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The Quartan Malarial Nephrotic Syndrome *

by

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Abstract

*The Nephrotic Syndrome as classically described is a disease of unknown aetiology with a peak incidence in the first three years of life, highly selective proteinuria, minimal histological changes in the kidney and usually responsive to steroid therapy. Studies in tropical Africa in recent years have revealed a high incidence of the nephrotic syndrome in childhood which shows many differences from the syndrome as described elsewhere. The vast majority of cases occur in association with *P. malariae* infection, the peak incidence occurs at 5 - 6 years of age, proteinuria is usually poorly selective, distinctive histological changes are found in the majority and response to steroids, and other forms of treatment, is in general poor.*

*Immunological studies, in particular immunofluorescence microscopy, indicate that the nephrotic syndrome in these children is an expression of an immunocomplex nephritis characterised by extensive intraglomerular deposition of immunoglobulins of the IgG and IgM classes and the third component of complement (C³). The only specific antigen that has been frequently demonstrated is that of Quartan Malaria. Correlation of clinical, pathological and immunological findings recorded to date indicate that Quartan Malarial Nephrosis is an immunologically mediated disorder initiated by *P. malariae* infection and which, when established, pursues a progressive course.*

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Introduction

The Nephrotic Syndrome occurs throughout the world and can be the expression of a wide range of disorders from infectious, toxics and allergic states to systemic diseases as varied as Amyloid, Diabetes and Sickle Cell Anaemia, conditions which obstruct renal venous drainage, and intrinsic renal diseases. In most cases seen in childhood, however, no specific cause can be identified and the pathogenesis of the renal lesion is poorly understood.

The syndrome poses many fascinating and challenging problems but, viewed in relation to the enormous health problems that beset the children of the Third World, could be regarded as largely irrelevant to the deliberations of a Congress like this. I would not wish to exaggerate the importance of the subject of this address, but I hope that the brief account I shall give of our experience of the nephrotic syndrome in Africa, will help to establish the fact that the disorder is much more prevalent in some tropical countries than is generally appreciated, and constitutes an important cause of morbidity and mortality in children over five years of age, in these countries. I hope also that this sequential account of our investigations, may be of some practical help to those undertaking medical research in developing countries.

Early Clinical Studies

In the mid 1950's, soon after the Clinical Departments of the University of Ibadan started functioning, it was noted that the nephrotic syndrome was very common in the local child population. Indeed, so many cases were seen, that it was necessary to set up a special clinic for their management. The presenting clinical features (Fig. 1) and biochemical findings in these patients were entirely similar to those described in the nephrotic syndrome elsewhere, but comparison of the age incidence, renal biopsy appearances and prognosis in our cases, with findings recorded elsewhere, revealed important differences. Our peak incidence occurred at 5 years of age, in contrast to a peak at two to three years recorded in Europe and America (Fig. II), (Gilles & Hendrickse, 1963; Hendrickse & Gilles, 1963). The vast majority of our patients showed significant renal pathology characterised by capillary wall thickening and progressive mesangial sclerosis, leading to total glomerular sclerosis in long standing cases. (Hendrickse & Gilles, 1963; Edington & Mainwaring, 1966). The characteristic 'minimal change' histology of the nephrotic syndrome in temperate climates (Churg, Habib & White, 1970; White, Glasgow & Mills, 1970) was rarely seen. Response to initial symptomatic treatment, judged by control of oedema was satisfactory

in many of our patients, but significant albuminuria persisted in the majority and many developed progressive renal failure and/or hypertension and died within a year or two. Prognosis in general was very much worse than recorded in Europe and America.

Investigation of the Role of P. Malaria in Etiology

References to an association between P. Malaria and renal disease can be found in the tropical medical literature dating back to the last century (Atkinson, 1884). Giglioli (1930) surveyed renal disease and its relationship to P. Malaria in British Guiana during 1923 - 29 and observed a close relationship between P. Malaria and the Nephrotic Syndrome. His observations were supported by subsequent reports from Indonesia, Africa, the Solomon Islands and New Guinea (Lambers, 1932; Carrothers, 1934; James, 1939; and Senecal et al., 1960).

In order to determine whether P. Malaria could be incriminated in the etiology of our cases, a comparative study of P. Malaria prevalence in 113 Nephrotic children, 920 ill non-nephrotic children and 340 'healthy' village children was undertaken. (Gilles & Hendrickse, 1963). The overall prevalence of P. Malaria in the three groups was 88, 24 and 18 per cent respectively. The results of this study, showed a highly significant selective increase in P. Mala-

riae parasitaemia in the nephrotic children ($P = 0.001$ for both sets of controls), confirming beyond any reasonable doubt, a relationship between P. Malaria and the nephrotic syndrome. Comparison of the peak age distribution of the nephrotic patients with the peak age specific prevalence of P. Malaria in the community (Fig. III) provided additional epidemiological evidence of a specific relationship.

Study of the renal histology in our patients failed however to show P. malariae or malarial pigment in the renal lesions and it seemed highly improbable therefore that renal changes reflected direct injury by the P. malariae parasite. (Hendrickse & Gilles, 1963; Edington & Mainwaring, 1966).

Therapeutic Trials

Having established a definite relationship between P. malariae and the nephrotic syndrome in our cases, it was logical to study the effect of antimalarial treatment on these patients. Children with the nephrotic syndrome were randomly allocated into two treatment groups. Group A (44 cases), received antimalarial treatment with chloroquine followed by weekly pyrimethamine, Group B (45 cases), received no antimalarials. All other aspects of management were similar for the two groups. A third group was subsequently included. These were 24 children, who in addi-

tion to chloroquine and pyrimethamine, received primaquine for 14 days to ensure eradication of *P. malariae* (Group C). Results assessed six months after the start of treatment showed no differences in the behaviour of the three groups. Only three patients in Group A, 3 in Group B and 2 in Group C showed a reduction in albuminuria to less than 50 mgm per 100 ml. (Gilles & Hendrickse, 1963).

We next studied the effect of treatment with prednisolone, either alone or in combination with anti-malarials to eradicate *P. malariae*. Controls were provided by patients treated for *P. malariae* only. Our intention was to randomly allocate 100 cases into the three treatment groups, but owing to serious untoward effects observed in the prednisolone treated patients the trial was discontinued after only 32 cases had been included.

Tables 1 and 2 summarise the findings in this study. It will be seen that not only was prednisolone ineffective in inducing a remission of symptoms in the majority of patients, its administration produced a very high rate of serious complications including permanent brain damage as a consequence of steroid induced hypertension. Furthermore, many of the deaths in the prednisolone treated groups were sudden and unexpected (Hendrickse, 1966). On the basis of these results it was

recommended that prednisolone was contraindicated in the majority of cases of the nephrotic syndrome seen in West Africa.

This trial was conducted on an outpatient basis. Patients were only admitted to the wards for initial assessment or when serious complications arose. Some of the lessons learned in this trial are of interest and may be of help to those who may undertake similar investigations.

(1) Continuity of follow-up is essential in patients receiving potentially dangerous drugs such as prednisolone. Selection of patients was therefore very carefully done with the aid of senior medical social workers, who investigated home circumstances and parental attitudes. In spite of very careful selection and elaborate safeguards to ensure continuity, 3 patients defaulted while on full prednisolone dosage and were lost to follow-up.

(2) Patients anywhere find it difficult to follow complex schedules of drug administration. The complicated treatment regime required in this investigation seemed to preclude a study based on outpatients. We were, however, able to overcome this problem by using the method of pre-packing of drugs shown in Fig. IV. Parents were simply taught to administer all the contents of each package at the times stated. The



FIG. 1 : *Nephrotic syndrome, presenting features*

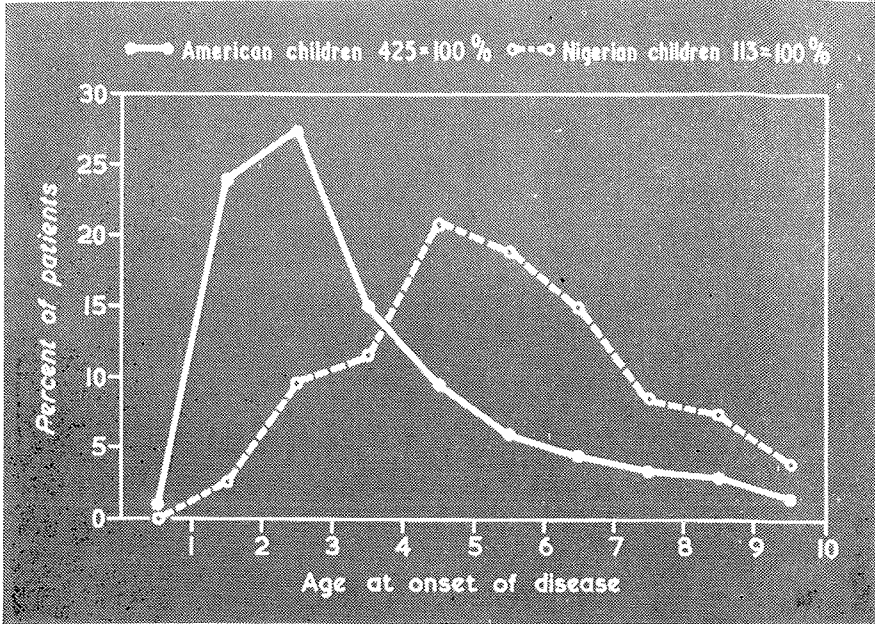


FIG. 2 : Comparison of age onset of the Nephrotic Syndrome in America and Nigeria.

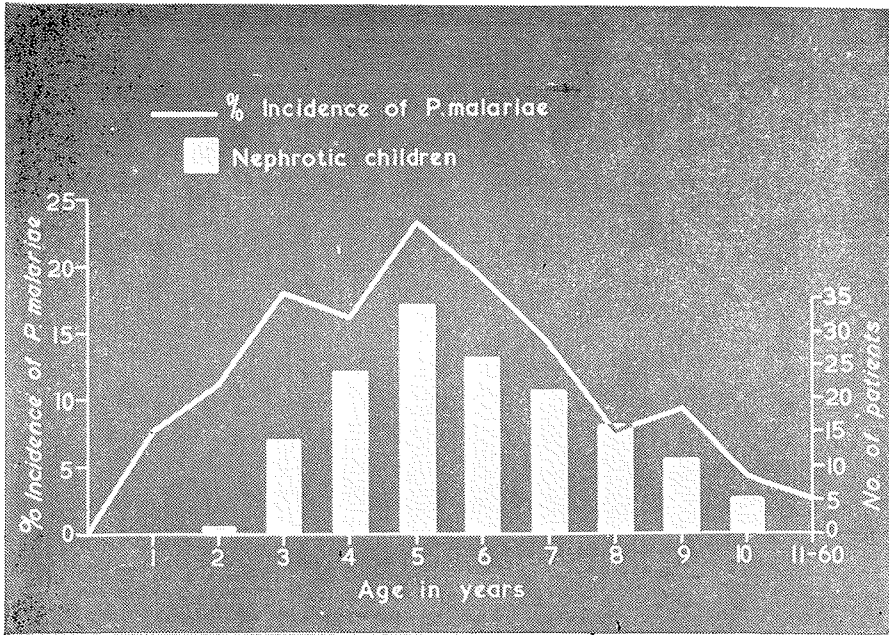


FIG. 3 : Age incidence of the nephrotic syndrome compared with age prevalence of P. Malariae.

SURNAME		AGE		SERIES No.		
Prednisolone mg. daily						
Primaquine mg. daily						
Nevirdrex mg. alt. days						
Sulphadiazine - 0.5 g. DAILY			Daraprim - 25 mg. WEEKLY		DEPARTMENT OF PEDIATRICS LUG MARRAS 1962	
DAY 1	DAY 2	DAY 3	DAY 4	DAY 5	DAY 6	DAY 7
even	ing	ing	ing	ing	ing	ing
mid	-	-	-	-	-	-
mor	ning	ning	ning	ning	ning	ning

SURNAME		AGE		SERIES No.		
Prednisolone mg. daily		45				
Primaquine mg. daily		75				
Nevirdrex mg. alt. days		35				
Sulphadiazine - 0.5 g. DAILY			Daraprim - 25 mg. WEEKLY		DEPARTMENT OF PEDIATRICS LUG MARRAS 1962	
DAY 1	DAY 2	DAY 3	DAY 4	DAY 5	DAY 6	DAY 7

FIG. 4 : Drugs pre-packed for patient of treatment with Prednisolone, Primaquine, Pyrimethamine, Sulphadiazine and a diuretic (Navirdrex). Removal of the appropriate staple delivers all drugs to be given at a particular time.

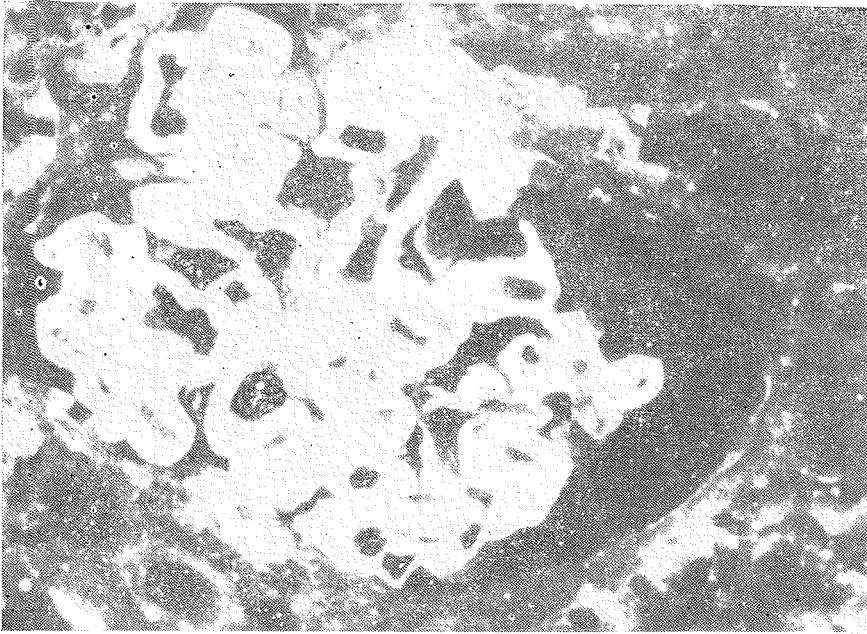


FIG. 5 : *First demonstration of Immune complexes, by immunofluorescence microscopy, in Quartan Malarial Nephrosis.*

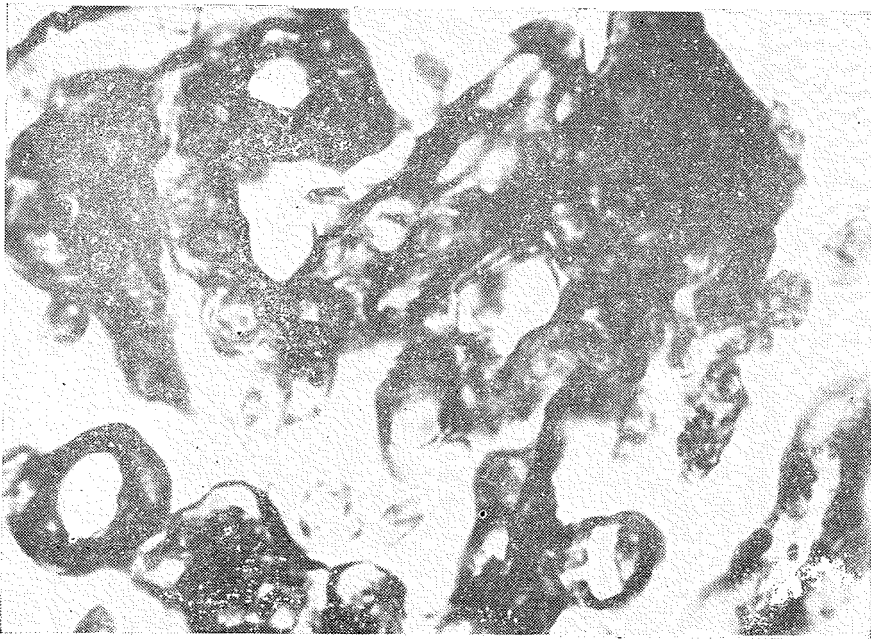


FIG. 6 : *Segment of a glomerulus showing capillary wall thickening and segmental sclerosis.*

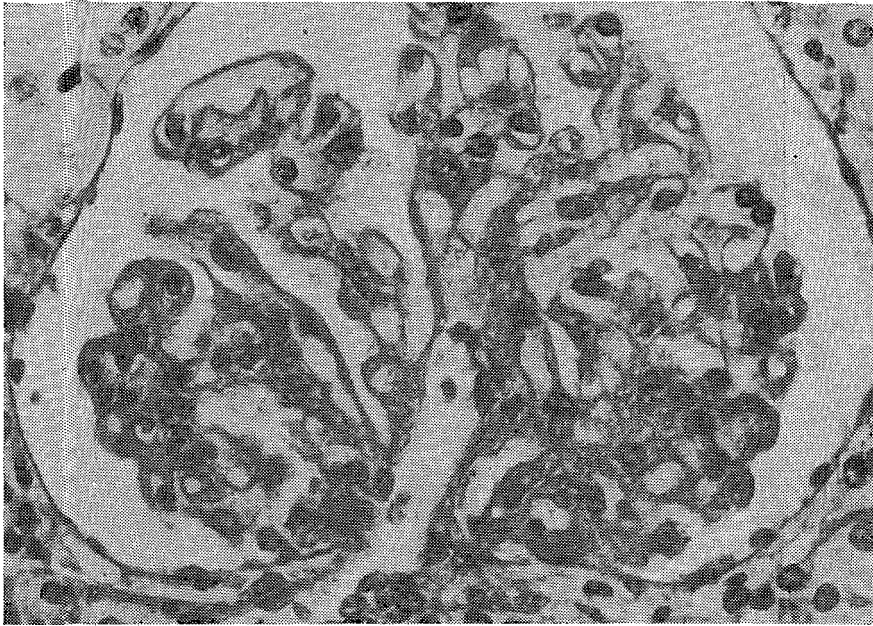


FIG. 7 : *Capillary wall thickening and "honeycomb" like mesangial sclerosis.*

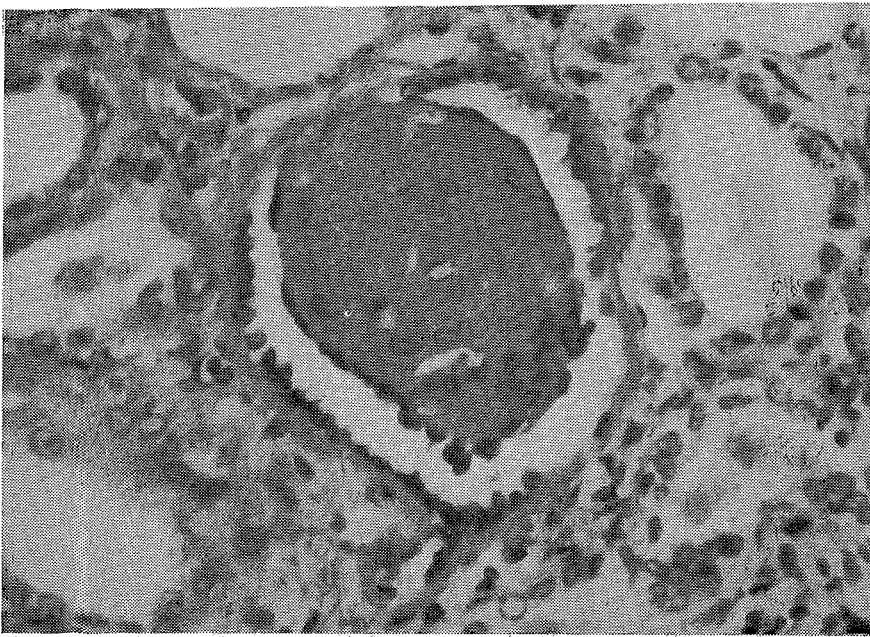


FIG. 8 : *Total glomerular sclerosis and tubular atrophy.*



FIG. 9 : *Electron microscopy showing Lacunae in thickened capillary basement membrane (X 30.000).*

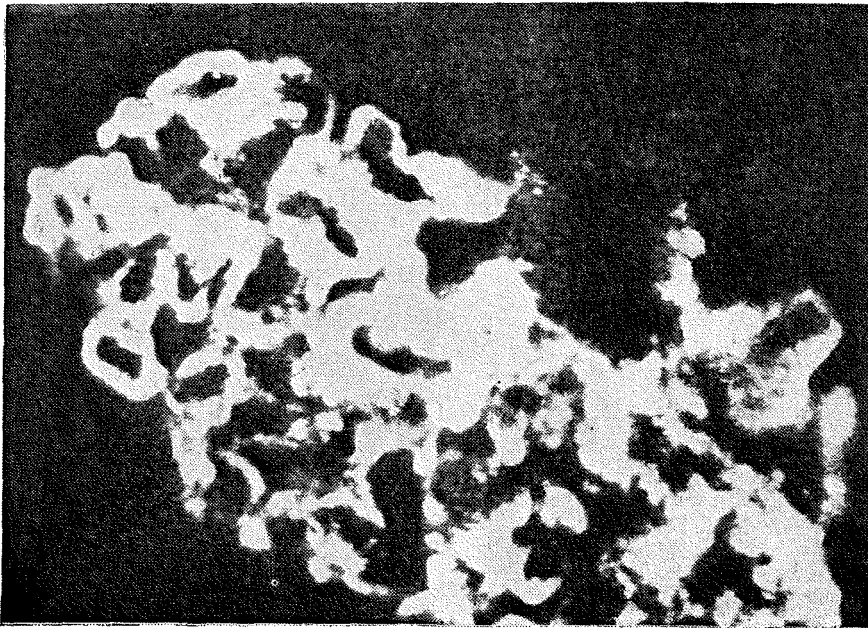


FIG. 10 : *Well marked, coarse, granular immunofluorescence observed in a patient with Quartan Malarial Nephrosis.*

system worked well in practice even with illiterates. Spot checks on the therapy cards during home visits provided health visitors with an easy means of checking whether the treatment schedule was being followed.

Hypothesis on the Relationship Between P. Malariae and the Nephrotic Syndrome

Summarising our main findings at this stage, we had established a definite relationship between P. malariae and the nephrotic syndrome but the parasite had not been detected in the renal lesions nor was antimalarial therapy of direct benefit to these patients, the majority of whom, were also non-responsive to prednisolone.

Bearing in mind various experimental models for immunologically mediated nephritis in animals (Dixon, 1962), we suggested that a possible explanation of the findings in our patients was that in some individuals, repeated attacks of P. malariae infection provokes an abnormal immunological response in which antigen-antibody complexes damage the glomerular basement membrane. It seemed that once the lesion had been initiated it tended to be progressive (Hendrickes & Gilles, 1963). If this hypothesis was correct then, using appropriate techniques, antigen-antibody complexes should be demonstrable in the glomeruli of our patients. We were at the time not

set-up to undertake the relevant investigations and found it singularly difficult to persuade colleagues elsewhere to test our hypothesis, until Dr. Frank Dixon of La Jolla, California, examined some of our renal biopsies by immunofluorescence microscopy in search of immune complexes. He found coarse, granular, immunofluorescent deposits containing IgG and C3 (Fig. V) in the specimens he examined (Dixon, 1966). This was the first-ever demonstration of immune complexes in the kidneys of patients with the nephrotic syndrome associated with Quartan Malaria and provided support for our hypothesis.

Encouraged by these findings new studies were undertaken in collaboration with colleagues in Pathology and Immunology. The main purposes of these studies were (i) to elucidate the pathogenesis and characterise the pathology of Quartan Malarial Nephrosis by correlating clinical findings with renal appearances studied by light, immunofluorescence and electron microscopy, (ii) to evaluate selectivity of proteinuria as a criterion for selecting patients for steroid therapy and (iii) to evaluate the role of cyclophosphamide and Azathioprine in treatment. The rest of this presentation will summarise these collaborative studies, details of which have been reported elsewhere. (Allison et al., 1969; Adeniyi, Hendrickse, Houba, 1970; Houba et al.,

1970; Houba et al., 1971; Hendrickse et al., 1972).

Recent Collaborative Studies

An earlier observation that two steroid responders, seen in relapse, had highly selective proteinuria, while all the non-responders had poorly selective proteinuria, (Soothill & Hendrickse, 1967) prompted us to use selectivity of proteinuria as a 'screening test' for possible steroid sensitive patients. Treatment with prednisolone was offered to all patients with highly selective proteinuria. Other patients were randomly allocated for treatment with Cyclophosphamide or Azathioprine, or acted as controls who received symptomatic treatment only. All patients were given antimalarials, and had similar clinical and pathological investigations including initial renal biopsy which was repeated, after treatment, whenever possible.

Renal Histology

Histological appearances were quite unlike those seen in the nephrotic syndrome in temperate climates and was characterised by a combination of capillary wall thickening and segmental sclerosis leading to progressive glomerular damage, secondary tubular atrophy and interstitial fibrosis. Cellular proliferation was inconspicuous or absent. Lesions were graded according to severity. (Hendrickse et al., 1972).

Grade I: Localised capillary wall thickening and segmental sclerosis affecting up to 30 per cent of glomeruli. (Fig. VI).

Grade II: Segmental or diffuse capillary wall thickening and sclerosis, often "honeycomb" like, affecting 30-75 per cent of glomeruli. (Fig. VII).

Grade III: More extensive lesions than Grade II affecting more than 75 per cent of glomeruli, with total glomerular sclerosis tubular atrophy and interstitial infiltration in many cases. (Fig. VIII).

On electron microscopy fusion of epithelial cell foot processes was invariable. The essential abnormality was thickening of capillary basement membrane. An apparently unique feature was the presence of small lacunae scattered throughout the basement membrane often containing islands of electron dense material (Fig. IX).

Immunofluorescence Microscopy

With only one exception, all patients studied by this method showed immunofluorescent deposits in their glomeruli on first biopsy (Fig. X). The pattern varied from coarsely granular and diffuse elements. IgG granular to 'diffuse', with some patients showing a mixed pattern with and IgM, either together or singly, were detected in all deposits but not IgA. The majority also showed complement (C₃). P. Malariae antigen

was detected in a third of the cases tested but no patient showed *P. falciparum* antigen or Streptolysin O. (Allison et al., 1969; Houba et al., 1970, 1971; Hendrickse et al., 1972).

Clinicopathological Correlations

Most of the younger patients had *P. malariae* parasitaemia, Grade I histological lesions, and a coarse or mixed pattern of immunofluorescence. Parasitaemia was less frequent in the older patients whose histological grading was usually II or III, and immunofluorescence appearances were more variable with some patients showing a diffuse pattern.

Prognosis was most favourable in younger patients with Grade I histology and coarse immunofluorescence. Prognosis was invariably poor, irrespective of age, in those in histological Grades II and III and with diffuse immunofluorescence.

Response to treatment

Response to all forms of treatment was in general poor. About 16 per cent of patients had highly selective proteinuria and were treated with prednisolone and of these about one third showed a good response. Patients with poorly selective proteinuria, treated with Azathioprine or Cyclophosphamide showed little response. Only 2 patients on Azathioprine, and one patient on cyclophosphamide, showed good responses. None of the controls showed spontaneous remission of albuminuria. (Adeniyi, Hendrickse & Houba, 1970).

Good response to treatment was commoner in younger than older patients and, irrespective of the drugs administered, was only observed in patients with Grade I histology and coarse or mixed immunofluorescence. No patient with Grade II or III histology, or showing diffuse immunofluorescence, responded well to treatment. (Hendrickse et al., 1972).

Comparison of immunofluorescence appearances in first biopsies with appearances in repeat biopsies after treatment, showed that immunofluorescent deposits disappeared or were greatly diminished in those with good response to treatment, but persisted or increased in non-responders, in a few of whom it was observed that initially granular deposits had become diffuse.

Conclusions

A casual relationship between *P. malariae* and the nephrotic syndrome, originally postulated on epidemiological evidence (Giglioli, 1930, 1962; Gilles & Hendrickse, 1963), was supported by clinical and immunological observations in this study. An immunological pathogenesis, which we first postulated in 1962 (Hendrickse & Gilles, 1963) was substantiated by demonstration of immunoglobulin deposits in the kidney, the presence of *P. malariae* antigen in several biopsies, alteration in immunofluorescence correlating with responses to treatment, and

TABLE 1 : *Results of Therapeutic of Prednisolone.*

Treatment Group	Died	Unimproved	Defaulted ? Died	Improved	Arrested
Prednisolone (12)	5	2	3	1	1
Prednisolone plus Primaquine (10)	4	2	—	1	3*
Primaquine alone (10)	4	2	1	2	1

* One patient improved after steroids discontinued.
One patient. hemiplegic and aphasic following steroids.

TABLE 2 : *Summary of Serious Complications*

Treatment Group	Total Needing Admission	Patients Treated For Infections	Total Episodes Of Infection	Serious C.N.S. Complications
Prednisolone	4	5	6	1
Prednisolone plus Primaquine	8	6	13	3
Primaquine alone	3	3	6	7

histological features which are compatible with immunologically mediated disease.

It would appear that Quartan Malarial infection causes an immune complex nephritis which, once established, is sustained by mechanisms not yet fully explained but which probably involve an auto-immune process. Anti-glomerular and anti-tubular antibodies have occasionally been detected in the serum of these patients. (Hendrickse, 1964; Hendrickse & Gilles, 1963; Houba, 1972).

Treatment of this disease is still very unsatisfactory. Few patients respond to prednisolone, Cyclophosphamide or Azathioprine, and serious side-effects of these drugs, in particular prednisolone, (Hendrickse, 1966, Aderele & Seriki, 1974) are so frequent that their use should be restricted to very carefully selected

cases treated in a carefully controlled situation.

The prevalence of Quartan Malarial Nephrosis in some tropical countries, its bad prognosis and poor response to treatment, underline the need for continued efforts to eradicate, or at least control, malaria in those parts of the world where it is still endemic.

Acknowledgements

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