CHILDHOOD NEPHROTIC SYNDROME IN KADUNA STATE

By

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To my wife

MARYAM ANUOLUWAPO ABDURRAHMAN

who has learnt to live with a

perpetual student as husband

ABSTRACT

The clinicopathological features of childhood nephrotic syndrome in tropical Africa are different from those in temperate countries of Europe and America. However, detailed clinico-pathological features of the disease have not been comprehensively described in all parts of Africa. Plasmodium malariae has been shown to be strongly associated with the disease in some parts of Africa, and the association has been postulated to be causal.

Childhood nephrotic syndrome was studied in Kaduna State of Nigeria in an attempt to define the clinicopathological features of the disease. In particular, the study set out to assess the role of P. malariae in the aetiology or pathogenesis of childhood nephrotic syndrome, and to look for other possible aetiological factors.

One hundred consecutive children with nephrotic syndrome who had had no treatment previously were studied. In addition to routine biochemical and haematological investigations, malaria parasitaemia, protein selectivity index, serum hepatitis B surface antigen and percutaneous renal biopsy were done.

As described in other parts of tropical Africa, children with nephrotic syndrome presented with massive oedema, prominent ascites, and very low serum proteins. P. malariae parasitaemia was present in 31% of nephrotic children, compared with 7% in the control group of children. The frequency of P. malariae parasitaemia was 40% in patients with membranoproliferative glomerulonephritis, 40% in quartan malarial nephropathy, and 21% in proliferative glomerolunephritis. Serum hepatitis B surface antigen was positive in the sera of 31% of patients compared with 30% in control but the concentration of antigen was stronger in the patients. Schistosoma mansoni ova were found in the stool or rectal snip of six patients: histology of renal biopsy showed membranoproliferative glomerulonephritis in four of these patients. Protein selectivity index was determined by comparing the clearances of albumin and immunoglobulin IgG. The index was good in 34% of patients. However, the test was not found useful in identifying those lesions likely to respond to corticosteroid therapy. Percutaneous renal biopsy was successful in 98 of the 100 patients. By light microscopy, the most common histological diagnoses were membranoproliferative glomerulonephritis (25 cases), quartan malarial nephropathy (20), and proliferative glomerulonephritis (19 cases). Together they formed 65% of the biopsies. Immunofluorescence was abnormal in 92%: there were deposits of immunoglobulins, C_3, P. malariae and hepatitis B

surface antigen. Schistosome antigens were not looked for.

Short-term prognosis of the disease was not as good as in children in Europe or North America, but did not seem to be as poor as in children studied in Ibadan. Quartan malarial nephropathy was not the predominant type of childhood nephrotic syndrome seen in Kaduna State, since it accounted for less than a quarter of the cases studied. This is in contrast to the finding in Ibadan where quartan malarial nephropathy was responsible for over 80% of cases of childhood nephrotic syndrome. There was some evidence that hepatitis B surface antigen could also play a role in the aetiology or pathogenesis of the disease in Kaduna State.

There is still no satisfactory treatment for childhood nephrotic syndrome in tropical Africa. Eradication or control of infectious diseases should result in reduced incidence of the disease.

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ABBREVIATIONS AND DEFINITIONS

Abbreviations

AGN	-	Acute glomerulonephritis
ASOT	-	Antistreptolysin-O titre
C_3	-	Complement C_3
CIC	-	Circulating immune complexes
CIE	-	Counter-current immunoelectrophoresis
CMI	-	Cell-mediated immunity
df	-	Degree of freedom
DPGN	-	Diffuse, proliferative glomerulonephritis
EM	-	Electron microscopy
ESRD	-	End-stage renal disease
FSGS	-	Focal segmental glomerulosclerosis
HB	-	Hepatitis B
HBeAg	-	Hepatitis B e antigen
HBsAg	-	Hepatitis B surface antigen
HBV	-	Hepatitis B virus
H & E	-	Haematoxylin and eosin
ISKDC	-	International Study of Kidney Disease in Children

MCN - Minimal change nephropathy

MGN - Membranous glomerulonephritis

MPGN - Membranoproliferative glomerulonephritis

PAS - Periodic acid-Schiff

PGN - Proliferative glomerulonephritis

PSAGN - Poststreptococcal acute glomerulonephritis

PSI - Protein selectivity index

QMN - Quartan malarial nephropathy

RIA - Radioimmunoassay

SD - Standard deviation

Definitions

Casturia — Presence of more than two casts per high power field of centrifuged urine.

Complete response — Disappearance of oedema

+

Urine protein $\leq$ 1+ by dipstick for three consecutive days

or

$<$500mg/24h for three consecutive days

+

Serum albumin $\geq$ 25g/l.

Eosinophilia — Eosinophil count $>$ 10% of total leukocyte count.

Erythrocyturia	Presence of ⩾5 red blood cells per high power field of centrifuged urine.
Hypertension	Hypertension was arbitrarily defined as: <5 years old: ⩾120/80 mmHg 5-10 years old: >120/90 mmHg ⩾11 years old: ⩾140/90 mmHg
Partial response	Urine protein 1+ or 2+ by dipstick, or 500-1000 mg/24h, for 3 consecutive days, + Serum albumin ⩾25g/l
Pyuria	Presence of >10 WBC per high power field of centrifuged urine.

CHAPTER 1

I N T R O D U C T I O N

The clinicopathological features of childhood nephrotic syndrome in Nigeria have been extensively studied and well described by workers in Ibadan (Hendrickse and Gilles, 1963; Adeniyi, 1972). The disease is characterised by paucity of minimal change nephropathy, pathological changes in majority of renal biopsies described as quartan malarial nephropathy (QMN), little or no response to corticosteroid therapy, and poor prognosis (Adeniyi, 1972; Hendrickse et al, 1972; Adeniyi, Hendrickse and Soothill, 1979). The reasons for suggesting that the association between Plasmodium malariae and childhood nephrotic syndrome is causal have been well articulated by Hendrickse and Adeniyi (1979). These reasons are epidemiological, clinical, histological and immunological. The pattern of nephrotic syndrome in Nigerian children is quite different from the pattern described in children living in temperate countries of Europe and North America. The majority of European and North American children with nephrotic syndrome have minimal change nephropathy (MCN) characterised by good response to cortico-

steroid therapy and a good prognosis (Churg, Habib and White, 1970).

Queiroz, Brito and Martinelli (1975) pointed out the influence of regional factors in the distribution of the histopathological patterns in nephrotic syndrome. In some tropical African countries with malaria pattern similar to Ibadan, QMN has not been established as an important type of childhood nephrotic syndrome. In Ghana, for example, Adu and his coworkers (1981) reported that in 25 children with nephrotic syndrome, minimal change nephropathy responsive to steroids was present in 14 (56%) cases. More important, the authors found no evidence to implicate P. malariae as a cause of the nephrotic syndrome. However, in that study, immunofluorescence and electron microscopic examination of the biopsies were not done, and no control children were included in the study of malaria parasitaemia. These weaknesses make it difficult to draw firm conclusions from the study. An earlier report from Lagos (Kibukamusoke, 1966), a town 150 km south of Ibadan, indicated that QMN existed in Lagos. However, in a more recent study of childhood nephrotic syndrome in Lagos, Noah and Olude (1979) biopsied 27 patients. Their findings, reported in an abstract and therefore without details, were: minimal change nephropathy (MCN) 9, membranoproliferative glomerulonephritis (MPGN) 8, focal segmental glomerulosclerosis (FSGS) 4, membranous

glomerulonephritis (MGN) 4 and end-stage renal disease (ESRD) 2. There is little or no information available on childhood nephrotic syndrome in other parts of Nigeria.

In addition to P. malariae, other infectious agents have been implicated in the aetiology of nephrotic syndrome. The infectious agents implicated include hepatitis B virus (Levy et al, 1982), S. mansoni (Andrade and Rocha, 1979), and Yersinia enterocolitica (Awunor-Renner, Lawande and Subbuswamy, 1984). Infectious diseases are prevalent in developing countries of tropical Africa.

Although the pattern of childhood nephrotic syndrome in tropical Africa has been shown to be different from that seen in temperate countries, the disease does not appear to be a uniform entity in Africa. Even within the same country, Nigeria, there is a suggestion that there are differences in the pathology of the disease. Kaduna State is situated about 850 km north of Ibadan and about 1000 km north of Lagos. The climate, vegetation and ethnic groupings in Kaduna State are different from those in Ibadan and Lagos.

With this background information on the epidemiology of childhood nephrotic syndrome in tropical Africa, it was decided to study the disease in Kaduna State. The study was to involve children with nephrotic syndrome presenting at Ahmadu Bello University Hospitals in Kaduna and Zaria. In addition to

describing the clinical features of childhood nephrotic syndrome in Kaduna State, the study was planned to define the pathology of the disease from examination of renal biopsies, and to define the role of *P. malariae* and other factors in the aetiology or pathogenesis of the disease.

CHAPTER 2

REVIEW OF THE LITERATURE

2.1 Nephrotic syndrome outside Africa

Reports from Europe (Habib and Kleinknecht, 1971; Arneil, 1971; Koskimies et al, 1982) and North America (Makker and Heymann, 1974; Grupe, 1979), as well as collaborative studies involving both continents (Churg, Habib and White, 1970), show that majority of children with nephrotic syndrome have certain characteristics which are summarised here. The peak age of onset is two to three years. The pathology of renal biopsy is predominantly minimal change nephropathy (MCN). The disease is characterised by highly selective proteinuria, prompt response to initial corticosteroid therapy, and a good prognosis. As a result of these findings, it is now a practice in many centres not to perform routine renal biopsy in children presenting with nephrotic syndrome. Renal biopsy is reserved for cases unresponsive to corticosteroid therapy, or cases in which the nephrotic syndrome is secondary to systemic disease.

In South America, nephrotic syndrome is characterised by paucity of MCN, presence of some form of glomerulonephritis on renal biopsy, and association with hepatosplenic schistosomiasis

(Queiroz, Brito and Martinelli, 1975; Andrade and Rocha, 1979). In India, Srivastava and his colleagues (1975) studied 206 children with nephrotic syndrome. Renal biopsy showed MCN in 77%, and the response to steroid therapy was good in 98% of those children with MCN. In Thailand, 11 out of 16 children with nephrotic syndrome had MCN (Tanphaichitr et al, 1974). It is of interest to note that granular deposits of IgM and/or β1C were detected in eight of the 11 cases with MCN. Strictly speaking, these cases cannot be accepted as MCN. Electron microscopy would have been most useful to resolve such a discrepancy between the findings on light and immunofluorescence microscopy. In Papua New Guinea (Powell and Meadows, 1971; Powel et al 1977; Duggin, 1981) MCN is uncommon. The dominant histological type reported was varying forms of proliferative glomerulonephritis (PGN), with deposition of IgM, IgG and complement in the glomeruli. Although the histology was similar to that described by Kibukamusoke and Hutt (1967) in Uganda, Powell et al (1977) found P. malariae parasitaemia in only two out of 18 patients.

2.2 Nephrotic syndrome in East Africa

In 1934, Carothers described 15 Kenyan children with "subacute nephritis". These patients presented with oedema, and 10 (67%) of them had P. malariae parasitaemia, compared with only 8% in other children. On the other hand, the prevalence of P.

falciparum was equal in both groups. He also observed that subacute nephritis occurred in 36% of all cases of quartan malaria in the hospital. In contrast, in a more recent study of 48 young Kenyan adults with nephrotic syndrome, there was no evidence to implicate malaria as a possible aetiology of the nephrotic syndrome (Rees et al, 1972). In another recent study, (Kinuthia et al, 1981), 162 cases of nephrotic syndrome were admitted to Kenyatta National Hospital, Nairobi, in five years. Of this number, 78 were children 1-15 years of age. Forty (51%) of the children were classified as nephritic-nephrotic, and 38 (49%) as pure nephrotics. Nephritic-nephrotic was defined as nephrotic syndrome plus azotaemia or histological evidence of PGN. Renal biopsy was done in 21 children: the histology was diffuse PGN 13, unclassifiable 4, MCN 2, FSGS 1 and MPGN 1. Malaria parasite was found in 8 out of 55 tested : P. malariae was not identified. It is difficult to assess the role of malaria in this study because the method of blood examination for the parasite was not stated, there were no controls, and the indications for biopsy were not stated.

Childhood nephrotic syndrome in Uganda was reported as part of a comprehensive study of the disease in hospital patients. In an analysis of medical admissions to Makerere Teaching Hospital, Kampala, over a 5-year period, Kibukamusoke (1973) reported that nephrotic syndrome accounted for an average of 2% of all

admissions per year. This figure was compared with figures compiled from malarious and non-malarious centres in different parts of the world. The figure for Makerere was 50-100 times higher than the figures for non-malarious areas. When the 53 renal biopsies performed in children were analysed, there were only three cases of MCN. The remaining 50 showed proliferative changes: mild in 39 and moderate or marked in 11. Features of mild PGN were a variable degree of segmental glomerulitis, occasionally with tuft adhesions, but sclerotic, hyalinizing lesions with mesangial and basement membrane thickening were also common. In moderate to marked PGN, there was mesangial proliferation or MPGN. In another report, Kibukamusoke and Hutt (1967) found a high P. malariae parasitaemia rate in children with nephrotic syndrome: 63% compared with 7.1% in control children. Surprisingly, this group of patients with high parasitaemia rate also had significantly higher serum malaria antibody titres than non-nephrotic controls (Kibukamusoke and Voller 1970), despite considerable losses of the antibody in urine (Kibukamusoke and Wilks, 1965). Some of the patients had glomerular deposits of immunoglobulins and complement, with IgM predominating (Ward and Kibukamusoke, 1969). However, plasma C_3 concentrations measured in 24 nephrotics were similar to those in controls (Cameron and Kibukamusoke, 1971). The response to corticosteroid therapy of these patients with P. malariae-

associated nephrotic syndrome was poor (Kibukamusoke and Wilks, 1967). Thus, workers in Uganda produced sufficient evidence to show that P. malariae is of aetiological significance in their population of children with nephrotic syndrome.

2.3 Nephrotic syndrome in West Africa

In 1963, Hendrickse and Gilles published the pattern of renal diseases seen in children less than ten years of age in Ibadan, Nigeria. Of a total of 196 children with renal disease seen in four years, 156 (80%) had nephrotic syndrome, 22 had acute glomerulonephritis and 7 had pyelonephritis. The peak incidence for nephrotic syndrome was 5 years of age, higher than the 2-3 years in Europe and America. Similar to the findings in Uganda, there was rarity of MCN; the vast majority of the patients had significant renal pathology. The pathology was characterised by capillary wall thickening and progressive glomerular sclerosis. There was also a high prevalence of P. malariae parasitaemia in nephrotic children compared with controls. The overall P. malariae infection rate was 88% in nephrotics, 24% in non-nephrotic outpatients, and 6% in unselected village children. The authors postulated an immunological pathogenesis for the renal pathology observed in their patients with nephrotic syndrome. Subsequent reports from the same centre confirmed the initial findings, and highlighted

the significance of P. malariae in the aetiology of childhood nephrotic syndrome in Ibadan. Some of these reports are summarised here. Hendrickse and his group (1972) biopsied 63 children with nephrotic syndrome: immunofluorescence study was done in 42 of the renal tissues, and electron microscopy in 22 cases. By light microscopy, the diagnoses were QMN 51, MCN 5, mesangial PGN 5, FSGS 1, and amyloidosis 1. Thus, QMN formed 81% of the biopsies. The authors described QMN as thickening of glomerular capillary walls, initially focal and segmental in distribution, with periodic acid-Schiff positive argyrophilic fibrils. The mesangium is also involved in the sclerosing process. Progression of the disease eventually leads to total glomerular sclerosis. Cellular proliferation is inconspicuous or absent. Immunofluorescence was abnormal in 41 of the 42 biopsies examined, with deposition of immunoglobulins in a predominantly granular pattern. P. malariae antigen was detected in 10 out of 30 cases. The response to prednisolone or azathioprine was poor in majority of patients. Moreover, each drug produced serious toxicity (Adeniyi, 1972; Hendrickse et al, 1972; Adeniyi, Hendrickse and Soothill, 1976). However, response to cyclophosphamide was encouraging (Adeniyi, Hendrickse, and Soothill, 1979).

The deductions from the Ibadan studies are that P. malariae is associated with nephrotic syndrome in some children (Gilles

and Hendrickse, 1963; Adeniyi, 1972), producing a peculiar renal histology called QMN (Hendrickse et al, 1972). The use of corticosteroid in such children is not only ineffective but could be dangerous (Adeniyi, 1972; Adeniyi, Hendrickse and Soothill, 1976). The course of the disease is characterised by progressive impairment of renal function associated with deterioration in histology, resulting in chronic renal failure within a few years of diagnosis. The overall prognosis is poor (Adeniyi, 1972; Hendrickse and Adeniyi, 1979).

There is scanty information on childhood nephrotic syndrome in other parts of Nigeria. Children were included in a review of 52 cases of nephrotic syndrome seen in Lagos over a two-year period, but the exact number of children was not stated. There was no minimal change in the 11 biopsies done; the indications for biopsying 11 of the 52 patients were not stated. P. malariae was found in the peripheral blood of seven of these patients, compared with two of 11 controls. Of the 22 patients treated with steroid only two responded. The author concluded that there was QMN in Lagos (Kibukamusoke, 1966). Thirteen years later came a report from the same centre indicating the rarity of QMN in childhood nephrotic syndrome. Noah and Olude (1979) analysed 27 consecutive cases of childhood nephrotic syndrome. The histological pattern of renal biopsies was: MCN 9, MPGN 8, FSGS 4, MGN 4, and ESRD 2. There was no mention about treatment

given. The report was contained in an abstract, which therefore gave no details of the criteria used for the histological diagnosis. Moreover, no immunoflourescence or electron microscopic studies were done. Unfortunately, there has been no subsequent report from Lagos on childhood nephrotic syndrome. In Enugu, out of 2170 children admitted in one year, there were only 17 cases of nephrotic syndrome (Kaine and Okolie, 1977). No further details were given. Before the present study was started, information was obtained for the previous three years about the number of cases of nephrotic syndrome admitted to children's ward in each of the three Ahmadu Bello University Hospitals. The average figures per year were Kaduna 35, Zaria 30, and Malumfashi 25 (unpublished data).

Other West African countries from which reports on childhood nephrotic syndrome are available include Ivory Coast, Senegal and Ghana. In Ivory Coast, Habib et al (1977) biopsied 96 children with nephrotic syndrome. Immunofluorescence was done in 40 and electron microscopy in 15 cases. The diagnosis was MCN in 13. Lesions compatible with QMN were described in 68% of the cases. There was one important omission in this study: malaria parasitaemia was not included. Twenty-four Senegalese children with nephrotic syndrome were extensively studied by Morel-Maroger and her colleagues (1975): serology (HBsAg, malaria antibodies, antiglomerular basement membrane, antitubular and antinuclear

antibodies) and renal biopsy for light, electron and immunofluorescence microscopy. There was no case of MCN. Fifteen biopsies were diagnosed as "tropical nephropathy", detailed description of which was compatible with QMN. However, only five of the 15 patients had high serum level of P. malariae antibody, whereas eight of them had high P. falciparum antibody. Unlike cases of QMN described in Ibadan children, immunofluorescence microscopy of renal tissue in Senegalese children showed segmental deposits of immunoglobulin and complement components only in occasional glomeruli of some patients. P. malariae was found in the blood smear of only one of the 24 patients. Four patients had MGN associated with glomerular nuclear proliferation and low serum complement. Immunofluorescence studies showed granular deposits of C_1q, C_3, C_4, properdin and IgG. Five patients had diffuse PGN associated with high ASOT. Thus, some of the 24 Senegalese children had renal histology similar to QMN but without the diffuse deposition of immuno-reactants seen in Nigeria, whereas a few had MGN but with immunofluorescence pattern of QMN. The remainder had renal histology compatible with poststreptococcal PGN. It is of interest to know that malaria is also endemic in Senegal.

In Ghana, a country close to Nigeria, a study of 25 children with nephrotic syndrome found no evidence to implicate P. malariae as a cause of the nephrotic syndrome (Adu et al, 1981).

MCN responsive to steroid was found in 14 (56%) patients. There were four cases each of diffuse PGN and MGN. It must be pointed out that the study was incomplete; it is therefore difficult to accept the authors' findings. The epidemiology of malaria in Ghana is similar to that of Nigeria.

Ngu and his coworkers (1985) in Cameroon studied 63 consecutive patients with severe proteinuria and/or renal failure; the number of children was not stated. The study included renal biopsy for light microscopy and immuno-fluorescence. Possible aetiologic factors identified included HBsAg (26.5%), O. volvulus (22%) and Loa loa (16%). Apart from immunoglobulins and complement, O. volvulus antigen was detected in nine out of 24 cases studied. The most frequent histological diagnoses were MGN (16 cases), MPGN (9 cases) and ESRD (7 cases).

2.4 Nephrotic syndrome in North Africa

Elzouki, Amin and Jaiswal (1983) carried out a 26-month prospective study to define the pattern of renal disease in Libyan children. Of the 343 children studied, nephrotic syndrome occurred in 71. Idiopathic nephrotic syndrome was diagnosed in 65 of the 71 cases. Sixty-four of the 65 patients responded to prednisolone, but 22 of them relapsed frequently. When biopsied, the 22 patients had MCN. MCN appears to be more frequent in Libyan children than in children in other parts of Africa, Europe

or America. The reasons for this difference are not clear. In Tunisia, a country close to Libya, the picture is different. A total of 304 adults and children with clinical evidence of glomerular disease were biopsied over a period of two years (Verroust et al, 1979). Of this number, 165 had nephrotic syndrome, but it was not stated how many of these were children. The most frequent histological diagnosis in children was PGN. MCN constituted less than 10% of all cases of childhood nephrotic syndrome.

2.5 Nephrotic syndrome in Southern Africa

In a study of nephrotic syndrome in 34 Malawi adults and children, Brown, Abrahams and Meyers (1977) found only five patients with QMN. There were 11 cases of FSGS and 10 of PGN. Malaria is hyperendemic in Malawi. Coovadia, Adhikari and Morel-Maroger (1979) studied nephrotic syndrome in children in Durban, a malaria-free area of South Africa. They found racial differences in the pattern of the disease among Africans and Indians. The frequency of MCN was 10/74 (13.5%) in Africans and 42/56 (75%) in Indians. The other histological types in African children were MGN 27, PGN 15, MPGN 6 and others 16. Indian children had PGN 5, MGN 2, MPGN 2 and others 5. No malaria parasite was detected in the peripheral blood of any patient. In a ten-year study of 180 adult patients (140 Africans and 40

Indians) in the same town, the most common histological pattern in both African and Indians was PGN, followed by MGN (Seedat, 1978). MCN was present in 4 Africans and 3 Indians. Older children, aged 12-15 years, constituted 15.7% of the African patients studied.

Seventeen children were included in a clinicopathological study of nephrotic syndrome in Zimbabwe by Seggie and her coworkers (Seggie et al, 1984). None of the children had malaria parasitaemia, and their serum malaria antibody levels were not significantly different from those of control children. Membranous nephropathy was the most frequent histopathological lesion, occurring in 7 (41%) cases. Every one of the children was HBsAg positive, compared with a positive rate of 5% in healthy children.

2.6 Nephrotic syndrome in other parts of Africa

In the Sudan, *S. mansoni*, and not malaria, appears to be a significant aetiological factor in nephrotic syndrome (Veress et al, 1978). QMN was not described in any of the 68 biopsies from 64 patients with nephrotic syndrome. There were 17 patients with PGN, 14 with MCN and 10 with amyloidosis. Fourteen of the 68 patients were children. There was a high frequency of *S. mansoni* infection in nephrotic patients - 32% compared with less than 1% in the general population. There were 27 cases of nephrotic

syndrome among 148 children clinically diagnosed as having glomerular disease in a five-year period in highland part of Ethiopia (Afework, Green-Abate and Tafari, 1980). Seventeen of the patients with nephrotic syndrome were treated with prednisolone: nine responded. No renal biopsy was done in the study. It appears, therefore, that malaria-associated nephrotic syndrome is uncommon in the horn of Africa.

2.7 Comments

This review of nephrotic syndrome in some countries of Africa shows that whereas MCN is uncommon in several countries, the pattern of the disease is not uniform in the continent. The evidence for possible aetiological role for *P. malariae* is strong in Ibadan and Kampala, though renal histology is different in both places. There is little or no such evidence in some malarious countries - Ghana, Kenya and Sudan. Although renal histology is compatible with QMN in Senegal and Ivory Coast, there is no supporting immunological evidence to implicate *P. malariae* as a cause of the nephrotic syndrome. Other infectious agents known to be nephrotic may be important in the aetiology and pathogenesis of childhood nephrotic syndrome in different parts of Africa. *S. mansoni* in the Sudan (Veress et al, 1978) and hepatitis B virus in South Africa (Adhikari, Coovadia and Chrystal, 1983) and Zimbabwe (Seggie et al, 1984) are examples of these infections.

Apart from Ibadan, there are no detailed studies of childhood nephrotic syndrome in Nigeria. The two reports from Lagos (Kibukamusoke, 1966; Noah and Olude, 1979) are far apart in time, and appear conflicting regarding the frequency of MCN and the importance of QMN.

CHAPTER 3

MATERIALS AND METHODS

3.1 Objectives of the study

The objectives of this study of nephrotic syndrome in children not older that 12 years were to:

1. Define the clinical and laboratory features of the disease.
2. Identify the pattern of the pathology of renal biopsies in children with the disease.
3. Assess the role of *P. malariae* in the aetiology or pathogenesis of childhood nephrotic syndrome.
4. Identify other possible aetiological factors associated with the disease.

3.2 Geography of study centres

The two main Ahmadu Bello University Hospitals are in Kaduna and Zaria, Kaduna State. Zaria is 80 km north of Kaduna. The hospitals serve as primary and referral hospitals for inhabitants of Kaduna State and other neighbouring states. Kaduna is about 900 km and 750 km north of Lagos and Ibadan respectively. Kaduna

State is different from Lagos and Ibadan with respect to vegetation, climate and ethnic origin of the inhabitants. Geographically, Kaduna and Zaria are located in the guinea savannah zone, whereas Lagos and Ibadan are in the forest zone of the country. Both Lagos and Ibadan are between 6° 30' and 7° 30' N latitude, compared with Kaduna and Zaria which lie between 10° 30' and 11° 30' N. Lagos and Ibadan are at low altitude above the sea level, whereas Kaduna and Zaria are about 610m above sea level. Rain falls throughout most of the year and is heavy in the southern parts of Nigeria, but in the north there is a definite rainy season from April to October. There is a high atmospheric humidity all year round in the south, compared with high humidity in the wet season and low humidity in the dry season in the north. The principal ethnic group in Lagos and Ibadan is Yoruba. In Kaduna State the principal ethnic groups are Hausa, Fulani and Kaje.

Nigeria is holoendemic for malaria. However, in the northern parts of the country there are seasonal differences in parasite and spleen rates, indicating seasonal variation in vector density and malaria transmission (Voller and Bruce-Chwatt, 1968; Molineaux et al, 1980). Vector density is low and malaria transmission reduced throughout the dry season.

3.3 Study population

The study population consisted of the first 100 consecutive

patients aged 12 years and below, with nephrotic syndrome which had not been treated previously. They were selected from children attending the children's outpatient unit of the Department of Paediatrics in Kaduna and in Zaria. According to hospital regulations, a person older than 12 years is an "adult".

Unless otherwise stated, the control group of children consisted of outpatients who had no historical or physical evidence of renal disease, and whose urinalysis by dipstick and microscopy was normal.

3.4 Methods

3.4.1 Criteria for diagnosis

The diagnosis of nephrotic syndrome was based on the following criteria: 1. Presence of oedema

2. Proteinuria of $\geqslant$ 2.0g/24h

3. Serum albumin $<$ 25g/l

3.4.2 Initial evaluation. History and physical examination were carried out as set out in the proforma in Appendix 1. Points specifically asked for in the history included previous episodes of oedema, presence of haematuria or oliguria, and treatment received before coming to the hospital. The signs particularly looked for in the physical examination were skin lesion, extent and severity of oedema and blood pressure.

Patients with dipstick proteinuria of $\geqslant$ 2+ were admitted for

further evaluation. Only those who satisfied the criteria for the diagnosis of nephrotic syndrome as stated above were included in the study.

3.4.3 Investigations. The investigations carried out were grouped as routine or special.

(a) Routine investigations.

1. Haemogram - haemoglobin, haematocrit, total and differential leucocyte count, and platelet count.
2. Peripheral blood film for malaria parasites on at least three occasions, about eight hours apart, within 24 hours of admission and before administration of chloroquine. This method was used in order to increase the yield of positive smear without undue delay in starting treatment.
3. Urine - dipstick for protein
   - microscopy for cells and casts
   - midstream specimen for culture
   - 24h specimen for protein
4. Stool microscopy for parasites.
5. Blood biochemistry - creatinine, urea, cholesterol, proteins (total and albumin), prothrombin time.
6. Intravenous urogram during the first half of the study.
7. ASOT. Serum ASOT was determined with Wellcome Streptolysin-O commercial kit.
8. Other investigations were done as indicated.

The routine investigations were done by appropriate standard laboratory methods in the hospital laboratories, except peripheral blood examination for malaria which was done by the investigator as well as by the laboratory staff.

(b) Special investigations

1. Protein selectivity index (PSI). Serum and urinary IgG and albumin concentrations were determined by single radial immunodiffusion using commercially prepared monospecific antisera (Behringwerke A.G., West Germany).

   The value of PSI was calculated from the formula:

$$\frac{\text{Urine IgG}}{\text{Serum IgG}} \div \frac{\text{Urine albumin}}{\text{Serum albumin}}$$

   and expressed as a percentage. PSI was classified as good (1 - 15%), moderate (16 - 30%), and poor (> 30%), using the classification of Adeniyi, Hendrickse and Soothill (1976).

2. Serum HBsAg. The first 50 serum specimens were tested for HBsAg by counter-current immunoelectrophoresis. The remaining 50 sera were tested by radioimmunoassay (Ausria 11-125. Abbott Laboratories, North Chicago, Illinois) when the test became available in our hospital.

3. Percutaneous renal biopsy (PRB). PRB was done early in the morning after an overnight fast. The patient was sedated, usually with a combination of intramuscular pethidine and

chlorpromazine given one hour before the biopsy. The site of biopsy was localised as follows. The lateral border of sacrospinal muscle was traced to the point where it crosses the lower border of the last rib. The biopsy site was 1 - 2 cm below this point along a perpendicular line parallel to the vertical axis of the spine. Franklin-Vim-Silverman biopsy needle was used initially, but this was replaced with Tru-cut needle when the latter became available in our hospital. Usually two cores of renal tissue were obtained: one for immunofluorescence and the other for both light and electron microscopy. Only some of the specimens were processed for electron microscopy. The patient was kept in bed for 24h after the biopsy, with frequent monitoring of pulse and blood pressure and observation of the colour of urine specimens passed. The renal tissue for light microscopy was fixed in 10% buffered neutral formol saline and embedded in paraffin. Sections were stained with haematoxylin-eosin, Masson's trichrome, periodic acid-Schiff and methenamine silver; Congo red stain for amyloid was used for the first 40 biopsies. Histological classification of biopsies on light microscopy was based on that of Edington and Gilles (1976). The portion of renal tissue for electron microscopy was fixed in cold buffered 3% glutaraldehyde, post-fixed in buffered 1% osmium tetroxide, dehydrated in a graded ethanol series, cleared with toluene and embedded in araldite. The araldite blocks were then

sent to E.A.E. Van Marck of Prince Leopold Institute of Tropical Medicine, Antwerp, Belgium. He carried out the electron microscopic examination. Renal tissue for immunofluorescence was snap-frozen using carbon dioxide snow and then kept at -20°C until examined. The time between biopsy and immunofluorescence microscopy was never more than ten days. Sections 6 µm thick were cut in a cryostat, washed for 30 minutes in phosphate-buffered saline pH 7.2, and then stained with the following fluoresceinated conjugate antisera at optimal concentration: IgG, IgA, IgM, C_3, P. malariae, P. falciparum and HBsAg. With the exception of P. falciparum and P. malariae the antisera used were obtained from two sources (Behringwerke AG, Germany, and Burroughs Wellcome, England). The anti- P. malariae and anti-P. falciparum conjugates were prepared from specific antisera provided initially by D.A. Voller and later by National Biological Standards Board, London, England. Tissue specificity of the HBsAg antiserum was confirmed by testing it against liver tissue obtained from a patient with chronic active hepatitis and positive serum HBsAg (positive control liver), and against liver tissue from a patient without liver disease and negative serum HBsAg (negative control liver). Control kidney tissues were obtained from previously healthy children and adults who died in road traffic accidents or from patients who died of non-renal diseases. Conjugated sections were examined with a Zeiss

fluorescent microscope using a BG 12 primary filter and a secondary filter at 440 angstrom units. Fluorescence was arbitrarily graded as + (present), ++ (strong), and +++ (intense or very strong). The pattern and distribution of fluorescence were also noted.

4. Malaria and schistosome antibodies. Blood was collected from the first 50 patients and 52 sex and age-matched control children. The sera extracted from the blood were stored at -20°C until transported in a flask of ice chips to C.C. Draper of the London School of Hygiene and Tropical Medicine. The malaria and schistosome antibodies were measured in his laboratory, using the indirect fluorescent antibody technique for malaria and the enzyme linked immunosorbent assay (ELISA) technique for S. haematobium antibody.

The investigations carried out personally were:

1. Examination of the blood smear for malaria parasites.
2. Protein selectivity index.
3. Serum HBsAg.
4. Percutaneous renal biopsy, and
   - 4.1 Processing the tissue for immunofluorescence and examination of the tissue under fluorescence microscope.

4.2 Histological examination under light microscope.

4.3 Preparation of some of the specimens for electron microscopy.

3.5 Management. All patients were admitted for initial evaluation. After discharge they were taken home to make tracing of defaulters easier. The patients were followed as outpatients in the Nephrology Clinic. They were readmitted if they had exacerbation of their symptoms which could not be controlled as outpatients, or electively for reevaluation, 6-12 months after the initial assessment.

3.5.1 Inpatient. The patient was weighed and the blood pressure recorded not less than once daily. A record of the fluid intake and output was kept. The urine was tested daily for protein by the disptick method. A diet of high protein and low salt was prescribed routinely. The practical translation of high protein diet depended on what was available in the kitchen. After blood had been taken for examination for malaria, each patient received a course of oral chloroquine 25mg/kg/day in two divided doses for three days, followed by weekly prophylactic pyrimethamine. The dose of pyrimethamine was 12.5mg for patients under five years of age, 25mg for those five years old and above. Each patient received oral furosemide 2mg/kg as a single dose

daily. If there was no diuresis, spironolactone 2mg/kg/day in two divided doses was added. The diuretics were discontinued when oedema subsided. The purpose of diuresis was to produce a cosmetic effect which was found necessary to discourage patients from absconding.

3.5.2 Outpatient. The following observations were made at each follow-up visit: history of general well-being, oedema, infection; presence of oedema, blood pressure, and urinalysis. Pyrimethamine was given routinely, but a diuretic (hydrochlorothiazide 2mg/kg/day in 2 divided doses) was prescribed if there was oedema.

3.5.3 Other drugs. It was decided at the beginning of the study that only patients with MCN would be treated with prednisolone according to the following regime:

(i) 2 mg/kg/day in three divided doses for 28 days, followed by;

(ii) 2 mg/kg as a single dose in the morning on alternate days for 28 days;

(iii) Thereafter, the prednisolone was tapered off over the next 28 days.

Total duration of prednisolone therapy: 12 weeks.

Towards the end of the study, a randomized cross-over trial was started of cyclophosphamide and levamisole in the treatment of nephrotic syndrome. The initial treatment consisted of either cyclophosphamide 3mg/kg/day for 12 weeks, or levamisole 3mg/kg thrice a week for 12 weeks. Only patients with non-minimal change disease were enrolled in the study.

3.6 Statistical analysis. Chi-square (X^2) was used to compare distributions of values between groups of patients. A P value of < 0.05 was regarded as statistically significant.

CHAPTER 4

R E S U L T S

One hundred consecutive children aged 12 years and below who had nephrotic syndrome were studied in Ahmadu Bello University Hospitals in Kaduna and Zaria over a six-year period from 1977 to 1983. The first 40 patients were studied in Kaduna while the remaining 60 were studied in Zaria. One hundred patients were admitted over a four-year period, but the duration of the study including follow-up was six years. The average number of children with nephrotic syndrome admitted yearly was 25, while the average figure for the total number of paediatric admissions per year during the study period was 7067. Nephrotic syndrome therefore formed 0.35% of all paediatric admissions per year.

4.1 Age and sex incidence.

Children with nephrotic syndrome ranged in age from one to 12 years, with a mean of 5.8 years. The peak incidence was 4-7 years. The sex incidence was about equal: 53 males and 47 females. The age distribution of the patients is shown in Fig. 4.1. The mean age of male patients, 5.9 years, was slightly

higher than the mean age of 5 years for the females. The age distribution of patients in the different histological subgroups was similar. Thus, the age range and mean age in years were: MPGN 3-11 (6.2); QMN 3-10 (6.0); PGN 1-9 (5.7); MCN 2-12 (5.8), others 3-12 (6.0).

4.2 Familial incidence.

There was no familial incidence - that is, no family had more than one child with nephrotic syndrome.

4.3 Ethnicity.

Eighty of the 100 patients were indigenes of Kaduna State who were normally resident in the State. Of the remaining patients, 14 came from neighbouring states, and only six were from states in the southern part of Nigeria.

4.4 Monthly incidence.

The monthly distribution of nephrotic syndrome in relation to rainfall and relative humidity in Zaria is illustrated in Fig. 4.2. Although nephrotic syndrome was seen throughout the year, more cases were seen in the first half of the year, during the dry season and when the relative humidity was low.

4.5 Clinical features.

4.5.1 Oedema. By definition, all the patients had oedema; this was the main presenting feature in all of them. The duration of oedema ranged from three days to three weeks, with a mean of one week. Oedema was generalised in 84 patients: one such patient is shown in Fig. 4.3a. Fig. 4.3b is the same patient after diuresis. Ascites was present in 80 patients. In seven patients, ascites was more prominent than peripheral oedema as shown in Fig. 4.4.

4.5.2 Fever. Forty-three patients complained of fever of 2-4 days duration. However, only 11 patients had a temperature of 38°C or more on admission. The high temperature was associated with pneumonia in seven patients, and urinary tract infection in two patients.

4.5.3 Haematuria. In addition to oedema, macroscopic haematuria was a presenting symptom in 11 patients. Eight of the 11 patients had high blood pressure, their urine microscopy showed red cells and/or granular casts. Five of the eight patients had high ASOT: histology of renal biopsy was diffuse PGN in all five patients. Four patients had QMN, one patient had MPGN, and the remaining patient had an unclassifiable histology with features of a slowly progressive glomerular disease. Thus, eight of 11 patients with gross haematuria had a nephritic component

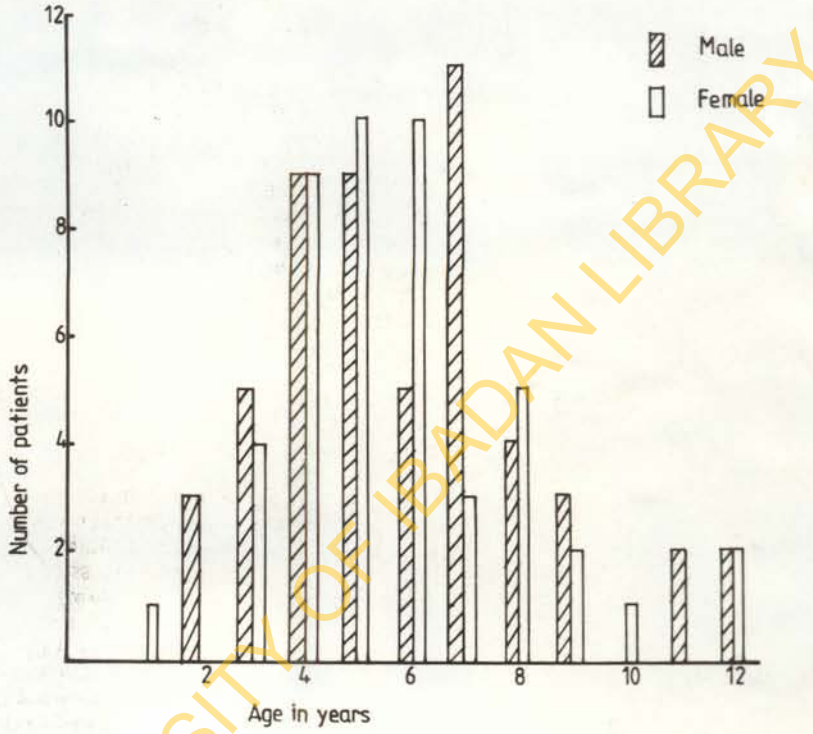

Fig. 4.1 Age distribution of children with nephrotic syndrome.

to their nephrotic syndrome - "nephritic nephrotic". One patient without haematuria also had a nephritic nephrotic syndrome.

4.5.4 Sorethroat/infected skin. There was a history of infected skin in 12 and of sorethroat in eight patients within a period not longer than three months before the onset of oedema. Two patients had both infected skin and sorethroat.

4.5.5 Hypertension. Twenty-eight patients had high blood pressure on admission, but hypertension was persistent in only four of them. One of these four presented with nephritic nephrotic syndrome.

4.5.6 Hepatosplenomegaly. There was hepatosplenomegaly in 22 patients, hepatomegaly alone in 12 and splenomegaly alone in three patients. Liver size ranged from 2 to 9cm and the spleen from 2 to 12cm. Hepatosplenomegaly was associated with S. mansoni in three patients.

4.5.7 Others. At the time of admission there was oliguria in 17, circulatory overload in 9 and pneumonia in 7 patients.

4.6 Investigations

4.6.1 Urine examination. Forty patients had erythrocyturia, 32 had pyuria and 32 had casturia. Urine culture grew pathogens in 20 patients: E. coli was isolated in 11 of

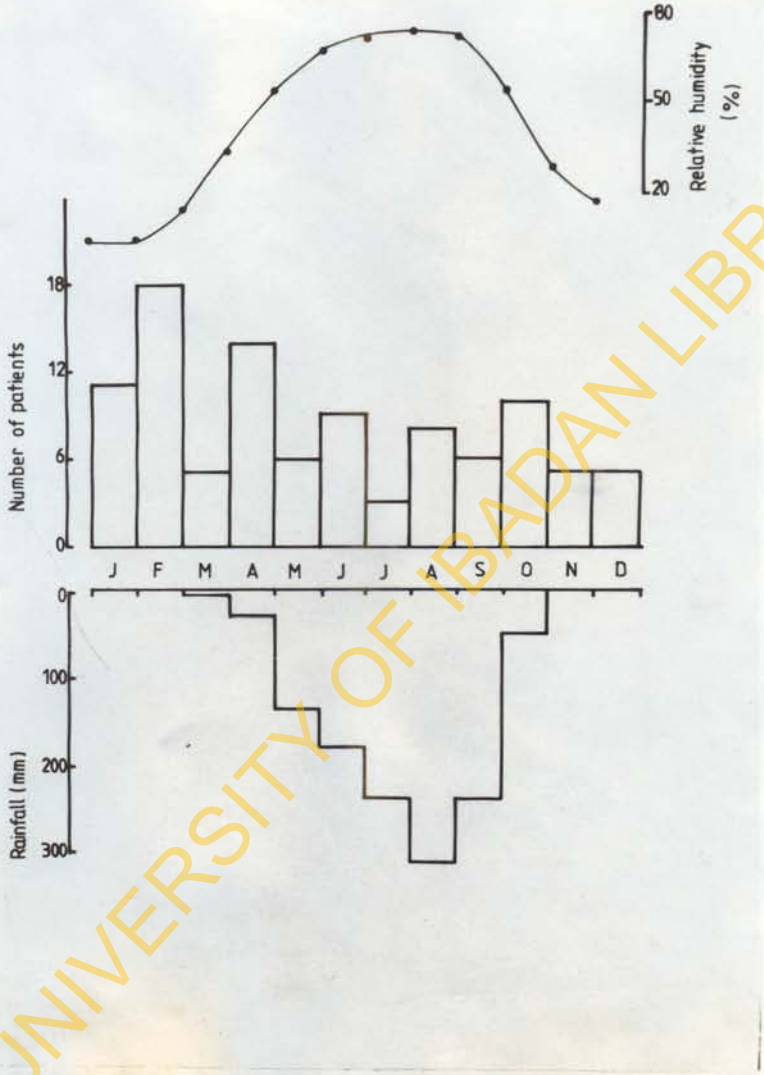

Fig. 4.2 Monthly distribution of cases of nephrotic syndrome in relation to rainfall and relative humidity.

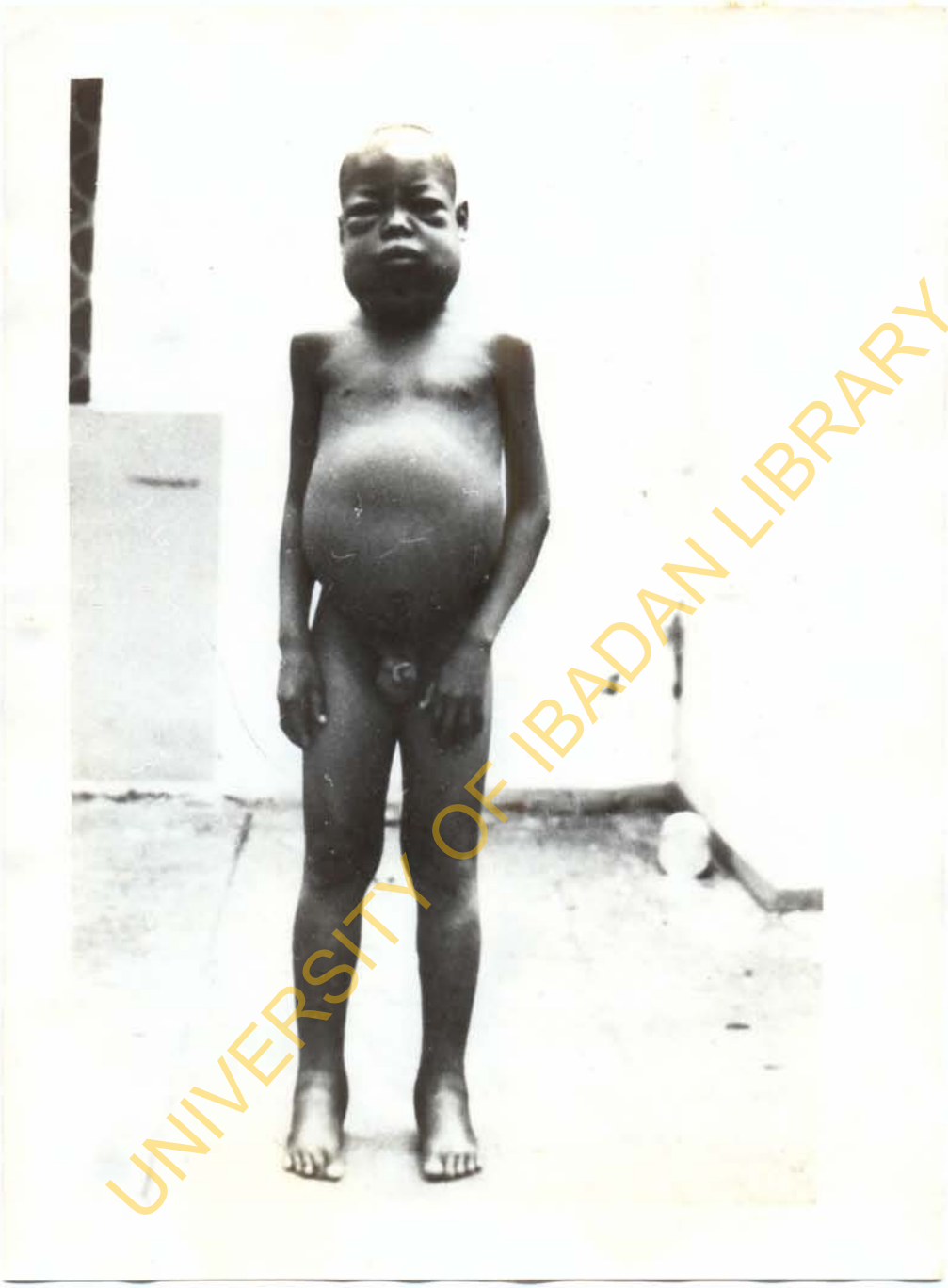

Fig. 4.3a. A child with nephrotic syndrome: on admission.

Fig. 4.3b. A child with nephrotic syndrome: after diuresis.

Same patient as in Fig. 4.3a.

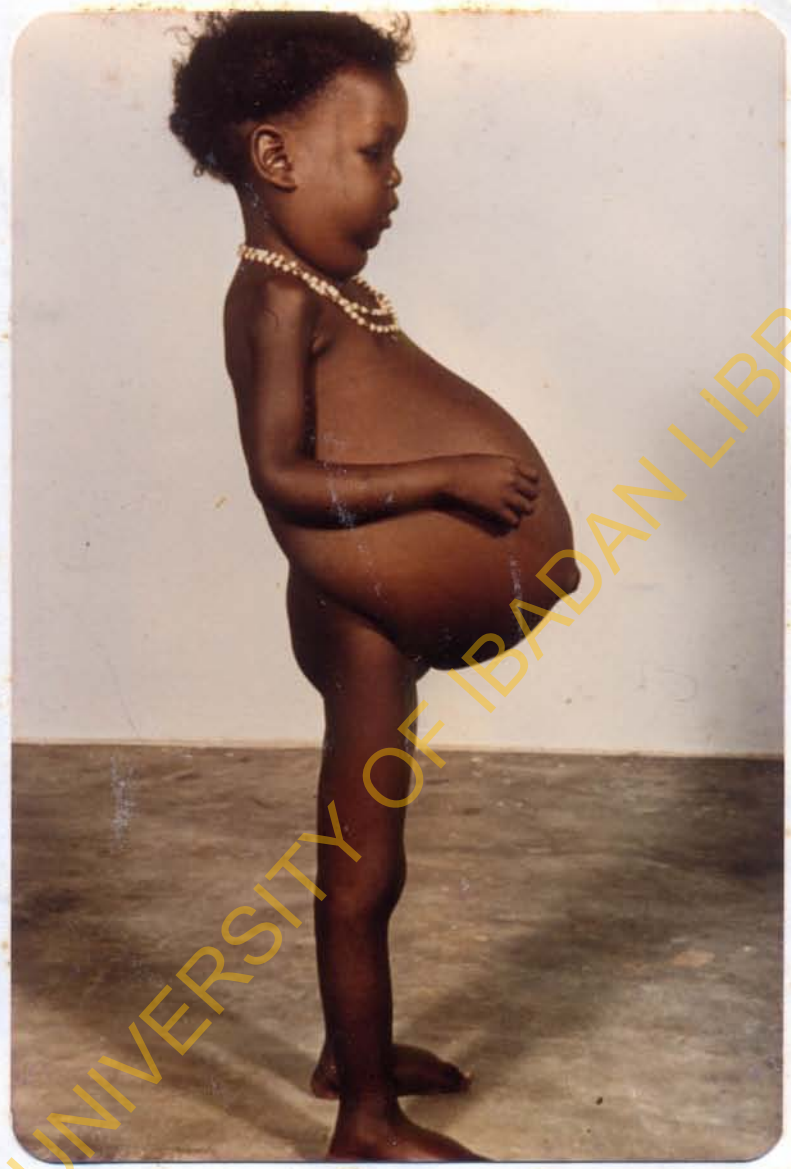

Fig. 4.4 A child with nephrotic syndrome in whom ascites was more prominent than peripheral oedema.

these. The frequency of bacteriuria in the different histological diagnosis was about the same. After ten days treatment bacteriuria was eradicated in 12 patients but persisted in eight patients who needed 20-30 days treatment. Bacteriuria was recurrent in 10 and persisted in 5 patients. Recurrent bacteriuria was due to relapse in four and reinfection in six patients. None of the five patients with persistent bacteriuria had remission of their nephrotic syndrome. 24h urine protein varied from 2.0g to 13.4g, with an average of 4.7g. There was no correlation between the amount of proteinuria and the histological diagnosis.

4.6.2 Blood chemistry. Total serum proteins ranged from 35g to 67g/l (mean 49.6g/l), with an albumin of 6-24g/l (mean 15g/l). Serum albumin was $\leqslant$ 15g/l in 30 patients. Serum proteins in control children were: total 55-80g/l (mean 65g/l), albumin 28-45g/l (mean 33g/l). There was a wide scatter in the values of serum cholesterol (1.1-17.2 mmol/l), with a mean of 7 mmol/l. The mean serum cholesterol in nephrotic children was significantly higher than 4.1 mmol/l obtained in control children. Thirty-three patients had serum urea above 6.5 mmol/l, the upper limit of normal for the hospital. At the time of discharge, only 13 patients still had raised urea. Twelve patients

had serum creatinine above 124 umol/l, the upper limit of normal for the hospital.

4.6.3 Throat and skin culture. None of the ten throat swab and two skin swab cultures yielded pathogens.

4.6.4 ASOT. ASOT was more than 200 iu/ml in 14 patients, with values ranging from 250 to more than 2560 iu/ml. The upper limit of normal for ASOT was 200 iu/ml. Histological diagnoses in these patients were: DPGN 5, QMN 5, MPGN 3, and congenital nephropathy 1.

4.6.5 Haemogram. Haemoglobin was less than 10g/dl in 44 patients, with levels ranging from 4.3 to 9.8g/dl. Nine of these patients required blood transfusion. Significant eosinophilia was present in nine patients. In three patients the eosinophilia was associated with the presence of parasites in the stool. The distribution of haemoglobin genotype in children with nephrotic syndrome is shown in Table 4.1. Since there are no data available on haemoglobin genotypes in Kaduna State, the pattern in the present study was compared with figures obtained in children in Kano State (Molinueaux and Gramiccia, 1980). Kaduna and Kano states are adjacent and have similar ethnic groupings. There was no significant difference in the frequency of genotypes between the patients and the children in the population. Moreover, there was no

nephrotic patient with sickle cell anaemia. Thus, haemoglobin genotype S did not appear to be associated with increased frequency of nephrotic syndrome.

4.6.6 Intravenous urogram. IVU was done in 60 patients: there was abnormality in 7 of them. The abnormalities found are summarised in Table 4.2. These abnormalities were considered to be unrelated aetiologically to the nephrotic syndrome.

4.6.7 Hepatitis B surface antigen. Sera from the first 50 patients were tested for HBsAg by counter-current immunoelectrophoresis. Thirteen nephrotic sera were positive, compared with two of 40 control children. The higher frequency of hepatitis B antigenaemia in nephrotic compared with control children was statistically significant (X^2 = 5.63, 1 df, $P < 0.02$). Sera from the remaining 50 patients were tested by radioimmunoassay when the reagents to do the test became available. Although the frequency of positive serum HBsAg was higher in control children (28 out of 61 or 45.9%) than in children with nephrotic syndrome (18 out of 50 or 36%), the difference was not statistically significant - X^2 = 1.1, 1 df, $0.30 > P > 0.20$. However, if only sera with radioactivity more than 2 SD above background radioactivity were considered HBsAg positive, 16 out of 50 (32%) nephrotics and only 2

out of 61 (3.3%) controls would be regarded as positive. Thus, the titre of antigenaemia, as judged by the amount of radioactivity, was significantly higher in nephrotics than in controls - X^2 = 16.68, 1 df, $P < 0.001$. Moreover, HBsAg was detected by immunofluorescence in 18 out of the 76 renal biopsies (24%) examined.

The frequency of positive HBsAg in the different histological lesions is illustrated in Table 4.3. HBsAg was most frequent in patients with MPGN: although MPGN formed 25.5% of all biopsies, patients with MPGN constituted 45% of all patients with HBsAg. As shown in Table 4.3, the high frequency of positive HBsAg in patients with MPGN was responsible for the statistically significant result obtained when all the histological diagnoses were considered together. None of the nine patients with MCN had positive serum HBsAg.

4.6.8 Malaria parasitaemia. The peripheral blood of eight patients was not examined for malaria because five of the patients had received chloroquine on admission before their blood could be tested, while the remaining three patients had been given chloroquine within one week before admission. Histology of renal biopsy in these eight patients showed MPGN (3), PGN (3), QMN (1) and ESRD (1). Table 4.4 shows that the yield of malaria parasitaemia

TABLE 4.1

Haemoglobin genotype in children with nephrotic syndrome and in children in the population.

Haemoglobin Genotype	Frequency (%)	
	Nephrotic children (n = 100)	Children in the population* (n = 895)
AA	76	70.2
AS	23	29.3
AC	1	0.4
SS	0	0.1

* Source: Molineaux and Gramiccia, 1980.

TABLE 4.2

Abnormalities found in intravenous urogram of children with nephrotic syndrome (n = 60).

Abnormality	Number
Double collecting system	3
Elongated calyces	1
Slightly enlarged kidneys	1
Poor concentration	1
Enlarged bladder	1
Total	7

increased with increased frequency of peripheral blood examination. The malaria parasitaemia rates in nephrotic and control children are shown in Table 4.5. Two nephrotic children had mixed infection with P. malariae and P. falciparum, while one patient had P. vivax infection. The patient with P. vivax was a 3-year old Fulani girl who presented with anasarca, circulatory overload and high blood pressure of 130/90 mmHg. She had erythrocyturia, pyuria and E. coli urinary tract infection. Each of the four peripheral blood specimens examined on different occasions showed P. vivax. Her renal biopsy showed QMN. Unfortunately she absconded after diuresis following diuretic treatment. The prevalence of malaria parasitaemia was much higher in nephrotic children than in the control group of children (X^2 = 24.018, 1 df, $P < 0.0005$). However, the prevalence of P. falciparum parasitaemia was not significantly different in the two groups of children (X^2 = 2.770, 1 df, $0.10 > P > 0.050$). The difference in the overall parasitaemia rates was due to a higher frequency of P. malariae in nephrotic patients than in control children (X^2 = 21.511, 1 df, $P < 0.0005$). The distribution of P. malariae parasitaemia among patients with different histological types is shown in Table 4.6. There is no significant difference in the frequency of P. malariae parasitaemia among the different histological lesions. In other words, P. malariae parasitaemia was not peculiar to any histological lesion.

TABLE 4.3

Renal histology and positive HBsAg

Histology	Serum HBsAg		Total
	Positive	Negative	
MPGN	14	11	25
QMN	8	12	20
PGN	4	15	19
Miscellaneous	3	6	9
MCN	0	9	9
ESRD	2	6	8
RPGN	0	4	4
FSGS	0	2	2
MGN	0	2	2
No biopsy	0	2	2
Total	31	69	100

X^2 = 17.634, 9 df, $0.050 > P > 0.025$

If MPGN is removed from the table, X^2= 10.33, 8 df, $0.30 > P > 0.20$

MPGN = membranoproliferative glomerulonephritis

QMN = quartan malarial nephropathy

PGN = proliferative glomerulonephritis

MCN = minimal change nephropathy

ESRD = end-stage renal disease

RPGN = rapidly progressive glomerulonephritis

FSGN = focal segmental glomerulosclerosis

MGN = membranous glomerulonephritis

TABLE 4.4

Number of blood smears positive for malaria parasite

	Nephrotic	Control
After the first examination	54	29
After the second examination	59	32
After the third examination	62	32

TABLE 4.5

Malaria parasitaemia in nephrotic and control children.

	Malaria parasite present	absent	X^2	P
Overall				
Nephrotic	62+	30		
Control	32	68	24.018	<0.0005
P. malariae				
Nephrotic	31	61		
Control	7	93	21.511	<0.0005
P. falciparum				
Nephrotic	30+	62		
Control	25	75	2.770	0.10 > P > 0.05

+ This figure include one patient with P. vivax infection.

4.6.9 Malaria antibodies. Serum malaria and schistosome antibodies were determined in 50 patients. This was a collaborative study undertaken by the staff of the Department of Paediatrics in Ahmadu Bello University, Zaria, and workers in London School of Hygiene and Tropical Medicine (Narayana et al, 1982). Since the author was not the principal investigator, details of the study are not given here. In a summary, significant P. malariae antibody was found in 48% of nephrotics compared with 7.7.% of controls. In contrast, the prevalence of significant P. falciparum antibody level was similar in the two groups of children. Thirteen out of 15 patients with QMN had high serum P. malariae antibody level, compared with seven out of 14 patients with MPGN. However, the difference was not statistically significant.

4.6.10 Schistosome antibody. Reagent was available to test for S. haematobium only. One of the 50 nephrotics and two of the 52 controls had significant S. haematobium antibody levels.

4.6.11 Protein selectivity index (PSI). The correlation between histological diagnosis and PSI is illustrated in Fig. 4.5. It was observed that none of the histological types showed a characteristic pattern of PSI. Instead, there

TABLE 4.6

Frequency of *P. malariae* parasitaemia among nephrotic patients with different histological lesions.

Histology	*P. malariae* +ve	*P. malariae* -ve	Total
MPGN	10	15	25
QMN	8	12	20
PGN	4	15	19
MCN	2	7	9
Others	7	12	19
Not tested			8
Total	31	61	92/100

$X^2 = 3.239$, 4 df, $0.60 > P < 0.50$

MPGN = membranoproliferative glomerulonephritis
QMN = quartan malarial nephropathy
PGN = proliferative glomerulonephritis
MCN = minimal change nephropathy

seemed to be an inverse relationship between PSI and severity of glomerular damage, irrespective of the histological diagnosis.

Renal biopsies

Renal biopsy was unsuccessful in two patients.

4.6.12 Light microscopy. Tables 4.7 and 4.8 show the classification of renal biopsies by light microscopy. A brief description of the major histological types and the unclassifiable biopsies is given here.

MPGN. The characteristics of this entity were prominent lobulation of the glomeruli, glomerular cell proliferation and irregular splitting or a plexiform arrangement of the basement membrane. The basement membrane lesion was most clearly demonstrated with the silver stain. In a few biopsies the lesion was focal and segmental. Fifteen of the biopsies were classified as severe, ten as moderate. Occasionally, the differentiation of MPGN and QMN was difficult.

QMN. QMN was diagnosed on the basis of varying degrees of severity of focal and segmental glomerulitis with thickening of glomerular capillary wall and, occasionaly, sclerosis. Endothelial cell proliferation was absent or inconspicuous, and there was focal and segmental

deposition of PAS positive material in the mesangium. The basement membrane is thickened: the thickening may give rise to a double contour, a honeycomb or a plexiform arrangement. This results in increased narrowing and, ultimately, obliteration of the capillary lumen. Ultramicroscopy confirms irregular thickening of capillary basement membrane. Some workers have described as a "unique feature" the presence of small lacunae in the basement membrane (Hendrickse et al, 1972; White, 1973).

PGN. In PGN, there was generalised increased cellularity of both endothelial and mesangial cells. In nine of the 19 cases of PGN there were inflammatory exudative cells, so that the lesion was indistinguishable from post-streptococcal acute glomerulonephritis. All the nine patients had nephritic features at admission, associated with ASOT above 200 iu/ml in six of them. However, subsequent follow-up showed that the patients had nephrotic syndrome as defined earlier.

Unclassified. Three biopsies could not be classified into any specific category. In one of these there were six glomeruli: two with complete hyalinization, two with segmental hyalinization and two glomeruli were normal. The second biopsy contained 25 glomeruli: about half of the glomeruli appeared normal, six showed focal

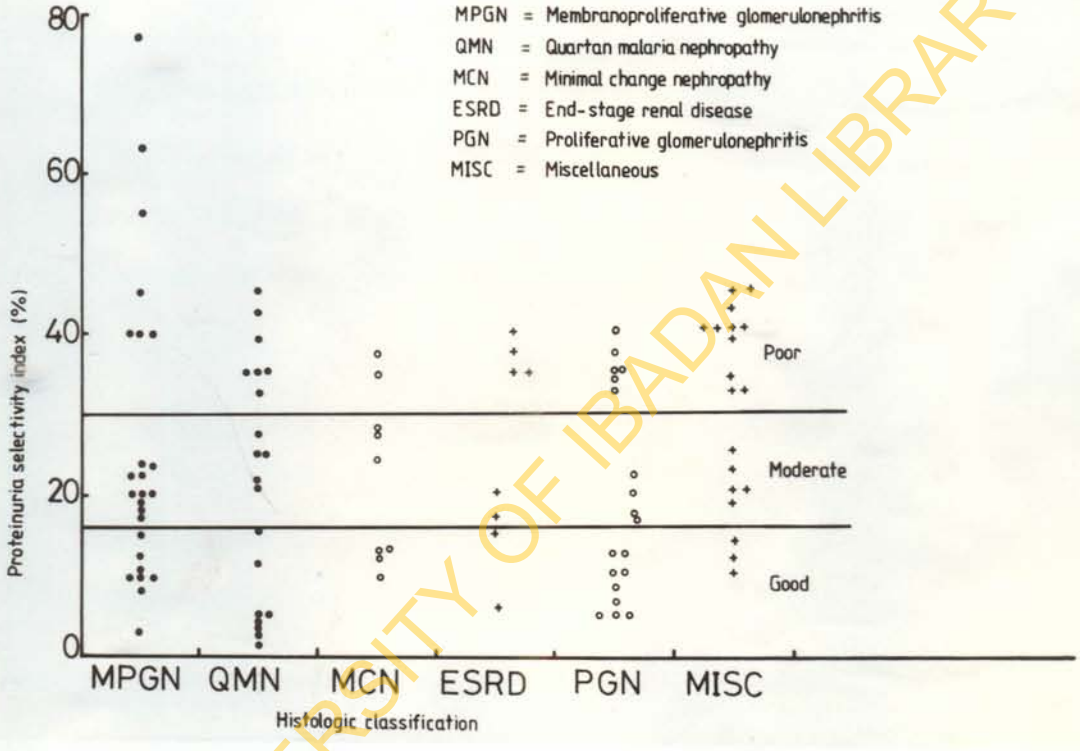

Fig. 4.5 Protein selectivity index related to histology.

TABLE 4.7

Histological classification of renal biopsies on light microscopy.

Histology	No. of patients
Membranoproliferative glomerolunephritis	25
Quartan malarial nephropathy	20
Proliferative glomerulonephritis	19
Minimal change nephropathy	9
Miscellaneous	9
End-stage renal disease	8
Rapidly progressive glomerulonephritis	4
Focal segmental glomerulosclerosis	2
Membranous glomerulonephritis	2
Total	98

TABLE 4.8

Analysis of nine renal biopsies classified as miscellaneous.

Histology	No. of patients
Interstitial nephritis	3
Unclassifiable	3
IgA nephropathy (Berger's disease)	2
Congenital nephropathy	1

hypercellularity at the hilum, mostly capsular. Some tubules contained protein casts, and there was moderate focal infiltration of the interstitium by mononuclear cells. The third biopsy was characterised by focal and segmental increased cellularity, and focal collections of eosinophils with focal loose fibrosis in the interstitium.

The most common histological types were, in order of frequency, MPGN, QMN and PGN. Only nine patients had MCN: the PSI was good in four, moderate in three, and poor in two. The two patients with MCN and poor protein selectivity were aged 9 and 12 years, compared with 6 years or less in the remaining seven patients with MCN. Although the histology was MCN by light miscroscopy, IgM and C_3 were detected by fluorescence microscopy in each patient, as shown in Table 4.9. Strictly speaking, therefore, these two patients should not be classified as MCN. Examples of histopathology of the biopsies are illustrated in Figs. 4.6-4.16.

4.6.13 Immunoflourescence. Immunofluorescence was carried out in 76 renal biopsies. Abnormal immunofluorescence with one or more conjugates was observed in 70 cases (92%). Four of the six cases without immunofluorescence had MCN. Immunofluorescence was predominantly coarsely granular (80%), but other patterns of immunofluorescence were also

observed: finely granular in 5%, linear in 4%, and mixed granular and linear in 11%. The findings on immunofluorescence microscopy are summarised in Table 4.9. Figs. 4.19 and 4.20 are two examples of the pattern of fluorescence observed.

4.6.14 Electron microscopy (EM). EM was performed in only 26 patients, as a collaborative study (Van Marck et al, 1983). Twelve cases of PGN by light microscopy were examined by EM: two of these turned out to be MPGN, one was QMN, while the remaining nine were confirmed as PGN. Of the 8 cases of QMN by light microscopy, only four proved to be QMN; two were MPGN while the remaining two showed sclerotic glomeruli. The latter could be advanced cases of QMN. Only 2 biopsies with MPGN were examined by EM. One of the two was MPGN while the other was QMN. The only case of MCN examined was also diagnosed as MCN on EM. These findings illustrate the usefulness of EM, in addition to light microscopy, for the complete histopathological evaluation of renal biopsies.

4.6.15 Repeat renal biopsies. A repeat renal biopsy was done in 18 patients, due mainly to deteriorating renal function. The findings are summarised in Table 4.10. There was progressive glomerular disease but the same diagnosis in 9 cases, no changes in diagnosis or severity between the

TABLE 4.9

Histological diagnosis related to immunofluorescence

Histological diagnosis	No. with immunofluorescence								Total no. of patients with immunofluorescence
	Whole	IgG	IgA	IgM	C_3	HBsAg	*P. falciparum*	*P. malariae*	
Membranoproliferative glomerulonephritis (n=23)	19	17	4	20	20	10	2	4	23
Quartan malarial nephropathy (n=15)	10	12	3	13	9	2	2	11	15
Proliferative glomerulonephritis (n=15)	12	9	0	10	10	4	0	0	14
Minimal change nephropathy (n=6)	2	0	0	2	2	0	0	0	2
Miscellaneous (n=6)	3	1	2	2	2	0	0	2	6
End-stage renal disease (n=5)	2	1	0	1	0	1	0	1	4
Rapidly progressive glomerulonephritis (n=3)	3	2	0	3	2	0	0	0	3
Focal segmental glomerulosclerosis (n=2)	2	2	0	1	1	0	0	1	2
Membranous glomerulo-nephritis (n=1)	1	0	0	0	1	1	0	0	1
Total (n = 76)	54	44	9	52	47	18	4	19	70

first and the second biopsy in seven cases, and in one child with PGN the repeat biopsy three years later was normal. In one patient with rapidly progressive glomerulonephritis, the repeat biopsy showed sclerosed glomeruli (Fig. 4.16 and Fig. 4.17).

4.6.16 Patients with S. mansoni. Six patients had S. mansoni in their stool. They were all male, ranging in age from four to 12 years. S. mansoni was associated with eosinophilia in three cases, hepatosplenomegaly in three, and mixed infection with S. haematobium in two cases. The three patients with hepatosplenomegaly had liver biopsy as part of another study of hepatosplenic schistosomiasis in children. The liver showed varying degrees of fibrosis, pigmentation, mononuclear cellular infiltration of portal tract, and tubercle formation. Two of the three patients with hepatosplenic schistosomiasis had high serum level of IgM and raised serum level of Widal agglutinating antibody; in one of them, both urine and blood grew S. typhi. Histology of renal biopsy in the three patients showed MPGN. In the remaining three patients renal histology showed MPGN 1, RPGN 1, and ESRD 1. The infection was treated with oxamniquine in three patients, with pyrazequantel in two, and with niridazole in one patient. The drug used depended on availability.

4.7 Treatment

4.7.1 Routine treatment. All patients were treated with high protein, low salt diet, chloroquine followed by pyrimethamine, and furosemide. Thirty three patients also received spironolactone because their oedema did not resolve with furosemide. The details of routine treatment of the patients are given in Chapter 3.5 (Management).

4.7.2 Additional treatment. Additional treatment was given as indicated. Thus, those patients who had pneumonia at admission received a course of penicillin, while patients with urinary tract infection were treated with cotrimoxazole or ampicillin, depending on which drug was readily available. Three patients with refractory oedema were given salt-poor albumin followed by intravenous furosemide. Diuresis was induced in two of them.

4.7.3 Specific treatment. Seven of the nine patients with MCN were treated with prednisolone. One of the remaining two MCN patients went into spontaneous remission before starting prednisolone, while the other one defaulted before therapy could be started. Five of the seven patients who received prednisolone responded. Three of the responders had good PSI, with values of 9, 12 and 13% respectively, while two had moderate PSI, with values of 23 and 26%, respectively. The glomeruli of the two non-responders had IgM and C_3 immunofluorescence. Of the five

TABLE 4.10

Repeat renal biopsy

Serial No.	Age at diagnosis (yr)/Sex	Diagnosis	Interval between biopsies (yr)	Comments
		Repeat biopsy worse		
1	4F	Quartan malarial nephropathy	1	Persistent proteinuria
2	9F	Quartan malarial nephropathy	0.8	In chronic renal failure
3	5M	Membranoproliferative GN	0.7	Persistent proteinuria
4	6F	Membranoproliferative GN	1	No response to cyclophosphamide
5	6M	Membranoproliferative GN	2	Slow deterioration in RFT
6	5M	Membranous GN	2	In chronic renal failure
7	4F	Interstitial nephritis	5	Persistent proteinuria but normal creatinine
8	4F	Rapidly progressive GN	0.2	Died in renal failure 0.4 years after onset
9	5F	Rapidly progressive GN	1.8	No response to cyclophosphamide
10	5F	Proliferative GN	2	Slow deterioration in RFT

Continued .....

TABLE 4.10 (Continued)

Serial No.	Age at diagnosis (yr)/Sex	Diagnosis	Interval between biopsies (yr)	Comments
		Repeat biopsy unchanged		
11	4M	Quartan malarial nephropathy	0.3	Persistent proteinuria
12	6F	Membranoproliferative GN	2	Persistent proteinuria but normal RFT
13	5M	Membranoproliferative GN	0.8	Responded to cyclophosphamide
14	4F	Membranoproliferative GN	0.6	Decreasing proteinuria
15	5M	Membranoproliferative GN	0.8	Persistent proteinuria
16	4M	Membranous GN	2.5	Has become hypertensive
17	5F	IgA nephropathy	1	In remission
		Repeat biopsy better		
18	4M	Proliferative GN	3	In remission for over 2 yrs

GN = glomerulonephritis
RFT = renal function test

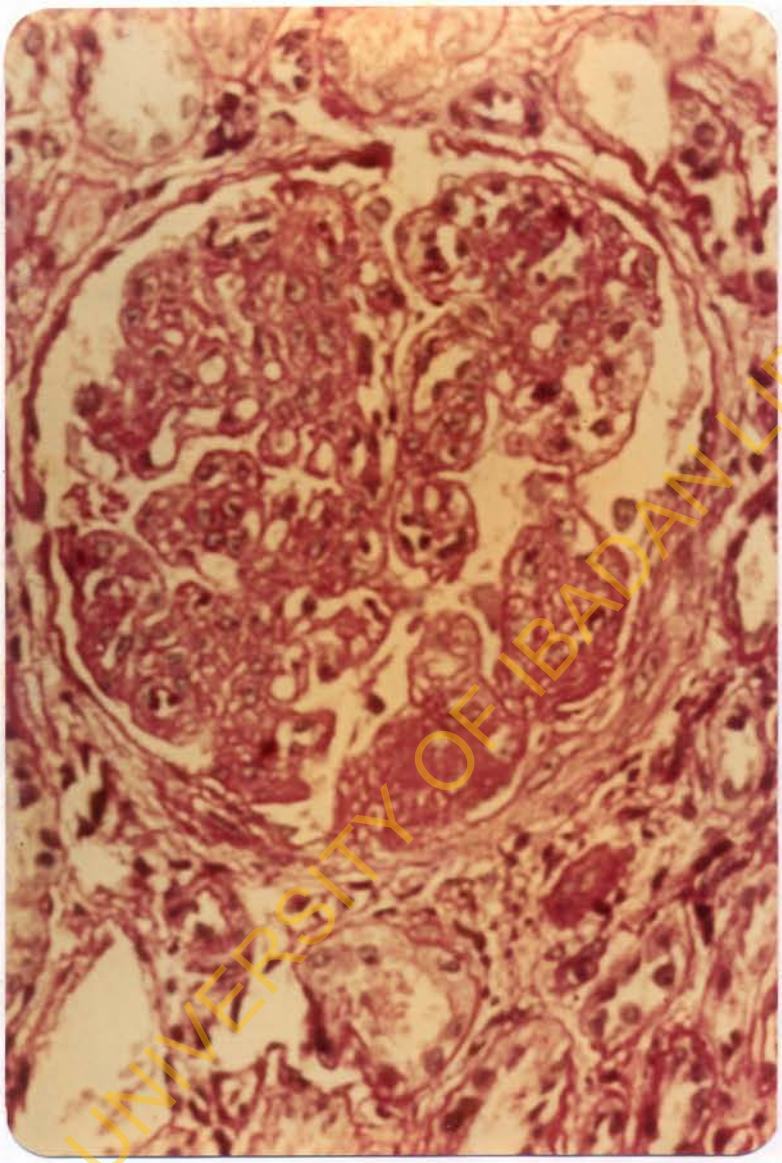

Fig. 4.6 Histopathology of membranoproliferative glomerulonephritis (PAS stain; x 200).

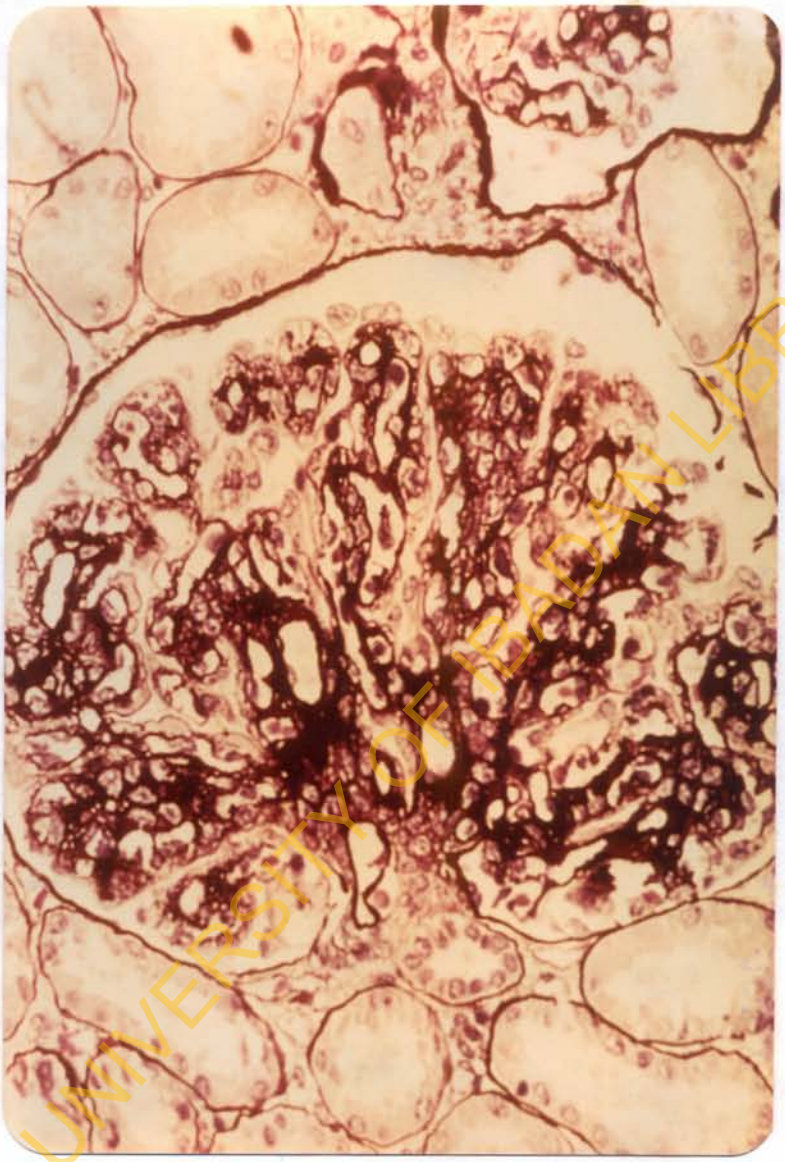

Fig. 4.7 Histopathology of membranoproliferative glomerulonephritis (Methenamine silver stain; x 200). Fig. 4.6 and Fig. 4.7 were from the same patient.

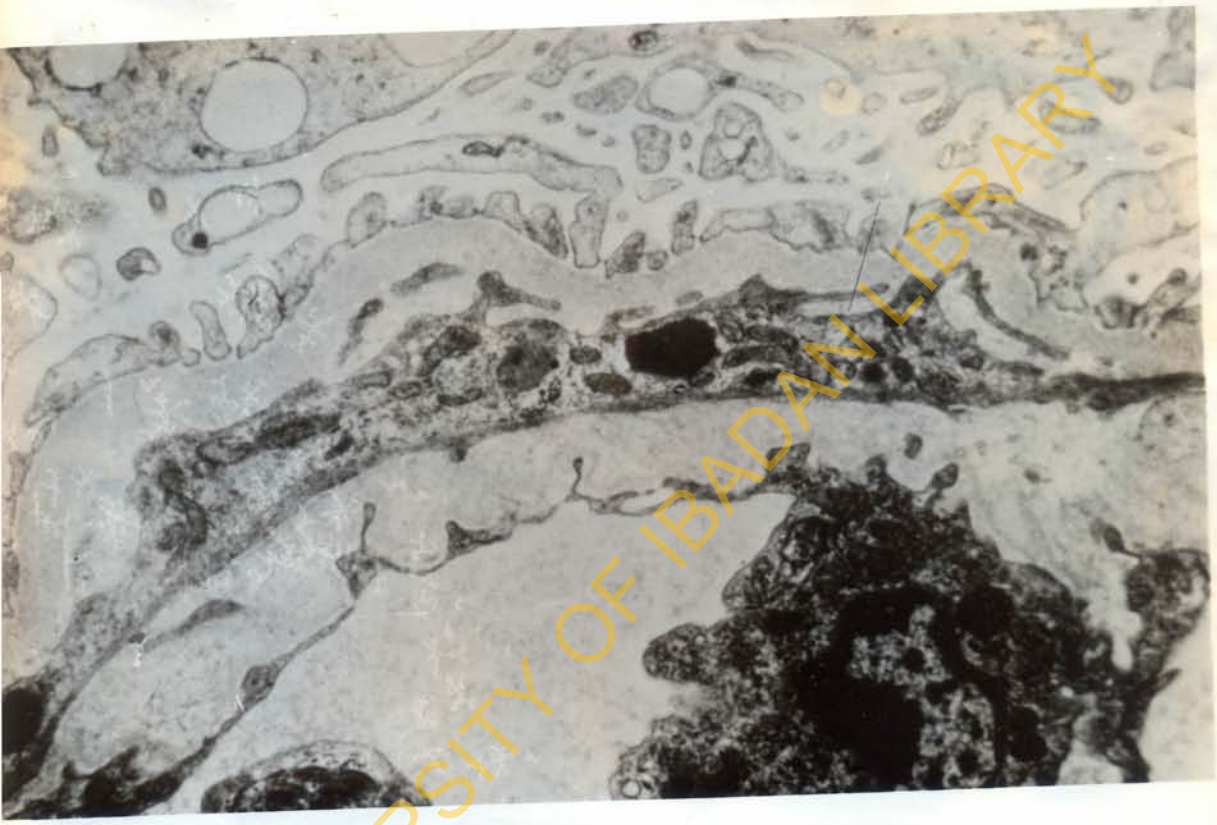

Fig. 4.8 Electronmicrograph of membranoproliferative glomerulonephritis, showing extension of mesangium into the basement membrane to give a double membrane (x10,000).

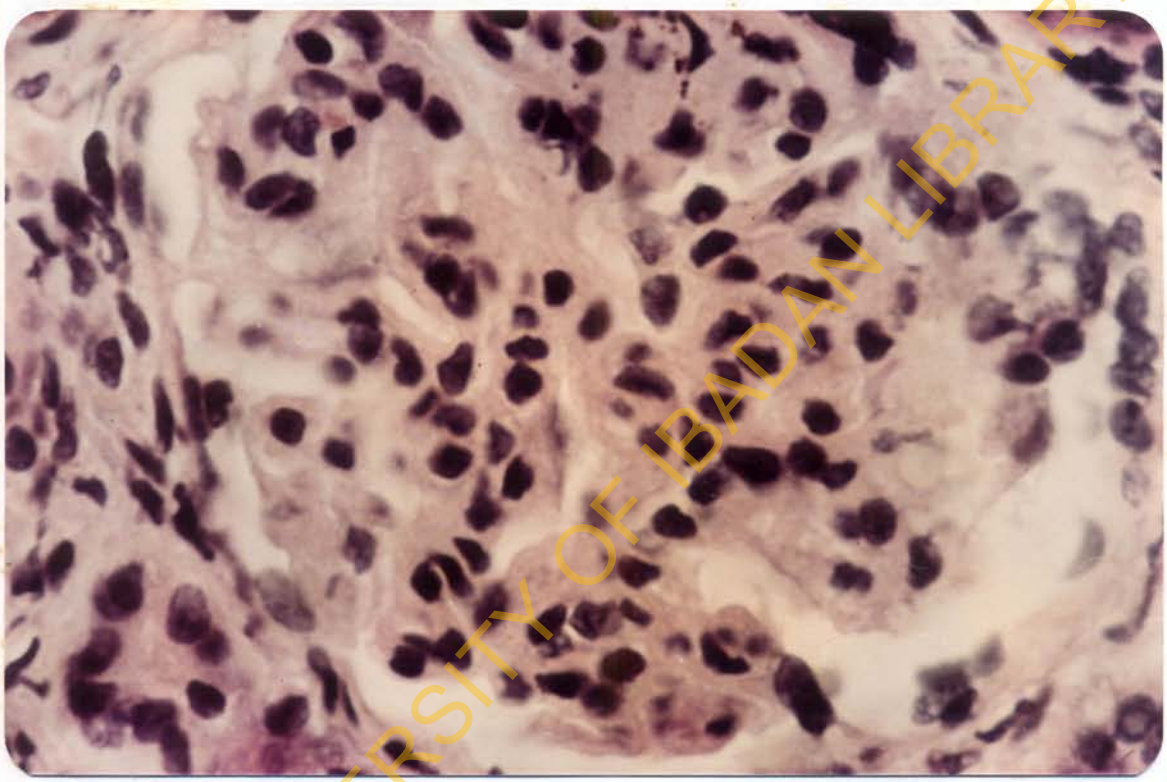

Fig. 4.9 Histopathology of quartan malarial nephropathy with uniform involvement of the glomerulus. (H & E stain; x 400).

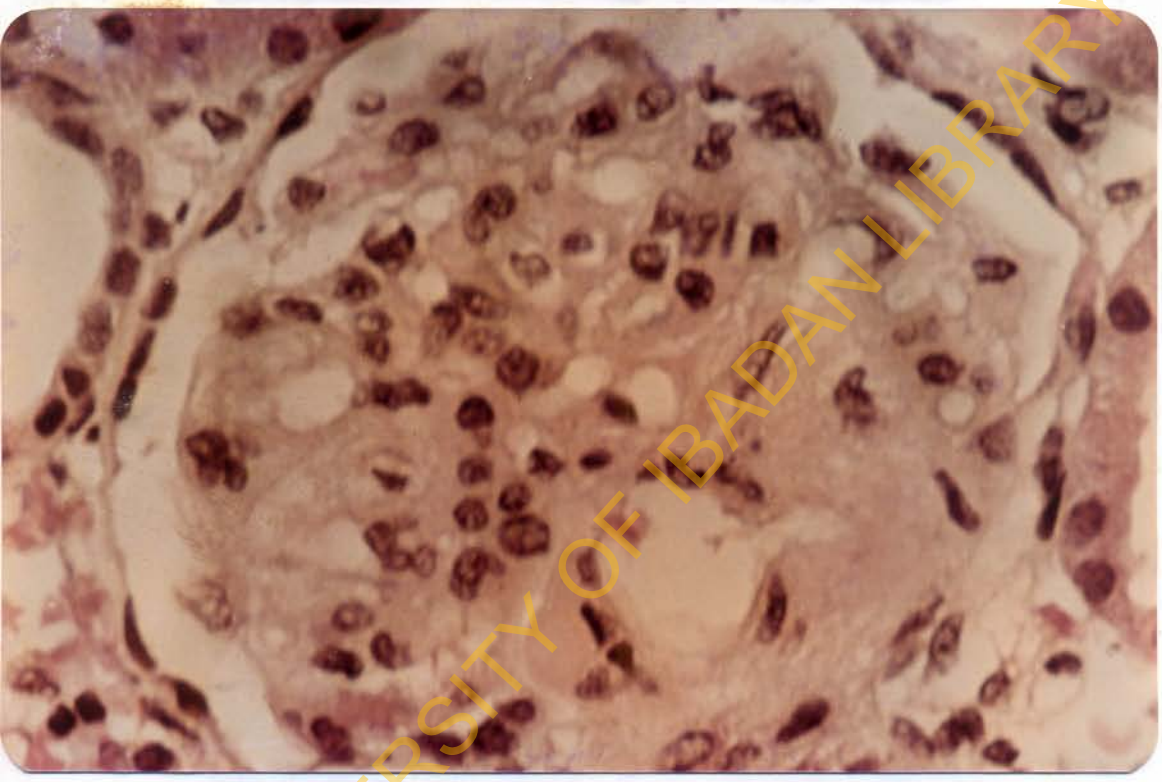

Fig. 4.10 Histopathology of moderately severe quartan malarial nephropathy with varying degree of involvement of the glomerulus (H & E stain; x 200).

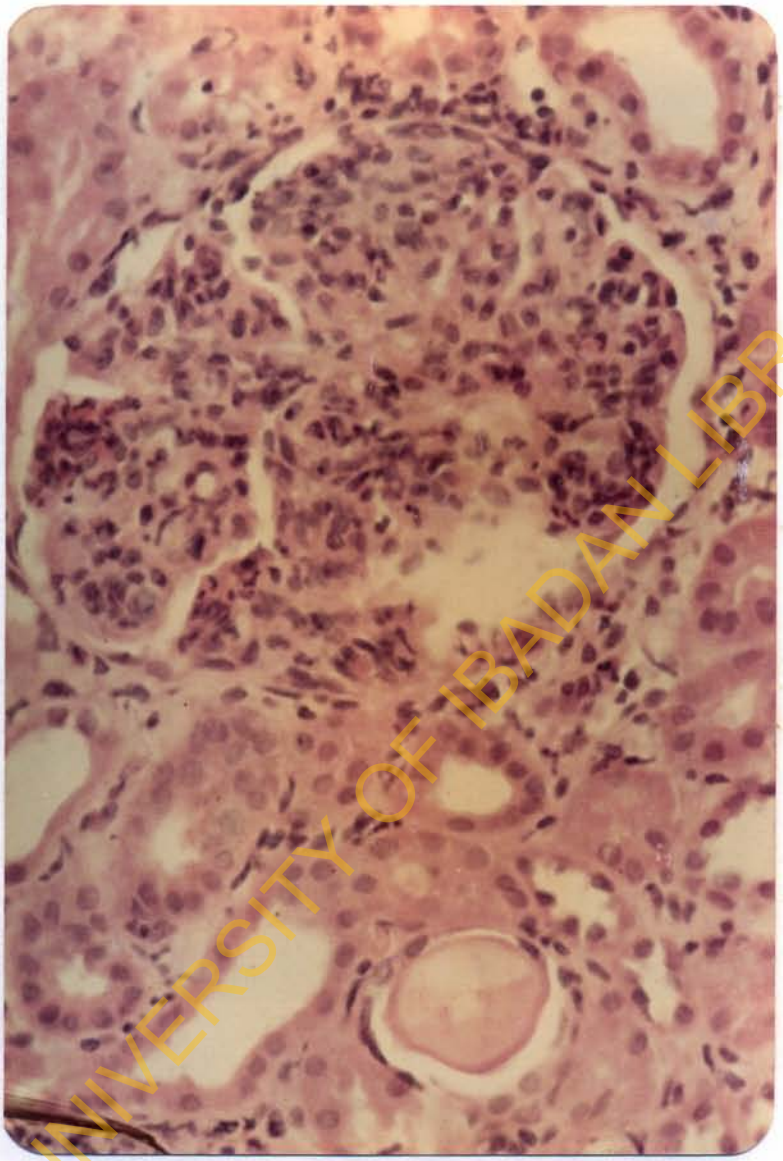

Fig. 4.11 Histopathology of diffuse, proliferative glomerulonephritis (H & E stain; x 200).

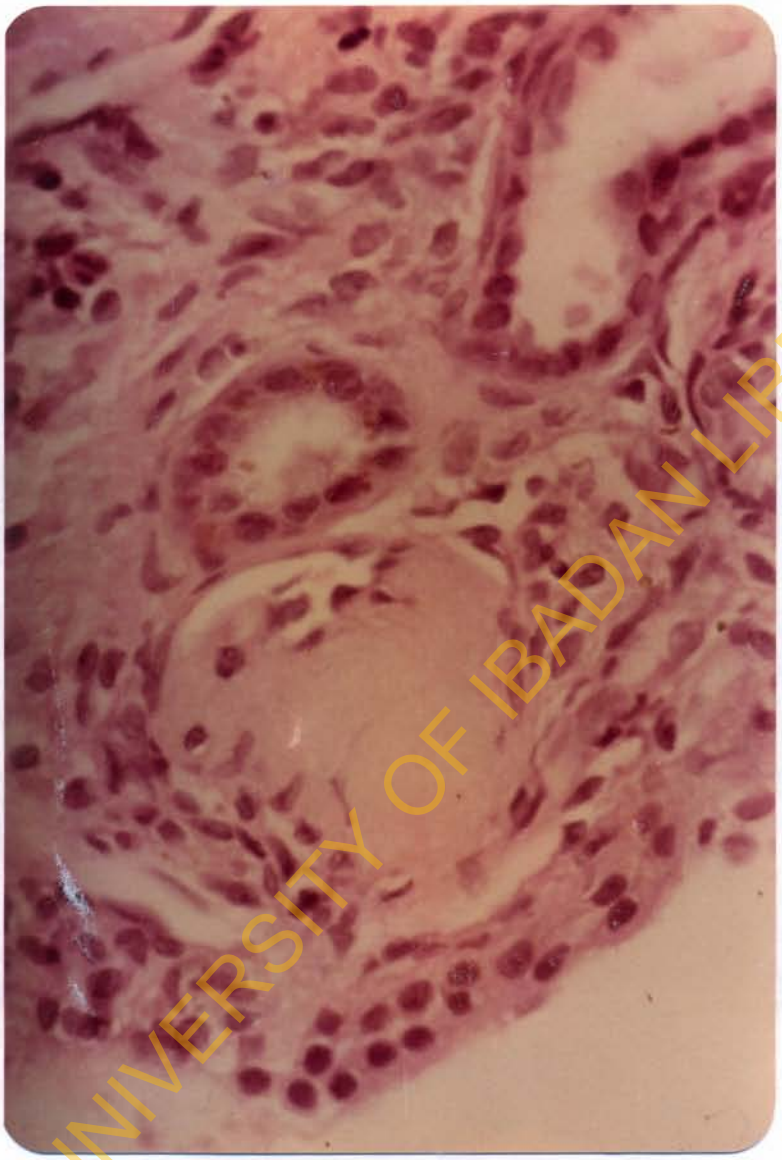

Fig. 4.12 Histopathology of end-stage renal disease, showing a sclerosed glomerulus and interstitial mononuclear cells (H & E stain; x 40).

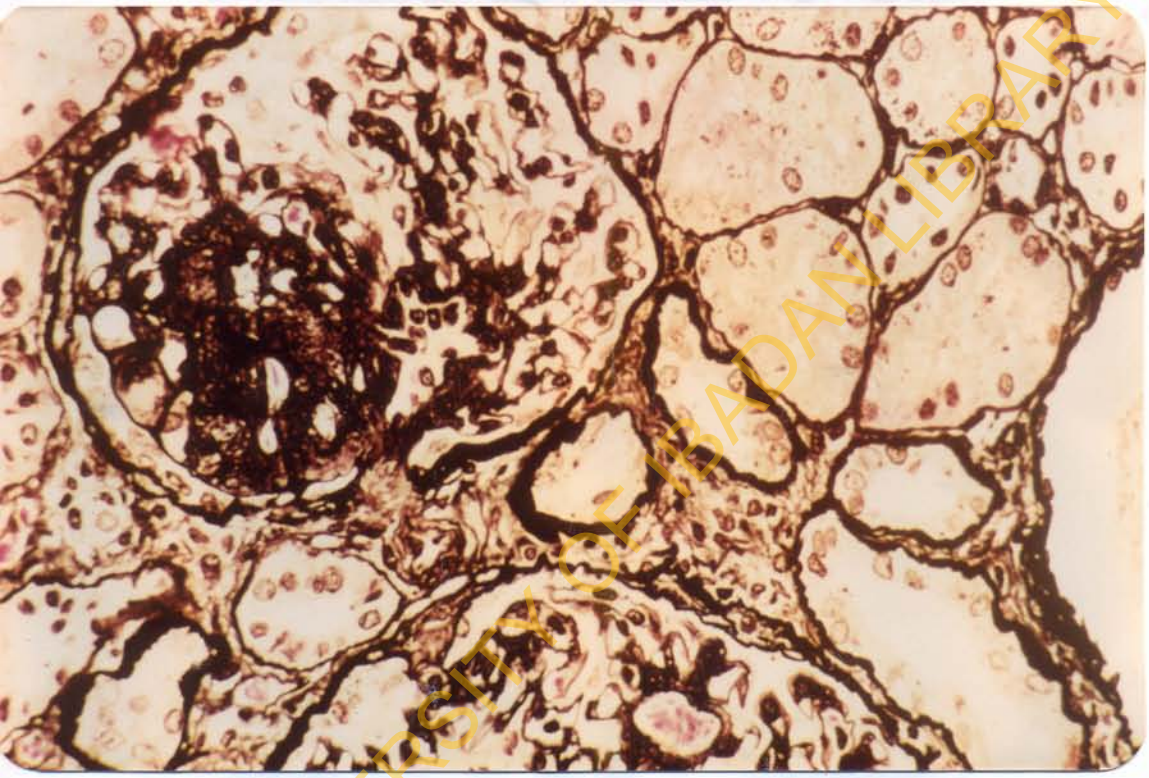

Fig. 4.13 Histopathology focal, segmental glomerulosclerosis (Methenamine silver stain; x 40).

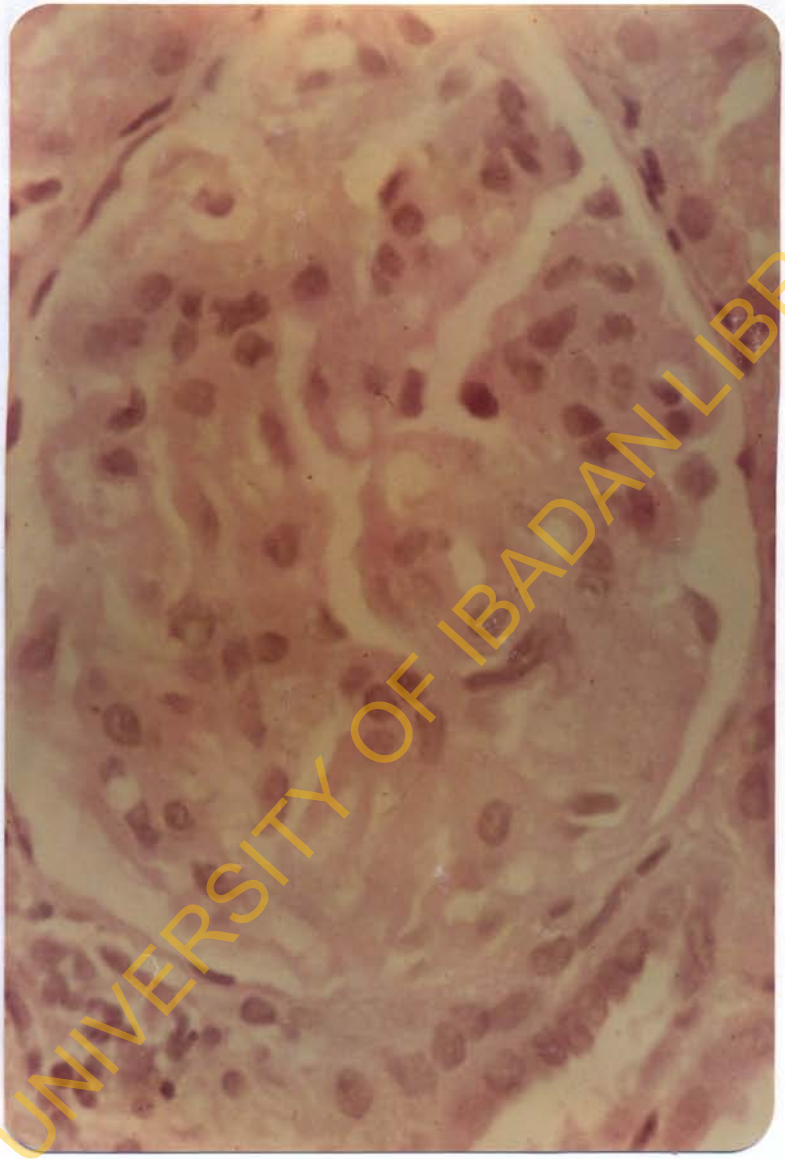

Fig. 4.14 Histopathology of membranous glomerulonephritis (H & E stain; x 400).

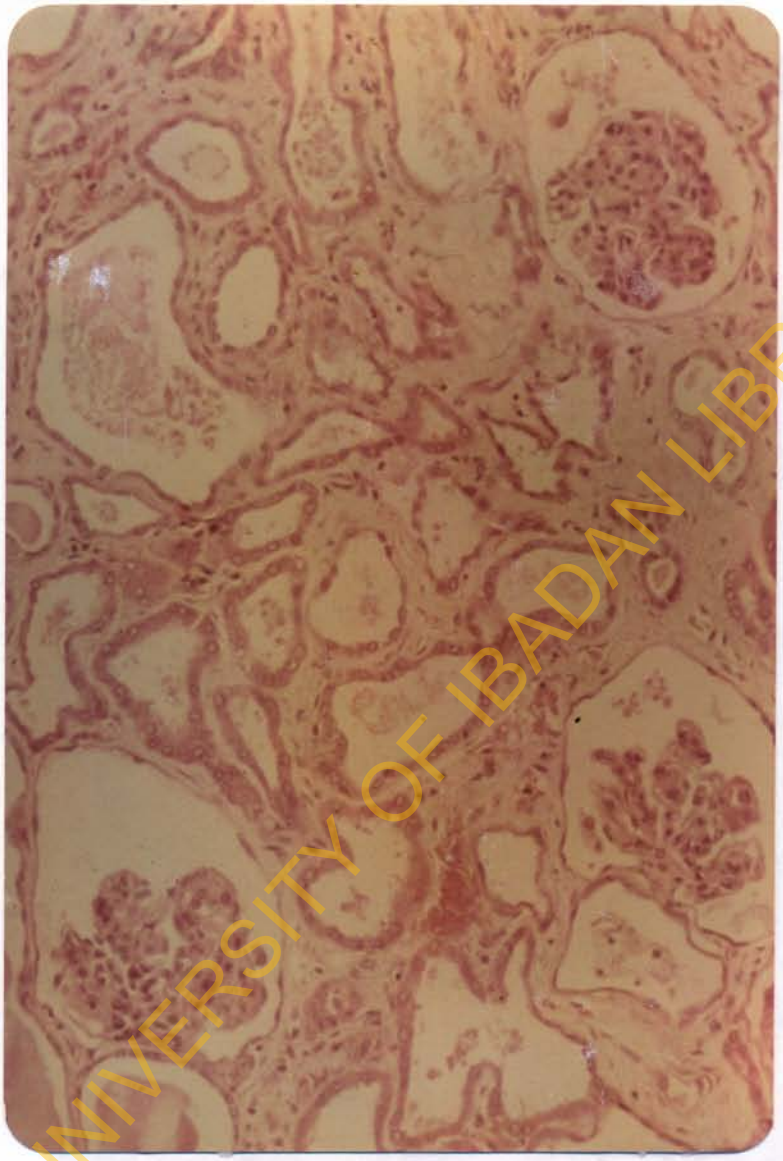

Fig. 4.15 Histopathology of congenital nephropathy, showing shrunken glomeruli and gross dilatation of the tubules (H & E stain; x 100).

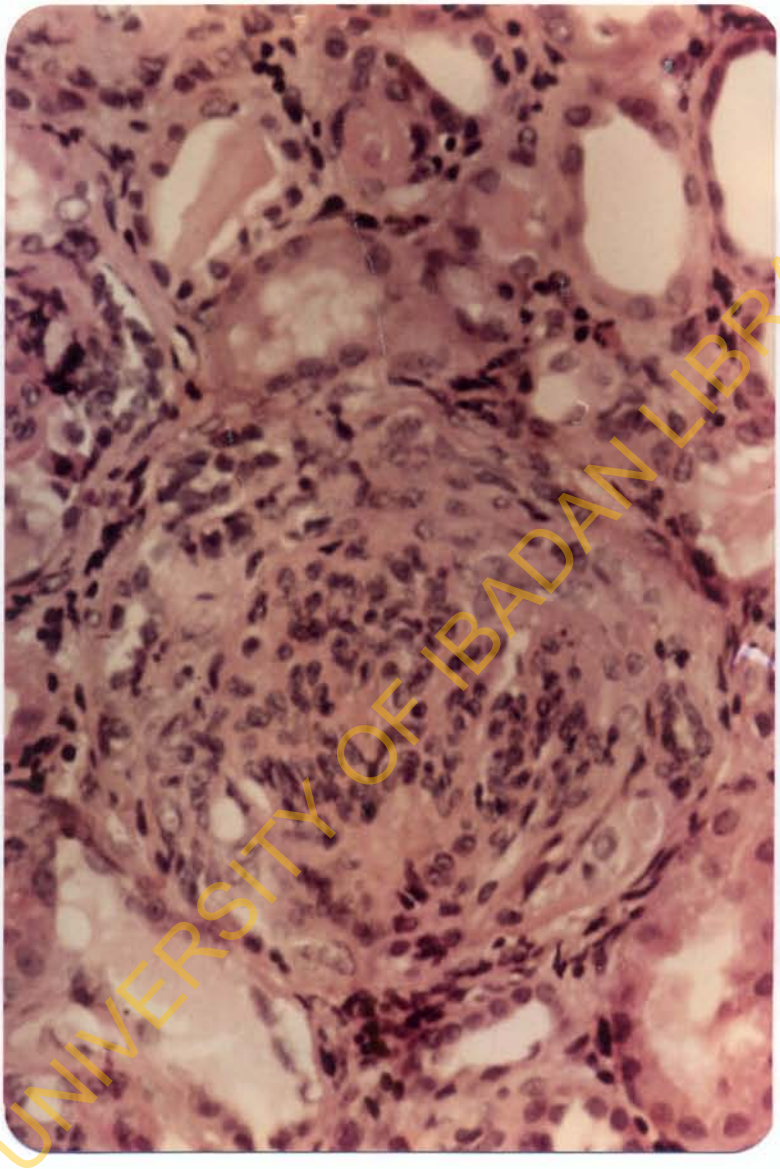

Fig. 4.16 Histopathology of crescentic, rapidly progressive glomerulonephritis (H & E stain; x 200).

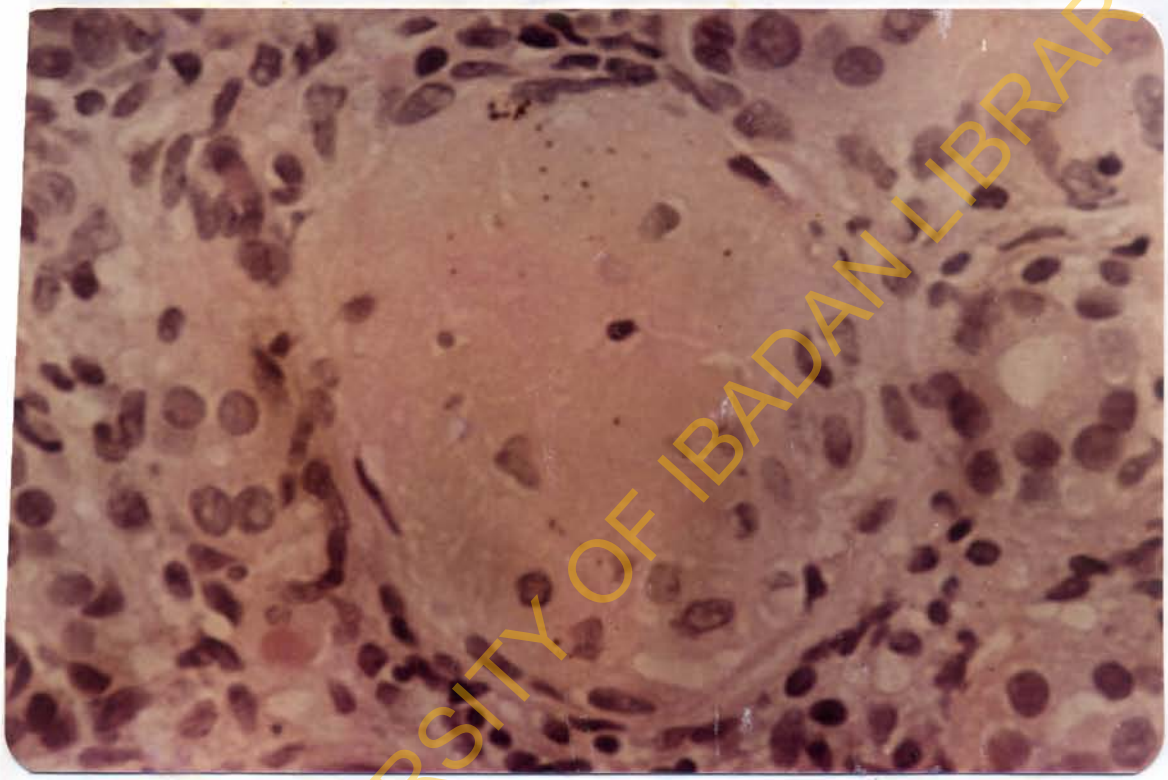

Fig. 4.17 Histopathology of a repeat biopsy in a patient with rapidly progressive glomerulonephritis (Fig. 4.16). The glomerulus is now almost completely sclerosed (H & E stain, x 100).

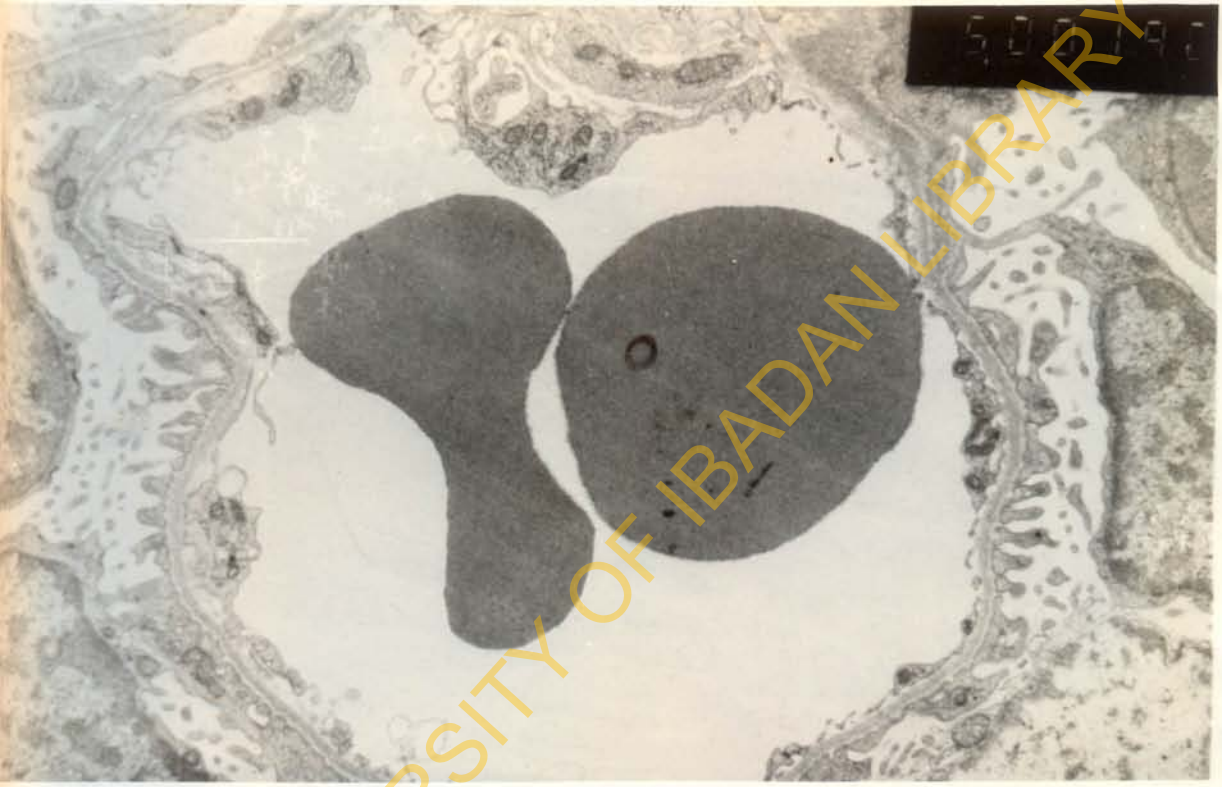

Fig. 4.18 Electronmicograph of minimal change nephropathy, showing normal basement membrane and only small areas of fusion of foot processes (x 4000). Two red blood cells are seen in the capillary lumen.

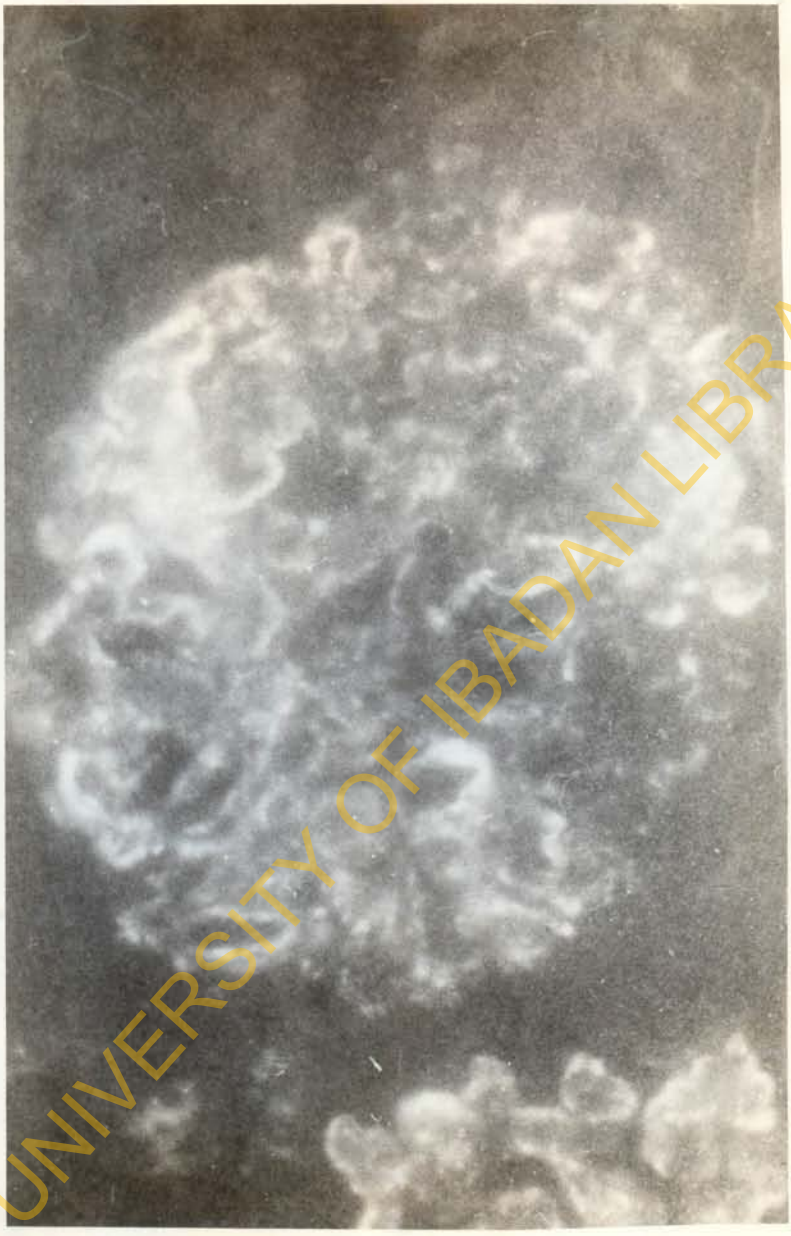

Fig. 4.19 Immunoflourescence showing a diffuse granular pattern (x 100).

Fig. 4.20 Immunofluorescence showing a mixed linear and granular pattern of fluorescence (x 100).

responders, three were still in remission at the last assessment 1.5 and three years after stopping prednisolone. Two patients had a relapse, six and nine months respectively after prednisolone was discontinued. They had PSI of 12% and 23% respectively. Both of them again responded to prednisolone therapy, but they became frequent relapsers, with more than two relapses per year. Seven of the patients in the present study were enrolled in the randomized clinical trial of cyclophosphamide and levamisole which began in 1982. The trial was started because of reports that Nigerian children with nephrotic syndrome did not respond to prednisolone (Adeniyi, 1972) or azathioprine (Adeniyi et al, 1979), and that other cytotoxic drugs (Adeniyi et al, 1979; Grupe, Makker, Ingelfinger, 1976) and levamisole (Tanphaichitr et al, 1980) were effective in some cases of nephrotic syndrome that had not responded to corticosteroid. Four of the seven patients received cyclophosphamide, while three received levamisole. The patients treated with cyclophosphamide had complete remission, and were still in remission six to ten months off therapy. None of the patients treated with levamisole responded. There were no serious complications encountered: two patients developed transient thrombocytopenia, and one patient had leukopenia on one occasion.

4.7.4 Course in the hospital. Diuresis was induced with diuretics in 87 patients and with albumin infusion in two others. Diuresis occurred from two to seven days (mean, four days) after starting diuretic therapy. However, this therapy had no effect on the proteinuria or other biochemical abnormalities. The duration of hospitalisation varied from eight to 21 days.

Two patients died in the hospital. One of them was a five-year old male who was admitted with oliguria, circulatory overload and a blood pressure of 130/100 mmHg. He had clinical and laboratory evidence of acute on chronic renal failure. Histology of his renal biopsy showed congenital nephropathy (Fig. 4.15) characterised by gross dilatation of tubules, shrunken glomeruli with increased Bowman's space; a few glomeruli were foetal in type. He had progressive oliguria to anuria, and died on the 12th day of admission. Autopsy was not allowed. The second patient was a four-year old girl admitted with anaemia and hypertension (blood pressure 120/100 mmHg). Histology of her renal biopsy showed features of end-stage kidney. She died suddenly a week after admission. The main findings at autopsy were: anasarca, generalised effusion in serous cavities, severe pulmonary oedema and enlarged, finely granular kidneys. Histologically, most

of the glomeruli were sclerosed, the tubules dilated and the interstitium oedematous with focal areas of lymphocytic infiltration and fibrosis.

Five patients developed measles in the hospital. The infection did not appear to alter the course of the nephrotic syndrome in two patients. The infection seemed to have induced diuresis in two patients, while the fifth patient's oedema increased and became refractory.

4.8 Follow-up

The duration of follow-up ranged from one to six years, with a mean of 2.5 years. The status of the patients as at the end of 1983 is shown in Table 4.11. The remission was spontaneous (that is, without any specific treatment) in 10 of the 19 patients in remission. The histological diagnosis, malaria parasitaemia and protein selectivity index in the patients with spontaneous remission is shown in Table 4.12. All of them were male, and four had PGN. Although the number of patients was too few to draw a conclusion, the table shows that spontaneous remission was more likely to occur within one year of onset of nephrotic syndrome in a young, male patient with PGN and highly selective proteinuria. In the remaining nine patients, remission was induced with prednisolone in five and with

cyclophosphamide in four. Although patients' homes were visited to make tracing easier, the default rate of 16% was high. The reasons for default were change of address (12 cases) and marriage (four cases).

There were 11 deaths during the follow-up period. If the two deaths that occurred during the first admission are added, the total number of deaths in children with nephrotic syndrome comes to 13. These are summarised in Table 4.13. Nine of the deaths occurred within one year of diagnosis. Death was due to renal disease in 10 and due to pulmonary cause in 3 patients.

Follow up of patients with nephritic nephrotic syndrome

Four of the nine patients had spontaneous remission: their biopsy showed PGN. The remaining five had persistent proteinuria. There was no death in this group of patients.

TABLE 4.11

Status of nephrotic patients after a mean follow-up period of 2.5 years.

Status	No. of patients
Persistent proteinuria without oedema	26
In remission	19
Defaulted	16
Persistent proteinuria with recurrent oedema	15
Dead	13+
Progressive deterioration	11
Total	100

+ This figure includes the two patients who died during their first admission.

TABLE 4.12

Renal histology, protein selectivity index and malaria parasitaemia in 10 nephrotic patients with spontaneous remission.

Age (yr)	Onset of remission (months)	Sex	Malaria parasitaemia	Histology	Protein selectivity index (%)
2	5	M	P. falciparum	Proliferative glomerulonephritis	5
3	7	M	P. malariae	Proliferative glomerulonephritis	6
4	13	M	Negative	Proliferative glomerulonephritis	33
9	9	M	Negative	Proliferative glomerulonephritis	35
3	12	M	P. malariae	Membranoproliferative glomerulonephritis	16
4	12	M	P. falciparum	Membranoproliferative glomerulonephritis	40
7	15	M	Negative	Quartan malarial nephropathy	5
7	13	M	P. malariae	Quartan malarial nephropathy	20
9	2	M	Negative	Minimal change nephropathy	28
4	15	M	P. falciparum	Interstitial nephritis	33

TABLE 4.13

Summary of the 13 patients who died.

Age (yr)	Sex	Histological diagnosis	Course	Interval between diagnosis and death	Cause of death
5	M	Congenital nephropathy	Acute on chronic renal failure	12 days	Acute renal failure
4	F	ESRD	Hypertension. Anaemia	7 days	Pulmonary oedema
4	F	RPGN	Progressive deterioration in renal function	9 months	Uraemia
8	M	ESRD	Acute on chronic renal failure	1 month	Acute renal failure
12	F	ESRD	Acute on chronic renal failure	1 month	Acute renal failure, hypertension
8	F	ESRD	Hypertension. Progressive deterioration in renal function	4 months	Uraemia, hypertension
9	F	MPGN	Deteriorating renal function	5 months	Uraemia

Continued .....

TABLE 4.13 (Continued)

Age (yr)	Sex	Histological diagnosis	Course	Interval between diagnosis and death	Cause of death
8	M	MPGN	Hepatosplenic schisto-somiasis. Hypertension	3 years	Uraemia, hypertension
4	F	MPGN	Stable renal function	4 months	Pneumonia
5	M	MPGN	Hypertension	3 months	Respiratory failure
6	M	QMN	Persistent proteinuria	2.5 years	Uraemia
9	F	QMN	Deteriorating renal function	2 years	Uraemia
6	M	MGN	Deteriorating renal function	1 year	Uraemia

ESRD = End-stage renal disease
MPGN = Membranoproliferative glomerulonephritis
MGN = Mambranous glomerulonephritis
RPGN = Rapidly progressive glomerulonephritis

CHAPTER 5

DISCUSSION

The clinical features of patients in this study were similar to those described in other African children with the disease. The oedema was more severe and the age of the patients higher than in children with the same disease in developed countries. The severity of the oedema could be due to a combination of two factors: low serum albumin in the general population (represented by the children used as controls) and late presentation to hospital. The low serum albumin would result in reduced serum oncotic pressure, making oedema formation easier and more severe. The frequency of childhood nephrotic syndrome was low, with an average of 25 cases a year, forming only 0.35% of all paediatric admissions. This figure is considerably smaller than 39 per year reported from Ibadan (Hendrickse and Gilles, 1963) and also smaller than 17 cases out of 2170 paediatric admissions (0.78%) in Enugu (Kaine and Okolie, 1977). In contrast, AGN is more prevalent in our hospital, with 202 cases seen in four years (Aikhionbare and Abdurrahman, 1984). In Ibadan, Hendrickse and Gilles (1963) reported 22 cases in four years. These

hospital-based figures are not strictly comparable since patient catchment areas and admission criteria might be different in the three places.

Nine patients had a mixed picture of nephrotic syndrome and acute nephritic syndrome. The latter was characterised by varying degrees of haematuria, circulatory overload, hypertension and raised ASOT. Histology of the kidney in five of these patients was indistinguishable from that of PSAGN. Four other patients who did not present with acute nephritic syndrome also had histology compatible with PSAGN. Four of the nine patients with nephritic nephrotic syndrome had spontaneous remission. In some cases it was not always possible to decide immediately on admission whether a patient had nephrotic syndrome or AGN. The serum albumin alone was not reliable for the differential diagnosis, since in children with AGN in tropical Africa serum albumin is often low and, at times, in the nephrotic range (Hendrickse and Gilles, 1963; Hutt and White, 1964; Aikhionbare and Abdurrahman, 1984). The relationship between AGN and childhood nephrotic syndrome in tropical Africa is not clear. Are children with AGN more likely to progress to nephrotic syndrome or develop the disease after a latent period? Are children with nephrotic syndrome more prone to develop AGN? There are no clear-cut answers to these questions. In several parts of Africa, PGN is a relatively common finding in nephrotic

syndrome, although evidence of a poststreptococcal origin of nephritis may be absent (Abdurrahman, 1984). In one report from Uganda (Wing, Kibukamusoke and Hutt, 1971) 12 of 156 cases of nephrotic syndrome had clinical, laboratory and histological evidence of PSAGN. The relatively high frequency of PGN in the present study could be a reflection of the high incidence of AGN in the locality. Compared with developed countries, PGN is a relatively frequent finding in nephrotic syndrome in developing countries both in Africa (Kibukamusoke, 1967; Brown, Abrahams and Meyers, 1977; Verroust et al, 1979; Kinuthia et al, 1981) and outside Africa (Sadiq, Jafarey and Naqui, 1978; Tanphaichitr et al, 1974; Duggin, 1981). This may not be unrelated to infectious agents that are prevalent in developing countries.

The 20% prevalence of urinary tract infection in the present study is far higher than the 1% found in primary school children in Kaduna (Abdurrahman, Chakrabarty and Ochoga, 1978). This suggests that children with nephrotic syndrome are more susceptible to urinary tract infection. Our data also showed that 1) nephrotic children were unable to clear their bacteriuria adequately even after antimicrobial therapy, and 2) nephrotic children with bacteriuria were less likely to have remission of their nephrosis. At least one study (Awwaad et al, 1979) even suggested that urinary tract infection causes nephrotic syndrome, but the authors' evidence was weak.

It is pertinent at this juncture to attempt to interprete the findings of, and define the correlation between, P. malariae parasitaemia, serum P. malariae antibody levels, histology and immunofluorescence. P. malariae parasitaemia was more frequent in nephrotic than in control children (Table 4.5). However, the parasite was detected not only in patients with QMN but also in patients with MPGN, PGN as well as MCN (Table 4.6). In addition, high serum P. malariae antibody levels were found in patients with different histological diagnoses (Narayana et al, 1982). Table 4.9 shows that detection of P. malariae antigen in the glomeruli by fluorescence microscopy was most frequent in, but not restricted to, patients with QMN. It should be pointed out that although one other specific antigen looked for, namely HBsAg, was found predominantly in patients with MPGN, the antigen was also detected in patients with PGN, QMN, ESRD and MGN. The author's comments on the findings are as follows. Presence of P. malariae parasitaemia alone in a patient with nephrotic syndrome cannot be interpreted as proof that P. malariae is the cause of the nephrotic syndrome, since 13-18% of apparently well children also have P. malariae parasitaemia (Hendrickse and Gilles, 1963; Gilles, 1965; Bell and Howells, 1973). With 13-18% prevalence of P. malariae in well children it is not unexpected that the parasite would be found in nephrotics with QMN as well as other histological lesions. The aetiological or pathogenetic

significance of high serum *P. malariae* antibody levels in nephrotics is difficult to define. This is because when compared with controls this group of patients has been shown to have high serum levels of various other antibodies or antigens such as HBsAg (Akinsola et al, 1984; Seggie et al, 1984; Adhikari, Coovadia, and Chrystal, 1983; the present study) Yersinia antibody (Awunor-Renner 1982); streptococcal antibody (Wing, Kibukamusoke, and Hutt, 1971; Seggie et al, 1984).

If detection of antigen in the glomeruli in the presence of supportive histology is taken as evidence of possible aetiological and/or pathogenetic role in children with nephrotic syndrome, not more than 19/76 (25%) patients in our study would be classified as QMN. Another nephropathic antigen, HBsAg, was also detected in 18 cases. Apart from malaria, no other antigen known or suspected to cause chronic renal disease was investigated in the studies on nephrotic children in Ibadan (Hendrickse et al, 1972) where QMN has been described in over 80% of cases.

There was no histological diagnosis that could be described as the predominant pattern. Instead, three lesions were almost of equal frequency: MPGN, QMN and PGN. Together they formed 65% of all biopsies. Only 20 out of 98 biopsies (20.4%) were classified as QMN. These figures contrast sharply with the findings in Ibadan where QMN was the dominant histological lesion

in children with nephrotic syndrome (Adeniyi, 1972; Hendrickse et al, 1972; Hendrickse and Adeniyi, 1979). The reasons for the differences are not obvious. In both centres, majority of the patients come from low income families, and the pattern of malaria is similar. In both parts of the country the prevalence of P. malariae parasitaemia in unselected village children is comparable - 14.1% (Gilles, 1965) and 18% (Hendrickse and Gilles, 1963) in Ibadan, compared with 13% in rural parts of Zaria (Bell and Howells, 1973). In contrast, Hendrickse and Gilles (1963) reported 88% P. malariae parasitaemia in nephrotic children, a figure much higher than 31% found in the present study. It is possible that the pathology of childhood nephrotic syndrome is truly different in Ibadan and Zaria. However, the alternative explanation that the difference is only an artefact and not real needs to be considered. It is possible that the histology described as characteristic of QMN is not peculiar to P. malariae- associated nephrotic syndrome, and that P. malariae can give rise to more than one type of kidney lesion. The presence of small lacunae in the basement membrane described on electron microscopy as diagnostic of QMN by some workers (Hendrickse et al, 1972; White, 1973) has not been confirmed in one other study (Houba, 1975). Moreover, a similar lesion had been described in schistosomal glomerulopathy (Andrade and Rocha, 1979). Thus, QMN may be regarded as a form of focal and segmental MPGN modified by

peculiar environmental nephropathic factors. In some malarious areas of West Africa, QMN has not been described (Noah and Olude, 1979; Adu et al, 1981). On the other hand, in Senegal, where malaria also occurs, renal biopsy of nephrotic children showed some similarities to QMN, but there were no characteristic deposition of immunoreactants typical of QMN. In Uganda, where QMN is also reported to be common, the predominant histological lesion is proliferative (Kibukamusoke and Hutt, 1967). It is of interest to note that in adults with nephrotic syndrome in Ibadan and Zaria, there is no evidence of QMN. The predominant histopathology is proliferative: it formed 45.7% of 81 biopsies in Ibadan (Akinkugbe and Hunton, 1968) and 70% of 67 biopsies in Zaria (Awunor-Renner, Lawande and Subbuswamy, 1984).

One possible reason why QMN occurs in children but not in adults with nephrotic syndrome in Ibadan and Zaria is that the aetiology of the disease may be different in adults and children. Secondary immunosuppression due to malnutrition and infections are less common and less severe in adults than in children. Moreover, immunity to malaria is better developed in adults who can therefore get rid of the parasite before an immune-complex or autoimmune glomerulopathy develops. An alternative explanation is that in Ibadan where QMN is common and has a poor prognosis, it is conceivable that most of the affected children die before reaching adulthood. In places where QMN is less common and less

severe in children, some of the patients may develop spontaneous remission.

There is now ample evidence that HBV and/or its antigens are associated with renal disease (Levy et al, 1982). The prevalence of HBsAg in Africa is high. In Zaria, for example, 45.9% of control children under 10 years of age had positive serum HBsAg (Fakunle, Abdurrahman, Whittle, 1981). Bowry, Ojwang and Lumba (1983) found positive HBsAg in 48% of 279 sera from urban Kenyan school children. The antigen has been associated with both nephritic (Aikhionbare and Abdurrahman, 1984) and nephrotic (Adhikari, Coovadia and Chrystal, 1983) glomerular disease in African children. Moreover, the antigen was detected in 41% of 39 sera from adult nephrotic patients in Ile-Ife, compared with 8% in controls (Akinsola et al, 1984). In the present study, nephrotic children had a stronger serum HBsAg reactivity than the control children. Patients with MPGN had the highest frequency of positive HBsAg. The most convincing evidence that HBsAg could play a role in the aetiology or pathogenesis of nephrotic syndrome in our patients was the finding on immunofluorescence. The antigen was detected in the glomeruli of 18 out of 76 biopsies (24%), in the same location as immunoglobulins and C_3. This suggests that the HBsAg was part of an immune complex deposited in the glomeruli, with resultant glomerular damage. In this study only one marker of HB infection, namely HBsAg, was

looked for in the glomeruli. It is known that other markers, particularly HBeAg, could be detected in the glomeruli (Takekoshi et al, 1979).

In the present study, the evidence that some cases of nephrotic syndrome were associated with S. mansoni was weak. The three patients with hepatosplenic schistosomiasis had MPGN, a lesion commonly found in the disease. S. mansoni antigens were not looked for in the glomeruli. In an earlier study of hepatosplenic schistosomiasis in 40 children from this institution, two of the four children who had MPGN presented with nephrotic syndrome (Abdurrahman, Attah and Narayana, 1981). Investigators from other areas of S. mansoni endemicity have produced strong evidence that the parasite is nephropathic (Andrade and Rocha, 1979).

Although 34% of our patients had good PSI, it was disappointing to find that none of the histological types had a characteristic pattern of PSI. In other words, PSI could not be used as a relatively simple test to identify patients who were likely to respond to steroid therapy. Several patients with MPGN or QMN had good PSI. Adeniyi (1972) noted that there was only a fair correlation between PSI and response to steroid. The finding of lack of usefulness of PSI is in contrast to the experience of workers in Europe and America (Churg, Habib and White, 1970, Grupe, 1979; Ellis and Buffone, 1981) who found the

test useful in predicting those patients likely to respond to steroid. Confirmation of our finding is needed before concluding that PSI is not of differential diagnostic value in African children with nephrotic syndrome. It will be particularly useful to determine PSI using several pairs of proteins in order to select the most discriminating pair of proteins. Such a study is being carried out by the author and his coworkers. It has been shown that different pairs of proteins give different PSI values (Ellis and Buffone, 1981).

The report by Adeniyi, Hendrickse and Soothill (1979) that cyclophosphamide is beneficial in some cases of nephrotic syndrome is supported by the finding in the present study. Four patients treated with the drug went into remission. Analysis of 50 patients enrolled in the clinical trial of cyclophosphamide and levamisole carried out in our institution showed that cyclophosphamide induced complete response in 6 patients and partial response in 10 patients. There was no response with levamisole (unpublished data). In view of the serious toxicity associated with the use of cyclophosphamide, and the fact that the response rate is not high, the drug cannot be regarded as the ideal drug for treating nephrotic syndrome in Kaduna State. Further investigation is therefore required to identify those patients who will respond to therapy, so that non-responders will not be exposed to the risk of toxicity.

At the initial part of this work, no attempt was made to offer any specific treatment to patients with nephrotic syndrome except those patients with MCN who were given prednisolone. This was because of our ignorance of the nature of the disease in our locality. Moreover, the lack of response of black African children to steroid therapy (Kibukamusoke, Hutt, Wilks, 1967; Adeniyi, Hendrickse and Soothill, 1976; Coovadia, Adhikari and Morel-Maroger, 1979) discouraged the use of the drug in our patients. There is still no satisfactory treatment for childhood nephrotic syndrome in Africa. In developed parts of the world drugs other than corticosteroid have been tried in cases of resistant nephrotic syndrome. Both indomethacin (Garin et al, 1978; Shehadeh et al, 1979) and dipyridamole (Ishikawa et al, 1982) have been tried with partial response. On a long-term basis, the most cost-effective way of reducing the incidence of childhood nephrotic syndrome in Africa is the eradication or control of infectious diseases. Improved standard of living and availability of vaccines against certain diseases, particulary hepatitis B and malaria, are solutions which are presently virtually impossible to achieve in several parts of Africa.

It is of interest to note that ten patients with different histological lesions had spontaneous remission. It could be argued that the patients with spontaneous remission were examples of delayed resolution in patients with AGN and severe

hypoalbuminaemia. Whereas such an explanation could be true in those patients with PGN, it cannot be applied to patients with MPGN or QMN. Spontaneous remission had been observed previously (Arneil, 1971). Therefore, assessment of the efficacy of any treatment must consider the possibility of spontaneous remission.

During a follow-up period of one to six years there was a total of 13 deaths. Eleven patients had progressive deterioration and 19 were in remission. From these figures prognosis of the disease cannot be described as good. However, the prognosis does not appear to be as bad as in Ibadan children where "the overall prognosis is poor with most patients developing hypertension and evidence of renal failure within 3 to 5 years of onset" (Hendrickse and Adeniyi, 1979). More specifically, in a group of 36 nephrotics with poorly selective proteinuria studied by Adeniyi and his coworkers (Adeniyi, Hendrickse and Soothill, 1979) 13 of them were dead at 2 years and 20 were dead by 5 years of follow-up.

Majority of African countries still have infections and infestations as their major health problems. Several of the infectious agents have been shown to be nephropathic: Treponema pallidum, M. leprae, filarae, HBsAg, S. mansoni and P. malariae. More recently, Yersinia enterocolitica has been added to the growing list of infectious agents which are nephropathic. The parasite has been associated with both AGN (Friedberg et al,

1981) and chronic glomerulopathy (Awunor-Renner and Lawande, 1982). The role of infectious agents in the aetiology and pathogenesis of childhood nephrotic syndrome in Africa has been reviewed recently (Abdurrahman, 1984). The difficult task faced by an investigator in Africa is to decide which of the several infectious agents prevalent in his locality has any role to play in patients with the nephrotic syndrome. In addition, he would like to know the effect of multiple infections and the interaction between these and non-infectious factors that affect the immune response of patients.

Certain precautions are necessary in the study of the role of infectious agents in the aetiology or pathogenesis of childhood nephrotic syndrome. Firstly, mere presence of an infectious agent is not synonymous with disease or with cause and effect relationship. Secondly, the kidney may be the primary or secondary target organ of an infectious process, or it may act merely as a "dumping ground" for the infectious agent. Detection of circulating immune complexes (CIC) is not proof of the presence of disease, since CIC are found in healthy subjects (Levinsky, 1981). The prevalence of CIC is higher in healthy Nigerians than in Caucasians (Onyewotu, 1978), probably related to prevalent infections and infestations. Moreover, immune complexes have also been found at autopsy in the glomeruli of patients without any clinical evidence of glomerulonephritis and

in whom light microscopy of the kidney was essentially normal (Sutherland, Markham and Mardney, 1974).

Although the role of humoral immunity in the pathogenesis of immune-mediated renal disease had been well studied, little attention had been given to cell-mediated immunity (CMI). There is experimental evidence that at least, in some glomerular diseases, CMI plays a major role in the pathogenesis (Bhan et al, 1978). The relevance of this finding to human situation is uncertain, since mononuclear cell infiltration is not a common finding in human glomerular disease.

In Africa, as elsewhere, the field of nephrology has been bedevilled by a lack of concordance between pathologists and considerable confusion among clinicians. This is manifested by interpersonal and intrapersonal differences in the interpretation of renal biopsies, and the lack of uniform meaning of terminologies. The situation is worsened by the considerable variation in "normal" kidney histology (Haynes, 1981), Moreover, although the causes and pathogenetic mechanisms of glomerular injury are heterogenous, the range of possible clinical, laboratory and morphological responses of the kidney is limited. In addition, in experimental animals, acute, subacute and chronic glomerulonephritis have been produced in the same animal species by altering the injection schedule of the same antigen (Dixon, Feldman and Vazquez, 1961). It is worth remembering these points

when analysing reports on childhood nephrotic syndrome from different parts of Africa. In Europe and America some of the problems mentioned here have been minimised, if not eliminated, with the formation of The International Study of Kidney Disease in Children (ISKDC, 1979). A similar body is strongly advocated for Africa, or at least for Nigeria as a start.

Hypothesis

It is proposed that childhood nephrotic syndrome in Africa be regarded as an example of partial immune paresis, with several secondary consequences. The secondary consequences are manifested largely as depression of surveillance function of the immune system, and decreased ability to process effectively several infectious agents. The cause of the immune paresis is unknown, but one possibility is a combination of chronic malnutrition and sustained antigenic stimulation from prevalent multiple infestations and infections. On the basis of this hypothesis, one expects to find in the nephrotic child serum antibodies in the presence of circulating antigens. Such a situation creates the right atmosphere for potential CIC formation. The CIC's become deposited in the kidney, with resultant glomerular injury. Paresis of CMI is manifested as anergy.

If this hypothesis is correct, a profitable approach to the

treatment of nephrotic syndrome is to stimulate or potentiate the immune system. This can be done with the use of immunomodulator and immunopotentiator drugs such as levamisole and isoprinosine. An attempt to test this hypothesis was started in our institution with the clinical trial of cyclophosphamide and levamisole in the treatment of nephrotic syndrome.

CHAPTER 6

SUMMARY AND CONCLUSIONS

A study was carried out to define the clinicopathological features of childhood nephrotic syndrome in Kaduna State, as represented by patients admitted to Ahmadu Bello University Hospitals in Kaduna and Zaria. The clinical features of the disease were similar to those described in other parts of the world, except that oedema was more pronounced and the patients older than children in temperate countries. Although QMN as described in Ibadan was recognised as a pathological entity, it was not the predominant histological type. This is in sharp contrast to Ibadan where QMN is reported to occur in more than 80% of children with nephrotic syndrome. Whether this difference is real or is an artefact is not clear. The most common histological types were, in order of frequency, MPGN, QMN and PGN. Together they formed 65% of all biopsies.

Apart from P. malariae, other possible aetiological factors identified in the study were HBsAg and beta haemolytic streptococci. PSI was not found to be a useful test in identifying those patients likely to respond to corticosteroid

therapy. Prognosis of the disease was poorer than in children in developed countries, but appeared to be better than the prognosis of the disease in Ibadan. Cosmetic treatment, the control of oedema, was the only treatment given to the patients for most of the study period. However, towards the end of the study a randomized clinical trial of cyclophosphamide and levamisole was started. Cyclophosphamide was beneficial in some cases, but levamisole was completely ineffective. A hypothesis is put forward that childhood nephrotic syndrome in Africa is a partial primary immune paresis with several secondary effects.

There is a need for a more comprehensive and coordinated country-wide study of the disease in Nigeria. There is an urgent need to evolve an effective therapy for childhood nephrotic syndrome in Africa. It is advocated that a body similar to ISKDC be set up to coordinate the study of renal disease in children in Africa. Control of infectious diseases will result in reduced incidence of childhood nephrotic syndrome in Africa.

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A P P E N D I X

NEPHROTIC SYNDROME IN CHILDREN

Serial No. Hosp. No. Date of Adm. Date of discharge

Surname Other names Father's name

Detailed address of usual place of residence

Age Sex Tribe

History

Symptom	Duration
Swelling - Face/Periorbital	
- Legs	
- Abdomen	
- Generalised	
Sore throat	
Infected Skin	
Fever	
Dysuria	
Haematuria	
Previous episode and treatment	
Others (specify)	

Physical Examination

Weight (kg) Height (cm) Temp.

Oedema - extent
severity

Skin

Throat

BP

Ascites Cardiovascular State

Others Liver (cm) Spleen (cm)

Investigations

1. Urinalysis - macroscopic haematuria
   - RBC
   - WBC
   - Casts
   - Albustix
2. MSU for C & S
3. 24 Hour Urine protein (Vol. of Urine =)
4. Serum proteins Total Alb. Glob.
5. Urea & electrolytes
6. Throat Swab for C & S
7. ASOT
8. C_3 (in EDTA bottle)
9. Blood for MP x - (i) (iii)
   (Before Chloroquine) - (ii) (iv)
10. Haemogram & Genotype
11. PSI
12. PT
13. IVU

14. Renal biopsy
15. HBsAG
16. Stool microscopy
17. 10 ml clotted blood for immune defence system
18. 2.5 ml blood in EDTA bottle for immune complexes
19. 5 ml clotted blood for Dr. Abdurrahman
20. 5 ml urine for Dr. Abdurrahman
21. Others (specify)

Course in Hospital

Condition at Discharge

Weight (kg) BP Any oedema?

Follow-up appointment date given

Others

NB IN CASE OF DIFFICULTIES PLEASE CONTACT DR. ABDURRAHMAN

NEPHROTIC SYNDROME IN CHILDREN : FOLLOW UP

Date	Duration after discharge	Wt (kg)	BP	Oedema	Others	Urinalysis	Others	Comments	Next Visit