THE NEPHROTIC SYNDROME

IN UGANDA

WITH SPECIAL REFERENCE

TO THE ROLE OF

PLASMODIUM MALARIAE

A dissertation presented for the degree of

DOCTOR OF MEDICINE

in the University of East Africa

by

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1966

MEMORANDUM

I hereby certify that the method of study employed in this work was my own, as were all the clinical observations. The renal biopsies were all taken by me, the dissertation was written by me and the views expressed therein are mine. The help I received from others in carrying out this comprehensive study is acknowledged in the preface to the dissertation.

I also hereby declare that this dissertation has not been submitted anywhere else for any purpose whatsoever.

J. W. Kibukamusoke

14th February, 1966.

I N D E X

PREFACE

Much confusion exists on the subject of Quartan Malaria and the Nephrotic Syndrome at the present time. Although many people have studied this subject in the past, a unanimous opinion is lacking on even whether the relationship between the two exists at all. The present study was undertaken in order to remedy this situation. The aim has been to present a comprehensive account of the clinical, biochemical and pathological features of this syndrome. An attempt has also been made to assess the effect of steroid therapy and the association between Quartan Malaria and the Nephrotic Syndrome. The study was conducted in the wards of the Department of Medicine between June 1961 and June 1965.

I wish to acknowledge the assistance I have received from many people during the course of this study. Interpretation of the renal biopsies was done by Professor M. S. R. Hutt of the Department of Pathology, Makerere College Medical School, who also gave me much advice on the arrangement and presentation of material. Thanks are also due to Professor G. M. Bull of the Department of Medicine, Queen's University of Belfast, for reading and critisizing the manuscript. Biochemistry was kindly done by the Department of Clinical Chemistry at Mulago Hospital, Kampala, Uganda. Special thanks are due to Dr. N. E. Wilks of the Department of Parasitology, Makerere College, for much devoted work on malaria parasites and antibodies. Dr. J. C. McAlpine very kindly produced the photo-micrographs for me.

I also wish to thank Professor J. A. Tulloch, the Head of the Department of Medicine, where this work was done, for his encouragement and also Makerere College for a grant which made it possible for me to conduct this work.

Kampala,

February 1966.

SUMMARY OF THE CONTENTS OF THE DISSERTATION

Quartan malaria has been known to be associated with the nephrotic syndrome since the days of Hippocrates. But whilst a large volume of literature has accumulated on the topic, there appears to be no unanimity about what relationship there might be between these two entities. There is even disagreement on whether the relationship exists at all.

The purpose of this study has been to re-evaluate the evidence for a relationship between Quartan Malaria and the Nephrotic Syndrome and to attempt to demonstrate the nature of such a relationship.

In order to do this, comprehensive clinical, biochemical, histopathological, immunological and parasitological studies have been made into 80 cases of the Nephrotic Syndrome as it presented at Mulago Hospital. These cases were seen between June 1961 and June 1965. They comprised only a small fraction of the total number admitted with the syndrome for treatment during this period.

No selection of cases was made for inclusion in the study but all the cases admitted to the author's unit were studied together with several that were referred to him by colleagues in the Departments of Medicine and Paediatrics.

A renal clinic was established for the continued follow up of the cases studied. It is intended to continue the clinic though the purpose of this study has been accomplished.

The main findings have been that the Nephrotic Syndrome in Uganda presents in the classical way it does in Europe or North America with one important exception: a high incidence of the Nephrotic Syndrome in acute nephritis and in pyelonephritis. The relationship between the Syndrome and Quartan Malaria has been established and evidence has been presented to show that this is causal in nature.

Therapy has presented a peculiar feature - of unusual resistance to steroids. Results on this aspect are considered to be provisional and confirmation from further work will be required.

INTRODUCTION

In his celebrated works, Hippocrates wrote of the Nephrotic Syndrome that "there was danger lest death should occur among young children and women and least of all among old people, and that the survivors should lapse into quartan fevers and from quartan fevers into dropsies .....". Numerous observers have since that time confirmed this observation repeatedly and the literature contains abundant evidence suggesting a relationship between malaria and the Nephrotic Syndrome.

REVIEW OF LITERATURE

EUROPE

In Europe, Rosenstein (1896) reported that he had found malaria parasites in 23% of 162 cases of nephritis. Rem-Picci working during the same period, (1894-1898) studied the urine in 80 cases of malaria. He found proteinuria of varying severity in a large number of the cases. In some of these, the proteinuria was very severe and suggested the presence of overt renal disease. Rem-Picci also stressed the importance of repeated attacks of malaria in those cases who presented with nephritis and the frequent association with P. vivax and P. malariae infection particularly in children.

NORTH AMERICA

In North America, Atkinson (1884) drew attention to "albuminuria

and nephritis of malarial origin". He quoted a long list of references in evidence of a relationship between malaria and nephritis. Hewetson et al (1895) working in the same country reported 133 cases of proteinuria and 4 of full blown nephrotic syndrome in a study of 335 cases of malaria.

SOUTH AMERICA

In South America, Giglioli (1930), in his valuable work in British Guiana described innumerable examples of nephrotic syndrome associated with malaria. In a comprehensive study published in booklet form he told of the evolution of the nephrotic syndrome through stages of intermittent proteinuria to persistent proteinuria and eventually to established nephrotic syndrome. In this work he also incriminated P. malariae specifically. More recently (1962a), he reviewed the literature on the subject and confirmed this association. He further presented work (1962b) to show evidence of a decline in the incidence of the nephrotic syndrome with effective malaria control. Bates (1913) in Panama discovered proteinuria in 42% of malaria cases. In Palestine, Goldie (1930) studied a number of cases who presented with the nephrotic syndrome and had experienced attacks of fever. He described in detail the findings in 4 of the most typical cases. P. malariae was found in two of these cases and P. vivax in two.

ASIA

In Asia, Watson (1905) reported two cases - one from India

and the other from Malaya - of nephrotic syndrome associated with malaria. Clarke (1912) wrote very vividly from Malaya "..... I believe that the occurrence of oedema in the tropics of such a nature as to make one think of parenchymatous nephritis is a reason for making a search for quartan malaria parasites imperative ..... Every medical man knows that given the malaria parasite he may find albuminuria but he does not know that given the albuminuria without any fever he may find malarial parasites in over 50% of cases and of this 50% almost 100% is quartan". He examined 62 cases of nephritis, five of whom had fever. Of the remaining 57, 29 (51%) showed P. malariae and 3 other forms of malaria. Manson-Bahr et al (1927) described two cases of the nephrotic syndrome treated at the Hospital for Tropical Diseases, London. Both had quartan malaria - one acquired in India and the other in Malaya. James (1939) reported similar observations in his work in Solomon Islands and New Guinea. Several other observers reported cases of the syndrome found in association with malaria: Bosch (1930) in Java; Surbek (1931) in Sumatra and Lambers (1932) in Surinam.

AFRICA

In Africa, McFie and Ingram (1917) reported nine cases of the nephrotic syndrome from Ghana (then called the Gold Coast). All the patients were children under 10 years of age and all had

P. malariae in their peripheral blood. Carothers (1934) working in Kenya reported that 67% of children with the nephrotic syndrome showed malaria parasitaemia whereas only 8% of children without the syndrome showed parasites. He concluded that "in so far as one could judge from the limited number of cases, it would appear that quartan malaria might be a factor in the causation of nephritis". More recently, Gilles and Hendrickse (1963a) reported comprehensive studies of 113 patients aged between 2 and 10 years suffering from the nephrotic syndrome. They found an overall incidence of 88% for P. malariae in their cases. Corresponding children in the hospital for other complaints than this gave a 24% incidence of the parasite. These workers concluded that "..... these epidemiological findings indicate a definite relationship between the nephrotic syndrome in Nigerian children and infection with P. malariae. They also considered that the most likely mechanism was sensitisation of the kidney with P. malariae and kidney damage resulting from auto-immune reactions. White (1964) was impressed with the frequency of the nephrotic state. He described 4 cases of acute nephritis who presented with the nephrotic syndrome.

DISSIDENT VIEWS

Many workers, however, are dissatisfied with the evidence for a causal relationship between malaria and the nephrotic syndrome. Raper (1953) studied a selection of 136 cases of renal disease

derived from 2,800 autopsies. His conclusions were cautious because the study was a retrospective and a highly selected one - only cases succumbing to renal disease being available for the study. However, he concluded that "No evidence was obtained that renal disease in Uganda is attributable to malnutrition or malaria .....". Leather (1960) was also unconvinced though he found malaria parasitaemia in 6 of the 12 children with glomerulonephritis. He thought that "this was a chance coincidence which would not be an unusual finding in a similar group of children in hospital in Kampala without nephritis, in whom the blood was searched periodically, over a period of many weeks". Unfortunately, he did not actually do this to a "control" group. However, his three cases of acute nephritis (Leather, 1958) presented in a nephrotic state. Luder (1958) thought that the association must still be considered unproven and Trowell (1960) was doubtful of the existence of "malarial nephritis".

RENAL REACTIONS IN ARTIFICIALLY INDUCED P. MALARIAE INFECTIONS

Boyd (1940) described a series of 43 cases of artificially induced quartan malaria (some mosquito transmitted and others by injection of infected blood). In 14 cases (32.5%) albuminuria was at some time very heavy; so much that in 12 instances the onset of the complication made termination of the infection imperative. Six patients developed oedema of the legs and in one of these the face and hands were involved. In another,

ascites was present. In four the proteinuria was heavy though in two this was only a trace. Boyd concluded that "the most common incident in the clinical course of the infection is the development of an albuminuria which probably represents a nephrosis rather than a nephritis. This always cleared up with termination of the infection". Unfortunately, no histological studies were done.

This important cause of nephrotic syndrome does not appear to have received international recognition. In an international meeting on the nephrotic syndrome organised by the Royal College of Physicians in London in 1960, this cause was not given as much as a mention. A comprehensive study was therefore deemed necessary in order to establish afresh clinical, biochemical, parasitological, histological, immunological and therapeutic data about it. This study was conducted at Mulago Hospital, Kampala, Uganda.

THE MULAGO HOSPITAL, KAMPALA, UGANDA

Mulago is the teaching hospital of Makerere University College Medical School. The present hospital has 900 beds and is comparatively new having been completed in 1962. It replaced the old hospital whose foundations were laid in the early ninenteen twenties. The hospital plays a dual role of Uganda's main consulting and teaching centre and of a district hospital for the surrounding area, serving an estimated population of half to three

quarters of a million people. It has one of the highest patient turnover rates of all teaching centres in the world.

Uganda itself is an independent state forming part of the British Commonwealth of Nations and situated some 800 miles from the East Coast of Africa. It lies across the equator at a height of 4,000 feet above sea level. It has an equable temperature of 65°-85°F and enjoys wet and dry seasons only. It has a population of just under seven million persons.

DEFINITION OF THE NEPHROTIC SYNDROME

Although the nephrotic syndrome was recognised by Richard Bright as early as 1827, a clear understanding of this disease has only come comparatively recently. Muller (1905) and Volhard and Fahr (1914) drew a clear distinction between 'nephrosis' and nephritis. This distinction was based on the presence of an inflammatory reaction in nephritis. Such inflammation was not present in 'nephrosis'. Ellis (1942) unfortunately called it a nephritis (type II nephritis) and this tended to blur the distinction a little more. It is however generally agreed now that the nephrotic state is a symptom complex comprised by massive proteinuria, hypoalbuminaemia and gross oedema (Black, 1962). Hypercholestrolaemia (Harrison et al; Lancet, 1959) and hyperlipidaemia (Allen, 1962; BMJ, 1962) are often added to the diagnostic picture. Hardwicke et al (1954) found that the nephrotic syndrome occurred when the level of serum albumen was 1.0-2.0 grams per cent (25-50% of normal). This level occurred with a proteinuria of 10-20 grams a day in a man of 70 kilograms. Squire (1960), however, showed that a loss of 7 grams per day would be capable of producing the syndrome in smaller sized patients. He emphasized, however, that during the oedematous phase the cube of the patient's height offered a better yardstick.

The syndrome can be produced by a wide variety of diseases.

Kark et al (1958) list 38 causes, 26 of which are proven while the rest are given as possible causes. Many authors are in agreement with this(B.M.J. 1962, Allen, 1962; Lancet, 1959, Smart, 1960).

In the present work, diagnosis was made if massive oedema, gross proteinuria and hypoalbuminaemia were present at the same time. The serum albumen level averaged 1.2 grams %. In the majority of cases, however, hypercholesterolaemia was also present.

CURRENT STUDIES AT MULAGO HOSPITAL

1. CLINICAL

A total of 80 unselected cases of the nephrotic syndrome were fully studied. The results are presented below:-

1. Age:

   (a) Children: 31 of the cases were children of 14 years or under. The average age was 8 years. The histogram (Fig.17) gives the distribution of the cases in the different age groups. It will be seen that the peak incidence occurs in the age 4-6. The actual peak occurs between the ages 5-6 years.

   (b) Adults: 49 of the cases were adults. The histogram (Fig. 18) shows that the largest number (33 cases) occurred in the age group 15-35 years. This pattern merely reflects the Mulago Hospital admission rates in reference to age (Hamilton, 1965). This in turn is a reflection of the adult population in Uganda (Uganda Census, 1959).

2. Sex:

   In children under the age of 14, the sex incidence was equal (16 males to 15 females). Among the adults (Table 1) however the male to female ratio was almost

2:1 (18 females to 31 males). Again this is considred to be a reflection of the hospital sex admission ratios than a true difference of incidence (Hamilton, 1965). Table 1 gives the actual number of cases in each age group.

ADULT CASES:

TABLE 1.

Age-Group	Females	Males
15 - 20	7	4
21 - 25	3	4
26 - 30	2	7
31 - 35	2	5
36 - 40	-	5
41 - 45	-	-
46 - 50	2	2
51 - 55	-	2
56 - 60	1	-
61 - 65	1	1
66 over	-	1
Total	18	31
Grand Total	49	

3. Racial and Tribal Distribution:

The series consists entirely of people of African

descent, with the exception of two children of Asian parentage. Fifteen tribes are represented; Ganda, Gishu, Lugbra, Rwanda/Rundi, Lango, Kiga, Etesot, Nkole, Toro, Nubia, Madi, Acholi, Luo and Kakwa. The largest numbers belonged to the Ganda tribe (35) and Rwanda/Rundi (17). This merely reflects the hospital admission ratios between these tribes (Hamilton, 1965).

4. Oedema:

This was present in all cases, being usually of great severity. The severity of the oedema is immediately suggestive of a nephrotic state at the first sight. In 28% of the cases, the oedema was of such severity that the patient was unable to open his eyes at all. This extreme severity of the oedema has already drawn comments from Leather (1958 and 1960) and White (1964). It was the symptom that led the patient to the doctor in two-thirds of the cases. Congestive cardiac failure was the reason for admission in most of the remainder.

5. Hypertension:

Among children under 10 years of age a diastolic pressure above 70 mm Hg. (taken under basal conditions) was regarded as hypertension (White, 1951; Pickering, 1955; Sheldon, 1955). For the older children (10-14 years), readings over 80 mm Hg under the same conditions were

similarly interpreted. Adults with sustained diastolic pressures of over 100 mm Hg under basal conditions were diagnosed as hypertensive.

Using these figures, 34 cases had hypertension. Table 2 shows the histological diagnoses in these cases.

TABLE 2

Histological Diagnosis	No. of Cases
Focal glomerulonephritis	2
Diffuse "	13
Chronic "	8
Lobular "	3
Membranous "	1
Pyelonephritis	1
Renal Vein Thrombosis	1
Renal amyloidosis	1
Chronic nephritis	3
Henoch-Schoenlein Syndrome	1
TOTAL	34

The proliferative lesion was one that was most frequently associated with hypertension, although there were some cases which showed this lesion but no hypertension.

When a diastolic level of 90 mm Hg is used as a level for the diagnosis of hypertension among adults, six more cases are added. Two of these cases showed proliferative glomerulonephritis. The third patient is an elderly person aged 70 years with membranous glomerulonephritis. (It is unlikely that this level of blood pressure was related to his renal pathology). Two patients showed membranous change in the glomeruli, and the sixth patient minimal change. It appears therefore that a diastolic pressure of 100 mm Hg would be a satisfactory one to adopt in reference to hypertension in renal disease. This level excludes all those cases which are classically unassociated with hypertension and includes all (except one) of those in whom hypertension is expected to occur (Ellis, 1942). 22 out of 27 cases (diffuse, chronic and lobular) were hypertensive using this level - a percentage of 81.5.

6. Retinal Changes

Only 10 cases out of 80 examined showed retinal abnormalities. All were associated with hypertension and were considered to be the result of it. Second degree retinopathy was present in six cases, and third degree changes in four. The incidence of retinal change

was, therefore, one in eight or 12.5%.

7. Congestive Cardiac Failure

Dyspnoea was the presenting complaint in 14 cases, and in all these cases congestive cardiac failure was present. It was secondary to hypertension in all cases except one who had mitral valve incompetence probably due to endomycardial fibrosis.

8. Haematuria

Six cases gave a history of haematuria in the recent past. All had proliferative glomerulonephritis and all were children. It was gross in two and repeated (up to six times) in two others. With the exception of three, all cases showing a proliferative lesion in the glomeruli had red cells in the urine on microscopy. Six of them showed only a few red cells. The histological detail in these cases was variable - ranging from mild proliferation to advanced glomerular sclerosis. The three cases who showed no red cells on repeated microscopy also varied in histological detail. One showed proliferation with secondary membranous change, one lobular glomerulonephritis and secondary pyelonephritis, and the third capsular proliferation and adhesions on top of glomerular hypercellularity and crescent formation. In conclusion, therefore, haematuria appears to be an almost invariable feature of proliferative glomerulo-nephritis

but is of much greater significance if it is macroscopic. This appears to occur more commonly among children than among adults.

9. Urinary Volume

Many cases had low urinary volumes. 24-hour volumes of 300-500 ml. were not uncommon. The low urinary volume was partly due to the nephrotic syndrome and partly due to increased insensible loss from the body as a result of a relatively high atmospheric temperature (70-80°F). Large volumes were passed when effective diuretic therapy was given.

10. Proteinuria

Heavy proteinuria (10-20 grams per day) occurred in only 20 (of 80)cases. The average proteinuria was 7 grams a day. In 11 cases proteinuria was 7 grams or less in the day. There was considerable variation in the daily protein output - differences of up to 15 grams being recorded in the daily values over a three-week period. The value for the case was taken to be the average of all the estimations unless a progressive diminution suggested the onset of a remission.

Urinary proteins contained large quantities of globulin. The globulin fraction was sometimes greater than that of albumen. This reversal of the usual

situation (Leutscher, 1940) is considered to be due to high serum gamm-globulin levels among East Africans (Kibukamusoke and Wilks, 1965b).

11. Urinary Deposit

Casts were present in all cases. Granular casts were invariably present. Hyaline casts were commonly found though not invariably. Pus casts were found in one case who was eventually proved to have an acute pyelonephritis. Red cells casts were found in one case who had an attack of acute glomerulonephritis. This type of cast therefore indicated true glomerular bleeding.

Red cells have already been considered under "Haematuria".

White cells - the majority of cases showed some white cells. These were usually few in number. In 5 cases, these were present in large numbers. Three of these cases had acute pyelonephritis when specimens were taken, while in the other two this finding could not be explained. Urethral strictures were not present in these two cases and repeated urine cultures were unrevealing. Such cultures were sterile on four occasions in one of the cases while in the other low bacillary counts were obtained on five occasions.

Renal biopsies in these two cases showed no evidence of pyelonephritis. The only changes to be found were those of proliferative glomerulonephritis.

12. Pregnancy

Pregnancy precipitated or aggravated oedema in every case where it was present. The same was also true for each subsequent pregnancy. Histology was irrelevant in this particular respect. In all cases, oedema remitted during the early puerperium up to the third pregnancy when it appeared to persist. In the majority of cases, the recurrence of oedema started during the third trimster although in a few cases it started as early as the second month of pregnancy.

DISCUSSION

The clinical presentation of these cases was in no essential way different from that seen in the Western hemisphere (Ellis, 1942; Squire, 1960; Arneil, 1961) except in one important respect - severity of oedema. The severity of this symptom is frequently so striking that it is not surprising that it has provoked comments before (Leather, 1958 and 1960: White, 1964). Diagnosis of a nephrotic state can often be made at the first sight of a case. What is significant though is that full blown nephrotic syndrome often presents with renal lesions usually unassociated with it:

2. BIOCHEMISTRY

Plasma Protein patterns among normal Africans differ from those seen in Europens (Holmes et al, 1951 and 1955; Leonard et al, 1965). Differences also occur within Africa one area from another (Edozien, 1961). It is therefore necessary to compare any abnormal results with figures obtained from "normal" subjects resident in the area under study. Table 3 (a) and (b) (below) has been compiled to facilitate such a comparison. Figures from normal European subjects have also been quoted to permit ease of reference.

The total protein content of the serum was estimated using the Biuret technique (Wootton, 1964). Protein fractions were done by paper electrophoresis in L.K.B. horizontal tanks using 0.125M veronal buffer pH 8.6. After running for 16 hours, the papers were stained with bromphenol blue and subsequently scanned and integrated on the Zeiss automatic instrument.

For serum cholesterol, the technique described by Wootton (1964) was used and for blood urea, the auto-analyzer method described by the same author (Wootton, 1964).

RESULTS:

Total Plasma Proteins

The average plasma protein total was 4.5 gm% with a range of 2.4 - 6.6 gm%. Only 10% of the cases had values of 3.0 gm or below and only 4% figure above 5.5%. The majority (86%) of

TABLE 3 (a)

PLASMA PROTEINS FROM DIFFERENT PARTS OF THE WORLD

	Source	Adults (A) Children (B)	Method	Total Protein	Albumen	$Alpha_1$	$Alpha_2$	Beta	Gamma
Normal East Africans (Ugandans)	Holmes et al (1951)	A	Chemical	7.6	3.27			0.78	1.98
	Holmes et al (1955)	A	Electro-phoresis	7.13	3.35			0.67	1.00
	ditto	C	ditto	7.16	3.80	0.27	0.62	0.64	1.89
	Lennard et al (1965)	A (students)	ditto	6.82	3.39	0.30	0.56	0.80	1.73
	ditto	A	ditto	6.74	3.15	0.21	0.52	0.90	1.86

Values given in grams percent

the cases were therefore in the range of 3.0 - 5.5%. This is distinctly lower than the average normal for Uganda African outpatients (Table 3 (a)).

Serum Albumen

The range was 0.4 - 2.6 gm% with an average of 1.2 gm%. 13% of the cases had 0.5 gm% or below and 6% of the values were above 2 gm%. These figures are all consistently below the normal (Table 3 (a) and (b)).

Alpha2-Globulin

The range was 0.5 - 1.6 gm% with only two cases below the normal range of 0.52 - 0.62 gm% (Table 3 (a) and (b)). Only 18% of the cases were below 0.7 gm%. 82% of all the cases, therefore, had values in excess of the normal range.

Beta-Globulin

In slightly more than half the cases the beta-globulin fraction was present in quantities larger than the alpha$_2$ fraction. The average value for the beta was however 0.83 gm%. These figures are not greater than those given for normal Ugandans (Table 3 (a) and (b)). In fact the highest figure quoted (0.90 gm% - Lennard et al, 1965) is greater than the average figure.

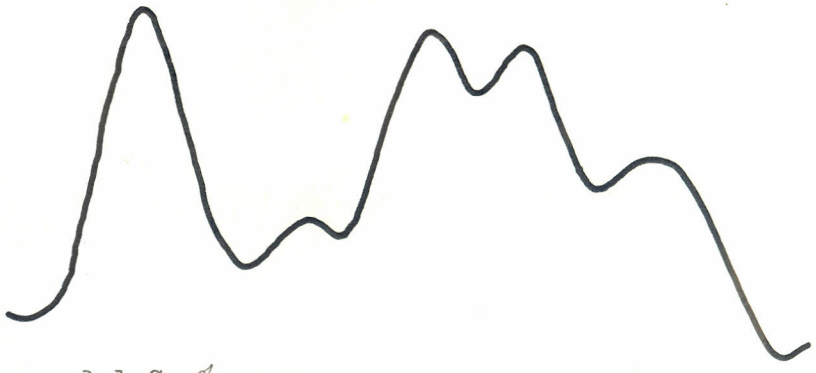
Gamma-Globulin

This was moderately reduced with an average of 1.45 gm% as

Fig. 1

PLASMA PROTEIN ELECTROPHORETIC PATTERNS

A. Case (4N): The Alpha$_2$Beta Pattern (85% of positive cases)



Total Protein: 3.1 Gm %

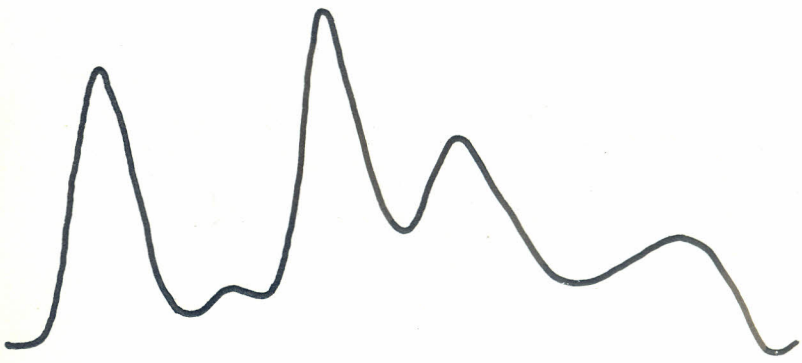
Albumen : 30% (1.0 Gm%)

Alpha$_1$: 10% (0.3 Gm%)

Alpha$_2$: 23% (0.8 Gm%)

Gamma : 19% (0.6 Gm%)

B. Case (66N): Lone Alpha Pattern (10% of positive cases)



Total Protein: 4.0 Gm%

Albumen : 25% (1.0 Gm%)

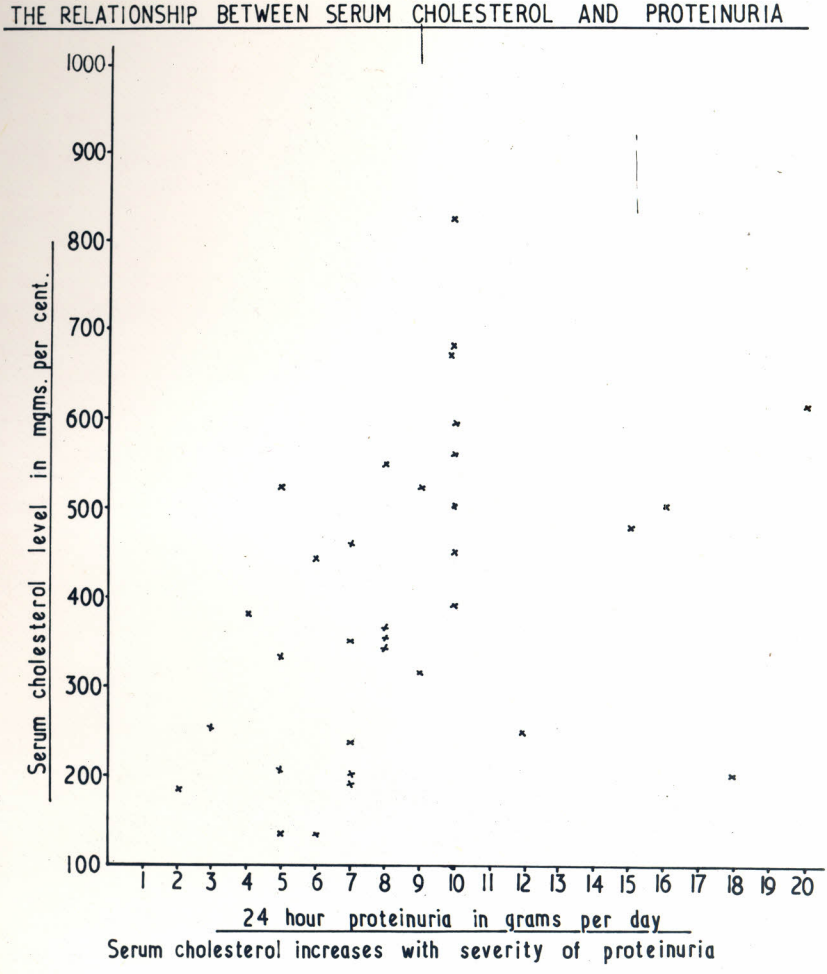
Alpha$_1$: 5% (0.2 Gm%)

Alpha$_2$: 30% (1.3 Gm%)

Beta : 24% (1.0 Gm%)

Gamma : 16% (0.5 Gm%)

Fig. 2


THE RELATIONSHIP BETWEEN SERUM CHOLESTEROL AND PROTEINURIA
Serum cholesterol level in mgms. per cent.
1000
900
800
700
600
500
400
300
200
100
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20
24 hour proteinuria in grams per day
Serum cholesterol increases with severity of proteinuria

compared with the normal range of 1.73 - 1.98 gm% (Holmes's figures of 1951 excluded - Table 3 (a) and (b)). The range was 0.3 - 4.0 gm%, 78% of which had values between 1-2 grams %.

Electrophoretic Pattern

95 of the cases showed the nephrotic pattern (a marked reduction of albumen level, a moderate gamma-globulin reduction and a lone alpha$_2$ (Fig. 1 (B)) or an alpha$_2$beta pattern (Fig. 1 (A)). 85% of the positive cases showed the alpha$_2$beta pattern, 15% the lone alpha$_2$ pattern. 5% had non-specific patterns. The appearance of the alpha$_2$beta pattern is, therefore, the commonest.

Serum Cholesterol

This averaged 485 mgm% as compared with a level of 144 mgm% in their normal equivalents (Shaper et al, 1959). The range was 140-1090 mgm% with only 33% below 300 mgm% and 12% below 200 mgm%. 95% were therefore above the normal serum cholesterol level. Fig. 2 shows that the serum cholesterol increased with the severity of proteinuria.

COMMENT

The confirmatory tests for the nephrotic sydrome that are used elsewhere in Europe and North America are therefore useful in the diagnosis of the Nephrotic Syndrome as it is seen in Uganda.

50 mgm of chlopromazine, both by the intramuscular route, an hour before the procedure. In obviously restless or agitated patients an additional dose of sodium amytal of 120 - 185 mgm was given 30 minutes before the operation. It was essential to obtain deep sedation before attempting biopsy as this ensures a high success-rate.

For children, intramuscular chlopromazine 1 mgm/Kg/body weight together with an oral dose of chloral hydrate was given. The dosage used was 120 mgm for children under 2 years, 240 mgm for 2 - 5 year olds and 360 mgm for those over 5 years of age. If further sedation was required another (similar) dose was given half an hour prior to biopsy.

The patient was then laid in the prone position with a tightly rolled blanket 4 inches in diameter across the upper abdomen. The angle between the quadratus lumborum muscle and the lower border of the 12th rib was then identified. This point coincided with a point, one centimeter outside the midpoint between the vertebral spines and the lateral side of the body. If the abdomen bulged laterally the side of the chest was used for purposes of this measurement. After skin cleansing and adequate local procaine anaesthesia, a thin lumbar puncture needle was inserted (to act as a sound for the kidney) through a small stab wound at the point determined

After paraffin embedding sections were cut 3 - 4 μ thickness and stained in two ways, one with Haematoxylin and Eosin and the other by the periodic-acid-Schiff technique for basement membrane histology.

Histological Findings

In assessing glomerular changes it was found useful to count the total number of nuclei in the glomerular tufts. Experience with a wide range of renal biopsies suggests that counts of over 120 nuclei in a single glomerular tuft (the largest that can be found in the biopsy) indicate a proliferative lesion (Hutt, 1965).

The basic histological groups encountered were as follows:

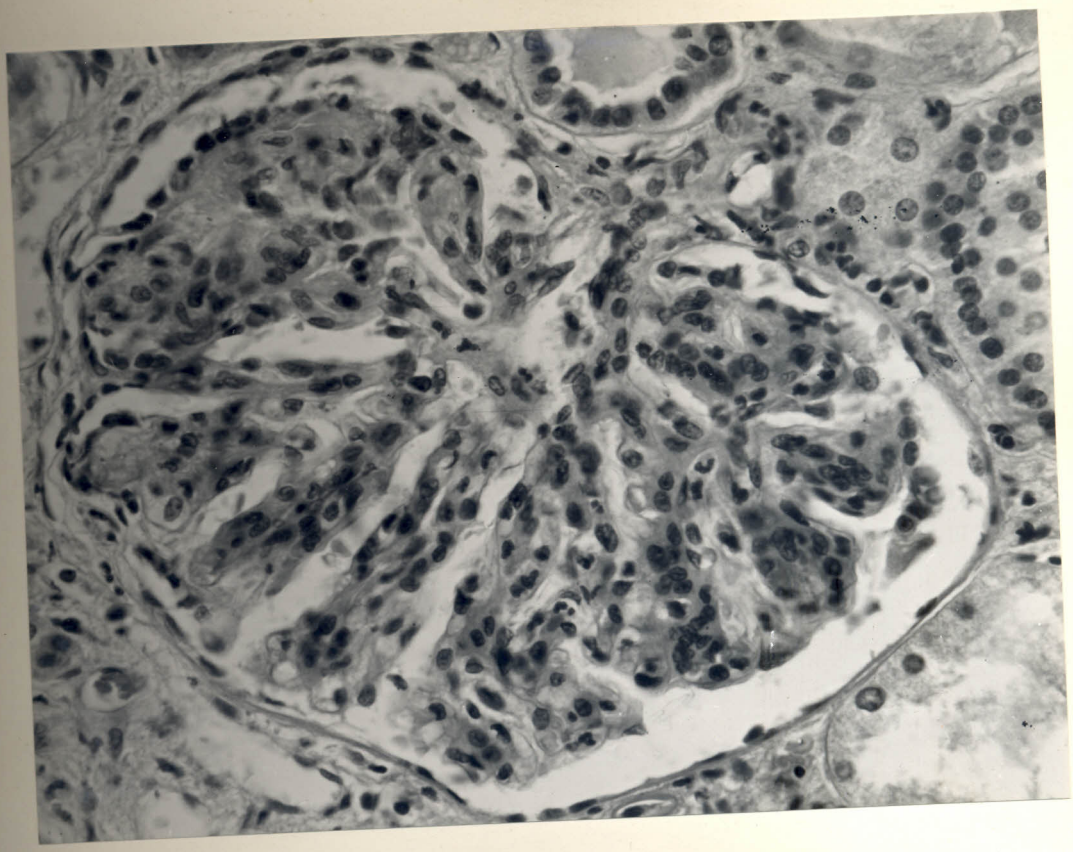
(1) Proliferative Glomerulonephritis

On histological grounds these cases were divided into five sub-groups under the general heading of proliferative glomerulonephritis. It is not suggested that this necessarily implies a differing aetiology. In many cases it was difficult to be certain into which sub-group a biopsy should be placed.

Diffuse

More than 50% of the glomeruli show an increase in the number of nuclei in the glomerular tufts. In most of these biopsies the proliferation was diffuse throughout the tufts (Fig. 3)and frequently all the glomeruli were involved.

Fig. 3

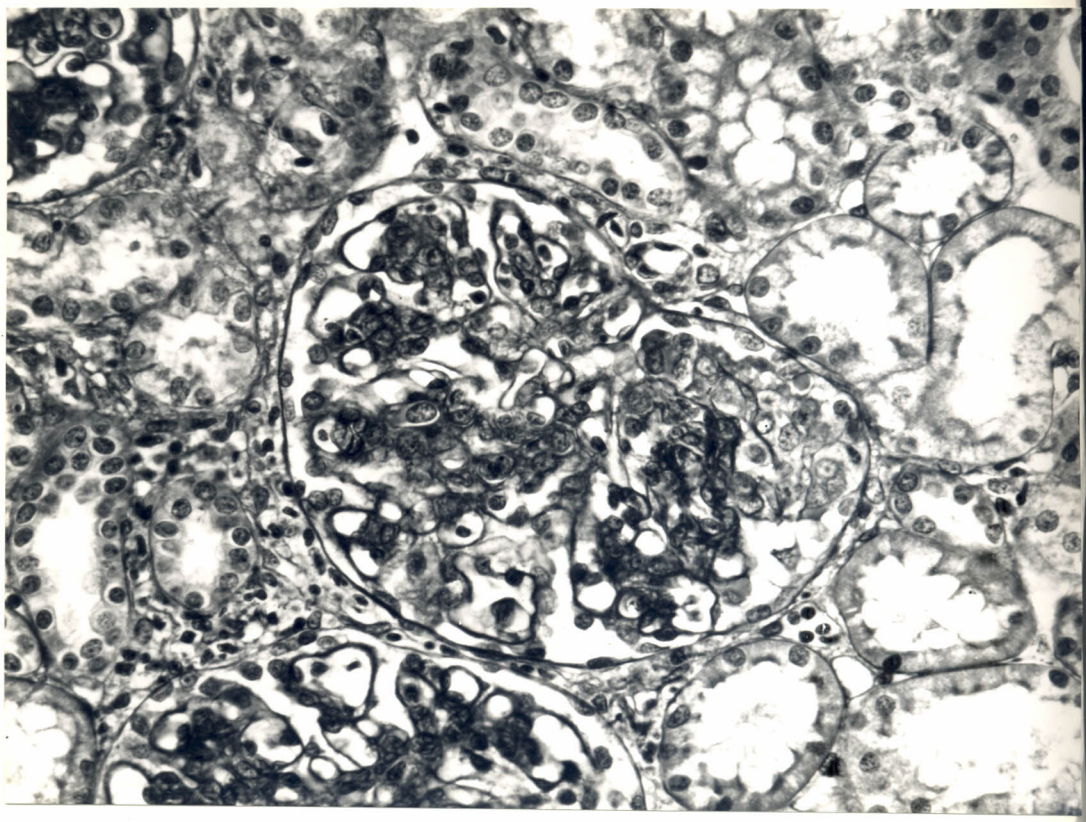


Proliferative glomerulonephritis.
Note lobulation and marked increase in size of glomerular tuft with proliferation of tuft nuclei.

Case No. 24N P.M. 73/64. This patient also showed focal areas of chronic pyelonephritis in both kidneys.

X390.

Fig. 4

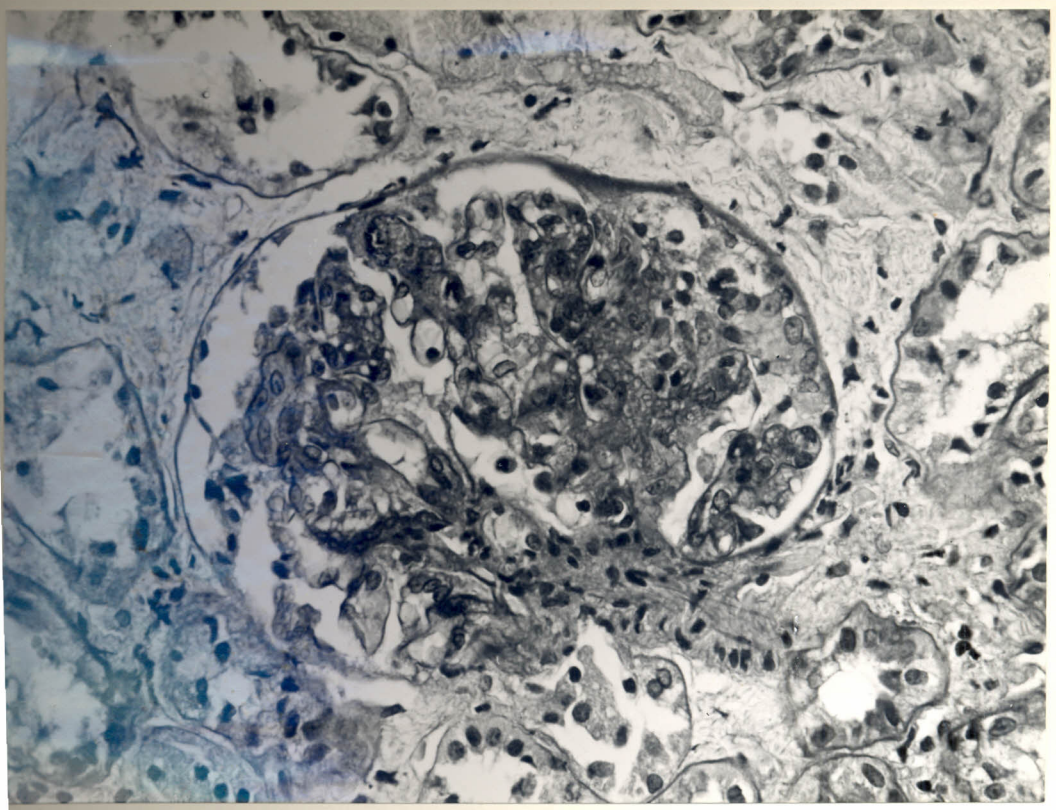


Proliferative Glomerulonephritis with early lobular pattern due to basement membrane increase.

Case No. 9N Biopsy 3698/63

X 390.

Fig. 5

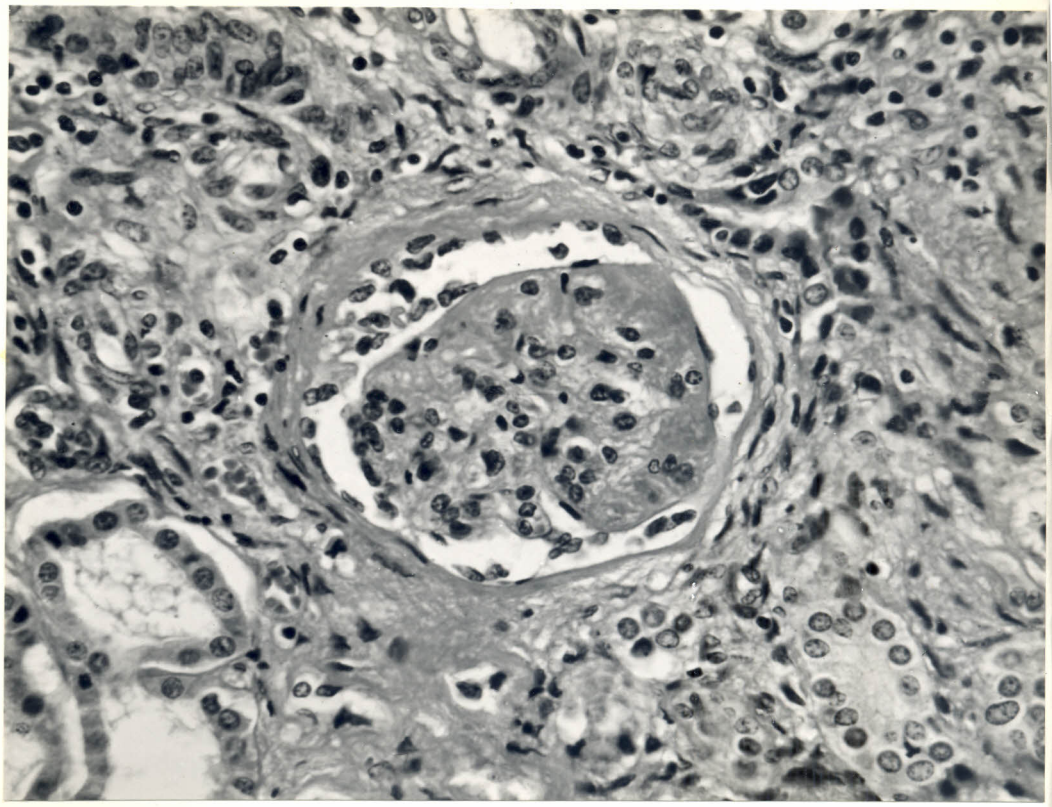


Proliferative glomerulonephritis with secondary membranous change and proliferation of Bowman's capsule.

Case No. 62N Biopsy 190/65 P.A.S.

X390.

Fig. 6

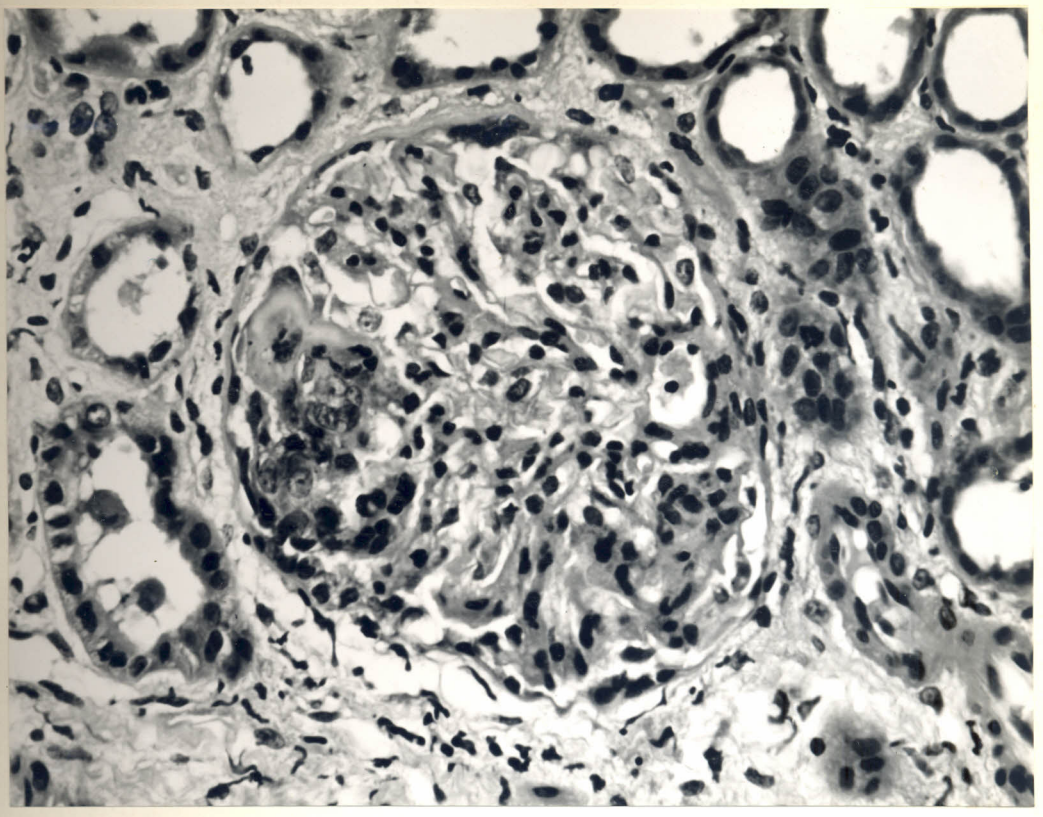


Proliferative glomerulonephritis with progression to sclerosis. This begins as an increase in basement membrane material.

Case No. 8N P.M. 211/65

X390.

Fig. 7

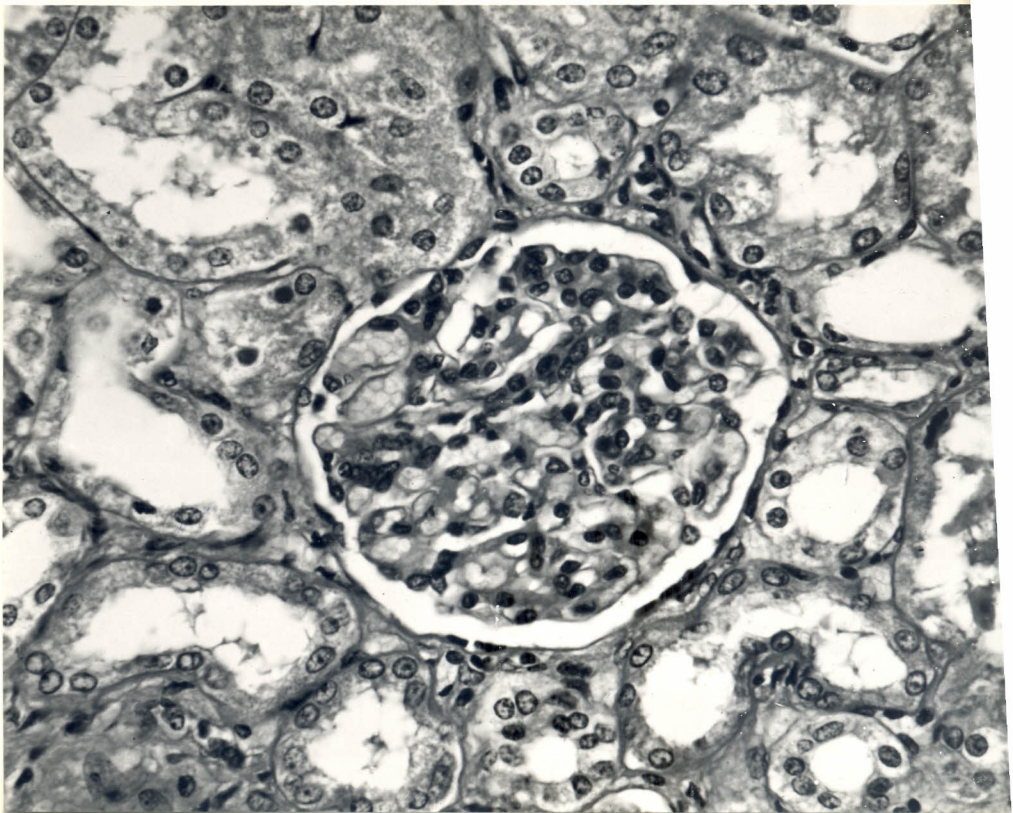


Proliferative glomerulonephritis with capsular proliferation. Note also atrophy of tubules and increase in interstitial tissue.

Case No. 62N Biopsy 190/65

X390.

Fig. 8



Focal glomerulonephritis. (see also Fig. 9 and 10
This is a normal glomerulus from Case No. 67N. P.M
(In focal glomerulonephritis many of the glomeruli
be normal).

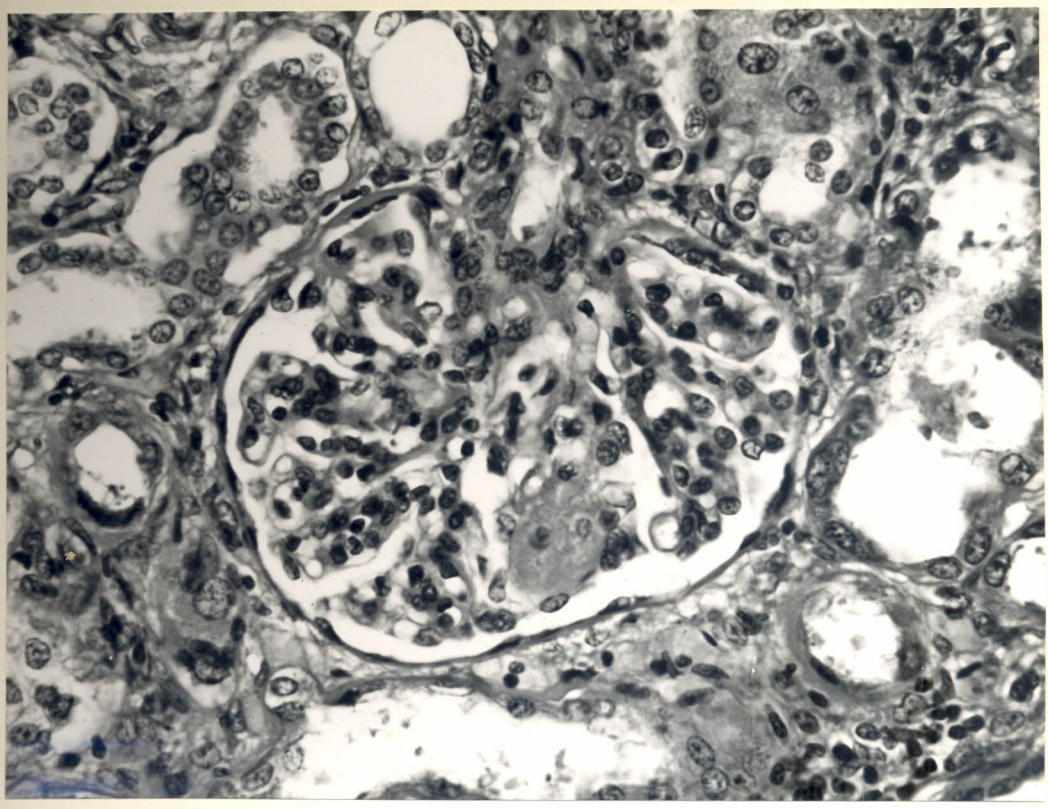
X390.

In some cases, proliferation was more pronounced in one lobule of a tuft than in others as in Rich's (1956) and Hutt et al (1958) cases. Secondary basement membrane change was visible in a number of cases (Fig. 4; Fig. 5) and progression of this lesion led to complete sclerosis of the glomerulus (Fig.6). Capsular proliferation was also present in a number of cases (Fig. 5; Fig. 7). Tubular atrophy and interstitial tissue changes were seen in some of the more advanced cases (Fig. 7).

Focal

In this variety, less than 50% of the glomeruli show changes (Fig. 8). Frequently the affected glomeruli show 'local' involvement (only part of the glomerulus being involved). In many cases, the 'focal' and 'local' lesions were proliferative but glomeruli with eccentric hyalinisation (Fig. 9; Fig. 11; Fig. 12) (Heptinstall and Joekes, 1961) or with local areas of basement membrane thickening (Hutt 1965) were included even if proliferation was not obvious. This is the type of lesion that was seen in many of the cases described as minimal. Partial sclerosis of the glomerulus was seen in some of the cases (Fig. 10). All these changes could be found in the same kidney and a single renal biopsy could be misleading. Figs. 8, 9 and 10 were in fact taken from a single case (67N).

Fig. 9

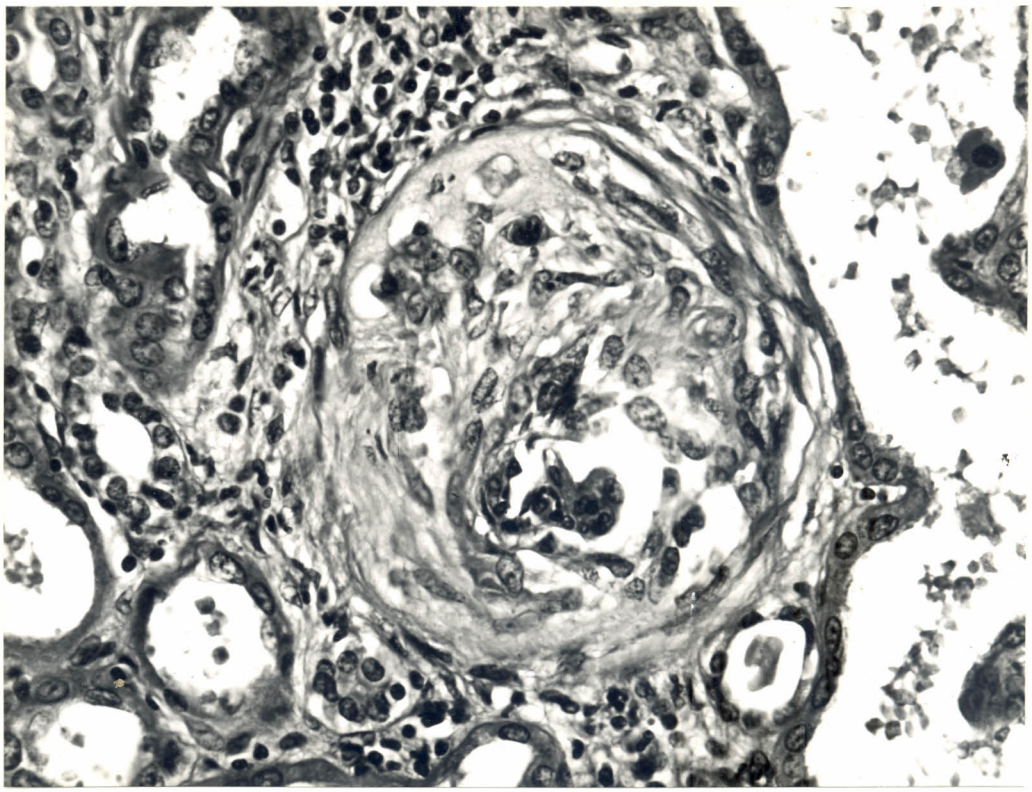


Focal glomerulonephritis (see also Figs. 8 and 10)
Note local area of hyalinisation with local increase in nuclei in one lobule. (this is the type of lesion seen in many of the cases described as minimal).

Case No. 67N P.M. 378/65

X390.

Fig. 10



Focal glomerulonephritis.
Partial sclerosis of glomerulus.

Case No. 67N P.M. 378/65 (see also Figs. 8 & 9

X390

Lobular

This variety showed a pattern in which the proliferation had a distinct lobular pattern with a central mass of hyalinisation (increase of basement membrane material) in the centre of the lobule (Fig. 3).

Chronic

In these cases, there were advanced lesions in the glomeruli with capsular adhesions, secondary membranous thickening, glomerular disorganisation and secondary tubular atrophy. Some of these biopsies showed crescent formation. In the group referred to in Table 4 as chronic nephritis there was almost complete destruction of the renal architecture with extensive fibrosis of the glomeruli.

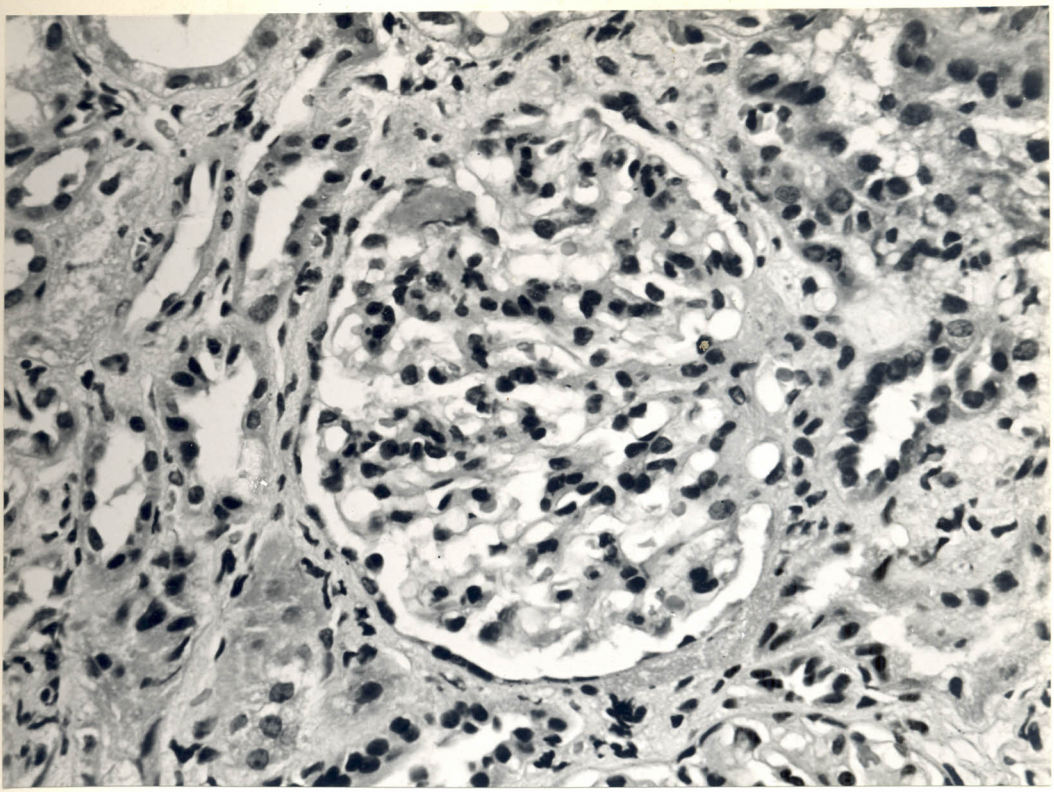
Minimal

This refers to biopsies in which there were slight but definite changes of the type described as diffuse or focal (Fig. 11, Fig. 12). In these cases, no pathological lesions could be found in the vessels, interstitial tissue or tubules (except, of course, hyaline granules due to leakage of protein).

(2) Membranous

Definite and usually uniform increase in the thickness of the glomerular basement membrane without significant increase of tuft cells (Fig. 13).

Fig. 11



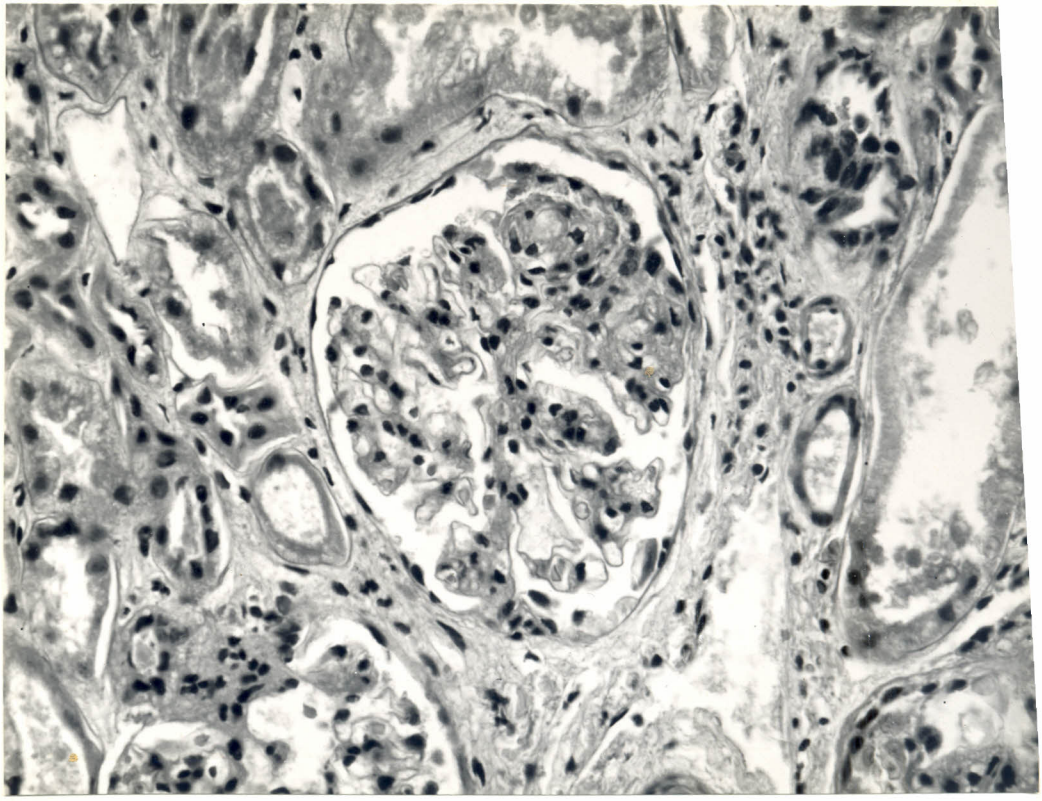
Minimal Lesion

Slight focal proliferation with a local area of sclerosis.

Case No. 67N Biopsy 166/65

X390.

Fig. 12



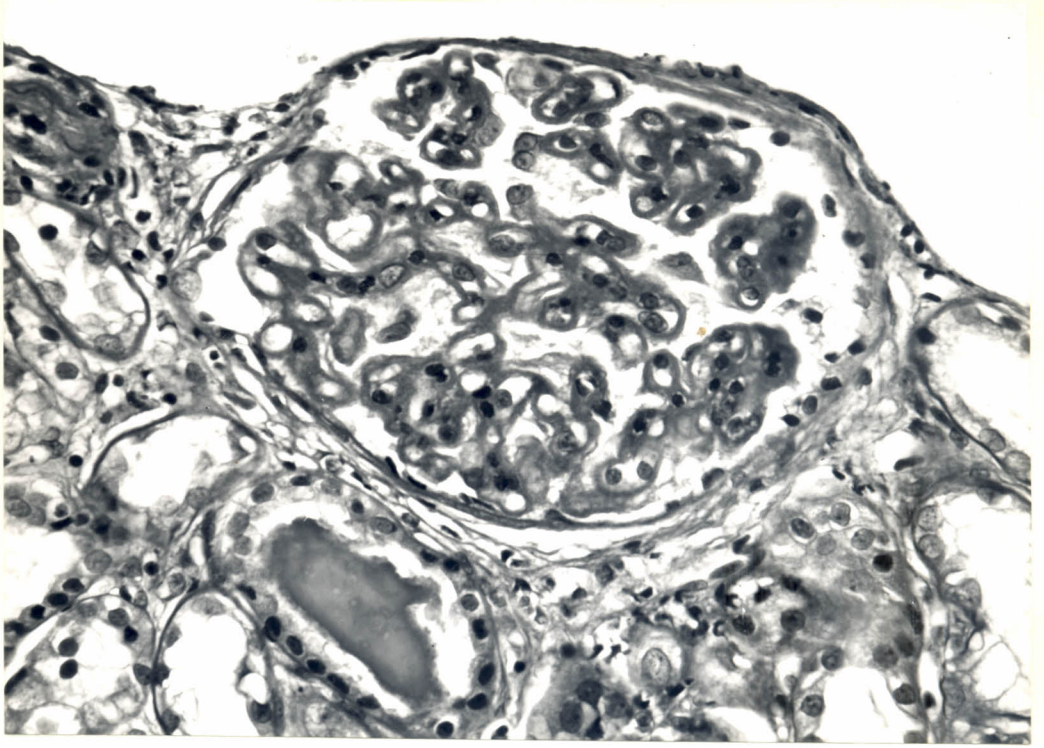
Minimal Lesion

Note focal area of sclerosis in glomerulus. Most of the glomeruli in this case were quite normal.

Case No. 22N Biopsy 200/64

X390.

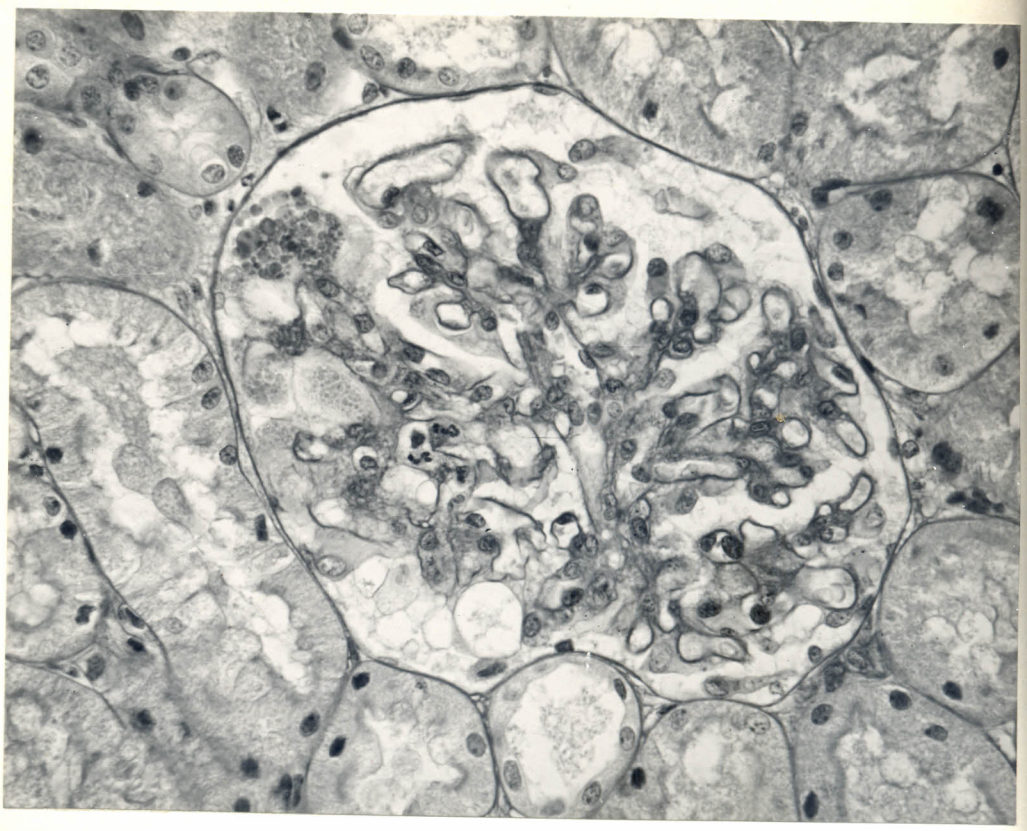
Fig. 13



Membranous Glomerulonephritis
Diffuse thickening of basement membrane with no proliferation. Case No. 18N Biopsy 5241/63

X390.

Fig. 14



Case of Pyelonephritis

Case No. 12N Biopsy 4991/63

Glomerulus from normal area of kidney showing hyaline droplet change in epithelial cells suggesting protein leak.

X390.

(3) Pyelonephritis

In small renal biopsies this may present many problems in diagnosis. Emphasis was laid on the focal nature of the lesions with normal renal tissue in the intervening areas (Fig. 14). The lesions are characterised by infiltration of the interstitial cells by chronic inflammatory cells (particularly plasma cells), periglomerular fibrosis and pus casts or 'thyroid like' tubules.

(4) Nil Change

When the four elements of renal tissue (glomeruli - including nuclear counts - tubules, interstitial tissue and blood vessels) are completely normal in all the glomeruli in the specimen, a diagnosis of 'nil change' is made.

RESULTS (Table 4)

1. Proliferative Glomerulonephritis

This was the largest histological group. It comprised 55 cases - more than half the total. Eleven of the cases showed focal glomerulonephritis, 17 minimal change, 16 the diffuse proliferative lesion, 8 chronic proliferative change and 3 the lobular variety. Contrary to tradition, the minimal change has been separated from the nil change group because of the important difference between these two groups in reference to steroid therapy. This difference will be discussed later.

In nearly all these cases, there was hyaline droplet formation

Table 4

THE HISTOPATHOLOGY OF 77 CONSECUTIVE CASES OF THE NEPHROTIC SYNDROME OF QUARTAN MALARIA

NO.	HISTOLOGY			NO. OF CASES
1.	PROLIFERATIVE GLOMERULONEPHRITIS	FOCAL	11	55
		MINIMAL CHANGE	17	
		DIFFUSE	16	
		CHORNIC	8	
		LOBULAR	3	
2.	MEMBRANOUS GLOMERULONEPHRITIS			9
3.	NIL CHANGE			3
4.	PYELONEPHRITIS WITH NEPHROTIC SYNDROME			2
5.	RENAL AMYLOIDOSIS			3
6.	RENAL VEIN THROMBOSIS			1
7.	DIABETIC GLOMERULOSCLEROSIS			0
8.	SYSTEMIC LUPUS ERYETHEMATOSUS			0
9.	CHRONIC NEPHRITIS			3
10.	HENOCH - SCHOENLEIN SYNDROME			1
TOTAL				77

Proliferative Glomerulonephritis is much the commonest histological lesion. All cases showing ar increase in glomerular cellularity whether local, focal or diffuse have been included in this group.

in the tubules. Those with more marked glomerular involvement often showed some tubular atrophy with dilatation of the lumen and flattening of the epithelium. Hyaline casts were present in some of these tubules and occasionally cellular casts. Red cells could be seen in the tubular lumens of many cases with severe proliferative lesions.

In those cases with minimal changes the tubules often appeared normal apart from some swelling of the cells and hyaline droplet formation. The interstitial tissue was normal or showed only a slight increase with occasional foci of lymphocytes.

In the advanced (chronic) group (8 cases) disorganisation of renal architecture was a very striking feature. Destruction of the glomerular elements with sclerosis and secondary membrane thickening was present in many cases. This feature, however, was seen in some isolated glomeruli in relatively mild cases. A whole glomerulus would appear completely sclerosed while its neighbouring fellows remained normal or only slightly proliferative. In the advanced case, the lesion was more widespread and was associated with severe atrophy of tubular elements. Epithelial crescents were seen only in three cases but capsular adhesions were present in practically all cases. Considerable interstitial infiltration with chronic inflammatory cells was seen in many cases together with varying degree of fibrosis. Arteriolar changes were present in 4 cases and these were attributable to hypertension.

Fig.15

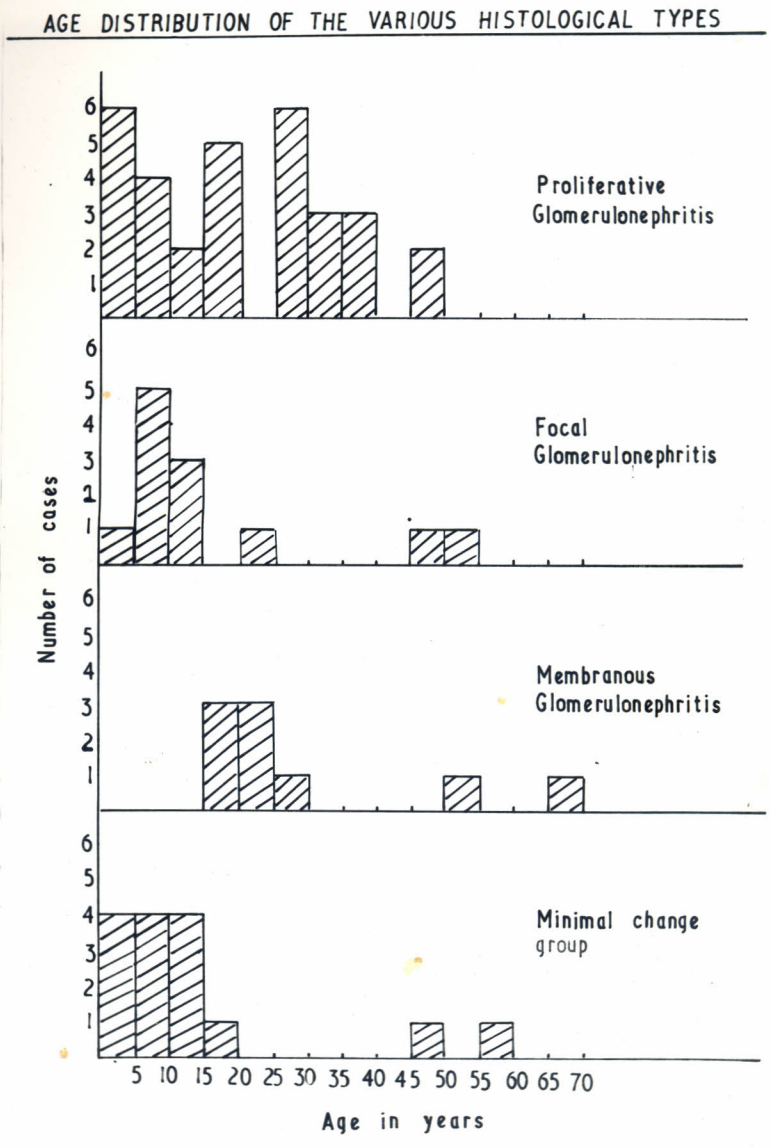

AGE DISTRIBUTION OF THE VARIOUS HISTOLOGICAL TYPES
Proliferative Glomerulonephritis
Focal Glomerulonephritis
Membranous Glomerulonephritis
Minimal change group
Number of cases
1 2 3 4 5 6
5 10 15 20 25 30 35 40 45 50 55 60 65 70
Age in years

Table 5

HISTOPATHOLOGY OF PEDIATRIC CASES
OF THE NEPHROTIC SYNDROME OF QUARTAN MALARIA

NO.	HISTOLOGY			NO. OF CASES
1.	PROLIFERATIVE GLOMERULONEPHRITIS	FOCAL	7	28
		MINIMAL CHANGE	14	
		DIFFUSE	5	
		CHRONIC	1	
		LOBULAR	1	
2.	MEMBRANOUS GLOMERULONEPHRITIS			0
3.	NIL CHANGE			3
4.	PYELONEPHRITIS WITH NEPHROTIC SYNDROME			0
TOTAL				31

Three cases showed a lobular pattern in the glomeruli and sclerosis was visible in many of the lobular stalks. Mild periglomerular fibrosis was seen in two cases.

Fig. 15 indicates that the nephrotic syndrome due to proliferative glomerulonephritis was commonest among children and young adults. The histogram shows two peaks: one in the age group 5-10 years and the other 25-35 years. The former coincides with the peak incidence of malaria infection among children (Fig. 17) and the latter peak merely reflects the age distribution of Mulago Hospital patients (Hamilton, 1965). The 17 cases showing the minimal proliferative lesion were all children, with the exception of three.

2. Membranous Glomerulonephritis

There were 9 examples of this lesion. Four cases showed mild thickening of the glomerular basement and 5 more sévere thickening. In two of these, glomerular sclerosis was also present. This ranged from slight to complete sclerosis of the glomerulus. The proximal tubular cells showed hyaline droplet formation. In one case, an elderly man of 70, tubular degeneration and infiltration of interstitial tissue with chronic inflammatory cells were present. Heavy bacillary growths were obtained on culture of the urine. Several cultures subsequent to treatment with Cephalosporin-C were sterile. This was undoubtedly a case with superimposed acute

pyelonephritis.

This lesion was found only in adult patients and apart from a man of 70, all were young adults (Fig. 15).

3. Nil Change

There were only three cases in this group and all were children. One of them showed P. malariae parasites in the blood and all responded satisfactorily to steroid therapy.

4. Pyelonephritis with the Nephrotic Syndrome

There were 2 cases in this category. Both were adults with urethral strictures. Heavy bacterial growths were obtained from cultures of urine in each of these cases. The following was the mode of presentation:-

(i) P.M., (12N), a male adult aged 60, gave an 8-year history of chronic gonorrhoeal infection. A suprapubic cystotomy had been performed two years previously for acute retention of urine and the stream had been diverted for a period of three weeks. He failed to attend bougie sessions subsequently. Perineal fistulae had appeared more recently and oedema which eventually involved the whole body had been building up during the year preceding admission. On admission, the urine was frankly purulent and heavy bacillary growths were obtained from the urine.

Blood slides showed P. Malariae and there was biochemical evidence of nephrotic syndrome. Renal biopsy which was taken two weeks after treatment of the urinary infection showed focal renal scars with periglomerular fibrosis, shrinkage of tuft, tubular atrophy and interstitial fibrosis. A piece of renal pelvis contained chronic inflammatory cells but otherwise inflammation was minimal. About 50% of the tissue was composed of normal cortex with normal looking glomeruli, except that some contained hyaline droplets in epithelial cells. The patient subsequently died and the necropsy findings were: hydronephrosis, hydroureters and a trabeculated bladder which was distended with infected urine. A stricture was present in the membranous part of the urethra. Histologically, microabscesses and extensive inflammation were seen.

(ii) M.L., (24N), aged 32, woke up five days before admission with oedema of the whole body. He had experienced difficulty with passing water for some years. His urine grew B. coli in considerable numbers and the urinary deposit showed numerous pus cells. His blood showed a very light infection with P. malariae parasites. He died a few days after admission and autopsy revealed bilateral atrophied kidneys and moderate hydronephrosis

and hydroureters. The urine was infected and there was an impassable stricture of the urethra. On histology, there was a "focus of chronic pyelonephritis together with evidence of inflammation in the pelvis. Looking at the apparently normal area, there was a striking proliferation of the glomerular tuft. In one of these 180 nuclei were counted, which is grossly abnormal. These glomeruli were a long way from an inflammatory process and the proliferation could not have been due to 'invasive glomerulitis'. This patient appeared to have two diseases: chronic pyelonephritis and proliferative glomerulonephritis".

5. The Rest of the Cases

Three cases of renal amyloidosis were found. Two had pulmonary tuberculosis but the third showed no primary cause of amyloid.

There was one case of primary renal vein thrombosis and one of Henoch-Schönlein syndrome. A further three cases showed glomerular changes that were too advanced for more accurate diagnosis and were therefore labelled chronic nephritis. No cases of either diabetic glomerulosclerosis or systemic lupus eryethematosus were seen. These two conditions though known to occur in East Africa do so much less commonly than is the case in Europe and North America (Tulloch, 1962 and 1965; Shaper, 1961).

TABLE 6

HISTOLOGICAL PATTERNS IN DIFFERENT CENTRES

NO.	HISTOLOGIC VARIETY	Berman et al (1958)	Kark et al (1958)	Kark et al (1955)	Blainey et al (1960)	Kibukamusoke (1966)
1.	Proliferative Glomerulonephritis	21	18	14	6	44
2.	Membranous Glomerulonephritis	10	28		6	9
3.	Focal Glomerulonephritis					11
4.	Nil Change		11	2	6	3
5.	Pyelonephritis with Nephrotic Syndrome				1	2
6.	Renal Amyloidosis	4	3	3	3	3
7.	Renal Vein Thrombosis	1			1	1
8.	Diabetic Glomerulosclerosis	3	15	11		
9.	Systemic Lupus Eryethematosus	4	18	7	1	
10	Chronic Nephritis				3	3
11.	Henoch-Schoenlein Syndrome					1
12.	Other	2	5		2	
13.	Non-classified			3		
	TOTAL	45	98	40	29	77

COMMENT

Comparison of the incidence of each histologic variety in different centres (Table 6) reveals no essential differences between Mulago Hospital and other centres. It is therefore inevitable to arrive at the same conclusion as did Grace in 1931 that "it may be said with certainty that if any difference exists between the nephritis of British Guiana and that of the temperate climates, this difference is one of aetiology and is not found in the developed disease."

HISTOLOGY OF PAEDIATRIC CASES

Gilles and Hendrickse (1963a) wrote that "the findings by light microscopy in 43 renal biopsies indicated that the renal pathology of the nephrotic syndrome associated with P. malariae was that of a non-specific membranous glomerulonephritis with progressive glomerular sclerosis and secondary tubular changes reflecting the degree of glomerular damage". Owing to the difference in the histology between Gilles and Hendrickse's series and our own, a detailed discussion of this group seems necessary.

Thirty-one of our cases were children with an average of 8 years. The bulk of these cases occurred in the age group 5-7 while the extremes were $2\frac{1}{2}$ and 14 years. Sixteen were males and 15 were females. The quartan parasite rate among

these was 71% while the malaria (all types included) parasite rate was 81%. Twenty-one showed minimal changes in the biopsy, all of the proliferative variety (Table 5). The lesion was diffuse but mild in 14 children and focal in seven. The glomeruli were involved either wholly or in part. In repeat biopsies many of these cases showed little change one way or the other during two years' observation. There was neither significant healing nor progression. It is however too early yet to comment on the prognosis in these cases.

One child, though, who showed a diffuse lesion involving all glomeruli on first occasion of admission showed significant healing with more than 50% of the glomeruli normal in a subsequent biopsy taken two years later. The second biopsy, therefore, showed a focal glomerulonephritis. He was not receiving malaria prophlaxis during this period. His biochemistry has remained normal and proteinuria 100-200 mgm in a 24 hour period. This shows therefore that a number of these cases do resolve to a considerable extent without malaria prophylaxis. It would be interesting to know whether prolonged malaria prophylaxis would influence the course of the disease. This aspect is being studied at the clinic at the moment. One child, however, had chronic glomerulonephritis and died of renal failure two years after his original admission with nephrotic syndrome.

Three cases presented as acute post-streptococal glomerulonephritis. In one, a beta-haemolytic streptococcus was recovered from throat cultures while high antistreptolysin-O-titres (ASOT) were obtained in the serum in all the three cases. Each of these three showed P. malariae in the blood. Renal biopsies showed acute diffuse proliferative glomerulonephritis. In addition, there was clinical and biochemical evidence of nephrotic syndrome. In these cases, therefore, acute nephritis presented with the nephrotic syndrome.

Focal Glomerulonephritis

One child had a series of three biopsies during the course of one year. The first showed entirely normal glomeruli. The second showed minor proliferative and some sclerotic changes and the third patchy lesions of diffuse proliferation (or focal glomerulonephritis, Heptinstall and Joekes, 1961). There was complete refractoriness to steroid therapy. Malaria parasites were absent in three ten-day sessions of search but subsequently discovered during a febrile episode. This then appears to have been a true case of focal glomerulonephritis in whom the needle missed a pathologic area on the first attempt. McGovern (1964) encountered similar problems in his series. This case was completely steroid resistant. Six others showed similar lesions (focal glomerulonephritis) and all were similarly steroid resistant.

4. STEROID THERAPY

Material

Twenty patients with the nil or minimal lesion were given steroid therapy (Table 7). Seventeen of these were children, 12 of whom had the disease for less than 6 months and five for periods between five days and three weeks. The disease had been present for over 6 months (1-2 years in all these cases) in 5 children. There were three adults with the minimal lesion; in all these the disease had been present for two months or less.

There were only three cases with the nil lesion. Two of them had suffered the disease for a year or more.

Ninenteen patients had severe glomerular damage. Seven had a pure membranous lesion and 11 a proliferative one. Seven of those with the proliferative lesion showed advanced changes in addition: sclerosis, secondary membrane thickening, or gross glomerular disorganisation. One was a case of renal vein thrombosis whose true diagnosis was revealed at necropsy. Four of these patients were children. In the rest of the cases, the disease had been present for a year, or more.

Therapy

All 39 patients received steroids; 25 for periods in excess of one month. Thirty patients received 60 mgms. of Prednisone a day: 6 for two weeks, 5 for 3 weeks, 14 for one month, 3 for 4-8 weeks and 2 for over two months. Three patients received 80 mgm.

Table 7

STEROID THERAPY IN THE NEPHROTIC SYNDROME OF QUARTAN MALARIA

	No.	Serial No.	Glomerular Pathology	Duration	Age In Years At Onset	Steroids	Response
I. MINIMAL CHANGE							
(a) Children - Disease under 6 months duration	1.	67N	Min. Prolif.	2½ months	7	Predn. 80/day, ACTH 100/day/ 2 months	Nil
	2.	61N	Min. Prolif.	5 days	5	Predn. 60/day/2 wks, ACTH 100/day/2 wks	Diuresis Only
	3.	58N	Min. Prolif.	2 months	7	60/day/3 weeks	Nil
	4.	57N	Min. Prolif.	1 month	14	60/day/one month	Nil
	5.	38N	Min. Prolif.	2 weeks	17	Predn. 60/day/Bet.3mgm/day/ 2 months	Nil
	6.	22N	Min. Prolif.	6 weeks	12	Predn. 80/day/one month	Partial
	7.	19N	Min. Prolif.	1 week	5	Predn. 60/day/one month	Nil
	8.	15N	Min. Prolif.	3 weeks	11	Predn. 100/day/one month	Nil
	9.	52N	Min. Prolif.	One month	5	Predn. 60/day/5 months	Nil
	10.	53N	Min. Prolif.	4 months	5	Predn. 60/day/2 weeks	Nil
	11.	29N	Min. Prolif.	3 weeks	8	Predn. 60/day/one month	Diuresis Only
	12.	79N	Nil	2 months	4 months	Predn. up to 60/day/one year	+++
(b) Adults - Disease under 6 months duration	1.	57N	Min. Prolif.	6 weeks	28	Predn. 60/day/one month	Partial 10G — 30/day
	2.	3N	Min. Prolif.	2 months	48	Predn. 60/day/one month	Nil
	3.	36N	Min. Prolif.	2 months	24	Predn. 100/day/one month	Nil
(c) Children - Disease over 6 months' duration	1.	66N	Min. Prolif.	2 years	5	Predn. 60/day/3 weeks	Nil
	2.	13N	Nil	1 year	1½	Predn. 60/day/one month	+++
	3.	14N	Nil	2 years (recurrence)	1½	Predn. 60/day/one month	+++ (dramatic)
	4.	55N	Min. Prolif.	1 year	12	Predn. 60/day/one month	Nil
	5.	54N	Min. Prolif.	1½ years	6	Predn. 60/day/3 weeks	Nil
II. MORE SEVERE CHANGE							
(a) Children	1.	34N	Diffuse Prolif. with Sclerosis	Several months	4½	Predn./60/3 weeks	Nil
	2.	33N	Diffuse Prolif. + Membr.	2 months	6	Predn./60/one month	Nil
	3.	27N	Diffuse Prolif.	3 weeks	8	Predn./60/day/one month	+++
	4.	73N	Diffuse Prolif. + Membr.	5 months	40	Predn./60/day/one month	Nil
(b) Adults	1.	69N	Membranous	6 years	21	Predn./60/day/2 weeks	Nil
	2.	68N	Membranous	1 year	26	Predn./60/day/16 days	Nil
	3.	65N	Membranous	7 months	18	Predn./60/day/one month	Nil
	4.	44N	Chronic Prolif.	2 months	36	Betameth. 4 mgm/day/one month	Nil
	5.	42N	Membranous	7 weeks	22	Predn./60/day/3 weeks	Nil
	6.	41N	Diffuse Prolif. + Membr.	? 1 year	35	Betameth/3 weeks	Nil
	7.	40N	Diffuse Prolif.	1 year	60	Betameth/one month	Nil
	8.	39N	Membranous	1 year	16	Predn./60/day/2 weeks	+++
	9.	31N	Renal Vein Thrombosis	2 months	60	Predn./60/day/one month	Nil
	10.	30N	Diffuse Prolif. + Membr.	5 months	48	Predn./60/day/one month	Nil
	11.	28N	Membranous	3½ years	20	Predn./100/day/6 weeks	Nil
	12.	21N	Diffuse Prolif.	3 months	28	Predn./60/day/6 weeks	Partial
	13.	17N	Diffuse Prolif.	3 years	28	Predn./80/day/one month	Nil
	14.	6N	Membranous	1 year	23	Predn./120/day/one month	Nil
	15.	4N	Chronic Prolif.	2 months	30	Predn./60/day/2 weeks	Nil

1. Only 2 of the 12 children with the disease under 6 months responded to Steroid therapy - one of whom only did so partially.
2. All the children with absolutely normal glomeruli responded fully to Steroid therapy.

Prednisone daily for a month. A further three received 100 mgm. daily for a month or six weeks and one received 120 mgm. a day for a month. Twenty-one of the patients were children, 19 of whom received 60 mgm. a day, two received 80 mgm. a day and one 100 mgm. a day. In two of the children, a course of adrenocorticosteroid hormone A.C.T.H.) was given (100 units a day) for periods of two and four weeks. Betamethasone was given in four cases; by itself in three (all adults) and for a month to follow a course of Predinsone of similar duration in one child.

RESULTS -(Table 7)

Response was reckoned to have occurred if both proteinuria and oedema had disappeared. "Diuresis only" was recorded where proteinuria persisted at the same level and "partial response" where there was a persistent but definite reduction in the 24 hour protein excretion.

Complete response occurred in one adult (with membranous lesion) and in four children (one with a diffuse proliferative lesion and three with a nil lesion). The overall response rate was, therefore, 12.8%. Among the children with the nil/minimal lesion under six months duration, this rate was only 8.3%. All the children who responded had the nil lesion and all patients with the nil lesion (3) responded - all these were children.

In two cases, only a diuresis occurred - one on A.C.T.H. and

the other on Prednisone. In the former case, Prednisone had failed to produce a diuresis. Both were children with the minimal lesion under six months duration.

A partial response was recorded in three cases: two with the minimal lesion, one of whom was an adult; the third case was an adult with the diffuse proliferative lesion.

COMMENT

Workers elsewhere have obtained high rates of response to steroids in the nil/minimal group of the nephrotic syndrome Vernier, 1961; Metcoff et al, 1961; Lange et al, 1957). The amount of steroid therapy in both groups was essentially similar but the response rate in the current series was 12.8%. Even in the most favourable group (disease under six months duration) there was considerable steroid resistance (8.3% response). However, all those patients with the true "nil" lesion on optical microscopy responded completely and did so to normal steroid doses regardless of the duration of the illness. From this experience it appears necessary to distinguish this group from the minimal change group thereby diverting from the established tradition where both are grouped together.

5. THE ASSOCIATION OF PLASMODIUM MALARIAE WITH THE NEPHROTIC SYNDROME

In order to throw light on the relationship that might exist between Plasmodium malariae and the nephrotic syndrome, extensive studies were undertaken. The results of these studies are presented below:

1. The Excessive Incidence of the Nephrotic Syndrome in Malarious Areas

(a) Figures from Different Parts of the World

Questionnaires were sent to many centres in different parts of the world. Table 8 was compiled from these and shows the incidence of the nephrotic syndrome calculated against the total number of medical admissions in various parts of the world. It is realised that this figure cannot be the best index of incidence since it may be influenced by factors which are independently variable such as the actual incidence of the disease in the area, the age structure of the population served, the amount of interest in the syndrome by the hospital and the quality and availability of medical facilities in the area involved. The figures, however, serve a very useful purpose of indicating the order of incidence in a given country.

It is remarkable that these figures fall into two definite categories: Africa with a precentage incidence

of 0.67 to 2.4 and North America and Red China with an incidence of 0.03 to 0.12%. This distinction corresponds to malaria distribution - being absent or very nearly so in North America and Red China and hyperendemic in Africa. There is one exception to this rule - Bulawayo, Rhodesia, which shows an incidence of 0.15%. It is, however, claimed that malaria has been eradicated from this area (Davies, 1964). The figures then give Africa an incidence of up to 80 times that of non-malarious countries. It is significant to note that the figures from British Guiana before and after malarial eradication (Table 8) correspond to the figures obtained from areas of malaria hyperendemicity and the non-malarious respectively.

(b) Figures from Mulago Hospital

Table 9 shows the analysis of medical admissions with renal complaints during the 5-year period: 1960 to 1964. It will be seen that the nephrotic syndrome was the commonest single group in each of the five years. This group comprised a third to a half of all the renal cases admitted to the medical wards during the period. The percentages against medical admissions are calculated from a total of chronic nephritis and nephrotic syndrome as a very large proportion of the former pass through a nephrotic phase.

Table 8

THE INCIDENCE OF THE NEPHROTIC SYNDROME IN DIFFERENT PARTS OF THE WORLD

			HOSPITAL		ADMISSION RATE	NUMBER OF NEPHROTICS	PERCENTAGE RATE	PHYSICIAN
1.	NORTH AMERICA		UTAH-University and County Hospital		8,400	10	0.12%	Dr. C. Nugent
			Southern California University Hospital		105,351	33	0.03%	Dr. B. Barbour
2.	AFRICA	Hyperendemic (malarial) areas	NIGERIA	Ibadan	2,472	60	2.4 %	Dr. A. Willis
			UGANDA	Fort Portal	1,065	18	1.8 %	Dr. M. Singh
				Mulago	5,761	170	2.0 %	Dr. J. W. Kibukamusoke
		Malaria Controlled Areas	RHODESIA	Bulawayo	15,840	24	0.15%	Prof. L. Davies
				Salisbury	759	5	0.67%	Prof. L. Davies
3.	PEOPLES REPUBLIC OF CHINA		Hunan Medical College		108,617	24	0.03%	Dr. Liu Young-Mo
4.	BRITISH GUIANA		Mackenzie Hospital (Pre-malaria Eradication)		3,617	102	2.8 %	Dr. G. Giglioli
			After Malaria Eradication	Demerara	9,801	0	0 %	Dr. G. Giglioli
				Mackenzie Hospital	6,408	0	0 %	Dr. G. Giglioli

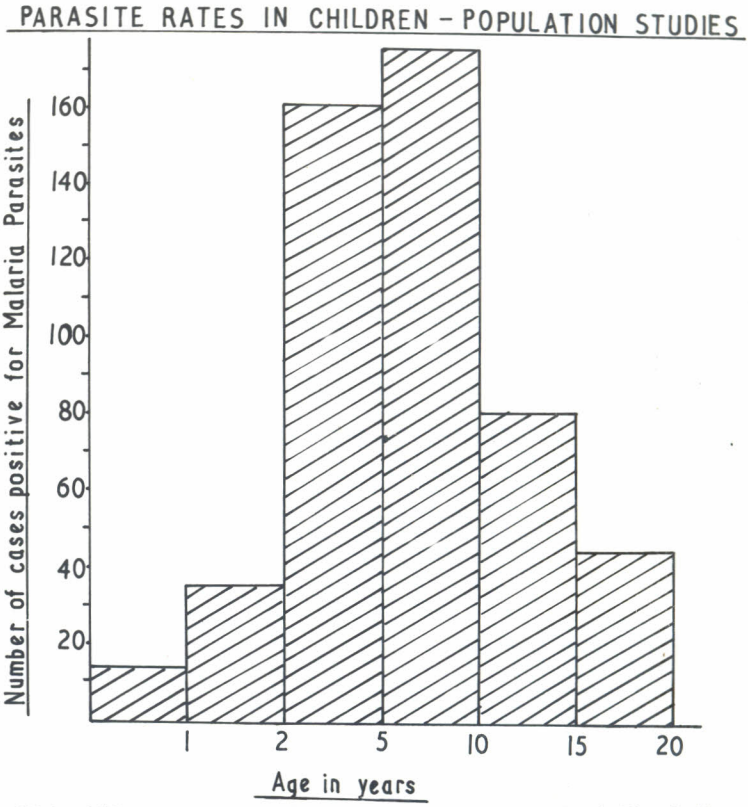
Table 9

ANALYSIS OF MEDICAL ADMISSIONS WITH RENAL COMPLAINTS
DURING A 5-YEAR PERIOD: 1960 - 1964 AT MULAGO HOSPITAL

YEAR		1960	1961	1962	1963	1964
Chronic Nephritis		42	36	46	37	57
Nephrotic Syndrome		70	48	59	50	117
Chronic Pyelonephritis	With Stricture	12	11	7	18	18
	Non-Obstructive	15	9	4	3	4
Acute Pyelonephritis		22	7	22	14	7
Acute Nephritis		5	3	14	20	18
Miscellaneous		10	4	19	12	10
Totals		176	118	171	154	231
Total Medical Admissions		5639	5274	5727	5925	6243
Percentage of Medical Admissions		2.0%	1.6%	2.0%	1.5%	2.8%

All these years are statistically comparable for renal disease.

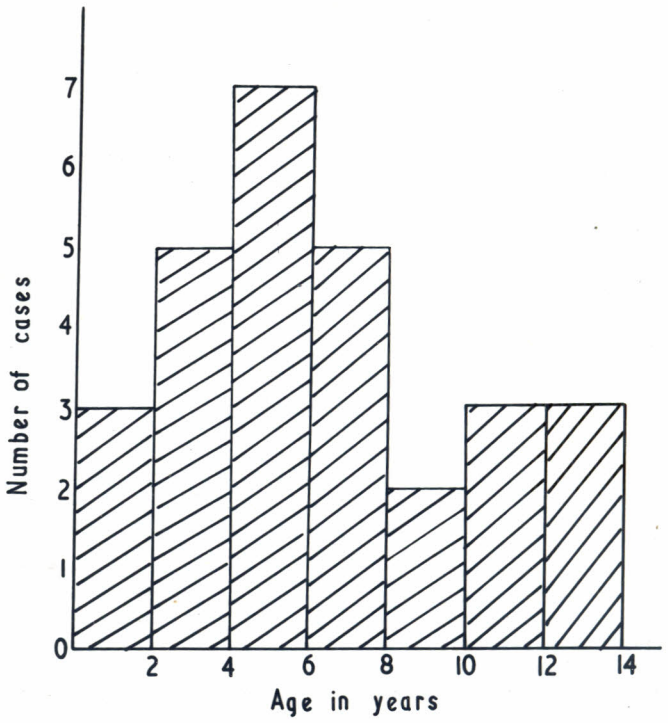
Fig. 16



504 children from 5 different villages were examined. The bulk of positive slides occured in the 4-9 year age group; studies done in Buganda.

Fig. 17

THE INCIDENCE OF THE NEPHROTIC SYNDROME IN CHILDREN



The peak incidence was between the ages 5-6 years.

This coincides with the peak malarial infection: 4-9 years.

The figures obtained are remarkably constant - in fact there is no statistical difference between them. It is noteworthy that these figures are similar to those obtained from Fort Portal (another part of Uganda - 1.8%), Ibadan (2.4%) and British Guiana - before eradication of malaria - (2.8%).

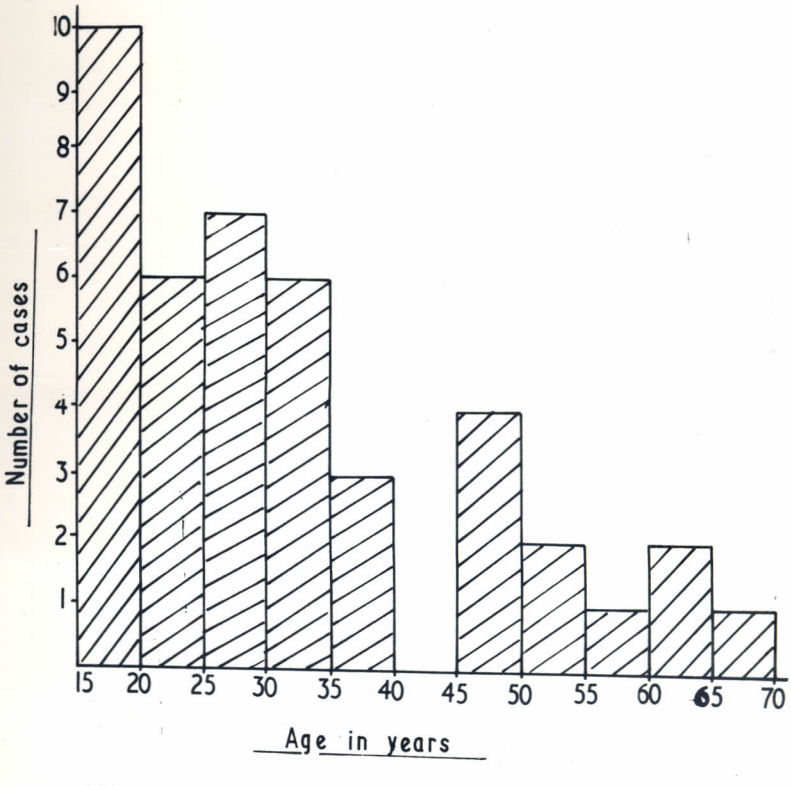
(c) The coincidence of the peak incidence of the nephrotic syndrome with that of malaria infection

Fig. 16 gives the results of a population study involving 504 children in five different villages. The highest incidence of malaria infection (single slide examination) was found in the age group 4-9 years.

Fig. 17 shows the incidence of the nephrotic syndrome among children at various ages. The peak incidence was between the ages 5-6 years, which coincides with the peak incidence of malaria infection. Studies elsewhere (Arneil, 1961) have shown that there are two peaks in the incidence of the nephrotic syndrome among children: at the age of two and five to six years. This study states that the peak at the age of two years is related to teething powders that contain mercury and that this peak is disappearing as mercury is withdrawn from teething powder preparations. Our own histogram (Fig. 17),

Fig. 18

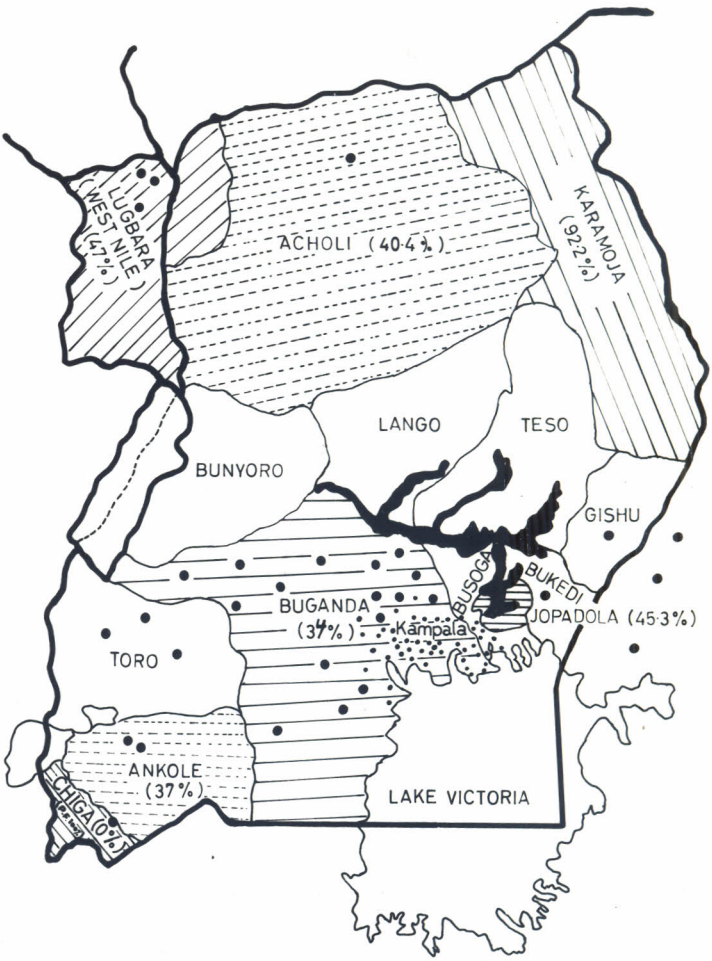
THE INCIDENCE OF THE NEPHROTIC SYNDROME AMONG ADULTS



This appears to be merely a reflection of age distribution in the population.

Fig. 19

INCIDENCE OF QUARTAN MALARIA IN UGANDA. DISTRIBUTION OF NEPHROTIC CASES.



1. ●● or ⁚⁚ → CASES OF NEPHROSIS.
2. SHADED AREAS → SURVEYED FOR MALARIA PARASITAEMIA.
3. % INDICATES PROPORTION OF QUARTAN MALARIA PARASITES IN POSITIVE SLIDES.

shows a single huge peak at the ages 5-6 years. Mothers in this country do not use teething powders and Arneil's contention appears to be a very reasonable one. It is however important to consider what it is that causes the peak at the ages 5-6 years. Whatever it is, it appears to be active in Africa, Europe and North America alike. All that the factor in Africa does is to produce much larger numbers.

Fig. 18 gives the incidence of the disease in the adults. The bulk of the cases occurred between the ages of 15 and 35 years. This, however, is no more than a reflection of the age distribution in the population (Hamilton, 1965). The difference once again is in the numbers - a proportionate increase at all age groups.

(d) The Geographical Distribution of the Cases Studied

Fig. 19 shows the origin of the cases included in this study. This figure reveals nothing more than the fact that they were derived from the cathment area of Mulago Hospital, where studies were conducted. One curious point is that the three cases that came from South-West Uganda were of the membranous variety, and this is the area in which a World Health Organisation malaria eradication team has been active for several

years. This lesion does not appear to be influenced by malaria endemicity.

2. Malaria Parasite Studies (Table 10)

(a) The Cases

Sixty-five cases were studied by examining a daily thick slide for 10-14 days. Cases showing a positive slide after the 14th day were not included among the positives. The whole field of the smear was examined under the oil immersion lens before a negative answer was recorded.

(i) The Children

There were 31 children (aged 2 - 14 years). All cases under the age of 14 (except five) were positive for Plasmodium malariae while in two only P. falciparum was found. Two cases in the P. Malariae group showed mixed infections. The percentage of cases positive for P. malariae was therefore 80 while the overall incidence of P. falciparum in the same group was only 13% - a figure not dissimilar to that obtained from population studies (12-23%) (Table 11).

(ii) The Adults

Thirty-four cases were studied and 13 were positive for P. malariae. This gives a percentage rate of 40.

Table 10

THE INCIDENCE OF QUARTAN MALARIA AMONG PATIENTS WITH THE NEPHROTIC SYNDROME

Age (in years)	% Of Positive Cases	Frequency of Positive Slides in a Positive Individual
0-10	80	1 in every 1.4
10-20	67	1 in every 3.4
Over 20	40	1 in every 4.5
TOTALS	60	

Children are more strongly and frequently positive than adults.

Table 11

PARASITE RATES AMONG CONTROLS AND PATIENTS WITH THE NEPHROTIC SYNDROME

Age	Cases	CONTROLS (Single Slide Examination)			
		Hospital Patients	Villages		
			(a)	(b)	(c)
Children (0 - 14)	81% (1:5)	16% (5:1)	12% ($2\frac{1}{2}$:1)	22% (4:1)	23% (2:1)
Adults (Over 20)	40% (2:3)	17% (1:1)	10%	6% (5:0)	6%

The figures in brackets indicate the ratio between Plasmodium Falciparum and Plasmodium Malariae (P.F : P.M.) Among the patients Plasmodium Malariae is the predominant organism, and the reverse is true for the control subjects.

Table 12

THE INCIDENCE OF MALARIA AMONG PATIENTS AND MATCHED CONTROLS

	TOTALS		P.M.	P.F.	Mixed PF/PM	% Incidence Of Malaria In Group
Children 0 - 14	Cases	16	8 (56.3%)	2 (19 %)	1	70.0%
	Matched Controls	16	1 (7.1%)	0	0	6.3%
Adults 18 and Over	Cases	21	3 (14.3%)	2 (9.5%)	0	24 %
	Matched Controls	21	1 (5 %)	2 (9.5%)	0	14.3%

(1) The difference in the incidence of parasitaemia is several times higher among cases of the Nephrotic Syndrome when compared with normal children matched for age, sex and residence.

(2) The same is true among the adults though the difference is smaller.

(3) The incidence of P. Falciparum is similar in both the adult cases and controls (9.5%). It is also similar to that found in the normal population. Among the children, the same is true for the cases (19%) and normal controls from the villages (18%).

A further three cases showed P. falciparum only. There were none with mixed infections. If, however, the 10-20 year group is considered separately, the number of positive cases rises to 67%.

(b) The Controls

(i) Village Population Studies

To ascertain the incidence of parasitaemia among village inhabitants from whom the majority of the cases came, population studies were done (Table 11). They were drawn from three villages (a, b and c). These villages were inhabited by labourers working on the sugar estates.

(ii) Hospital Outpatients Studies

A further group was taken from patients coming to the hospital outpatient department for complaints other than fever. The results are also included in Table 11.

The results obtained from these groups are so similar that they could be pooled together. This would give an average percentage of 18 for the children (0-14) and 10 for adults over 20. It was, however, impossible to do more than a single day (one thick slide) examination among these villages.

(iii) Matched Controls

Patients admitted with cardiac, neurological, respiratory and dyspeptic disorders were matched with 37 of the cases for age, sex and length of residence (exposure) in a hyperendemic area. Sixteen of these were children and 21 adults. Daily thick slides were taken from each case and its control for 10 days. The results are given in Table 12.

It will be seen that:

(1) The difference in the incidence of parasitaemia is several times higher among cases of the Nephrotic Syndrome when compared with normal children matched for age, sex and residence.

(2) The same is true among adults though the difference is smaller.

(3) The incidence of P. falciparum is similar in both the adult case and controls (9.5%). It is also similar to that found in normal population. Among the children, the same is true for the cases (19%) and normal controls from the villages (18% - pooled figures).

(c) Parasite Density - (Table 10)

As a rough measure of parasite density, the number of slides positive for malaria parasites were calculated against the total number examined, in each patient. In the 0-10 year group, each slide was positive for every 1.4 examined, while for the 10-20 group this figure was 1 : 3.4 and 1 : 4.5 for the over 20 group. It therefore appears that repeated slide examinations are essential for the discovery of parasites particularly among adult patients.

Apart from a few exceptions, parasite densities were much heavier in children than among adults. It was therefore relatively easy to find the parasites in a thick film from a child whilst it was often necessary to examine the entire smear for several days in an adult before parasites could be found. In one case (Case 2 (N)), 19 such smears were examined before a small number of parasites were detected. The infections were often, therefore, very light indeed. This was true of all adults except two.

Among children, three exceptions occurred: Cases 15 (N), 16 (N) and 67 (N) where standard examinations of 10 daily thick films failed to reveal the presence of parasites. These were to be discovered a few weeks later during a mild febrile illness. In one case, 67 (N),

there had been no chance of exposure to infection at all as the child had remained in the hospital the whole time. The second case, 15 (N), returned to the follow-up clinic a few weeks after discharge with a temperature of 102°F and quartan malaria parasites were found in his blood. The third case, 16 (N), had showed a positive slide for P. malariae during the first attack of the nephrotic syndrome three years previously. She was consistently negative for parasites during the current investigations.

(d) Selective Increase of Quartan Malaria in the Nephrotic Syndrome

(i) Reversal of Frequency Ratio between P. falciparum and P. malariae

Table 11 shows that among the controls P. falciparum always occurs in excess of P. malariae (see bracketed ratios - the first figure refers to P. falciparum in each case). Only one exception was found to this rule: the adult hospital group - where the incidence was equal. One other group, however, (Village b), all parasites that were found were P. falciparum.

Among the cases, however, P. malariae was by far the commonest parasite. This was equally true among the adults as among children.

(ii) Specific Increase of P. malariae among Patients with the Nephrotic Syndrome - (Fig. 12)

The incidence of P. falciparum is similar in both the adult cases and their matched controls (9.5%). It is also similar to that found in the normal village population (pooled figures). When figures for P. malariae on the other hand are considered among cases and matched controls, definite increases are found in the former (Table 12). Among children, 16 cases were matched in this way and the incidence of P. malariae was found to be 56.3%, using the multiple slide examination method. Matched cases showed an incidence of 14.3% against 5% in the controls.

(3) MALARIA INTIBODY STUDIES

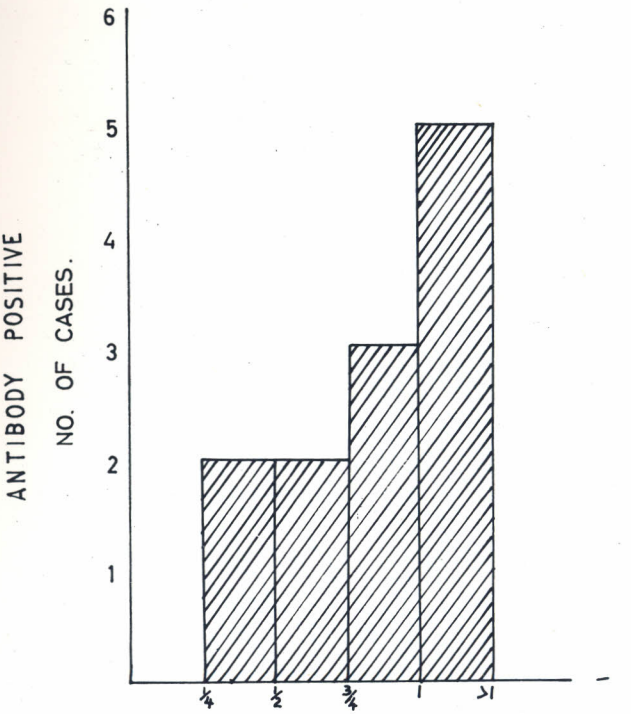
(a) SERUM

A controlled study was made on 37 cases of the nephrotic syndrome and a similar number of matched controls using the indirect florescent antibody test of Voller and Bray (1962). The cases were matched for age, sex, and period of exposure to malaria in a hyperendemic area. The results are presented in Fig. 20. Applying the X_2 text, it was found that the proportion of patients with a titre in excess of 1 : 800 in the two groups was significantly different at the 5% level. There was an excess of patients with the nephrotic syndrome in titresover 1 : 800 over their matched controls.

Fig. 21

[redacted].

PRESENCE OF MALARIA ANTIBODIES IN THE URINE AND SEVERITY OF GLOBULINURIA.

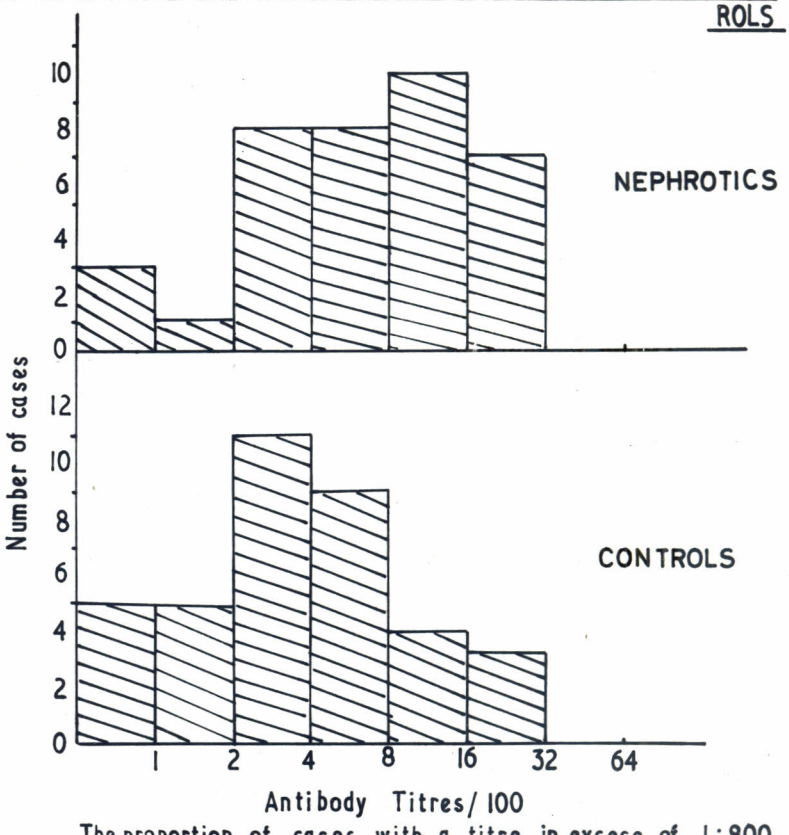


Globulin expressed as a fraction of Albumin passed in the urine.

Most antibody-positive cases occur when Globulinuria is heaviest.

Fig. 20

MALARIA ANTIBODIES AMONG NEPHROTICS AND MATCHED CONTROLS



The proportion of cases with a titre in excess of 1:800 in the two groups is significantly different at the 5% level (x^2 test).

(b) URINARY ANTIBODY LEAKAGE

The urines from patients with the nephrotic syndrome were screened for presence of malaria antibody. The results are presented in Fig. 21. It will be seen that urinary leakage of antibody occurred to a much larger extent when globulinuria was heavy. Most antibody positive tests on the urine occurred in the group where globulinuria was heaviest (Kibukamusoke and Wilks, 1965 (b)). Despite this loss in the urine there was a significantly higher level of malaria antibody in the serum of cases in comparison with their matched controls.

BIG SPLEEN DISEASE

In a study of idiopathic splenomegaly, Marsden and others (1965) found an unusually high malaria antibody titre in the sera of the affected people. They further found that liver biopsies from these patients showed sinusoidal infiltration with lymphocytes and macrophages. There was also an increase in the incidence of Quartan Malaria parasitaemia in this group as compared with controls. They therefore concluded that this type of splenomegaly was due to chronic malaria.

Because the same parasite is incriminated in the nephrotic syndrome, the liver biopsies were examined in 13 patients with this syndrome. Only one of these cases showed definite changes

Table 13

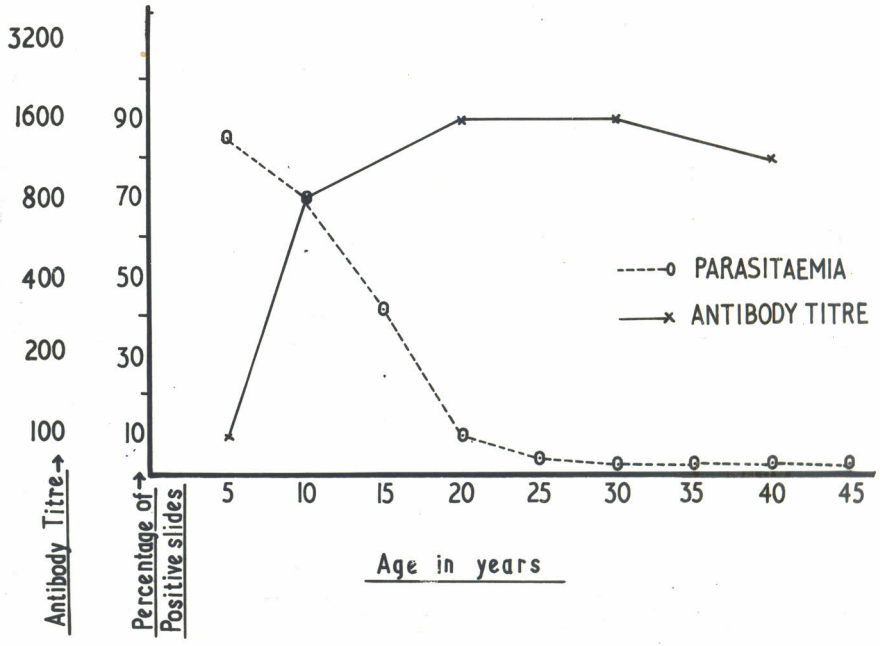
THE INCIDENCE OF QUARTAN MALARIA AMONG PATIENTS WITH THE NEPHROTIC SYNDROME IN DIFFERENT COUNTRIES

AUTHOR	COUNTRY	INCIDENCE IN NEPHROTICS	COUNTRY INCIDENCE
GIGLIOLI (1929)	BRITISH GUIANA	43%	11.1%
LAMBERS (1932)	SURINAM	16.1%	-
CAROTHERS (1934)	KENYA	67.0% (CHILDREN)	8.0% (CHILDREN)
GILLES & HENDRICKSE (1960)	NIGERIA	89.6% (CHILDREN)	18.0% (CHILDREN)
KIBUKAMUSOKE (1964)	UGANDA	81% (CHILDREN)	12.0% (WILKS) - CHILDREN 23.0% (JELLIFFE) - CHILDREN
		40% (ADULTS)	6-10% (WILKS) - ADULTS
		60% (OVERALL)	

IN EACH INSTANCE THE INCIDENCE IS DECIDEDLY HIGHER AMONG THE NEPHROTICS; BEING EVEN MORE SO IN CHILDREN THAN IN ADULTS

Fig. 22

BEHAVIOUR OF PARASITAEMIA AND ANTIBODY TITRE WITH AGE



but his blood slides showed Plasmodium falciparum. Two others showed doubtful changes one of whom had light Plasmodium malariae infection (only one of 15 slides being positive in the thick smears taken daily). In all the rest of the patients (10). absolutely nothing was found to suggest sinusoidal change. Three of these showed Plasmodium malariae infection, one P. Falciparum and the rest no malaria parasites at all. These results, though from a small series, do not appear to suggest concurrent liver changes during the course of the nephrotic syndrome.

large numbers of manifest renal disease. If this concept is accepted then such an agent would be Plasmodium malariae. The presence of P. malariae in the body appears to create a state in which the kidneys' threshold to damage is lowered (in reference to damage). If x was the percentage of cases showing manifest renal damage during a pathological process, say, beta-haemolytic streptococcal infection, then xy would be the incidence if P. malariae was concurrently present in the body. y in this study has been found to be of the order of 80. This concept where the agent sets the stage for pathological damage to occur is an interesting one and it is suggested that it should be termed the "SET-STAGE THEORY".

Gilles and Hendrickse (1963a) were the first to suggest the use of the term sensitisation in connection with malaria and the nephrotic syndrome. They had observed an excessive incidence of the syndrome in Nigeria and an overwhelming rate of quartan malaria parasitaemia among their cases. This was in sharp contrast with controls. These two workers also found that there was not only a coincidence of the peak incidence of malaria infection with the nephrotic syndrome but also what they interpreted as a shifting of the peak incidence of the nephrotic syndrome from the age of two to the age 5-7 to coincide with the peak incidence of malaria infection. It seemed to them that P. malariae infection must be causally related to the nephrotic syndrome as they were seeing it. They came to the conclusion that

TABLE 14

THE AGE INCIDENCE OF NEPHROTIC SYNDROME IN CHILDREN

Age	Minnesota U.S.A.	Glasgow England	Mayo Clinic U.S.A.	Ibadan Nigeria	Mulago Uganda
0- 1			1		
1- 2	3	31	14	3	2
2- 3	10	29	21	11	3
3- 4	9	24	18	13	1
4- 5	3	10	29	26	8
5- 6	6	16	12	22	3
6- 7	2	13	6	17	3
7- 8	0	18	11	9	3
8- 9	1	5	3	8	1
9-10	2	4	7	4	1
10-11	1	5	3		2
11-12	1	3	3		1
12-13	3	5	3		1
13-14		1	1		1
14-15			3		1
TOTAL	40	165	135	113	31
Source	Vernier et al J. Ped. (1961) 58; 620	Arneil G.C. Lancet (1961) 2, 1103	Brown et al. Mayo Clinic Proc. (1965) 40; 5 384	Gilles et al B.M.J. (1963a) 2; 27	Kibukamusoke (current series)

"in some individuals repeated untreated attacks of infection with P. malariae sensitise the kidney, which produces an auto-antibody". The current series has confirmed the excessive rates of quartan malaria parasitaemia among cases of the nephrotic syndrome but a different interpretation for the peak incidence seems necessary. Table 14 shows that there are in fact two peaks in Western countries the first at the ages of 1-4 and the second during the early period of schooling (5-8). The first peak has been attributed to mercury containing teething powders in the U.K. (Arneil, 1958; 1961).

The current study and the Ibadan series (Gilles et al, 1963a) do not show this early peak. The peak that we appear to get, therfore, may not reflect so much a shift from the age 1-4 as an exaggeration of the peak occurring during early school-age. It is felt that this exaggeration is of cardinal importance in relation to the incidence of the nephrotic syndrome as we see it (Table 8). The causal relationship between the nephrotic syndrome and quartan malaria seems practically proven. The figures submitted here show a selective and significant increase of P. malariae parasitaemia among the cases. This is shown by comparison with matched controls (Table 12). It confirms Gilles and Hendrickse's work (1963a) and also numerous other reports in the literature (Table 13). Giglioli's work (1930; 1962 (a) and (b)) is of considerable significance in this connection. It presents investigations in British Guiana in

the pre and post malaria eradication periods. The difference between the figures is a very striking one (Table 8). They show a drop of the incidence of the nephrotic syndrome from a percentage similar to that currently found in hyperendemic (malarial) Africa to that obtaining in Europe and North America. If the reason for the high rates of parasitaemia among the cases was susceptibility of this group to infection with P. malariae then the numbers in British Guiana should have remained high and the difference would have been in parasitaemia rates alone. Boyd's work (1940) provides further confirmation of a causal relationship. He showed that experimental P. malariae can produce the nephrotic syndrome among normal volunteers. The only feasible explanation is that the presence of P. malariae is the cause rather than the effect of the nephrotic syndrome, and it has already been shown how the absence of a distinct histology does not invalidate this concept.

Experience with malaria over a large number of years leads to the development of considerable immunity to malaria. Immunological studies have shown that this immunity is mediated through humoral factors (McGregor, 1963; 1964). Parasite densities tend to be very low among adult immunes. Fig.22 shows the relationship between parasite density and the malaria antibody titre in the serum as the age increases. It is evident that parasitaemia becomes very light in the presence of high levels of serum antibodies. This conforms

to the classical concepts of immunity to stable malaria. It is not surprising therefore that parasite densities are considerably greater in children than in adults (Table 10).

Plasmodium malariae tends to produce lower parasite densities than Plasmodium falciparum (McGregor, 1965). A repeated search for parasites is therefore necessary if P. malariae is to be discovered. This is especially true among adults and it may well be the reason why some workers have not found parasites in adult cases of the nephrotic syndrome (Willis, 1964: Danaraj, 1964) in malarious countries.

If P. malariae is causally related to the nephrotic syndrome, it is necessary to consider the mechanism by which this occurs. It is almost certain that this does not occur by a direct process of action of the parasite on the glomerulus. A diligent search for malaria parasites in biopsy material failed to reveal the parasites or recognisable portions of them. It is possible, of course, that the staining methods employed were unsuitable for such a demonstration. This, however, is an unlikely possibility as the infliction of direct damage to a portion of the glomerulus would be expected to produce localised change and reaction which was not the case. The fact that this particular parasite (P. malariae) has been incriminated in another syndrome (Big Spleen Disease - Marsden et a l 1965) where direct damage has also been considered

unlikely helps to strengthen this concept. Lovell Becker's suggestion (1961) of "immune mechanisms" in both the membranous and proliferative forms of glomerulonephritis, is worthy of serious consideration.

Immune Reactions in the Kidney

Intravenous injection of anti-rat kidney sera induces a nephrotic type of renal disease in rats. This disease closely simulates the pathological changes, clinical course and outcome of the disease as observed in infants and children (Heymann and Lund, 1951). Six out of seven rats subjected to unilateral nephrectomy and injected 5 to 11 weeks later with adjuvant and kidney suspensions prepared from their own (previously removed) kidneys developed severe nephrotic renal disease after two to eight treatments Heymann, 1961). The presence of precipitating antibodies to kidney proteins has also been demonstrated in the sera of animals so treated (Hunter et al, 1960).

Lange et al (1961) suggested that auto-antibody formation may be a significant factor in nephrotoxic nephritis. They demonstrated the transfer of autogenous gamma-globulin from rats previously given anti-rat kidney serum, to parabiotic partners which also developed nephritis though of a mild form. Rat (but not rabbit) gamma-globulin was found in the glomeruli of the partner and the authors concluded that this was auto-antibody trnsferred by the parabiotic

anastomosis from the rat injected with the serum that was nephrotoxic. It could have been formed against altered kidney or a complex of kidney and rabbit antibody.

Vogt and Kochem (1961) found that complement was fixed rapidly in the glomeruli after injecting rats with rabbit anti-rat kidney serum and the onset of proteinuria was equally rapid.

Several workers (Mellors, 1955; Mellors et al, 1955 (b); Baxter and Goodman, 1956) have noted that nephrotoxic antigenicity was located principally in the kidney, though also in other organs: placenta, lung. Ortega and Mellors (1956) demonstrated nephrotoxic gamma-globulin in renal glomeruli. This persisted for as long as three months after injection. Seegal et al (1962) and Triedman et al (1962) confirmed this observation. Location of nephrotoxic antigenicity in other organs may be due to antigenic relationship that appears to exist between reticulin and basement membrane (Cruickshank and Hill, 1953a). This relationship is based on cross-reactivity rather than identity (Tamanai et al, 1961).

Baxter and Goodman (1956) inferred that the preponderant renal injury which occurred was due to the presence in the kidney of large amounts of antigenic material in a position where it was exposed to large amounts of circulating antibody - the kidney being in receipt of an abundant supply of blood. Ortega and Mellors (1956) showed that after the in vivo localisation of heterologous nephrotoxic

antibodies in the glomeruli of rat kidney, there was an acute reaction associated with local accumulation of native non-antibody plasma-globulin. Autogenous antibodies appeared later with a distribution closely similar to that of the nephrotoxins and at a tim interval in keeping with an immunisation process.

In work on humans, gamma-globulin has been located in glomerular lesions of glomerulonephrtitis, lipid nephrosis, systemic lupus erythematosus, sclerodema, polyarteritis nodosa, amyloidosis and diabetic glomerulosclerosis (Mellors and Ortega, 1956; Mellors et al, 1957; Freedman et al, 1960). Available evidence in the form of decreased complement activity of sera from nephrotic patients (Lange, 1954; Wedgewood and Janeway, 1953) increased amounts of globulins demonstrable in the glomeruli of nephrotic kidneys (Mellors and Ortega, 1956) and haemagglutination titres together with the demonstration ofprecipitating antibodies in nephrotic sera from children (Liu and McCrory, 1958) is at best compatible with a hypothesis of an autoimmune process but,thus far,has failed to show that antibodies to kidney proteins are demonstrable in man (Heymann, 1961).

In the nephrotic syndrome associated with P. malariae no antibody work has been done to reveal the antibody status within the glomerulus. The situation, however, is such that it would not be unreasonable to imagine the occurrence of an immune reaction

involving the basement membrane. Gamma-globulin turnover rates have been shown to be considerably increased in immunity to stable malaria (Cohen et al, 1961). Our current work on malaria antibodies in patients with the nephrotic syndrome (Fig.20) has shown significant increases in this group compared with matched controls despite a urinary loss in the former.

It is important to note that in none of the nine cases of membranous glomerulonephritis were parasites found and the serum antibody titres wer generally lower than in the other cases. It is considered that this lesion may probably not be causally related to malaria.

Steroid Therapy

Early reports on the use of steroids in the nephrotic syndrome (Arneil and Wilson, 1952; 1953) were encouraging. Unfortunately, cortisone and corticotrophin proved to be of limited benefit (Holland, 1960; Arneil, 1961). This was because of concomitant fluid and salt retention. The agents could provoke diuresis but fail to reduce the albuminuria consistently. Arneil (1966a) reported that cortisone appeared to cause diuresis more frequently than corticotrophin and that it produced fewer side effects. There was disagreement however on this point as other workers notably in North America considered that corticotrophin was of great value. Lange et al (1957) in fact advocated a regime which commenced with corticotrophin. Calcagno et al (1961) however

thought that there was no clear evidence of a beneficial effect of corticotrophin over steroids.

The use of the newer steroids has improved therapy to a considerable extent. Arneil (196) wrote that ".... in Glasgow we still regard prednisolone as the best steroid available". This steroid is 4-5 times as effective as cortisone. Arneil (1958, 1961) recommended a dosage 60-80 mgm/day of predinsolone irrespective of size. Diuresis occurred in the majority of children within three weeks of starting therapy, both oedema and ascites usually completely clearing. This dosage was reduced over a period of six weeks and maintained at 10-20 mgm/day for 6 to 40 weeks. Thereafter, it was discontinued if proteinuria had ceased or was very slight (100 mgm/day). Chinard (1960) used a dosage of 2 mgm/Kg/day of predinsolone up to a maximum of 100 mgm/day during the first 10 days. The dose was then gradually reduced over the next 30 days. During the first seven days of therapy, either nothing noticeable happened or there was a slight worsening of the oedema. Diuresis then "always set in together with dimunition of proteinuria". Calcagno (1961) and Chinard (1961) also appear to agree with this conclusion. Failures occurred in a number of cases particularly in adults and among those cases showing hypertension and haematuria in the early phase of the disease. Occasionally, a second course succeeded. Arneil considered predinisolone superior not only to cortisone and corticotrophin but

also to the newer deltasteroids: triamcinolone, methylprednisolone and dexamethasone (Arneil, 1961).

Prednisone was also considered to be of great value. Riley et al (1959) thought it was the "logical drug of choice". They found that it was superior to corticotrophin in the majority of cases and that in the few where corticotrophin appeared to be better this was attributable to better absorption of an injected material. These authors found no better advantages accruing from the use of triamcinolone and 6-methyl-prednisolone and Chinard (1961) agrees with them. Hellman et al (1959) also thought the same of triamcinolone. Riley and his co-worker (1959) recommended a prednisone dosage of 40 mgm/day for patients under three years of age and 60 mgm/day for older children. With this regimen diuresis began after 10-14 days but they continued treatment for 3-4 weeks when proteinuria in early cases had as a rule cleared. Prednisone was then tapered to zero in three or four days. They found that prolonging treatment over a period of four weeks was rarely helpful if diuresis had not already occurred. However, they found that in a few instances raising the dosage to 80 mgm/day worked when the lower dosage had failed.

It is unfortunate that no valid comparison has yet been made between prednisone and prednisolone though most authors state a preference. On balance, however, it appears that these two agents are the best to use and that there is little to choose between them.

In the current series, it was therefore decided to use only one of these - prednisone - for all cases in which steroids were given. In three cases, however, this was not possible and betamethasone was given. Normal doses of prednisone (60-80 mgm/day) were given to all patients (in the prednisone series) except four who had 100 mgm/day (3 cases) and 120 mgm/day (1 case). The drug was given for periods ranging from two weeks to over two months.

In Western Europe and North America, response to steroids can be expected in the majority of children with the nil or minimal lesion in whom the disease has been present for less than six months (Arneil, 1961) Vernier et al (1961) reported that 65% of their cases gave complete response when these criteria were satisfied. Failures or an incomplete response was seen among cases that showed definite membranous thickening or cellular proliferation. Metcoff et al (1961) reported that 70-80% of cases in the minimal group benefited from steroids, while Lange et al (1957) returned a response rate of 82% to the initial attempt. Similar results have been reported by several other workers - Arneil (1958), Calcagno et al (1961), Vernier et al (1961).

Results are poorer in children who have had the disease for six months or longer. Cases giving the complete response are then in the region of 18% (Vernier et al, 1961). Likewise, adults with this lesion tend to respond less satisfactorily (Lange et al (1957).

If these antibodies have anything to do with the disease, then their continued production can perpetuate its manifestations and establish antagonism to recognised forms of treatment. In any case, we consider that this is a peculiar characteristic ofthis form of the nephrotic syndrome.

Classical Presentation of "Malarial Nephrtitis" as the Nephrotic Syndrome

All the cases that have been reported in the literature where quartan malaria has been associated with kidney disease have presented the clinical picture of the nephrotic syndrome. Boyd's (1940) experimental cases also developed the nephrotic syndrome. All the cases the author has seen at Mulago in association with P. malariae have also all presented with the nephrotic syndrome. This then appears to be the clinical manifestation of "malarial nephritis". In cases where P. malariae has been found with well recognised renal entities, acute post streptococcal nephritis, for example, the nephrotic state has supervened. It is therefore considered that this is the clinical expression of the involvement of the kidney by malaria.

It israre for post streptococcal glomerulonephritis to present with the nephrotic syndrome in the acute phase. Lawrence et al (1963) after an extensive review of the literature wrote that "well documented cases are rare". Kassirer et al (1959) came to the same conclusion after a similar effort. Wilson et al (1959),

however, reported five cases out of 111 children with acute glomerulonephritis. Joekes (1965) has also seen an occasional case. In this study of 31 children with the nephrotic syndrome, three cases were recognised. The author is fully aware of the difficulty of ascertaining that the attack of acute nephritis is in fact the initial one. Attacks of the nephrotic syndrome occurring later in the disease are, however, well documented (Lawrence et al, 1963; Kassirer et al, 1961). The three cases in the current study all showed P. malariae parasites in the peripheral blood. It is considered that this indicated a high incidence of the nephrotic syndrome in the acute phase of post streptococcal glomerulonephritis and that quartan malaria was concerned in its production.

Pyelonephritis is another condition which is disputed as a cause of the nephrotic syndrome. In this series, two bonafide cases of pyelonephritis presented with the nephrotic syndrome. Both had urethral strictures and acute pyelonephritis on top. Again, both these cases showed P. malariae in their blood. It is hard to think that if pyelonephritis was a commoner cause of nephrotic syndrome, it would not have been reported more frequently and definitely. The moral here, however, is that the nephrotic syndrome has presented in unusual circumstances on several occasions.

Conclusion

The high incidence of the nephrotic syndrome in malarious

countries and its aetiologic association with Plasmodium malariae has been known for many years. This work presented evidence to confirm this observation. The peculiarity of clinical presentation of this form of renal disease particularly in unusual circumstances and the unusual pattern of steroid resistence provides a resonable basis for suggesting a separate group for this type of nephrotic syndrome. It is submitted that the term NEPHROTIC SYNDROME OF QUARTAN MALARIA be adopted for this disease entity.

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