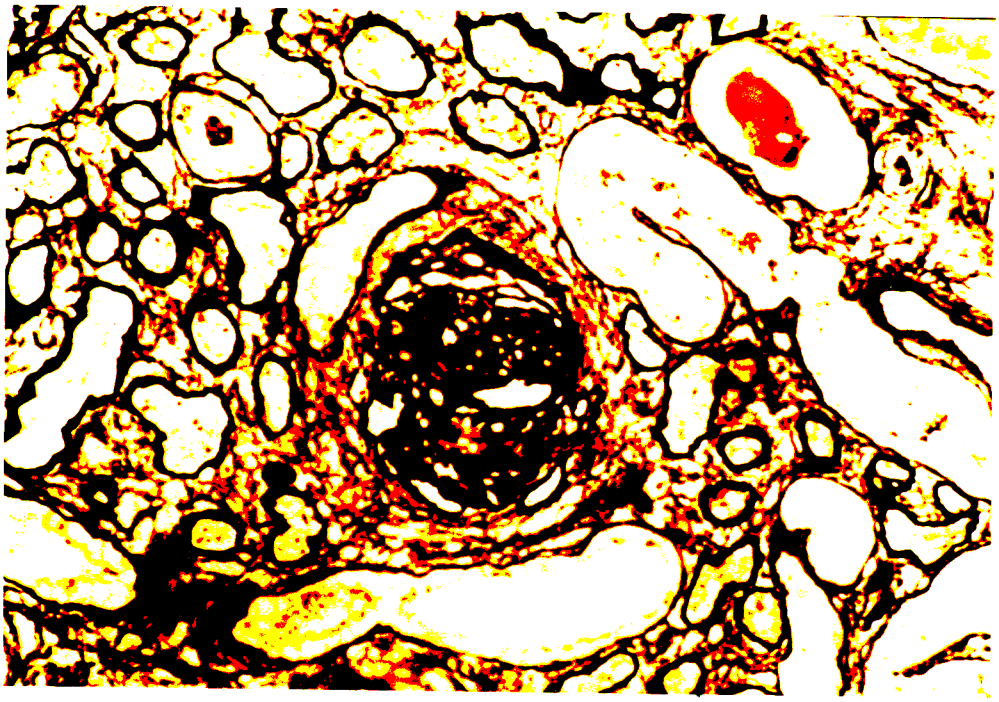
END STAGE KIDNEY - POSTMORTEM BIOPSY

(Haematoxylin and Eosin stain, Magnification x 250)



PERIGLOMERULAR FIBROSIS - SCLEROSED GLOMERULAR TUFT WITH ADHESIONS AND FIBROTIC CRESCENT

(Silver Methanamine Stain, Magnification x 250)



5.12 SECONDARY NEPHROTIC SYNDROME

TABLE XXXIV

NEPHROTICS - PRIMARY AND SECONDARY

HISTOLOGICAL GROUP	IND.	AFR.	TOTAL
A Minimal Change	48	15	63
B Extramembranous	2	31	33
C Proliferative			
(i) Diffuse mesangial	4	7	11
(ii) Diffuse exudative	1	9	10
(iii) Diffuse endocapillary	0	7	7
(iv) Membranoproliferative	2	9	11
(v) Focal proliferative	1	10	11
D Focal glomerulosclerosis	6	4	10
E Tropical extramembranous	0	6	6
F Tropical nephropathy	1	2	3
G Unclassified	1	4	5
TOTAL	66	104	170
Unbiopsied nephrotics	48	12	60
	114	116	230

Secondary Nephrotics

Rapidly progressive glomerulonephritis	4
Acute post-streptococcal nephrotic syndrome	7
HB_sAg associated nephrotic syndrome	9
Henoch Schönlein Purpura	1
Systemic lupus erythematosus	1
TOTAL	22

5.12.1 Summary

Secondary nephrotic syndrome occurred in 10% of the patients studied. Half of the patients suffered nephrotic syndrome following acute streptococcal infection as rapidly progressive glomerulonephritis or transient nephrotic syndrome. Collagen vascular diseases occur very rarely and the patients with SLE and HSP were both Indians. HB_sAg carriers were the remaining patients with secondary nephrotic syndrome.

5.12.2 Introduction

Glomerular lesions which occur secondarily to systemic illness are generally uncommon and are found in fewer than 10% of all cases of glomerular diseases in children (Habib 1974). Similarly in the nephrotic syndrome of childhood no more than 10% are secondary to other causes (Habib 1974c). In this study there were 22 (10.9%) secondary nephrotics of a total of 192 biopsied nephrotics.

The causes of the secondary nephrotic syndrome in these 22 children were as follows:

4 - were rapidly progressive glomerulonephritis following poststreptococcal infection - all African.

7 - acute poststreptococcal glomerulonephritis with nephrotic syndrome - all African.

9 - HB_sAg Positive Nephrotics - all African.

1 - child with Henoch Schönlein Purpura - Indian.

1 - girl with systemic lupus erythematosus.

Each of these secondary categories will be discussed.

RAPIDLY PROGRESSIVE GLOMERULONEPHRITIS

5.12.3.1 Summary

Four African children with rapidly progressive glomerulonephritis are described. All had

evidence of a preceding streptococcal infection and crescents in more than 80% of glomeruli seen on histological examination. The clinical presentation was dominated by oligo-anuria in a setting of nephritis or nephrotic syndrome with a relentless progression to chronic renal failure and death. Quadruple therapy with cyclophosphamide, steroids, heparin and dipyridamole in 3 patients was of no lasting benefit and attended by severe complications.

5.12.3.2 Introduction

Rapidly Progressive Glomerulonephritis (RPGN) is uncommon in adults and even rarer in children. A current review of the disease in American children is based on 13 cases seen over a period of about 16 years (Cunningham et al 1980). Post-Streptococcal Glomerulonephritis (PSGN) is one of the commonest renal diseases seen in African children admitted to hospital and is recognised as an antecedent event in the development of RPGN. The Syndrome of RPGN, however, has not been adequately described in African children. In fact, in a recent synposium (Hendrickse 1980, Hutt 1980) renal disease in the tropics, the disease

has not been mentioned. The patient details are summarised in the table.

5.12.3.3 Case 1

A nine year old African boy was admitted from a peripheral hospital with a history of having been treated for acute glomerulonephritis. The duration of the illness was unknown. A history of previous hospitalisation or a relevant family history was not available.

On admission he had evidence of healing impetigo, generalised oedema, a blood pressure of 110/70 mm Hg and he was anuric. The rest of the systematic examination was normal. The initial blood urea and electrolytes done on admission were: blood urea 58 mmol/l, serum sodium 122 mmol/l, potassium 8,4 mmol/l, chlorides 96 mmol/l and plasma bicarbonate 15 mmol/l. A peritoneal dialysis was therefore commenced. The blood urea had decreased to 15,2 mmol/l with normal levels of serum sodium, potassium, chlorides and plasma bicarbonate. Subsequently the urea stabilised at 30 mmol/l. The patient remained anuric for three weeks and oliguric till death. Examination of the first available specimen of urine revealed 3+ albumin with the subsequent urinary examinations being

non-contributory. In particular there were no cells or casts.

The serum osmolality was 329 m osmol/kg whilst the urine osmolality was 313 m osmol/kg. The glomerular filtration rate was not done. The serum creatinine level was 675 mmol/l. Serum protein electrophoresis revealed an albumen concentration of 24,4 g/l and the following globulin levels: α^1 globulin 2,5 g/l, α^2 globulin 9,3 g/l, β globulin 15,6 g/l and γ globulin 15,2 g/l. The serum cholesterol was 4,27 mmol/l. The streptozyme test was positive; the anti-streptolysin O titres were 100 u/ml on admission and became negative after ten days. The 'C'-reactive protein test was positive on admission and on subsequent examination. The chest radiographs done on admission and after 10 days revealed lamellar effusions at both bases. Enlarged kidneys were demonstrated on ultrasonogram examination.

Antinuclear factor, parietal cell, smooth muscle and mitochondrial antibodies were negative. The hepatitis B (surface) antigen was not detected in the serum. The C3 level was 0,04 g/l (normal - Mean 0,90 $\pm$ Standard Deviation 0,19 g/l) and C4 level was 0,72 g/l (normal - Mean 0,47 g/l $\pm$

Standard Deviation 0,18 g/l) initially. Seven days later the C3 level had risen to 0,98 g/l and the C4 level was 0,90 g/l. The haemoglobulin 11,1 g/dl and the white cell count was 36,9 x 10^9/l with 94% neutrophils, 4% lymphocytes and 2% monocytes. The Factor VIII procoagulant acitivity was 156% (normal range 50 - 150%). S. Typhi was cultured from the blood after two weeks of hospitalisation. The Widal, stool and urine examinations for Salmonella typhi were negative on several occasions. The repeat blood culture after 17 days of treatment with Amoxycillin was negative. Two weeks later Shigella flexnerii was cultured from the stools. The bilharzia CFT was negative. The liver enzymes were within normal limits. The blood pressure was elevated one day after admission and stabilized at 150/100 mm Hg despite anti-hypertensive medication. The patient had persistent generalized oedema throughout the period of hospitalisation and became progressively anaemic. At a haemoglobin level of 6,3 g/dl, packed cells and 20% albumin and frusemide were administered slowly to the patient in order to correct the anaemia and attempt to induce a diuresis. The patient died 20 hours later.

The histology of the renal tissue taken at autopsy showed rapidly progressive glomerulonephritis (RPGN) with more than 80% of the glomeruli showing crescents. The probable cause of death at post mortem examination was terminal heart failure with left ventricular hypertrophy. The patient died six weeks after admission. The patient was treated with diuretics, anti-hypertensives together with the routine care.

5.12.3.4 Case 2

An 11 year old African boy was admitted from a peripheral hospital with a 2 day history of generalised oedema. He had been admitted to that hospital 7 months prior to transfer to King Edward VIII Hospital with acute glomerulonephritis which had responded well to penicillin, frusemide, hydrallazine, fluid and protein restriction. There was no relevant family history.

On admission he had generalised oedema and gross ascites, a blood pressure of 100/70 mm/Hg. The rest of the systemic examination was negative. He was anuric for three days and thereafter became oliguric. The examination of the urine revealed 30 leucocytes/HPF, 30 red blood cells/HPF with

hyaline casts and granular casts. Serum protein electrophoresis revealed an albumin of 12,4 g/l and the following globulin levels: 1,4 g/l α^1 globulin; 14,1 g/l α^2 globulin; 5,9 g/l β globulin and 10,2 g/l γ globulin and a total protein of 44,0 g/l. The serum cholesterol was 11,61 mmol/l. The serum and urine osmolality were 308 m osmol/kg and 385 m osmol/kg respectively.

The blood urea level on admission was 19,0 mmol/l. The serum creatinine level was 155 mmol/l. The glomerular filtration rate by C50 EDTA was 17 ml/min. Serum sodium, potassium, chlorides and plasma bicarbonate were within normal limits. One month later the blood urea level had increased to 35,0 mmol/l and persistent generalised oedema with evidence of fluid overload developed. A peritoneal dialysis was performed. Gradually over a period of 3 weeks the blood urea steadily increased to 35,4 mmol/l and fluid overload developed again. A second peritoneal dialysis was done followed by a renal biopsy.

The streptozyme test was positive initially and became negative after two months. The anti-streptolysin O titre on admission was negative. The C-reactive protein was positive; the Wasserman

reaction and Widal test were negative. Anti-nuclear factor, parietal cell, mitochondrial and smooth muscle antibodies and hepatitis B (surface) antigens were not detected in the serum. The bilharzia CFT was positive. The rectal mucosa biopsy did not reveal bilharzia. The haemaglobin was 8,3 g/dl and the white cell count was 13,1 x 10^9/L with 66% neutrophils, 24% lymphocytes, 5% monocytes, 4% eosinophils and 1% basophils. The patient was transfused with packed cells prior to the renal biopsy. The Factor VIII procoagulant activity was 182%.

The complement levels on admission and two months later were respectively: C3 0,68 g/l and 0,58 g/l; C4 0,60 g/l and 0,68 g/l; Factor B 0,22 g/l (normal 0,34 $\pm$ 14 g/l) and 0,14 g/l. The chest x-ray on admission was normal. The ultrasonogram revealed normal sized kidney on admission and progressive enlargement 6 weeks later. Renal biopsy showed rapidly progressive (crescentic) glomerulonephritis. Not one of 13 glomeruli was normal. Nine glomeruli showed extensive sclerosis and in some of these residual crescents were detectable. IgA deposits were present along the basement membrane of some tubules but no glomeruli were present for

immunofluorescent examination. During his stay in hospital he remained oligo-anuric, had persistent generalised oedema and became hypertensive after an initial normotensive period. He received the following treatment in hospital: anti-hypertensive drugs, diuretics and quadruple chemotherapy (Brown et al 1974), i.e. heparin, dipyridamole, cyclophosphamide and prednisone. Ten days after treatment with the quadruple chemotherapy, the patient developed a pericardial friction rub. The cardiac shadow was enlarged, lung fields congested with a small right-sided pleural effusion on chest radiograph done at this stage. The ultrasonogram showed cardiomegaly with no pericardial effusion. The quadruple chemotherapy was therefore stopped. The patient died after three months of hospitalisation.

5.12.3.5 Case 3

A 4 year old African female child was admitted with a three day old history of puffiness of the face. There was no relevant past or family history of illness. On examination she had oedema of the legs and face, healing impetigo on the lower limbs and a blood pressure of 150/100. There was no evidence of fluid overload. The

other systems were normal.

Throughout the period of her first admission of 2 months she remained oligo-anuric, hypertensive, oedematous and azotaemic. Three peritoneal dialyses were performed and a renal biopsy was done after the last dialysis.

Examination of the first available urine specimen was normal, in particular there were no cells or protein. Subsequent urine samples revealed at most a plus of protein. Three subsequent urine cultures isolated Klebsiella pneumoniae. The blood urea level was 33,1 mmol/l on admission, the serum creatinine was 580 mmol/l. Serum sodium, potassium and plasma bicarbonate were normal. Serum protein estimation showed a total protein of 62 g/l with albumin 27 g/l and globulin 35 g/l. The streptozyme test was positive but the anti-streptolysin O titre was negative. The C-reactive protein was positive. Antibuclear factor, parietal cell, mitochondrial and smooth muscle antibodies and hepatitis B (surface) antigen were not detected in the serum. The Wasserman reaction and Widal test were negative. The bilharzia CFT was positive.

The haemaglobin was 10,3 gm/dl and the white cell

count was 12,5 x 10^9/L with 61% neutrophils, 33% lymphocytes, 2% monocytes, 1% eosinophils and 1% basophils. Factor VIII procoagulant activity was 180%. The blood cultures were negative. The serum and urine osmolality were 285 m osmol/kg and 195 m osmol/kg respectively. Immunochemical assay of complement revealed a Factor B level of 0,38 g/l (normal 0,34 $\pm$ 0,14 g/l), C3 0,12 g/l and C4 0,54 g/l. Subsequent C3 determinations remained low.

Renal biopsy showed RPGN. Of the 31 glomeruli seen, only 6 were free of crescents. The patient was treated with anti-hypertensive drugs, diuretics and quadruple chemotherapy (Brown et al 1974) and transfused when necessary. Whilst on the quadruple chemotherapy she developed bilateral bronchopneumonia and a pericardial friction rub. The initial chest radiograph was normal; chest radiographs taken after treatment with quadruple chemotherapy showed infective changes of both lung fields. The ultrasonogram examination showed bilateral enlargement of the kidneys. The ultrasonogram examination done after the development of the pericardial friction rub showed cardiac enlargement with no evidence of pericardial effusion.

After two months of hospitalisation the patient was signed out of hospital by her parents. The patient was subsequently admitted a second time for 14 days with urinary tract infection which was successfully treated. The blood pressure and blood urea were normal.

Within a week after the second discharge the patient was admitted for the third time with features suggestive of chronic renal failure and congestive cardiac failure. She was hypertensive, oedematous and azotaemic; she had a systolic murmur of the apex most probably secondary to the cardiomegaly which had followed the elevated blood pressure. There was no evidence of rheumatic heart disease. The patient is presently alive and is being treated for chronic renal failure.

5.12.3.6 Case 4

An 8 year old African female was admitted from a peripheral hospital with a history of having been treated for acute glomerulonephritis with hypertension. The duration of the illness was three months. There was no relevant past or family history of illness.

On examination she had generalised oedema, a blood pressure of 160/110 mm Hg, oliguria and macroscopic haematuria. There was no evidence of fluid overload. The other systems were normal.

The examination of the urine revealed 80 leucocytes/HPF, 800 red blood cells/HPF and a 2 plus proteinuria. Urine cultures revealed no organisms. The total protein in a 24 hour specimen of urine was 6,32 g. The patient remained oliguric until death, except for a 10 day diuretic phase immediately following initiation of quadruple chemotherapy.

The blood urea level on admission was 24,6 mmol/l and the serum creatinine was 508 mmol/l. Serum sodium, potassium, chlorides and plasma bicarbonate were within normal limits.

Ten days after admission the blood urea level had increased to 26,1 mmol/l and the generalised oedema had increased despite adequate doses of diuretics. A peritoneal dialysis was performed followed by renal biopsy.

Serum protein estimation showed a total protein of 56 g/l with albumin 24 g/l and globulin 32 g/l.

The serum cholesterol was 5,08 mmol/l. The serum and urine osmolality were 310 m osmol/kg and 257 m osmol/kg, respectively.

The streptozyme test was positive but the anti-streptolysin O titre was negative. The C-reactive protein was positive, the Widal test was negative. The initial haemoglobin was 8,2 g/dl and the white cell count was 13,2 x 10^9/l with 65% neutrophils, 20% lymphocytes and more than 12% eosinophils. The platelet count was normal.

Parasites were not detected on stool and urine examination. The patient was transfused with packed cells on two occasions because of a falling haemoglobin level. The factor VIII pro-coagulant activity was 201%.

The complement levels on admission and a month later were respectively: C3 0,70 g/l and 0,64 g/l; C4 0,44 g/l and 0,40 g/l; Factor B 0,68 g/l and 0,32 g/l. The chest x-ray on admission and subsequently showed features that were compatible with acute glomerulonephritis.

Renal biopsy showed RPGN. All the ten glomeruli that were seen showed crescents. IgM granular

deposits were seen along the basement membrane of the glomeruli on immunofluorescent examination.

The patient was treated with anti-hypertensive drugs, diuretics, quadruple chemotherapy, together with routine care. The patient was drowsy and acidotic one day prior to her death, after being in the ward for eleven weeks.

Post mortem examination revealed large pale kidneys which on light microscopy showed fibrosis and sclerosis of all glomeruli with progressive tubular atrophy and interstitial fibrosis.

5.12.3.7 Discussion

This report has described the features of RPGN in four African children who were all seen within a one year period. This temporal aggregation of cases of an extremely rare disease is not easily explained. It is possible that some combination of circumstances enhanced the pathogenicity of a particular sub-type of streptococcus resulting in severe renal disease. In most series about a third of adult patients with RPGN are associated with systemic vasculitis syndromes (Cameron 1979) and a minority follow infections. Only 1,6% are related to an antecedent streptococcal glomerulo-

nephritis (Whitworth et al 1976). However, in 2 series (Cunningham et al 1980, Habib 1974b) of children with RPGN, APSGN was the antecedent event in 32% and 63% respectively. The four children reported here did not have evidence of systemic vasculitis syndromes which are in any case infrequent among our patients. It was not unexpected that all our patients were detected in a setting of PSGN as the latter is an extremely common disease seen in African children admitted to King Edward VIII Hospital. The evidence for a post-streptococcal aetiology was the combination of healing impetigo (2 patients), a positive "streptozyme" test and diminished levels of C3. Cunningham (1980), on the basis of his results, speculated that RPGN may follow only pharyngeal and not skin infection by streptococci. Our data do not support this. Rapidly progressive glomerulonephritis is said to be an extremely rare complication of acute post-streptococcal glomerulonephritis, the incidence being <1% (Brown et al 1974). We admit approximately 250 cases of PSGN every year and the 4 cases reported are the first we have seen. Therefore our experience accords with that of other units.

In case 1 the second blood culture done after 11 days of hospitalisation isolated Salmonella typhi. However, the clinical presentation did not resemble the typical picture of typhoid glomerulonephritis (Buka & Coovadia 1980) and we therefore believe that the patient was cross-infected in the ward.

The clinical manifestations in crescentic glomerulonephritis are usually variable, with oligo-anuria, nephritis, proteinuria or the nephrotic syndrome (Cameron 1979, Habib 1974b). The 4 children reported here illustrate these typical presentations with all being oligo-anuric, 3 having nephritis and 2 demonstrating the features of nephrotic syndrome. More than 90% of African children in Durban with post-streptococcal glomerulonephritis (PSGN) will have clinical recovery (i.e. from hypertension, oedema and oliguria) by the second week of admission to hospital (Hallett et al 1977). Therefore, in our circumstances, any child with this syndrome who does not recover within a fortnight of admission must be considered for renal biopsy in order to establish the diagnosis of RPGN. There has been a suggestion, not entirely supported by our data, that in children with PSGN clinical pointers to a diagnosis of

RPGN are anaemic, marked azotaemia and hypergammaglobulinemia (Cunningham et al 1980). Increased levels of Factor VIII procoagulant activity can be used as an index of the extent of immunopathological injury to the glomerular capillaries (Adhikari et al 1978). This can be an additional factor in assessing severity of renal disease. In all the 4 cases of RPGN the Factor VIII levels were increased beyond that found in children with PSGN who generally do well (Adhikari et al 1978). (Appendix p. 270).

RPGN following streptococcal infections is thought to have a better outcome (Leonard et al 1970). The study by Cunningham (1980) and our data do not support this. As suggested by Cunningham the prognosis of RPGN does not depend on aetiology but on the extent of renal damage as reflected in the number of glomeruli showing crescent formation.

All 4 cases had severe RPGN on renal biopsy with more than 80% of glomeruli involved. This denotes a poor prognosis as pointed out by Kincaid-Smith (1975). If over 50% of glomeruli in an adequate sample show crescents, spontaneous recovery is rare while if more than 80% glomeruli

show crescents, recovery does not occur (Kincaid-Smith 1975). Our patients had a uniformly protracted course and poor outcome.

Untreated RPGN is known to have a very poor outcome, death occurring within weeks to months from the time of presentation. Anticoagulant therapy has been known to have a striking effect on the renal pathology in experimental nephritis and an immediate clinical improvement in some clinical trials (Arieff & Pinggera 1972, Kincaid-Smith et al 1968).

Three of the 4 patients were tested with the quadruple therapy. The expected improvement in renal function (Arieff & Pinggera 1972, Kincaid-Smith 1968), however, did not occur in two patients, and was transient (10 days) in one child (Case 4). In this latter case the histological changes showed marked progression to glomerular sclerosis and fibrosis and interstitial fibrosis. Complications of therapy were life-threatening. Two patients developed pericarditis with the appearance of a pericardial friction rub on treatment. Pericardial fluid, however, was not demonstrated on ultrasonography, suggesting a fibrinous pericarditis. Azotaemia is an

explanation for the development of the pericarditis. Haemorrhagic complications have been encountered with anticoagulant therapy in 2 studies (Brown et al 1974, Kincaid-Smith et al 1968). Haemorrhagic pericarditis should therefore be considered a possibility in both patients. One of these 2 patients also developed severe bilateral bronchopneumonia while on quadruple therapy. Although previous studies have demonstrated benefit from quadruple therapy (Brown et al 1974) in the patients reported here, this treatment was attended by grave hazards which required discontinuation of the drugs. In Cunningham's (1980) series 2 patients with prolonged oliguria did not respond to anticoagulant therapy. All 4 patients described had prolonged oligo-anuria and this may account for the failure to respond to anticoagulant therapy.

TABLE XXXV

CLINICAL FEATURES IN RPGN

PATIENT	ACE (YRS)	SEX	PEAK B.P.	HAEMATURIA	PROTEINURIA	OLIGO-ANURIA	SKIN LESIONS
1	9	M	150/100	Nil	3+.	Yes	Present
2	11	M	140/100	Microscopic	3+	Yes	Absent
3	4	F	150/100	Nil	+	Yes	Present
4	8	F	180/140	Macroscopic	2+	Yes	Absent

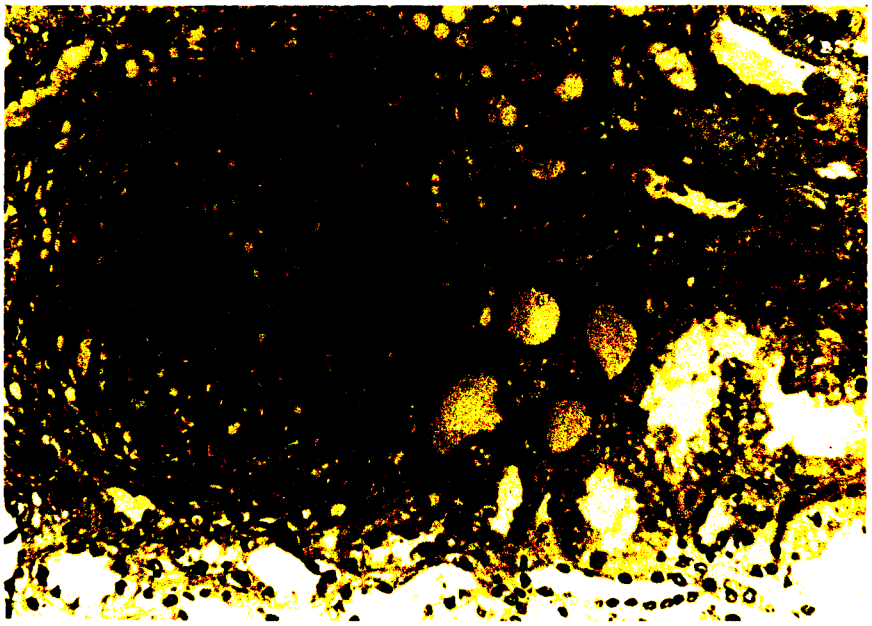
TABLE XXXVI

INVESTIGATIONS AND OUTCOME IN RPGN

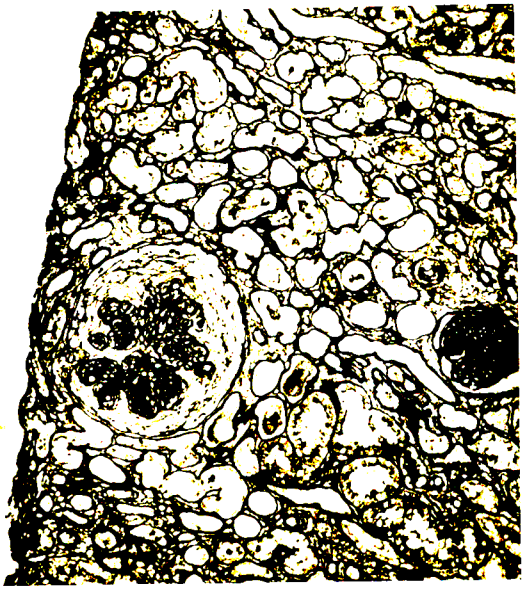
PATIENT	BUN mmol/L	SERUM CREATININE mmol/L	ASOT/ STREPTOZYME	C3 gms/L	FACTOR VIII(%)	% CRESCENTS ON BIOPSY	TREATMENT	OUTCOME
1	58	675	Positive	0,04	156	80	Supportive	Died
2	19	155	Positive	0,68	182	100	Q.C.D.	Died
3	33	580	Positive	0,12	180	80	Q.C.D.	Alive
4	26	508	Positive	0,70	201	100	Q.C.D.	Died

Q.C.D. = Quadruple Chemotherapy

RAPIDLY PROGRESSIVE GLOMERULONEPHRITIS WITH CIRCUMFERENTIAL CRESCENT



Haematoxylin and Eosin Stain, Magnification x 640



Silver methanamine Stain, Magnification x 100

5.13 ACUTE POSTSTREPTOCOCCAL GLOMERULONEPHRITIS AND NEPHROTIC SYNDROME

5.13.1 Introduction

Acute post-streptococcal glomerulonephritis (APSGN) is a very common disease in the Paediatric wards of King Edward Hospital. However, the nephrotic syndrome which may occur in association with APSGN is a rare complication of this disease. (0.3% of cases with APSGN). (Diedericks & Coovadia 1978). This complication in children is mild and transient (Wilson & Heyman 1959). The diagnosis of APSGN was made on criteria which have been described by Hallett et al 1977.

Over the past 4 years, 7 cases of nephrotic syndrome associated with APSGN have been seen. The number of ASPGN seen over this period was 836. The incidence of nephrotic syndrome associated with APSGN is therefore 0.80% at King Edward Hospital.

5.13.2 Patient's Details

The ages of these 7 children ranged from 3 to 11 years and 2 were males. They presented with a 1 to 4 months history of oedema, 1 child had a raised blood urea and 2 had hypertension. These physical signs settled within 1 - 2 weeks of admission in most of the children. Four

children had acute or healed impetigo on admission. The C_3 levels were normal in three patients and depressed in 4. All had raised antistreptolysin O titres or positive streptozyme tests, elevated serum cholesterol levels, low serum albumin and massive proteinuria, (>3 gms/m^2/24 hours). Urine testing revealed significant haematuria in 4 patients.

Biochemical improvement occurred over 4 to 6 weeks. On discharge 4 to 6 weeks after the onset of the disease, the urinary abnormality had settled completely in 1 child and definite improvement had occurred in 5 other patients. One remained nephrotic at 6 weeks after the onset of his illness.

5.13.3 Comment

In a study of APSGN in East African children 4 of (Hutt & White 1964) 24 children (16.6%) developed the nephrotic syndrome. In another study the incidence was 4.5% (Wilson & Heymann 1959). The incidence reported here appears to be extremely low in spite of a high incidence of ASPGN compared to other centres. The outcome in the East African Children (Hutt & White 1964)

was less favourable than the Americal study (Wilson & Heymann 1959). The children in this study appeared to be similar to the American study. The disease appeared to be mild and transient in almost all the patients. Parameters of the disease had settled in most patients by 6 weeks.

The factors responsible for the development of nephrotic syndrome in APSGN are not understood. The nature of the immune response to streptococcal antigens may determine progress from APSGN to the nephrotic syndrome (Diedericks & Coovadia 1978).

5.14 HB_SAg POSITIVE NEPHROTICS

5.14.1 Introduction

Nine of 15 African children with nephrotic syndrome were tested and found to have HB_SAg in their serum. The method used to detect the antigen was the haem-agglutination inhibition test. Only very recently (in 1981) was it possible to detect HB_SAg by radio immuno-assay and unfortunately could not be applied to any of these patients. Detection of HB_SAg is important as it may be associated with the development of membranous nephropathy (Takekoshi et al 1979). The details of the patients are given in Table XXXVII.

5.14.2 Patient Details

Of 15 patients tested 9 were positive for HB_SAg. The majority were males, 6 were over 5 years of age and the histology was variable. Three of 6 patients with membranous nephropathy were HB_SAg positive, and 5 of 8 patients with proliferative glomerulonephritis were HB_SAg positive. Seven patients had moderate to heavy immune deposits on the glomerular basement membrane. Five of the patients were observed for a period of 6 months or more. The outcome was poor in 4 and 1 remitted spontaneously.

TABLE XXXVII

HB_sAg POSITIVE NEPHROTICS

AGE (YRS)	SEX	CARRIER/HEPATITIS	HISTOLOGICAL GROUP	IMMUNOFLUORESCENCE						OUTCOME
				IgG	IgM	IgA	C3	C4	C1q	
4	M	Carrier	Membranoproliferative	+++	+++	+++	+++	+++	+++	Persistent relapse for 6 months
5	M	Carrier	Extramembranous	+++	+++	+++	+++	+++	+++	No follow-up
11	M	Carrier	Extramembranous	+++	-	-	+++	-	+++	Persistent relapse for 60 months
8	F	Carrier	Extramembranous	-	-	-	-	-	-	No follow-up
10	M	Carrier	Diffuse mesangial	-	++	-	++	-	-	No follow-up
9	M	Carrier	Diffuse Endocapillary	-	-	-	-	-	-	Persistent relapse for 16 months
8	M	Acute Hepatitis Carrier	Diffuse Exudative	++	-	-	++	-	-	Relapse for 6 months - spontaneous remission
11	M	Carrier	Diffuse Exudative	-	+	-	++	-	-	No follow-up
3	F	Carrier	Tropical Nephropathy	+++	-	-	++	-	++	Died 14 days after admission

5.14.3 Comment

Patients with extramembranous nephropathy associated with HB_sAg did not differ in their clinical features and outcome from those who were HB_sAg negative (Kleinknecht et al 1979). Membranoproliferative glomerulonephritis has also been associated with Australia antigenaemia (Myers et al 1973, Stratta et al 1975). Only 1 of our patients had membranoproliferative changes.

In South Africa, African children have an HB_sAg carrier rate of 7.4%. (Vos et al 1980). However, the incidence of HB_sAg among the nephrotic children described here cannot be causally implicated, in particular a direct association with extra-membranous nephropathy is not justified.

5.15 HENOCH SCHÖNLEIN PURPURA

5.15.1 Case Report

P.S. was a 5 year old girl who presented 1 month after the onset of her illness. Her illness commenced with a sore throat which was diagnosed as tonsillitis and she was treated with Penicillin. One week later she developed haematuria, abdominal pain with malaena stools and an urticarial rash over the buttocks and extensor surfaces of the arms and legs. She had no joint pains. Three weeks after this she developed oedema and was referred to hospital.

On examination she was noted to have facial, sacral and ankle oedema. The rash had faded and the joints were normal. Her blood pressure was 130/85 with a heart rate of 100/min; the abdomen was normal, the stool on rectal examination was normal and central nervous system was normal. The ear, nose and throat examination were normal.

Urine examination revealed 50 red blood cells per high-power-field and 3 plus proteinuria.

Investigations demonstrated a blood urea 2.1 mmol/L, serum creatinine 50 mmol/L, normal electrolyte pattern, a serum albumen of 18 gms/L, cholesterol 10.92 mmol/L, Hb 11.4, white cell count of 24000/dl

(neutrophils 71%, lymphocytes 23%, monocytes 6%), stool occult blood test was negative, the ASOT was not elevated, the C_3 level was 110 mgs%, serum immunoglobulin levels were as follows IgG 380 mgs%, IgA 168%, IgM 228 mgs%. the glomerular filtration rate was 90 mls/min.

Light microscopic examination of renal biopsy tissue showed a focal proliferative glomerulonephritis and occasional adhesions to Bowman's capsule. Intervening glomeruli were normal. Some of the tubules were dilated and atrophic, some foam cells were present.

Immunofluorescent examination demonstrated course granular deposits of IgA and C_3 on the glomerular basement membrane.

Her progress in the ward was as follows: she gradually lost her oedema, the proteinuria decreased to 1+ on daily urine testing, the blood pressure settled to 100/60 but on discharge she still had biochemical abnormalities of nephrosis. A few months later she was normal clinically and biochemically.

5.15.2 Comment

Henoch-Schönlein Purpura is a disease of childhood.

The peak age incidence occurring between 2 - 8 years. The clinical features are fever, a purpuric skin rash, joint pain with or without swelling, abdominal pain which may be accompanied by malaena, haematuria is a constant feature of renal involvement, proteinuria may be absent (Cream et al 1970).

The incidence of nephropathies in Henoch-Schönlein Purpura is said to vary from 22 - 66% (Habib 1974c). Renal complications are said to occur more often in boys and an upper respiratory tract infection precedes the Henoch-Schönlein Purpura in one third of cases (Habib 1974c). The renal disease is usually mild, the majority of children recovering. Progressive glomerulonephritis may occur in 5 - 10% of children.

The nephrotic syndrome may occur in nearly 50% of cases and is nearly always purely biochemical (Habib 1974c). The appearance of the nephrotic syndrome may vary from an early onset up to 18 to 19 months after the disease (Habib 1974c). The nephrotic syndrome is short-lived, renal insufficiency may occur at the onset as may hypertension. The serum complement is normal. The natural history of the nephropathy is very

variable, however, a permanent nephrotic syndrome indicates poor prognosis (Habib 1974c).

Histologically a number of glomerular lesions are possible, minimal change, diffuse endocapillary glomerulonephritis, endo- and extra-capillary glomerulonephritis membranoproliferative, segmental and focal glomerulonephritis. The prognosis is related to the histological findings.

Immunofluorescence studies typically show IgA, IgG and C_3 mainly in the mesangium but the glomerular basement membrane may be affected.

The aetiology and pathogenesis of this disease is unknown. However, immune mechanisms are believed to be important in tissue injury. Streptococcal infections have been shown to be no more frequent in these patients as compared to controls (Vernier et al 1961). The best evidence for the immune mechanism is the presence of immunoglobulins and complement in the glomerular lesions and the nature of these deposits (McCluskey and Vasalli 1971).

The patient described appeared to have all the features of Henoch-Schönlein Purpura. She was obviously mildly affected and recovered fully. Fortunately she had no recurrent episodes which

would have altered her ultimate prognosis (Habib 1974c). Her illness occurred shortly after an upper respiratory tract infection, her renal lesion appeared early in the course of her illness, the nephrotic syndrome was transient and the histology a favourable one.

Henoch-Schönlein Purpura is rarely seen at King Edward Hospital. There was one other patient, an African boy, who presented as a nephritic, with a fading rash in the typical distribution.

5.16 SYSTEMIC LUPUS ERYTHEMATOSUS

5.16.1 Introduction

Systemic lupus erythematosus (SLE) is relatively rare in children (Habib 1974c). In the period 1960 - 1980, of the 129, 743 admissions to the paediatric wards of King Edward VIII Hospital only 4 Indian children below the age of 12 years were diagnosed as having SLE. At the present time, one patient's records were not available. However, the remaining three had signs and symptoms which complied with the preliminary criteria of the American Rheumatism Associated (Cohen and Canaso 1972). One of these 3 had the nephrotic syndrome.

5.16.2 Case Report

R.M. was a 10 year old Indian girl who presented with a history of headache, swelling of the body and backache for two weeks. She had not been seriously ill previously and had not been taking any medication. There was no relevant family history. On admission she was grossly oedematous with hypertension (170/115 mm Hg) oliguria, chest examination revealed a pneumonia and pleurisy. Investigations were compatible with

nephrotic syndrome and renal failure. They were as follows urea 28 mmol, albuminuria 29 $m/m^2/24$ hours, a normochromic, normocytic anaemia, EST 126, total globulin 28 g/L, albumen 10 g/L, IgG 400 g/L, IgA 75 g/L, IgM 190 g/L, C_3 1 mg %. Fluid overload and a rising blood urea necessitated peritoneal dialysis. Fourteen days after admission a erythematous facial rash with butterfly distribution peri-ungual vasculitis as well as arthritis. The diagnosis of SLE was suspected and supported by the presence of anti-nucle factor in the blood. Skin biopsy of uninvolved skin demonstrated IgM plus C_3. Renal biopsy showed focal glomerulonephritis. The patient was discharged but returned three weeks later in renal failure. Repeat peritoneal dialysis was necessary. On this occasion it was noted that the patient had alopecia and was dis-orientated. Treatment with 80 mg prednisone daily was started. The parents requested discharge and the patient was sent home on the same dose of prednisone. There was little or no response to therapy and she succumbed from renal failure eight months after presentation. This child had therefore SLE and focal glomerulonephritis presenting with a nephrotic syndrome.

5.16.3 Discussion

Indian patients accounted for 8.2% of the 129,743 patients admitted to the paediatric wards in the 20 years 1960 - 1980. However, all 4 children with SLE were Indians and not a single African child presented with this disease in these 2 decades. SLE is generally rare in children (Habib 1974c) and has not been described in an African child in Durban. Stein (personal communication) has a very limited experience of this disease in Black children in Johannesburg. There are some reports from South Africa of SLE in African, Indian and Coloured adolescents and adults (Seedat and Pudifin 1977, Jessop and Myers 1973). SLE does occur in American Negro children but the exact prevalence is unknown (Cook et al 1960).

SLE nephropathy occurs in a situation which includes skin and joint lesions and sometimes other system involvement. The skin and joint manifestations occur in 80% of cases (Habib 1974c). The gravity of the renal involvement and the severity of other system involvement may not parallel each other (Habib 1974c).

The histological changes in SLE are diverse

including minor disorders of the renal parenchyma, segmental and focal nephritis, diffuse porliferative glomerulonephritis and extramembranous glomerulo-nephritis.

It appears that each histological type corresponds to a certain clinical picture and a particular pattern of evolution (Baldwin et al 1970). Similarly Habib (1974c) in her small series of cases found a correlation between the clinical nature, histological type and pattern of evolution. However, renal involvement is not always clinically evident. Fourteen patients in one study (Cook et al 1960) who died and had a post mortem performed had significant histological changes despite the absence of clinical evidence of disease during life.

This young girl presented with severe renal impairment and the nephrotic syndrome but the classical rash and vasculitis appeared only a fortnight later. Yet her renal biopsy revealed focal proliferative changes. This category of SLE is generally regarded as being associated with mild renal disease (Ginzler et al 1980). Hypertension, nephrotic syndrome and renal insufficiency are rare in the focal proliferative

group and the prognosis is said to be good (Habib 1974c). The clinical course of this patient was of rapid decline and death within 8 months of her initial presentation. It is also unusual for the renal aspect of the disease to be the presenting problem (McLean et al 1975).

During the course of her illness this patient did not appear to respond to large doses of steroids. She appeared to have a fulminating form of the disease.

SLE is a systemic disease with exacerbations and spontaneous remissions (Estes & Christian 1971, Jacobs 1963, Cook et al 1960). It is an immunological disease which has an unknown immunopathological basis (Gladman et al 1980, Coovadia et al 1981a. The outcome of the disease is variable and partially influenced by the therapy used (Estes & Christian 1971, Hughes 1979). High doses of steroids may result in bleeding and septicaemia resulting in death (McLean et al 1975).

Moderate to severe renal involvement usually requires more aggressive treatment and steroids in combination with azathiaprine have been advocated. Other immunosuppressive agents have also been used (McLean et al 1975). The most

important guide to treatment is the clinical response. A satisfactory test to monitor disease activity is as yet not available (Caerus et al 1980). Once remission has been induced drug doses are gradually reduced.

6 DISCUSSION

DISCUSSION

The nephrotic syndrome in Africa is a very different disease in childhood as compared to that experienced in other continents. Differences are striking in the incidence, aetiology (in some parts of Africa), histological categories, natural history, prognosis and response to treatment.

In temperate climates the incidence of the nephrotic syndrome is less frequent, the majority of affected children are males under 5 years of age and 80% have minimal change nephrotic syndrome which almost always responds to steroid therapy and has a very low association with uraemia, haematuria and hypertension.

African children in malarial endemic areas suffer from the nephrotic syndrome much more frequently than in non-malarial areas. The evidence for the causal relationship between malaria and the nephrotic syndrome is based on epidemiological (Kibukamusoke et al 1967, Giglioli 1962), clinical, histological, immunological (Hendrickse et al 1972) and experimental features (Houba 1979).

However, in Senegal (Morel-Maroger et al 1975) an histological picture similar to that in quartan malaria nephrotic syndrome (Hendrickse et al 1972) did not demonstrate an association with malaria.

In South Africa where malaria is not of significance, African children with nephrotic syndrome in contrast to children in temperate climates have distinctly different histological findings (predominantly extra-membranous) on renal biopsy, experience a natural history often similar to adults of the same histological categories, tend to be older, have a higher incidence of hypertension, uraemia and haematuria, respond very poorly to conventional steroid and immunosuppressive agents and do less well or badly in certain histological categories.

In marked contrast Indian nephrotic children in South Africa have the typical minimal change nephrotic syndrome as experienced in temperate zones and also in India. (Srivastava et al 1975).

African children in South Africa are most frequently and often severely exposed to conditions of poverty, malnutrition and frequent infections. Indian South Africans, although better off than Africans, also are often subjected to similar living conditions. The nephrotic syndrome however, expresses itself quite differently in these two groups more than can be accounted for by differences in socio-economic status. This suggests that environmental factors are certainly not the only, and most likely not the crucial issues in this

disease. It is possible that many and varied factors both hereditary and environmental play a role in determining the immuno-pathological processes and consequent renal damage in the 2 race groups.

The unexpected findings among African children with the nephrotic syndrome are relevant not only for this disease but also underscore and emphasize another very important observation. The observation which is based on the accumulated experience of different workers in the Paediatric Unit in Durban, is that conventional textbook descriptions of diseases derived mainly from Caucasian children, often do not apply locally. The usual becomes unusual and the common becomes singular. The best example is measles. This is a damaging disease in Africa and much of its severity has been ascribed to the concomitant presence of protein-calorie-malnutrition. However, it has been shown quite clearly that the clinical spectrum and outcome of measles is related to the degree of immune suppression and not nutritional status at the onset of the illness (Coovadia et al 1977). While protein-calorie-malnutrition disturbs immune function and adversely affects the outcome in measles resulting in high morbidity and mortality this is not always the explanation for severe measles. It has been shown that when protein-calorie-malnurition has been carefully excluded, measles

may still be a severe disease in a small number of African children. (Coovadia et al 1978). This poor outcome of measles in the well-nourished African child has been shown to be significantly associated with HLA - AW 32. (Coovadia et al 1981). Accordingly, in addition to environmental factors, there are genetic determinants of severe disease in measles in African children.

Deviations from the expected pattern also occur in haematological malignancies. In leukaemia the acute lymphoblastic subgroup accounts for the vast majority of children with this disease in the west. Myeloid leukaemia is generally held to be rare. In contrast, acute lymphoblastic and myeloblastic leukaemia occur with almost equal frequency in the African child. (Kusman et al 1978, Naidoo 1979). This obviously influences the therapy and outcome for these children, as within specialised units in developed countries acute lymphoblastic leukaemia is emerging as a curable disease.

Hepatosplenic schistosomiasis on the other hand is a relatively benign disease in the African child in Durban. There is firm hepatomegaly predominantly of the left lobe together with splenomegaly. In addition there are raised globulins, mild enzyme derangements and an associated eosinophilia. (Mackenjee et al 1981b). The clinical outcome of this parasitic

infestation seems very different from the severe disease reported from Brazil (Andrade & Rocha 1979) and other parts of Africa (Abdurahman et al 1981) where hepatosplenomegaly with portal hypertension, liver decompensation, severe ascites and oedema in association with renal involvement occurs. In Brazil it has been shown (Bina et al 1978) that Negroes suffered a milder form of the disease than Whites. It was predicted that the disease would also be mild in Africa among races ancestral to the Brazilian negroes on the basis that natural selection would have diminished or eliminated those susceptible to severe bilharzia. The evidence for mild bilharzia in Durban supports this contention. Man, therefore, may be genetically protected from developing severe forms of many parasitic diseases. This is well known for sickle cell disease and malaria (Allison 1954).

In this study, examination of some of the renal biopsy material for schistosoma antigens demonstrated that these could not be implicated as aetiological agents in the glomerulopathy of the African child in Durban, which is an area of endemic schistosomiasis (Schutte et al 1977). It is probable that the nephrotic syndrome due to S. mansoni which has been described in other endemic areas occurs only with the severe form of the disease.

Asthma is rare in rural African children and uncommon in urbanised African children (van Niekerk et al 1979). Similarly neuromuscular diseases are rare in African children. When they occur neurogenic disorders are more frequent than muscular dystrophies and the clinical presentation is often unusual. This contrasts with the emphasis on muscular diseases in Caucasian children (Moosa - personal communication).

It appears that the clinical and pathological expressions of certain diseases as discussed above are influenced by many different factors including genetic components.

Environmental factors, in particular the presence of protein-calorie-malnutrition and the debilitating effect of frequent infections are without doubt of extreme importance and may be pre-eminent in determining some disease patterns.

This study of the nephrotic syndrome is the most detailed examination of these diseases which appear to manifest in unexpected ways in southern Africa. It is also a cautionary note to physicians who tend to generalise from the particular and end up being surprised by the unsurprising. The majority of glomerulopathies appear to be mediated by immunopathological mechanisms. All of the known causes of glomerulonephritis have a background of classical autoimmune disease, infections

or parasitic infestations. Till the present no specific factor or factors have been demonstrated for most of the patients in this study. Well known causative agents such as malaria, schistosomiasis and collagen vascular diseases have been excluded.

Perhaps the aetiology and pathogenesis are not related to one or two factors but rather to the overall host response of the African child to multiple frequent infections. These would produce immune complexes which are not readily cleared from the blood or the kidney resulting in antigen-antibody deposition in the kidney. The Indian child, although exposed to similar conditions, may "handle" the immune complexes more effectively and presents most often as minimal change nephrotic syndrome.

Detailed further studies into HLA associations, factors in the residential environment parasitic and bacterial burdens, natural history and effective therapy need to be undertaken.

ADDENDUM

The uniform pattern of obvious glomerular lesions seen in Black children in Africa with the N.S. which has been the main thrust of this thesis has been complicated by a recent, fairly small sample of Ghanaian children (Adu et al 1981, Quarterly Journal of Medicine, 50, 297) who had a surprisingly high incidence (56%) of MCNS by light microscopy only, which in addition responded to steroids. While this interesting finding warrants further study it is at present diminished by a lack of precise detail and long term follow-up.

7. RECOMMENDATIONS

RECOMMENDATIONS

1. Biopsy

The most pertinent question now is whether renal biopsies are in fact indicated in African children. It has been firmly established that the histology is either of the membranous or proliferative groups and that steroids are of no value in altering the course of the disease. The only available form of treatment is supportive. Of greater benefit to the patient would be to establish the pathogenesis of the glomerular lesions and attempt newer forms of therapy.

2. Immunological Aspects

a) HLA typing may be important in indicating genetic markers in patients who are at risk for the development of the nephrotic syndrome.

b) T cell function, in particular suppressor cell function, in the African as compared to Indian.

c) Establish that circulating immune complexes are present in the nephrotics studied. Immune complexes are deposited on the glomerular basement membrane in the majority of the African patients and the possibility of the development of auto-antibodies has been considered.

d) Isolation of a causative antigen in the patients discussed appears an impossible task for the present and would probably not be worthwhile.

3. Therapeutic

a) Plasma Exchange

If circulating immune complexes are established as pathogenetic in our studies, plasma exchange will be considered. A carefully controlled study with good sequential monitoring of patients would enable a reliable assessment of the role of plasma exchange in obvious glomerular lesions where the conventional forms of therapy have failed.

Plasma exchange is now being widely used for a number of conditions (Pinching 1978), in particular for fulminant glomerular diseases, namely Good Pastures syndrome and rapidly progressive glomerulonephritis. Not only is this of possible therapeutic value but could provide the means to study pathogenetic factors in this disease.

As was discussed in the pathogenesis of schistosomiasis a heavy load of immune complexes may saturate the RES and inhibit or reduce the

capacity of the RES to clear antigen or immune complexes. Removal of plasma reduces the load for the RES which may then recover the ability to clear antigen or complexes (Lockhood - quoted in article by Pinching 1978).

b) Drugs

Antiplatelet drugs have been used in certain glomerular diseases e.g. rapidly progressive glomerulonephritis (Cameron et al 1975) with some encouraging results. Whether platelets are involved in the primary pathogenic process or are secondarily involved in response to the vascular injury occurring in the nephritic process is not perhaps so important as the fact that once platelets are stimulated they exacerbate the vascular damage.

The most recent, most potent antiplatelet agent is prostacyclin which prevents platelet activation.

8. APPENDIX

8.1 Tables of Patients' Details

ABBREVIATIONS USED IN TABLES IN APPENDIX

HT	=	Hypertension
H	=	Haematuria
R.F.	=	Renal Failure
Creat	=	Creatinine
chol	=	Cholesterol
Alb	=	Albumen
glob	=	Globulin
TP	=	Total Protein
Hb	=	Haemoglobin
WCC	=	White Cell Count
GFR	=	Glomerular Filtration Rate
ASOT	=	Antistreptolysin O Titre
ANF	=	Antinuclear Factor
Treat	=	Treatment
S	=	Steroids
E	=	Cyclophosphamide
C	=	Chlorambucil
N/G or O	=	Not Given
+	=	Response
-	=	No Response
$\pm$	=	Equivocal
D	=	Duration
R	=	Relapse
PP	=	Persistent Proteinuria
SR	=	Spontaneous Remission

UTI	=	Urinary Tract Infection
TT	=	Trichiuris Trichiuria
FR	=	Frequent Relapses
SE	=	Single Episode

NB GFR = Not all the figures were recorded as corrected for age of patients but were within the normal range. Those figures in the unclassified group have been corrected.

INDIAN MINIMAL CHANGE NEPHROTIC SYNDROME – SINGLE EPISODE

Pt	Age (yrs)	Sex	HT	H	RF	Urea μmol/L	Creat. μmol/L	Chol. mmol/L	Serum Protein Alb	Glob	TP	Hb gms/dl	WCC X10^9	GFR mls/min	ASOT	C_3 mg%	C_4 mg%	CH_{50} mgs%	ANF	LE cells	HB_sAg	Immunofluorescence	Treat. S	E	Follow-up (month) D		Miscellaneous
AM	1.5	M	–	–	–	2.4	–	14	–	–	–	12.7	9.7	–	–	72	–	–	–	–	–	No deposits	–	N/G	42	SE	–
KS	3	M	–	–	–	3.4	–	10.1	11	24	35	11.3	20	–	–	44	–	–	–	–	–	No deposits	+	N/G	44	SE	Measles on S – Rem
SG	1.5	M	–	–	–	2.5	60	10.4	–	–	–	12.1	15	26	< 166	94	–	–	-ve	–	–	Light IgM in mesangium	+	N/G	73	SE	Febrile convulsions
PS	7	F	–	–	–	4.8	–	11.1	7	26	33	15	24	–	< 166	98	–	–	-ve	–	–	No deposits	–	+	67	Relapse for 1 year	Cushingoid Alopecia, UTI, Klebsiella pneumoniae
PC	9	F	–	–	–	3.1	55	10.5	28	34	62	13.6	12	–	–	102	–	–	–	–	–	No deposits	+	N/G	4	SE	Cushingoid
AA	4	F	–	–	–	2.5	65	7.8	22	36	58	10.4	11	–	100	96	–	–	–	–	–	No deposits	+	N/G	26	SE	–
ES	3	M	–	–	–	5.5	45	8.9	14	23	37	12.4	9	52	< 166	–	–	–	-ve	-ve	–	No deposits	+	N/G	34	SE	–
VM	7	F	–	–	–	4.9	–	–	27	28	55	13.0	11.5	89	–	–	–	–	–	–	–	No deposits	+	N/G	20	SE	Chicken pox in relapse on S – remitted
RM	10	M	–	+	–	1.7	60	11.2	–	–	–	6	12	–	–	50	28	–	–	–	–	No deposits	–	N/G	11	Persistent proteinuria and haematuria.	
TD	11	M	–	–	–	11	–	17.9	8	33	41	15.7	13	27	< 166	150	–	–	–	-ve		–	+	N/G	4	SE	–
JA	9	M	–	–	–	3.3	–	9.6	13	31	44	16.2	16	–	–	–	–	–	–	–	–	–	–	+	7	SE	–
DM	3	F	–	–	–	2.1	75	11.2	6	40	46	11.6	7	40	< 166	262	–	–	-ve	-ve	–	–	+	N/G	54	SE	–
AP	9	M	–	–	–	3.5	125	12.48	9	36	45	11.7	11	–	< 166	230	–	–	-ve	–	–	–	+	N/G	3	SE	–
SI	3	F	–	–	–	2.9	55	–	12	29	41	11.8	12	26	< 166	140	–	–	-ve	-ve	-ve	Weak deposits IgG, IgM, IgA	N/G	N/G	72	SE	Spontaneous remission
FN	4.5	M	–	–	–	3.9	55	26.1	3	30	33	15.5	15	30	–	160	–	–	-ve	–	–	–	+	N/G	72	SE	–
JG	2.5	F	–	–	–	3.8	35	9.4	29	32	61	10.9	13	–	<166	112	–	–	-ve	-ve	-ve	No deposits	+	N/G	65	SE	UTI – E. coli, tonsillitis
INDIAN MINIMAL CHANGE NEPHROTIC SYNDROME – MULTIPLE EPISODES																											
DN	4.5	M	–	–	–	2.1	80	12.4	11	26	37	15.4	10.4	–	–	90	56	–	–	-ve	–	Fine IgM	+	+ C+	18	2 episodes C+	C for severe S Toxicity Alopecia dark nails, URTI, diarrhoea – relapse
RM	4.5	M	–	–	–	3.2	–	10.9	17	26	43	13.5	3.2	–	–	–	–	–	–	–	-ve	Light IgM, IgG + C_3	+		10	2 episodes	
SS	3.5	M	–	–	–	4.8	60	13.7	9	23	32	13.0	14	–	–	102	–	–	–	–	-ve	Light IgM	+	±	53	2 episodes	Severe S Toxicity, UTI, (Klebsiella pneumoniae)
DS	4	M	–	–	–	4.2	50	16.7	9	27	36	13.3	18	40	–	144	–	–	-ve	–	–	No deposits	+		53	2 episodes	–
FM	5	M	–	–	–	5.3	35	11.4	12	30	42	13.5	19	64	<166	98	–	–	–	–	-ve	No deposits	+		31	2 episodes	Cushingoid
PG	8	M	–	–	–	13.5	60	13	13	23	36	12.8	10	44	<166	120	–	–	–	–	-ve	No deposits	+		122	2 episodes	Severe S Toxicity, Oral moniliasis.
SN	3	F	–	–	–	5.7	–	10.2	15	34	49	10.0	30	18	–	98	52	76	–	–	–	No deposits	+	–	18	Initially S– 12 relapse – S+	Initially E. coli Sept. UTI (Klebsiella pneumoniae) on E – septic arthritis. Calcified hilar glands.
VS	8	F	–	–	–	–	–	10.9	9	31	40	13.0	12	27	<166	190	–	–	-ve	-ve	–	No deposits	+		12	2 episodes	URTI E.coli UTI
LM	7	M	–	–	–	1.7	–	–	–	–	–	13.4	15	–	<166	–	–	–	–	–	–	–	+		33	2 episodes	Measles with initial presentation, rem. spont. Later R.
SM	7	M	–	–	–	2.8	6.5	14.3	13	35	48	13.9	90	–	<166	98	–	–	–	-ve	–	–	±		17	2 episodes	–
TN	11	F	–	–	–	1.6	–	14.7	17	23	40	16.6	16	–	-ve	96	26	48	–	–	-ve	Light IgM + C3	+		42	3 episodes	Cushingoid HTT. PTB, INH neuritis. Bulbar palsey.
AN	3	M	–	–	–	5.6	80	10.8	8	31	39	10.3	11	18	<166	230	–	–	–	-ve	–	–	+	0	120	3 episodes	Measles in R.

INDIAN MINIMAL CHANGE NEPHROTIC SYNDROME – MULTIPLE EPISODES

Pt	Age (yrs)	Sex	HT	H	RF	Urea mmol/L	Creat. µmol/L	Chol. mmol/L	Serum Protein Alb	Glob	TP	Hb gms/dl	WCC X10^9	GFR mls/min	ASOT	C_3 mg%	C_4 mg%	CH_{50} mgs%	ANF	LE cells	HB_sAg	Immunofluorescence	Treat. S	Treat. E	Follow-up (month) D		Miscellaneous
SM	3	M	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	No deposits	0		30	4 episodes	–
SZ	5	M	–	–	–	16	–	12.48	10	32	42	14.2	–	–	–	>1	–	–	–ve	–	–ve	No deposits	+		36	4 episodes	–
AP	2	M	–	–	–	2.4	105	20.5	8	30	38	13.4	13	48.75	< 166	–	–	–	–ve	–ve	–	–	+		91	10 episodes	Peritonitis 7 years after onset of Rem.
JS	6	M	–	–	–	3.3	–	17.8	4	34	38	11.8	13	39	< 166	–	–	–	–ve	–ve	–	No deposits Light IgM	±		120	6 episodes	URTI, Amoebic dysentery.
RR	4	M	–	–	–	8.0	–	25	40	48.4	44	12.1	9	–	< 166	100	–	–	–	–	–	–	+		33	4 episodes	Died, meningitis – no organism on S.
																						INDIAN MINIMAL CHANGE NEPHROTIC SYNDROME – FREQUENT RELAPSERS					
NG	5	M	–	–	–	–	–	–	24	31	55	12.8	4.2	–	–	–	–	–	–	–	–	Fine granular IgM	+	–	60	FR	Chicken pox in R (no S). Remitted. Alopecia.
IS	12	M	–	–	–	5.0	50	7.12	5	42	47	12.0	13.4	–	–	–	–	–	–	–ve	–	No deposits	+ C+	–	36	FR	Pneumococcal pelvis abscess on S. Klebsiella pneumoniae, buttock abscess in Remission. Otitis media
DG	6.5	M	–	–	–	2.3	–	11.49	13	29	42	12.7	2.3	–	–	126	84	111	–ve	–	–ve	Light IgM	+	+	41	FR. (24 mths after E)	URTI before R. Chicken pox in R on S.
SS	3	F	–	–	–	4.8	–	14.9	10	32	42	12.3	4.8	–	–	88	–	–	–ve	–ve	–ve	Light IgM	+	+	40	FR. (15 mths after E)	Haemorrhagic chicken pox on S – Severe measles pneumomiae on E.
SM	3	F	–	–	–	12.4	–	16.25	14	32	46	12.4	12.4	–	–ve	–	–	–	–	–	–	–	+	–	120	FR	
SR	2	M	–	–	–	2.4	–	38	10.5	29.5	40	15.7	16	50	–ve	136	–	–	–ve	–ve	–	Scanty IgM + C_3 on GBM	+	+	46	FR (20 mths after E)	Cushingoid Alopecia dark nails. URTI. Otitis media.
NP	4.5	M	–	–	–	2.8	105	10.4	18	25	43	12.8	11	34	–ve	154	38	–	–ve	–ve	–	No deposits	+	+	63	FR (32 mths after E)	Cushingoid Alopecia dark nails.
LN	2	M	–	–	–	3.5	–	21.5	8	24.9	33.1	13.2	5	53	< 166	190	–	–	–ve	–ve	–	No deposits	±	+	122	FR (30 mths after E) Subsequent relapse.	Chicken pox not on S. Cushingoid Herpes Zoster on E.
PG	6	M	–	–	–	12	–	22.8	23	11	34	13.8	9	–	< 166	155	–	–	–ve	–	–	–	+ C+	+	79	FR (34 mths after E)	Haemophilus influenza. Cushingoid.
SG	1.5	M	–	–	–	5	90	9.62	12	36	48	10.6	9	–	< 166	240	–	–	–	–	–	No deposits	+	+	103	FR (53 mths after E) Subsequent episodes S+	Cushingoid
PP	8	F	–	–	–	8.1	65	7.0	18	36	54	15.6	13	–	12	–	–	–	–	–	–	–	+	+	29	FR	Not seen after E.
MG	3	M	–	–	–	6.2	–	15.6	–	–	–	12.7	27	–	–	–	–	–	–	–	–	–	+		15	FR	–
PO	5.5	M	–	–	–	11	–	10.9	–	–	–	12.8	9	–	< 166	–	–	–	–	–	–	No deposits	+ C+	± (24m)	87	FR	

AFRICAN MINIMAL CHANGE NEPHROTIC SYNDROME

Pt	Age (yrs)	Sex	HT	H	RF	Urea mmol/L	Creat. μmol/L	Chol. mmol/L	Serum Protein Alb	Glob	TP	Hb gms/dl	WCC X10^9	GFR mls/min	ASOT	C_3 mg%	C_4 mg%	CH_{50} mgs%	ANF	LE cells	HB_sAg	Immunofluorescence	Treat. S	Treat. E	Follow-up (month) D	Follow-up (month) R	Follow-up (month) PP	Follow-up (month) SR	Miscellaneous
AN	8	M	–	–	–	3.8	–	7.8	10	32	42	9.2	14	56	–ve	136	–	–	–	–ve	–	–	–	N/G	16	3		13	
NM	7	F	–	–	–	5.0	–	13.39	14	35	49	13.8	13	29	–ve	88	46	39	–	–	–ve	No deposits	–	N/G	8	4	4		
OG	8	F	–	+	–	2.8	–	12.22	5	36	41	13.6	7	17	<166	130	–	–	–ve	–ve	–	Scanty IgG + IgM, IgA (mesangial)	–	N/G	48	11	25	12	
XM	2	M	–	–	–	3.1	33	12	19	36	55	12.4	9	22	320	122	–	–	–	–ve	–ve	Heavily, finely, granular IgG. Scattered C_{1q}	N/G	N/G	8	1	7		
DZ	8	M	–	+	–	3.4	–	8.03	12	32	44	12.6	9	–	–ve	116	–	–	–	–	–	No deposits	–	N/G	42	9,3	8	2,20	
LN	5	F	–	+	–	2.4	–	11.67	11	37	48	12.7	11	56	–ve	144	–	–	–	–	–ve	Coarsely granular deposits IgG, C_{1q}, IgA.	N/G	N/G	15	4		11	
RN	7	M	–	–	–	3.1	–	8.7	40	22	66	12.4	17	60	<166	175	–	–	–ve	–ve	–	–	–	N/G	99	4,1	8,4	24,48	
JG	1.5	M	–	–	–	2.0	–	8.18	11.5	19	30.5	10.6	10.9	–	–ve	92	52	139	–ve	–ve	–ve	No deposits	–	–	12	9	3		
BM	7	M	–	–	–	4.5	45	9,05	8	39	47	9.6	14	–	–ve	–	–	59	–ve	–ve	–ve	Focal IgM	N/G	N/G	<1				
MD	7.75	M	–	2+	–	–	47	7.78	14	31	45	12.7	11.0	68	–ve	94	72	–	–ve	–	–	Light deposit of IgM	N/G	N/G	<1				
TM	3.5	F	–	–	–	2.7	70	9.42	12	31	43	11.0	12.7	–	–ve	170	–ve	104	–	–	–ve	No deposits	–	–	12	12			
NC	2.25	M	–	–	–	3.6	–	13.25	12	33	45	9.4	10	–	–ve	90	108	–	–	–	–ve	No deposits	N/G	N/G	36	2,3	4		
JD	7	M	–	–	–	3.0	38	10.5	10.6	47	57.4	–	–	72	–	188	88	–	–ve	–	–	No deposits	–	N/G	12	12			
SJ	11	M	–	–	–	2,1	65	15,61	10	31	41	12.7	10.2	–	–ve	84	36	43	–ve	–ve	–	Heavy coarse IgG, IgA, IgM, C_{1q}	+	N/G	7	1		6	
NM	11	F	–	–	–	7.3	–	12,95	17	33	50	14.9	6.5	11	–	110	48	86	–ve	–	–	No deposits	N/G	N/G	<1				
															AFRICAN – EXTRAMEMBRANOUS													
BL	7	M	–	–	–	7.5	–	11.96	12	–	–	19.8	21	93	<166	49	–	–	–	–	–	–	0	0	30	8		22	Calcified hilar glands
CL	2.5	M	–	–	–	2.2	132	8.3	18	30	48	11.4	8	–	<166	122	–	–	–	–	–	Granular IgG, C_3	0	0	3			15	–
TM	3	F	–	–	–	2.8	36	9.7	18	3	–	11.8	11	45	<166	60	–	–	–	–	–	Heavy coarse IgG, C_{1q}, light IgM, IgA, C_3.	–	0	3	3			–
DM	8	M		+	–	4.6	100	13.8	17	55	–	8.8	–	134	<166	170	–	–	–ve	–ve	–	Heavy coarse IgG, C_3 Weak IgM, C_{1q}, C_4	0	0	60	60			E. coli UTI, 3 biopsies – progressive lesions.
SM	5	M	–	–	–	6.5	45	24	17	–	–	12.0	11	–	50	70	–	–	–ve	–	+ve	Heavy IgG, C_3, C_4. Light IgM, C_{1q}.	0	0	3	3			–
NB	8	F	–	–	–	2.8	–	14.4	13	35	48	12.2	12	37.5	–	105	–	–	–	–	+ve	–			0				–
TN	10	F	+	–	–	8.1	65	9.3	14	28	42	13.5	9	28	<166	175	–	–	–	–	–	–	–	0	64	5.9	15	20.5	UTI
LS	11	F	–	+	–	3.5	55	9.2	15.1	28.9	44	12.7	4.2	–	<166	72	–	–	–ve	–ve	+ve	Heavy coarse IgG, C_3 Minimal focal IgG, IgM, C_3.	–	–	60				Epilepsy fungal infections 2 biopsies progressive.
TS	11	M	–	+	–	3.5	45	12.8	25	38	63	11.6	11	–	<166	76	–	–	–	–	–	Heavy granular IgG, C_3. Weak IgM	0	0	48		48		UTI (E.coli) cellulitis (R) foot.
TT	9	M	–	–	–	2.0	–	12.4	12	40	52	11.3	9	47	–ve	–	–	–	–ve	–ve	–	Coarsely granular IgG. Light C_4.	0	0	4	4			–
CG	7	M	–	+	–	3.0	35	10.6	12	32	44	11.4	9.4	70	–ve	62	26	–	–	–	–	Moderate IgG, C_{1q}, C_3	0	0	6	6			E. coli peritonitis pelvic abscess.
LL	9	M	–	+	–	7.0	60	7.9	13	42	55	11.5	11	–	–	70	28	–	–ve	–	–	Discontinuous IgG, IgM, + C_3	0	0	15	6	9		Pneumococcal peritonitis. S. haemotobium in urine.

AFRICAN – EXTRAMEMBRANOUS

Pt	Age (yrs)	Sex	HT	H	RF	Urea mmol/L	Creat. µmol/L	Chol. mmol/L	Serum Protein Alb	Glob	TP	Hb gms/dl	WCC X10^9	GFR mls/min	ASOT	C_3 mg%	C_4 mg%	CH_{50} mgs%	ANF	LE cells	HB_sAg	Immunofluorescence	Treat. S	Treat. E	Follow-up (month) D	R	PP	SR	Miscellaneous
SM	5	F	–	+	–	5.9	–	22.2	15	33	48	8.6	2	49	–ve	88	36	–	–ve	–	–	–	0	0	16	3	8	5	–
SM	6	M	–	–	–	4.5	–	9.67	12	43	55	12.1	–	–	–	–	–	–	–ve	–ve	–	Heavy granular IgM, IgG, C_3. Tubular C_3.	0	0	9	2	7		–
WG	3	M	–	–	–	5	–	13.8	15	13	46	11.8	19.1	66	–ve	56	26	–	–ve	–ve	–ve	Heavy IgG granular IgM, C_{1q}, C_3, C_4.	0	0	3	3			–
BP	8	M	+	–	–	2.8	–	8.0	43	34	77	11.4	16	54	<166	190	–	–	–ve	–	–	–	+	0	54	6		48	HPT 6 months after Rem.
PM	5	M	–	+	–	7.0	2.4	10.8	13.3	34.7	47	9.7	12.5	56	–	62	44	–	–	–ve	–	Scanty IgG, IgM, C4.	0	0	10		10		–
SN	8	F	+	+	–	4.4	–	9.19	15	35	50	12.2	1.5	–	–	110	34	–	–	–ve	–	Heavy IgM, C_{1q} + C_3	0	0	15	15			–
TN	6	M	–	+	–	6.5	–	11.18	13	4	17	12.1	9	42.6	<166	92	–	–	–ve	–ve	–ve	Coarse granular IgG, IgM. Heavy C_{1q} + C_3.	0	0	45	9	33		HPT when last seen.
KS	5	M	+	+	–	3.3	–	14.3	11	34	45	12.6	13.2	50	–	15	36	–	–ve	–ve	–ve	Heavy IgG + C_3. Moderate IgA, C1q + C_4.	0	0	6	2	4		–
VM	1	M	–	+	–	3.1	0.6	10.4	10	44	54	7.5	9	–	–	78	–	–	–ve	–	–	–	0	0	72	Repeated episode.			Initial E.coli UTI, measles in rel – no response. Chicken pox – no response, Shigella, dysentery.
AK	10	M	–	+	–	6	–	–	29	40	69	11.9	9.1	82.8	<166	16	–	–	+ve	–	–	–	0	0	4				Hepatosplenomegaly. Heaf gr. IV. S. typhimurium enteritis. Liver biopsy – ? bilharzia.
BN	8	F	–	–	–	4.6	–	14.3	13	35	40	12.2	12	37.5	–	105	–	–	–	+ve	–	–	0	0	2.5	1	1.5		–
TG	11	M	+	–	–	5.0	1	12.2	26	30	56	13.0	11	–	<166	195	–	–	–	–ve	–	Granular IgM, IgA, IgG + C_3.	+	0	5	0.5		4.5	–
DH	11	M	+	–	–	9	–	14.3	8	33	41	11.8	17	–	–	143	–	–	–ve	–	–	Granular IgM	0	0	3	3			–
MN	5	M	–	+	–	4.6	–	12.3	17	23	40	13.1	11	55	<166	80	–	–	–ve	–ve	–	IgM, IgA, IgM	0	0	48				PTB
RN	4	M	–	–	–	–	0.5	–	17	40.6	57.6	11.5	8.8	–	–	190	–	–	–ve	–ve	–	No deposits	0	0	3				–
LC	5	M	–	+	–	9.5	–	9.88	11	34	45	12.1	8	–	<166	100	–	–	–	–	–	Coarse heavy IgG, IgM, IgA, C_3 + C_4.	0	0	4.5			0.5	–
TS	4	M	–	–	–	–	–	–	28	–	–	–	–	–	–ve	–	–	–	–	–	–	–	0	0	0				–
OD	7	M	–	–	–	2.6	–	9.1	17	41	58	12.7	7	–	–	–	–	–	–ve	–	–	–	0	0	3.5	3.5			–
SM	10	M	–	–	–	4.6	–	12.74	10	0	–	11.8	11	–	<166	74	–	–	–	–	–	Coarse granular IgG, IgM + C_3.	0	0	1	1			–
SD	2	M	–	+	–	6.8	–	10.23	14	23	37	12.8	1.5	36	<166	99	–	–	–ve	–ve	–	–	+	0	60	2		58	–
RK	5.5	M	–	–	–	2.1	–	23.0	9	33	42	13.1	19	–	<166	–	–	–	–ve	–ve	–ve	–	+	0	3				2 admissions. Died 4 days after commencing steroids.
AFRICAN													DIFFUSE	MESANGIAL	PROLIFERATIVE														
NM	3	M	+	+	–	10	35	18.46	7	25	32	12.2	13	19.51	<166	100	–	–	–ve	–ve	–	Focal IgM in mesangium.	N/G	N/G	6	6			–
MM	4	F	–	+	–	6.8	–	13.26	21	33	54	10.4	10	16.5	<166	270	–	–	–ve	–ve	–	–	–	0	1				–
TS	4	F	–	–	–	3.6	45	8.7	17	27	44	12.1	11	31	–ve	72	–	–	–	–	–	Heavy granular IgG, C_3, C_{1q}.	N/G	N/G	24	4	5	15	–

DIFFUSE MESANGIAL PROLIFERATIVE

Pt	Age (yrs)	Sex	HT	H	RF	Urea mmol/L	Creat. µmol/L	Chol. mmol/L	Serum Protein Alb	Glob	TP	Hb gms/dl	WCC X10^9	GFR mls/min	ASOT	C_3 mg%	C_4 mg%	CH_{50} mgs%	ANF	LE cells	HB_sAg	Immunofluorescence	Treat. S	Treat. E	Follow-up (month) D	Follow-up (month) R	Follow-up (month) PP	Follow-up (month) SR	Miscellaneous
AFRICAN																													
ZM	8	F	+	+	–	9.0	70	24.2	5.7	25.2	30.9	12.2	9.4	–	200	82	30	80	–	-ve	–	IgG, C_3 in mesangium.	N/G	N/G	3	3			–
EZ	10	M	+	+	–	3.0	55	11.6	6.6	15	21.6	13.5	9	–	–	70	4	96	–	–	+ve	IgM + C_3 on GBM and mesangium.	N/G	N/G	3	3			AN present, HB_sAg + PTB
TN	2	M	–	–	+	3.3	40	–	10	28	38	10.8	6.3	26	–	90	66	–	–	–	–	–	0	0	1				–
MN	9	M	–	–	–	3.1	–	13.3	15	45	60	13.4	13	25	–	102	72	–	-ve	–	–	Finely granular IgG, IgM, C_3, C_{1q} in mesangium.	0	0	54	8	37	9	Heaf Grade IV.
INDIAN																													
IP	8	F	–	–	–	6.3	60	8.88	22	34	56	9.7	10	–	644	–	–	–	–	–	–	Weak IgM + C_3 in mesangium	+	N/G	18	1		17	–
FK	9	F	–	+	–	4.3	121	9.76	–	–	–	11.7	7.0	–	–	123	–	–	–	–	–	Granular IgM, C_3 in mesangium.	N/G	N/G	12		12		Urinary tract infection.
RG	10	F	–	–	–	5.9	132	9.1	9	26	35	13.6	11	66	<166	97	–	–	-ve	–	–	–	+	N/G	12	1		11	–
AM	2.5	M	–	–	–	1.3	40	8.16	12.3	34.7	47	13.4	11	–	<166	138	–	–	-ve	-ve	-ve	IgM in mesangium	–	N/G	27	Fluctuated between relapse and proteinuria			Recurrent upper respiratory tract infection.
															DIFFUSE ENDOCAPILLARY														
PM	12	F	+	+	–	2.5	–	16.7	12	31	43	13.4	9.5	91	<166	120	–	–	-ve	-ve	–	1. IgM weak IgG, IgA, C_3, C_4, C_{1q}. 2. Granular IgA, IgG, IgM, C_{1q}, C_3, C_4.	N/G	N/G	84	48	36		Neurofibromatosis. Short stature. Endocrine function normal.
AM	11	F	–	+	–	2.8	–	–	–	–	–	–	–	41	–	–	–	–	–	–	–	–	N/G	N/G	24	2	24		–
SM	10	M	–		–	3.6	–	–	7	20	27	–	–	81	<166	123	–	–	-ve	-ve	–	–	N/G	N/G	16		16		–
JS	9.5	M	–		–	4.3	45	9.3	9.4	19	29.1	12.5	2.7	–	–	–	–	–	-ve	-ve	–	Heavy granular IgG, IgM, lighter C_{1q}, C_3, C_4.	N/G	N/G	–		–		–
BS	8	F	–		–	4.2	–	15.2	8.7	22	30.7	12.9	9.4	–	-ve	124	94	196	–	–	+ve	No deposits	N/G	N/G	7		7		–
TB	9	M	+		–	6.7	–	7.36	21	43	64	–	–	–	-ve	100	38	0	–	–	–	Light C_3.	N/G	N/G	1		1		–
SK	3	F	–	–	–	7.7	45	10.14	9.7	53.3	63.0	10	9.1	–	<166	54	56	70	–	–	–	IgG, IgM, IgA, C_3, C_4, C_{1q}.	N/G	N/G	96		96		Old PTB. Cirrhosis – severe ascites. Died Postmortem: Staph. aureus sept., pyaemic abscesses in lung and liver. PI 20, terminally.
AFRICAN															DIFFUSE EXUDATIVE														
MN	4	F	–	–	–	2.6	–	26	19	32	51	12.8	6	–	<166	–	–	–	-ve	-ve	–	Granular IgM +	N/G	N/G	–		–		–
SS	9	M	+	+	–	9.5	106	6.8	20	–	–	7.9	9	22	<166	507	–	–	-ve	-ve	–	Weak gran. dep – IgM.	N/G	N/G	3		3		–
MD	11	M	+	–	–	10.0	–	9.0	12	2	55	10.3	6	–	800	80	–	–	–	–	+ve	Moderate C_3, IgM on GBM.	N/G	N/G	23	23			Scabies AGN HFT x 4/7 Haem. Urea.
MS	8	M	–	–	–	21.5	–	–	–	–	42	14.2	10	–	-ve	104	–	–	–	+ve	–	Gran. deposits IgG, C_3 in all, glom.	N/G	N/G	30	6		24	Bilat – pleural effusion Hepatitis – 1977.

DIFFUSE EXUDATIVE

Pt	Age (yrs)	Sex	HT	H	RF	Urea mmol/L	Creat. µmol/L	Chol. mmol/L	Serum Protein Alb	Glob	TP	Hb gms/dl	WCC X10^9	GFR mls/min	ASOT	C_3 mg%	C_4 mg%	CH_{50} mgs%	ANF	LE cells	HB_sAg	Immunofluorescence	Treat. S	Treat. E	Follow-up (month) D	R	PP	SR	Miscellaneous
AFRICAN																													
MS	9	F	–	+	–	6.0	–	7.12	–	–	–	11.3	8	–	<166	114	–	73	-ve	–	–	IgM, C_{1q}, C_4, IgG, C_3.	N/G	N/G	42	3	9	30	AN no HPT ↓C_3 1 x 3/52 Asot +ve.
CN	11	F	–	–	–	–	–	8.7	21	30	51	5.7	15	60	250	41	–	–	–	-ve	-ve	IgM + C_3.	N/G	N/G	0				Hepatic bilharziasis. Haem. E.coli urinary tract infection.
DC	10	F	+	–	–	11	90	11.7	15	10	25	14.8	12	86.25	<166	145	–	–	–	-ve	–	–	N/G	N/G	0				–
MR	10	M	–	–	–	2	–	13.0	1.5	1.0	2.5	–	–	58	-ve	–	–	–	–	–	–	IgG smooth linear deposits – IgM focal granular deposits.	–	–	0				–
KS	5	F	–	+	–	10.8	–	–	21	32	53	3.1	7.9	40	-ve	118	–	96	–	–	–	IgM + C_3 on GBM	–	–	0				
INDIAN																													
AB	13	M	–	+	–	5.6	–	8.45	12	29	41	11.6	8	30	<166	–	–	–	–	–	–	–	N/G	N/G	12		12		E.Coli UTI
MEMBRANO-PROLIFERATIVE																													
AFRICAN																													
MM	5	M	–	+	–	2.8	45	15.5	7.7	17.3	25	11.4	10	–	–	52	46	–	–	-ve	–	IgG, IgM, IgA, C_3	N/G		3	–	3		Left pleural effusion.
KM	8	F	–	–	–	4.0	73	17.3	21	37	58	11.5	5	49.3	<166	138	–	–	-ve	-ve	–	–	–		1	1			–
BM	11	M	+	–	–	2.1	–	–	21	4	61	8.5	–	30.8	<166	83	–	–	–	–	–	Granular IgM, IgG and complement.	N/G		2		2		–
ZN	4	F	–	+	–	4.5	–	9.6	8	33	41	11.1	3.4	–	–	–	–	–	–	–	–	–	–	–	8	8			–
MK	4	M	–	+	–	5	33	11.83	10	30	40	12.8	7	–	–	170	–	–	-ve	-ve	–	–	N/G	N/G	5	5			–
DB	2	M	–	–	–	3.3	–	8.71	9.0	28	37	9.2	20	–	<166	96	–	–	–	-ve	–	–	–	–	3		3		–
ZM	9	M	–	–	–	4.0	74	11.9	11.8	35.2	47	9.5	7.8	–	–	74	50	–	-ve	–	–	Finely granular IgG, IgM, IgA, C_3.	N/G	N/G	1		1		–
SM	4	M	–	–	–	3.1	39	18.8	11.4	35.7	47.1	11.4	22	–	–	94	–	–	–	–	+ve	Coarsely granular dep of IgM, IgG, IgA, C_3, C_4, C_{1q}.	N/G	N/G					TB lymphadenitis groins . and pelvis. (R) ectopic kidney.
AS	10	M	–	+	–	4.4	48	4.16	15.0	17.4	32.4	10.4	11.2	–	400	64 1	1	–	–	–	–	IgM, C_3, lesser IgG + C_4.	N/G	N/G	12	12			Cirrhosis. Died in hepatic and renal failure Terminal E.coli sept. and oral herpes.
INDIAN																													
RJ	2.5	M	–	–	–	3.8	–	13.0	–	–	–	14.1	8	–	–	–	–	–	–	–	–	–	±	N/G			5		–
DN	8	F	–	–	+	1.2	–	16.9	24.5	–	–	–	–	67.5	–	160	–	–	–	–	–	–	–	–			4		Pneumonia E.coli Cellulitis L foot.
FOCAL PROLIFERATIVE																													
AFRICAN																													
NN	11	F	+	–	–	5.0	70	14.0	9.0	92	70	13.3	10.00	54	< 166	80	–	–	–	–	–	IgM, C_3 on GBM	0	0	–		0.25		F VIII 246 Heaf III. S. haematobium urine.
ZM	3	M	–	–	–	3.2	–	14.7	6	42	48	9.8	20	28	–	72	–	–	–	–	–	IgM, C_3 focal in mesangium.	0	0	12	12	12		PTB on INH Ethambutol.
BM	9	F	–	–	–	8.2	–	17.6	13	34	47	12.6	7.1	–	<166	100	–	–	–	–	–	No deposits	0	0	6	6			Duplex ureter on right
MN	10	F	–	+	–	5	–	–	6	45	51	11.9	7.9	–	–	60	–	0	–	–	–	IgG, C_{1q}, C3	0	0	9	9		Died	Right upper lobe pneumon. + shrinkage.

FOCAL PROLIFERATIVE

Pt	Age (yrs)	Sex	HT	H	RF	Urea mmol/L	Creat. μmol/L	Chol. mmol/L	Serum Protein Alb	Glob	TP	Hb gms/dl	WCC X10^9	GFR mls/min	ASOT	C_3 mg%	C_4 mg%	CH_{50} mgs%	ANF	LE cells	HB_sAg	Immunofluorescence	Treat. S	Treat. E	Follow-up (month) D	R	PP	SR	Miscellaneous
AFRICAN																													
GL	1.5	M	-	+	-	2.7	-	8.2	21	-	-	11.9	9.0	54	-ve	96	-	-	-	-	-	IgM scattered	0	0	30	30			-
SG	8	F	+	-	-	-	-	9.55	9	36	45	11.5	10.4	33	-ve	150	54	-	-ve	-	-ve	Focal IgM	0	0					Rectal biopsy bilharzia
MV	5	M	-	+	-	8.8	122	18.27	11	35	46	13.10	2.0	41	-ve	126	48	92	-	-	-	Minimal C_3	0	0	4	4		Died	Stool - giardia, ascaris TT. UTI (Klebsiella pneumoniae) + peritonitis
NE	9	M	-	-	-	-	45	10.9	27.6	26	53.6	12.8	2.1	-	-	114	88	113	-ve	-ve	-	Heavy coarse IgG, IgA, IgM, C_{1q}, C_3 + C_4.	0	0	32	6	24		Asthmatic
AN	10	F	-	+	-	5.3	45	10.0	21	34	55	10.6	14	90	160	160	-	-	-ve	-ve	-ve	No deposits	0	0	108	24	84		-
ZN	3	M	-	-	-	1.3	-	20	18	23.8	41.8	11.7	6.1	-	-	118	-	-	-	-	-	No deposits	0	0	4	4			Subcapsular haematoma after biopsy - resolved.
INDIAN																													
NM	10	F	-	-	-	1.5	60	12.9	7	-	-	13.0	11.0	-	-	120	42	-	-	-	-	IgM deposits	0	0	4	1	3	3	Stools-ova of TT
AFRICAN														FOCAL GLOMERULOSCLEROSIS															
ZB	2.5	M	-	-	-	11.1	25	103	24	44	68	11.3	15.8	53	-	-	-	-	-ve	-ve	-	-	-	N/G	8		8		-
BN	9	M	-	-	-	12.6	55	11.4	13	27	40	11.3	16	18.5	-	-	-	-	-ve	-ve	-	Heavy IgG slight IgM, heavy tubular fluorescence.	-	N/G	4	4			E.coli sept. + UTI. Died severe oedema.
HM	10	F	-	+	-	1.5	-	9.9	17	41	58	12.2	7	-	-ve	-	-	-	-ve	-ve	-ve	Weak IgM, C_3.	-	-	24		24		3F hegar stool TT
SM	10	M	+	-	-	2.9	55	9.0	13	38	51	-	10	73	-	80	-	-	-	-	-	Fine focal granular IgM.			<1				
INDIAN																													
KK	1.3	M	-	-	-	8.0	-	17.49	12	34.2	46.2	14.0	24.9	13.2	-ve	106	50	149	-ve	-ve	-	Heavy mesangial IgM. Light mesangial C_3.	+		36	2 episodes			Measles.
FS	7	F	-	+	+	2.0	-	12.73	23	22	48	12.8	13.2	35	-	94	44	-	-ve	-ve	-	No deposits	-	-	12		12		-
MM	7	M	-	+	+	35.2	860	8.95	13.1	42.9	56	8	19.3	-	-	58	40	56	-ve	-ve	-	IgM + C_3,	N/G	N/G	24		4		A.N. Klebsiella pneum. sept. + UTI.
KR	8	F	-	+	-	3.2	85	18.4	23.5	42	65.5	-	-	-	-	-	-	-	-ve	-ve	-	Focal IgM	-	N/G	24		24		-
RS	8	F	+	-	-	2.0	-	9.36	23	51.0	74	-	-	-	< 166	66	45	-	-	-	-	-	N/G	N/G	120		120		-
LP	4	M	-	-	-	12	33	9.9	23	37	59	11.7	25	78	< 166	56	40	-	-	-	-	-	-	-	125		125		No response to Chloramb-ucil. 2 biopsies MCNS 3rd biopsy FGS.
														TROPICAL EXTRAMEMBRANOUS NEPHROPATHY															
SB	9	M	-	+	-	2.0	-	17.9	17	30.1	47.8	12.8	13	-	-	-	-	-	-	-ve	-	Heavy coarse granular IgG, C_3, C_{1q}, C_4, weak IgM.	N/G	N/G	48	48			-
HM	5	M	-	-	-	9.5	45	10.5	7	38	45	9.2	18	26	-ve	74	-	-	-ve	-ve	-	Coarse gramular IgG + C_3.	N/G	N/G	3	1	2		Bronchopneumonia.
GM	8	M	-	-	-	2.3	124	9.2	14	32	46	11.6	17	-	<166	54	-	-	-	-ve	-	No deposits	N/G	N/G	48				-
MN	6	M	-	-	-	2.7	35	14.4	17	31	32	13.2	9	98	-ve	100	-	-	-ve	-	-	Heavy, coarse, gramular IgG, weak C_{1q}, C_3, C_4. IgM in mesangium.	N/G	N/G	2	1	1		-

TROPICAL EXTRAMEMBRANOUS NEPHROPATHY

Pt	Age (yrs)	Sex	HT	H	RF	Urea mmol/L	Creat. μmol/L	Chol. mmol/L	Serum Protein Alb	Glob	TP	Hb gms/dl	WCC X10^9	GFR mls/min	ASOT	C_3 mg%	C_4 mg%	CH_{50} mgs%	ANF	LE cells	HB_sAg	Immunofluorescence	Treat. S	E	Follow-up (month) D	R	PP	SR	Miscellaneous
MX	7	M	–	–	–	5.1	–	7.7	22	33	55	11.1	9	52	200	86	–	–	–ve	–ve	–	Fine, granular IgG, C_{1q}, C_3.	N/G	N/G	2	2			Large liver – biopsy normal.
AG	4	M	–	–	–	3.4	–	8.7	25	43	68	12.3	18.7	–	–ve	86	–	–	–	–	–	Heavy granular IgG, IgM, C_{1q}, C_3, C_4.	N/G	N/G	6	1	5		Bilateral lower lobe consolidation. Klebsiella pneumoniae and Salmonella septicaemia.
AFRICAN																TROPICAL NEITHROPATHY													
DE	3	F	+	–	+	12.3 15.2 19.1 28	90	8.3	8	–	–	12.4	11	–	–ve	–	–	–	–ve	–ve	+ve	Marked granular IgG on GBM + mesangium moderately granular C3, C_{1q}.	– Died in 14 days.		0.5				Deteriorated on steroids. Died.
GN	10	M	+	–	–	1.2	–	20.05	12	33	45	11.1	13	–	–	110	–	–	–	–	–	Light IgM, scattered C_{1q}.	N/G		27	2	25	–	–
INDIAN																													
KN	6	M	+	+	–	3.9	–	10.4	28	29	57	12.5	14	36	100	102	–	–	–	–	–	–	+		46	4	–	42	Renal abscess following biopsy. Gross VUR – nephrectomy.
AFRICAN																UNCLASSIFIABLE GLOMERULAR LESIONS													
XN	4	M	–	–	–	4.7	–	12.35	18	26	44	11.1	10	45	–	120	–	–	–	–ve	–	–	–		5	5	–	–	–
FM	5	F	+	+	–	9.4	–	–	23.5	41.3	54.8	10	9.8	–	200	–	–	–	–	–	–	Heavy C_3, coarse granular pattern on GBM.	–		2	?			–
ND	7	F	+	+	–	7.1	1.3	13.52	24.0	44	68.0	12.7	10	–	50	–	–	–	–	–ve	–	–			6	6		Died	
FM	12	F	+	+	–	12.7	0.45	11.6	12.6	37.4	50	10.5	8.7	16	–	1	–	0	–ve	–ve	–	–	–		8	8			–
INDIAN																													
NR	7	M	–	+	–	1.4	0.1	8.4	23	32	41	5.0	10	23	–	100	–	–	–ve	–ve	–ve	–	–	N/G	9	9		Died	UTI (Klebsiella pneumoniae).

8.2 FACTOR VIII PROCOAGULANT ACTIVITY IN CHILDREN WITH NEPHROTIC SYNDROME

Summary

Plasma factor VIII procoagulant activity has been shown to be significantly elevated in 32 children with the nephrotic syndrome. This increase is more marked in those with obvious glomerular lesions on histology than in patients with minimal change nephropathy. Fluctuations in factor VIII levels corresponded to changes in the clinical condition of the nephrotic syndrome. Factor VIII levels may reflect the extent of immuno-pathological injury to glomerular capillaries and be useful in management of children with glomerular disease.

Introduction

Factor VIII (F VIII) which is believed to be normally produced by vascular endothelial cells (Bloom et al 1973, Holmberg and Nilsson 1974, Hoyer et al 1973) has been reported to be present in abnormal amounts in damaged renal tissue (Hoyer et al 1974). Elevated levels of plasma F VIII have been reported in cases of nephrotic syndrome (Kendall et al 1971) and glomerulonephritis (Ekberg et al 1975). These results have dealt mostly with adults and the level of plasma F VIII was found to correlate with response to treatment (Kendall et al 1971) and outcome (Ekberg et al 1975). This study reports on F VIII (factor VIII procoagulant activity) in children with the nephrotic syndrome (NS).

Patients

32 patients were studied. The diagnosis of NS was based on criteria given on page 73 and the type of lesion was identified by renal biopsy. 20 patients were African (16 males, 4 females, aged 2 - 11 years) and 12 Indian (8 males, 4 females aged 4 - 11 years). All the Indian patients showed the histological changes of

minimal change nephropathy by light microscopy and immunofluorescence. All the African patients had obvious glomerular lesions on histology (Table XXXVIII). F VIII levels in NS patients were measured during relapse, complete remission, and in partial remission. Deterioration refers to worsening of the diagnostic features of NS. 10 NS patients (3 African and 7 Indian) had repeat F VIII levels done at intervals of 35 - 210 days.

Methods

The glomerular filtration rate (assessed by ^{51}Cr EDTA excretion), blood urea, serum creatinine and intravenous pyelogram or renal ultrasonogram were normal in all the NS patients.

F VIII (procoagulant activity) was assayed by the two-stage method of Biggs et al (1955) and expressed as a percentage of the mean normal level using normal pooled human plasma as a standard.

Controls were race-matched with all patients.

Statistical analysis of results was carried out by the paired and unpaired Student's t tests and Spearman's product-moment correlation coefficient.

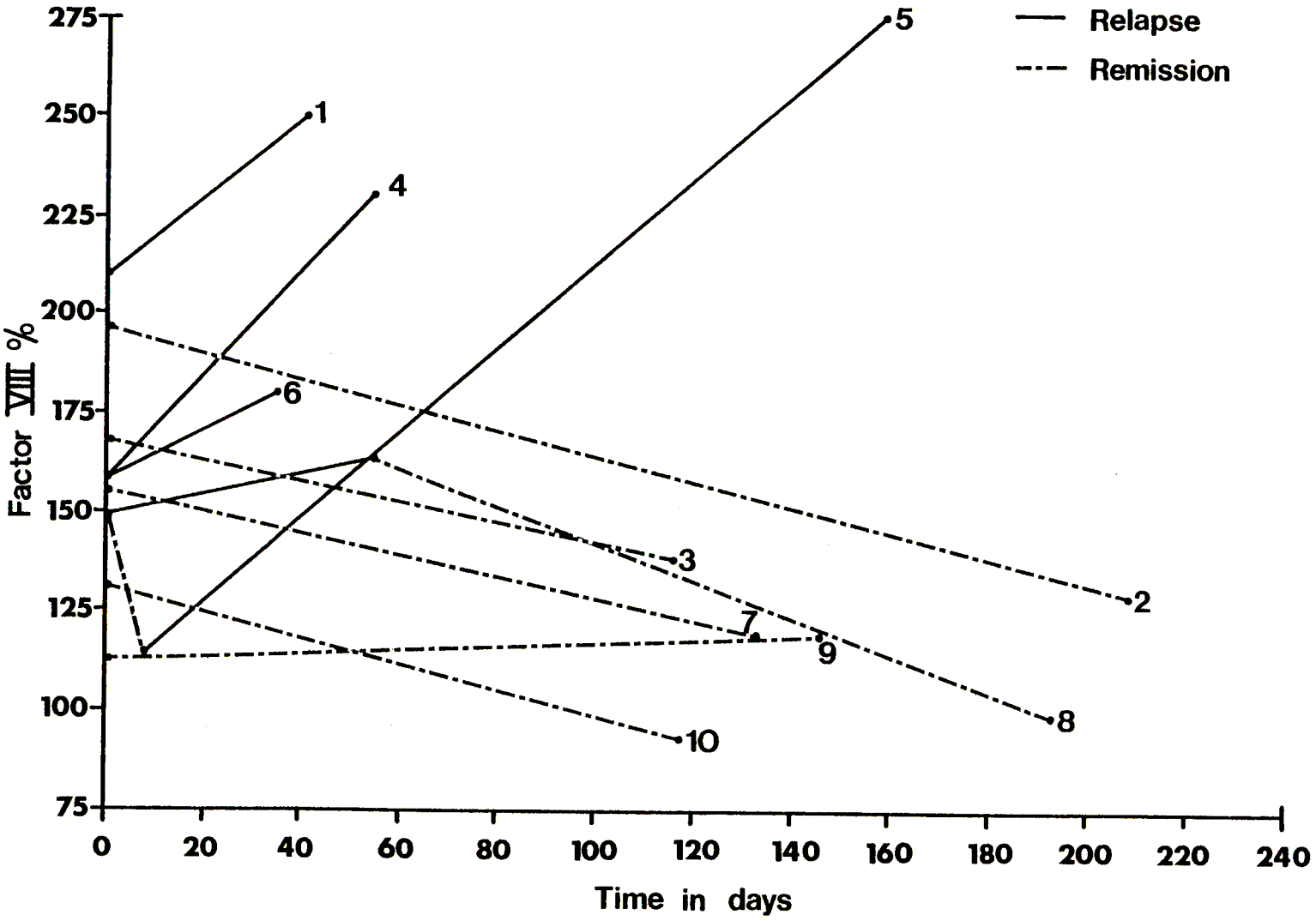
Results

The mean F VIII level in both African and Indian children with NS in relapse was significantly higher (197% ± 28 and 145% ± 20, respectively) than the mean control values (127% ± 20, 116% ± 27, respectively). The level of significance for African cases was $p < 0.0005$ and for Indian cases $p < 0.01$.

4 patients (3 Indian and 1 African) were studied only during nephrotic remission. The 3 Indian patients had F VIII levels within range of the control value ± 2 standard deviations. F VIII in the African child was lower than 2 standard deviations below the mean value of the African nephrotics in relapse.

Changes in F VIII levels during follow-up of 10 children with NS are shown in figure 15. Patients 1, 2 and 6 were African. Initial results were obtained during relapse in all patients except patient 9, who was in cyclophosphamide-induced remission. African patients were on no treatment at the time of F VIII assay, whereas the Indians were on steroids. The mean initial F VIII level (162% ± 22) in 6 patients (No. 2, 3, 5, 7, 8 and 10) who improved clinically was

FIG. 15: THE FACTOR VIII LEVELS DURING REMISSION AND RELAPSE IN NS.



significantly greater ($p < 0.0025$) than the subsequent level (115% ± 17). F VIII levels in these 6 patients fell during complete (patients 7 and 10), partial (patients 2 and 3) and steroid-induced (patients 5 and 8) remissions. In those who deteriorated (patients 1, 4, 5, 6 and 8) the F VIII level rose; the mean initial F VIII (158% ± 31) was significantly lower ($p < 0.025$) than the follow-up value (220% ± 42). F VIII levels in patient 8 are reported during periods of improvement and deterioration. Patient 4 died due to possible infeciton and steroid toxicity; autopsy was not performed. F VIII remained unaltered in case 9, who was studied during cyclophosphamide-induced remission and complete remission. There was no significant correlation ($p > 0.05$) between F VIII and serum albumin, serum cholesterol and $_2$-globulin in all the nephrotic patients, nor was there a significant difference ($p > 0.05$) in serum albumin, serum cholesterol and $_2$-globulin between Indian and African patients with NS.

Discussion

Plasma F VIII levels have been shown to be significantly elevated in children with NS and

this increase is accentuated in those with obvious glomerular lesions. The latter group, which has evidence of immunologic injury to the glomerular basement membrane and a poorer prognosis (Habib and Kleinknecht 1971) can clearly be distinguished from patients with minimal change in whom there is an absence of immune deposits and who have a better prognosis.

These findings suggest that the degree of elevation of plasma F VIII is related to severity of glomerular damage mediated by immunological mechanisms. This interpretation of the results is supported by fluctuations in levels of F VIII during the course of the NS in individual patients. Remissions resulted in a fall, confirming the results of Kendall et al (1971), whereas worsening of the clinical condition was associated with a marked rise in F VIII. These changes in F VIII appeared to occur independently of steroid therapy. The mechanisms of elevated F VIII in NS are not clearly understood. F VIII is produced in glomerular endothelial cells and is found in increased amounts in damaged renal tissue (Hoyer et al 1974). Intravascular coagulation which can be activated by immune complexes (Zimmerman and Muller-Eberhard 1971) may result in glomerular

endothelial cell swelling and proliferation (Vassalli et al 1963). Immune injury to glomerular capillaries may provoke, by this mechanism, accelerated F VIII production or release. This can only be a partial explanation for elevated F VIII, as in minimal change NS the glomerular damage appears not to be mediated by immune complexes but possibly, through sensitized T cells (Shalhoub 1974). Differences in the scale of F VIII increase in the NS with minimal change or obvious glomerular lesions may also reflect differences in immunopathological mechanisms responsible for these diseases.

Generally, biochemical abnormalities of blood in patients with NS correlate poorly with severity of glomerular damage (Hayslett et al 1973) and clinical outcome. However, in one report (World 1976), serum cholesterol has been shown to be important in differentiating minimal change from the other histological types of NS.

Mechanisms giving rise to elevated F VIII may be different from those involved in abnormalities of other biochemical factors in NS because F VIII is produced by glomerular capillaries which are actively involved in this disease. This is

This is partly borne out by the finding of lack of correlation of F VIII with serum albumin, serum cholesterol and α_2-globulin.

F VIII assay may prove a useful tool in prognosis and management of children with glomerular lesions.

TABLE XXXVIII (continued)

F VIII LEVELS AND GLOMERULAR LESIONS IN CHILDREN WITH NS (continued)

Patient No.	Age years	Sex	Race	Renal biopsy		FVIII %	
				histology	Immunofluorescence	remission	relapse
17	5	F	A	diffuse proliferative	coarse, granular deposits IgG and C_{1q} on GBM	-	151
18	11	F	A	focal proliferative	focal IgM and C_3 on GBM	-	246
19	11	F	A	membrano-proliferative	heavy IgG and C_3 on GBM, weak IgM	-	200
20	4	F	A	diffuse membrano-proliferative	heavy, granular deposits IgG and C_3 C_{1q} on GBM	-	182
21 (8)	8	M	I	MC	no deposits	99	150;163
22 (5)	5	M	I	MC	no deposits	115	158;276
23 (9)	8	M	I	MC	no deposits	111;120	-
24 (3)	7	M	I	MC	no deposits	146	168
25 (10)	4.5	M	I	MC	no deposits	93	132
26	11	M	I	MC	no deposits	112	-
27	6	M	I	MC	no deposits	-	160
28	8	M	I	MC	no deposits	-	154
29 (7)	4	F	I	MC	no deposits	119	157
30 (4)	9	F	I	MC	no deposits	-	158;231
31	10	F	I	MC	no deposits	131	-
32	7	F	I	MC	no deposits	-	156

Numbers in parentheses refer to patients' corresponding number in figure 1. A = African : I = Indian : MC = minimal change : GBM = glomerular basement membrane.

TABLE XXXVIII

F VIII LEVELS AND GLOMERULAR LESIONS IN CHILDREN WITH NS

Patient	Age	Sex	Race	Renal biopsy		FVIII %	
No.	years			histology	Immunofluorescence	remission	relapse
1 (2)	11	M	A	diffuse extramembranous	heavy, coarse IgG, lighter C_3 and C_{1q}	128	197
2	7	M	A	diffuse proliferative	coarse IgG and C_{1q}	-	182
3	11	M	A	membrano-proliferative	heavy, coarse, granular KgG and C_3 on GBM, weak IgM	-	170
4	9	M	A	diffuse extramembranous	heavy IgG, lighter C_3	-	170
5	5	M	A	diffuse extramembranous with proliferation	coarse, granular IgG, C_{1q}, C_4 and C_3 on GBM	-	197
6	7	M	A	diffuse mesangial proliferative	finely granular IgG, C_{1q} and C_3 on GBM	-	180
7 (1)	9	M	A	diffuse mesangial proliferative	finely granular IgG, C_3, C_{1q} and IgM on GBM	-	211;251
8	10	M	A	extramembranous	heavy, coarse IgG and C_3 on GBM weak C_{1q}, C_4 and IgM	-	205
9	6	M	A	diffuse membrano-proliferative	heavy, coarse IgG, weal C_{1q}, C_3 and C_4 GBM, IgM on mesangium	-	187
10	5	M	A	diffuse proliferative	coarse, granular IgG, C_3 and C_4 weak IgM and C_{1q} on GBM	-	220
11 (6)	9	M	A	diffuse extramembranous	granular deposits IgG and C_3 on GBM	-	158;181
12	2	M	A	diffuse proliferative	heavy, granular IgG on GBM, weak C_{1q}	-	157
13	2	M	A	diffuse extramembranous	granular deposits IgG and C_3 on GBM	-	212
14	11	M	A	diffuse extramembranous	not available	86	-
15	8	M	A	diffuse extramembranous	heavy IgG and C_3 on GBM, weak C_{1q} and C_4	-	227
16	11	M	A	diffuse extramembranous	granular deposits IgG and C_3 on GBM	-	174

8.3 SCHISTOSOMIASIS

Nephropathy has been associated with hepatosplenic schistosomiasis (Andrade & Rocha 1979). Schistosoma mansoni is endemic in the Durban area (Schutte et al 1977). Preliminary epidemiological evidence suggests that hepatic schistosomiasis may be as high as 12 -20% in the general childhood population in this area (Mackenjee et al 1981b).

It was therefore important to exclude Schistosoma mansoni as an aetiological factor in nephrotic patients. The biopsies of 19 African patients (5 FPGN, 5 MPGN, 1 DE, 2 endo, 3 MCNS, 2 EM, 1 TN) were tested by immunofluorescent techniques for schistosoma antigen on the GBM. Indian nephrotics were used as negative controls.

Schistosomal antigens were sought in frozen sections of kidney biopsies by an indirect immunofluorescent technique using rabbit antiwhole worm schistosomal antibody (kindly supplied by Prof. Andre Capron) as the first reagent and fluorescein - conjugated anti rabbit antibody as the second layer.

Schistosoma antigens were not detected in any of the biopsies. Therefore Schistosoma mansoni could not be proven as an aetiological agent in the nephrotic syndrome of African children in South Africa.

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