MALARIAL NEHPROSIS

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EPIDEMIOLOGICAL DATA

Convincing evidence of an association between "Plasmodium malariae" and the nephrotic syndrome in children has accumulated over the years. The epidemiological data include (1) case-history reports of the relative prevalence of "P.malariae" in nephrotics and controls (2), comparisons of the incidence of the nephrotic syndrome in the tropics with that in temperate countries, and (3) time-trend studies of the effects of malaria control on the incidence of nephrosis.

Case-history studies:

Watson (1905) reviewing the clinical features of "P.malariae" infections, remarked on the presence of oedema and albuminuria in several of his patients.

Clarke (1912) wrote 'I believe that the occurrence of oedema in the tropics of such nature as to make one think of parenchymatous nephritis is a reason for making a search for quartan malaria para sites imperative'. Out of 62 cases of 'nephritis', 29 of them (48%) had "P.malariae".

McFie et Ingram (1917) reported nine cases of the nephrotic syndrome from the Gold Coast, all the patients were under 10 years of age and all had "P.malariae" in the peripheral blood.

Giglioli (1930) made a survey of kidney disease and its relation to malaria in British Guiana during 1923-29 and noted the close relationship between 'P.malariae" and the nephrotic syndrome. Subsequent reports from Sumatra, Surinam, Kenya, New Guinea and Senegal (Surbek, 1931; Lambers, 1932; Carrothers, 1934; James, 1939; and Senecal et al., 1960) supported Giglioli's hypothesis.

In Nigeria, Gilles and Hendrickse (1963) studied 113 nephrotic children, 920 ill non-nephrotic children, and 430 'healthy' village children. The vast majority of the patients were seen at or referred from the General Practice Clinic at University College Hospital and were mainly Yorubas resident in and around Ibadan, though some patients came from further afield. All the ill children (nephrotics and non-nephrotics) were collected over the same period of time, they were of similar age (2-10 years) and had a similar sex distribution. The 'healthy' children were all Yorubas living in a village 11 miles from Ibadan (Akufo), of similar age and, sex, and also examined over the same span of time. Only one thick and thin

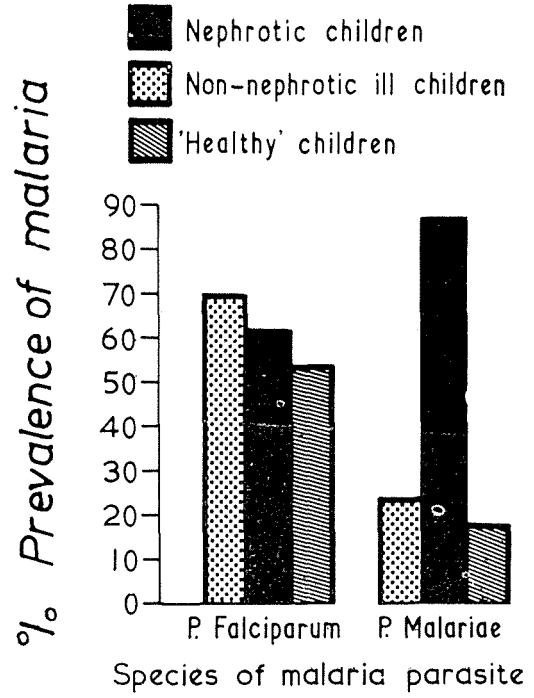

FIG. 1. Prevalence of P.falciparum and P.malariae in nephrotic children (113); non-nephrotic ill children (920) and healthy' village children (320), in the Western State, Nigeria (Gilles and Hendrickse 1963).

blood film was taken from each individual in all three groups of children. The results of this study are summarized in Table I and are shown graphically in a histogram (Fig. 1.). They show a highly significant greater prevalence of "P. malariae" parasitaemia in the nephrotic children ($p < 0.001$ for both sets of controls). Thus as many as 88% of the 113 nephrotic children examined were infected with "P.malariae" either alone or in combination with "P.falciparum," whereas, the overall "P.malariae" rate was 24% in the 920 non-nephretic ill children and 18% in the 340 'healthy' village children.

Kibukamuscke and al. (1967) have also reported a higher prevalence of "P. malariae" parasitaemia in 16 children with the nephrotic syndrome seen in Uganda.

Thuriaux (1971) working at a children's hospital in the Yemen Arab Republic reported that 10 out of 16 nephrotic children aged 2-10 years showed "P.malariae" in their blood (62.5%) while the overall prevalence of "P.malariae" in the same age group among outpatients at the same hospital over the same period (April 1967 — March 1968) was about 3%.

It is clear, therefore, that despite some shortcomings, prevalence data from parts of the globe as wide apart as New Guinea in the East and Guyana in the West, provide convincing evidence of an association between childhood nephrosis and "P.malariae" infection (Fig. 2).

The natural history of "P.malariae" infection in the Western state of Nigeria was studied by Bruce-Chwatt et al., 1953, and Gilles, 1967. It will be noted that the peak age distribution of the nephrotic syndrome in Ibadan corresponds closely to the peak age specific prevalence of "P.malariae" This complementary epidemiological evidence is interesting even though it is not conclusive.

The peak age at onset of childhood nephrosis in the Nigerian studies occurred at between five and seven years (Gilles and Hendrickse, 1963). In contrast the peak age at onset in temperate countries has been between one and three years, (Barnett et al., 1952; Lawson et al., 1960; Arneil, 1961; and White et al., 1970). It is highly unlikely that ,at University College Hospital, Ibadan, where admissions of ill children under two years of age are very numerous, nephrotics are selectively being missed.

Incidence studies:

Incidence studies based on hospital data are notorious for their bias and cannot be directly applied to the community. Thus,

TABLE I

Prevalence (%) of malaria parasitaemia in nephrotic and non-nephrotic nigerian children (aged 2-10 years).

Group	Number examined	Prevalence of parasitaemia (%)					No. parasites seen
		P.falciparum	P.malariae	P.falciparum & P.malariae	Overall P.falciparum	Overall P.malariae	
Nephrotic children	113	2	28	60	62	88	10
Non nephrotic ill children	920	52	6	18	70	24	24
"Healthy" village children	340	44	6	12	56	18	38

Overall Infection Rate :	*P. malariae*	*P. falciparum*
Nephrotic/Non-nephrotic ill children	$x^2 = 183.3$ n = 1 P = < 0.001	$x^2 = 2.3$ n = 1 P = < 0.1
Nephrotic/Healthy children	$x^2 = 177.1$ n = 1 P = < 0.001	$x^2 = 1.03$ n = 1 P = < 0.3

the incidence and prevalence of the nephrotic syndrome in tropical populations is unknown and comparisons with temperate countries cannot legitimately be made. In contrast, comparisons between data derived from hospital series in Europe and elsewhere and hospitals in the tropics, despite certain snags, may not be as unrepresentative as might appear at first. Thus, in Ibadan, 50 cases of childhood nephrosis were encountered yearly in one of the two hospitals in the city (Gilles, 1967). In Durban, where "P.malariae" does not exist, fewer than 12 cases were observed over an eighteen month period among all children attending the three largest general hospitals, one of which has a turnover of African children three times that of University College Hospital Ibadan, (Klenerman 1960; Walt, 1960). Similarly, in a series from Glasgow, where there were about 500,000 children at risk, the average yearly number of admissions with nephrosis was only ten (Arneil, 1961). Kibukamusoke (1966) has also stressed the high incidence of the nephrotic syndrome in Kampala and Lagos. It is true that hospitals such as the University College Hospital Ibadan and Mulago Hospital, Kampala, enjoy a rather special position in their local environment and may attract patients from far and wide. A similar situation however can exist to some extent in temperate countries, in relation to a renowned renal unit at a children's hospital in a big city such as London or Glasgow.

Time-trend studies:

Giglioli (1950) predicted that when malaria in Guyana was eradicated the nephrotic syndrome would become less frequent. Thirty years later, following the eradication of malaria from that country, Giglioli (1962b) reported a decline in the prevalence of albuminuria, and the virtual disappearance of nephrosis in children. Thus, in one area of the country where malaria had been hyperendemic, 108 cases of 'chronic or subchronic nephritis were recorded, mainly in children' by Giglioli between 1923 and -1929 (pre-eradication years). In contrast, in the same area between 1958 and 1960 (about 10 years after successful eradication of malaria) only 12 cases of acute, sub-acute and chronic nephritis were recorded out of a total of 6,408 admissions. There was no case of 'nephrosis'. Even allowing for the

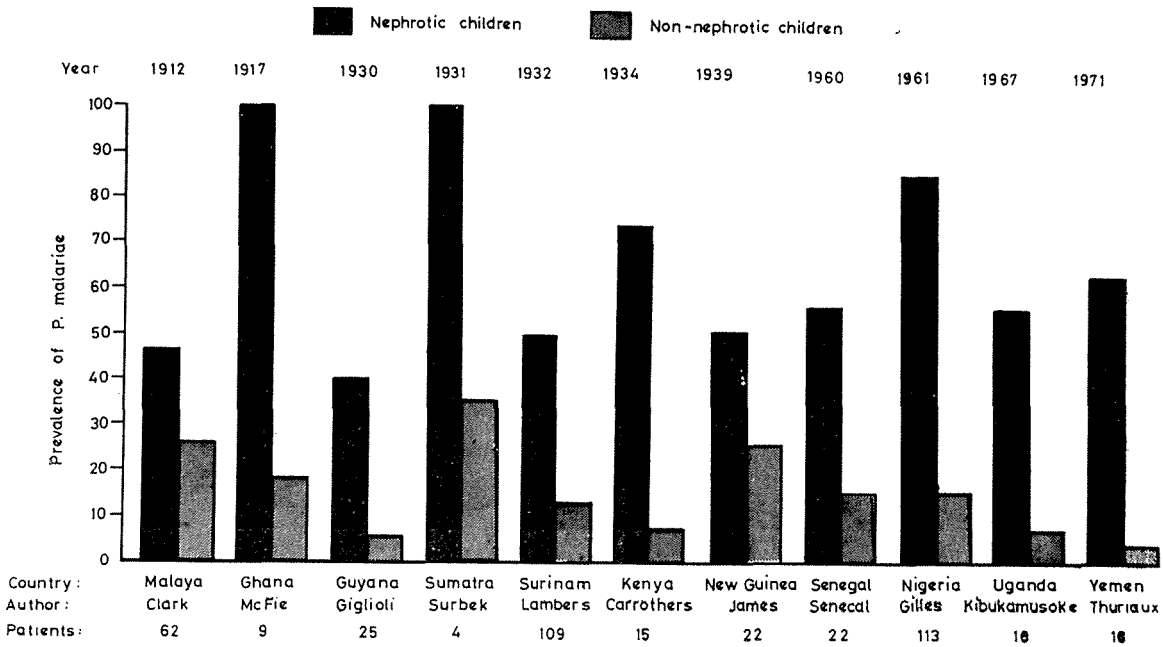

FIG. 2. Worldwide reports on the associ ation between P.malariae and the nephrotic syndrome.

relative imprecision of the renal terminology used and the lack of accurate renal morbidity data for the period between 1929 and 1958, these results can hardly be shrugged off. The possibility that 'other factors', e.g. the introduction of antibiotics and improvement in basic health services, might have been responsible for the decline, rather than the eradication of malaria, could be relevant to renal diseases such as acute nephritis or pyelonephritis, but hardly to 'nephrosis', since no evidence is forthcoming that such 'other factors' have significantly affected the incidence of childhood nephrosis in Europe and America during the past century .

In this context the observations of Carter (1961) from Freetown, Sierra Leone are interesting. He observed that in the city where malaria had been brought under control, the nephrotic syndrome was rare, although in other respects the paediatric problems resembled those in Ibadan. Unfortunately, unlike Giglioli's observations, the prevalence of the syndrome in the years before malaria control is not known.

In Ceylon, James and Gunesekara (1913) reported a high proportion of cases of kidney disease in the colony; it would be interesting to know what effect if any malaria eradication has had on the incidence of nephrosis especially among children.

Mandle (1970) has recently reported that in the thirty-year period preceeding malaria eradication in Guyana, there was a decline in deaths from all causes including renal disease and malaria, but that following malaria eradication there was a notable acceleration in the decline in deaths from renal disease and tuberculosis. The evaluation of morbidity and mortality of such time-trends of disease in the tropics are notoriously difficult to assess.

McGregor et al. (1956) followed up 52 Gambian children from birth, half of whom were protected from malaria with weekly doses of chloroquine while the other half were left unprotected. Three years later these workers were able to examine 16 protected and 13 unprotected children in detail. 61,5% of the unprotected children had "P.malariae" parasitaemia, but only one unprotected child (who had "P.malariae) had heavy proteinuria. This child had no oedema or other evidence of renal dysfunction.

If this low 'attack rate' is applicable in other areas of the tropics, community based cohorts to determine the incidence and prevalence of albuminura and of the nephrotic syndrome in persons with "P.malariae infection and controls, will be extremely difficult to construct because of the large number of children needed and the length of observation that will be required. In this context, it is of interest that over a period of 10 years Giglioli (1962a) has been able 'on more than one accasion, to follow through the different evolutionary stages of the disease from an uncomplicated and mild quartan malaria with simple intermittent albuminuria, to quartan malaria with persistent albuminuria and hyaline and granular casts in the sediment, to established nephrosis with extreme generalized oedema and ascites'.

MORPHOLOGY

The morphological changes in renal biopsies in Nigeria differ in the frequency with which the different types of lesion are encountered, from those described in non-malarious areas (Chung et al., 1970; While et al., 1970).

Thus, in Nigeria, the most common renal lesion is 'segmental capillary wall thickening of the tuft associated with a mesangial increase of PAS positive material leading to sclerosis of peripheral capillary loops." These lesions appear to progress to total glomerular sclerosis. "Minimal change' kidney, (seen in the majority of European childhood nephrosis cases), proliferative and membranous nephritis are not common.

Electron microscopy studies reveal "segmental fusion of foot processes of the epithelial cells with thickening and irregularity of the lamina densa of the basement membrane of the capillaries". Small lacunae are noted in the basement membrane. Deposits of basement membrane like material are seen in the mesangium and luminal surface of the basement membrane. The

detailed pathological appearances have recently been published and correlated with the clinical and immunological findings (Hendrickse et al., 1972).

PATHOGENESIS

Four possibilities come readily to mind. Firstly, the notion of a fortuitous association between quartan malaria and the nephrotic syndrome is highly unlikely in view of the universitality, consistency and degree of the correlation. Secondly, there is no evidence to suggest that "P.malariae" damages the kidney by direct action.

The third, and perhaps the most difficult argument to refute, is that nephrotic children merely exhibit a greater susceptibility to infection with "P.malariae". On general logistic grounds, one could argue that since "P.falciparum" and "P.vivax" are the two malaria parasites most widely distributed throughout the tropical world, it would seem reasonable to suppose that if a nephrotic were to exhibit a propensity for a malaria parasite, it would be to the more predominant rather than to the less common protozoal agent. Furthermore, no increase in the overall incidence of nephrosis in the tropics (despite the loopholes in the available data) would be expected. Finally, the results previously mentioned of malaria eradication in Guyana (despite certain flaws), together with the observations from Sierra Leone cannot easily be shrugged off as meaningless. The magnitude and exactitude of the community cohort studies that would be needed to dispose of this third hypothesis, is a daunting thought.

Fourthly, Hendrickse and Gilles (1963) advanced the suggestion that the nephrotic syndrome might be due to glomerular damage caused by the deposition of immune complexes.

IMMUNOLOGY

Preliminary evidence in support of the view that immunoglobulins and complement deposits occur in the glomeruli of nephrotic Nigerian children was presented by Dixon (1966). Soothill and Hendrickse (1967) showed that part of the complement component (beta-1-C) was found in the macro-molecular fraction of serum in affected children suggesting that it might be bound to soluble antigen-antibody complexes.

In renal biopsies from 93 Nigerian patients (50 children and 43 adults) immunofluorescence showed that immunoglobulins G and M were present in 96%, the third component of complement in 66%, and "P. malariae" antigen in 25% of cases (Houba et al. 1970). Examination of eluates from nephrotic kidney specimens confirmed that specific antibodies against "P.malariae" were present in most of them (Houba et al. 1971). The immunoglobulin deposits varied from a coarse to a fine granular pattern (Fig. 3) and the distribution of IgG sub-classes in glomerular deposits was related to the pattern (Houba and Lambert, 1974). Both morphological and electron microscope changes showed considerable variation (Allison et al. 1969; Hendrickse et al. 1972).

TREATMENT

The results of treatment of this quartan malaria nephrosis are unsatisfactory. There

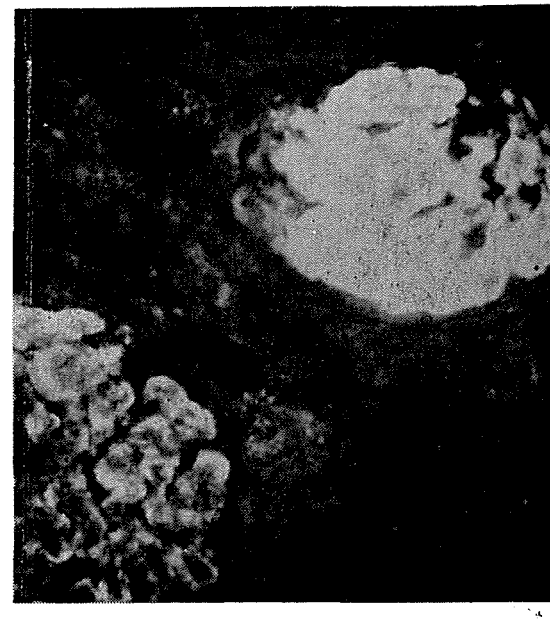

FIG. 3. Note fine granular pattern on left and coarse on right.

is no response to radical treatment with antimalarials and a poor response to corticosteroids (Adenyi et al. 1970). Good responses to azathioprine and cyclophosphamide have been reported in patients with coarse or mixed granular patterns of immunofluorescence but not in patients with a fine, granular pattern (Houba et al., 1974; Hendrickse et al. 1972).

Several important questions remain unanswered. Why do only some individuals develop the nephrotic syndrome when at some time or another in endemic areas all the children are infected with "P.malariae?" How does the lesion start? What factors are responsible for the chronicity of the syndrome? Many unsolved problems still remain over this nephropathy associated with "P.malariae" infection.

SUMMARY

There now exists overwhelming evidence of an association between quartan malaria and the nephrotic syndrome in childhood, and all the clinical, laboratory, morphological, immunological and epidemiological data available strongly support the concept of 'malarial nephrosis' as an immune-complex disease. This syndrome responds poorly to all forms of treatment which have been tried so far and usually progresses to renal failure and early death.

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