PAPERS AND ORIGINALS

"Tropical Nephropathy" and "Tropical Extramembranous Glomerulonephritis" of Unknown Aetiology in Senegal

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British Medical Journal, 1975, 1, 541-546**Summary**

A study of renal biopsy specimens obtained in Senegal from 24 children and six adults with the nephrotic syndrome showed two unusual varieties of nephropathy—namely, an extramembranous glomerulonephritis associated with hypocomplementaemia (four cases), a combination previously described only in systemic lupus erythematosus, and a "tropical nephropathy" (16 cases). The latter, though lacking the diffuse glomerular deposits of immunoglobulin described in quartan malarial nephropathy (Q.M.N.), showed a curious progressive and segmental glomerulosclerosis, characterized by a "flaking" or fibrillary splitting of the glomerular capillary wall, seen in Q.M.N. Serological evidence of malaria was lacking in a third of the childhood cases.

Introduction

Plasmodium malariae has been suggested as a major cause of the nephrotic syndrome in children in Nigeria (Gilles and Hendrickse, 1963) and Uganda (Kibukamusoke *et al.*, 1967). The causative role of this parasite is of particular interest—firstly,

because the incidence of the syndrome should be reduced by prophylactic measures (Giglioli, 1962 a, 1962 b; Gilles and Hendrickse, 1963), and, secondly, because it seems to be one of the few forms of immune complex nephritis in which antigens of the causative organism have been found by immunological techniques lying along the glomerular capillary basement membrane (Houba *et al.*, 1970; Houba *et al.*, 1971). In this nephropathy there is an unusual form of progressive and segmental glomerulosclerosis, recognized in the Ivory Coast (Paillerets *et al.*, 1972) as well as in Nigeria (Hendrickse *et al.*, 1972), and now held to be characterized by a fibrillary "splitting" or "flaking" ("feuilletage") of the capillary basement membrane and by the absence of nuclear proliferation in the glomerular tufts (Habib, 1973; White, 1973).

The question arises whether this form of renal lesion occurs solely in patients infected with *P. malariae*. An investigation has therefore been carried out in Senegal, where though the prevalence of quartan malaria is low the nephrotic syndrome is common in children (Saté *et al.*, 1970). Thirty cases were investigated, 24 of them children. Five of the children and four of the six adults had forms of nephropathy seen in non-tropical areas. The remainder suffered from two unusual forms. One of these was a hypocomplementaemic type of extramembranous glomerulonephritis that was unassociated with systemic lupus erythematosus. This we term "tropical extramembranous glomerulonephritis." The second form of nephropathy differed from any described hitherto, and this until it has been further analysed we term "tropical nephropathy." Preliminary analysis (Morel-Maroger *et al.*, 1973) by light microscopy showed the renal lesions in tropical nephropathy to be typical of the progressive and segmental glomerulosclerosis found in the Ivory Coast and Nigeria. The glomeruli, however, lacked both the diffuse deposition of immunoglobulin noted by Hendrickse *et al.* (1972) and, save rarely, the areas of lacunar basement membrane resorption emphasized by White (1973), changes regarded as characteristic of quartan malarial nephropathy (Q.M.N.).

More-detailed investigation yielded no single cause of the tropical nephropathy found in Senegal. The obvious lesion was the curious fibrillary abnormality of the glomerular capillary basement membrane.

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Materials and Methods

All the patients presented with the nephrotic syndrome, some being in remission. The gross degree of anasarca was striking. The blood urea and plasma proteins were measured and the urine was analysed. Blood smears were examined for plasmodia; faecal specimens for hookworm, ascaris, and trichuris; and urine specimens for *Schistosoma haematobium*.

Blood from each patient was conveyed to Europe. Apart from routine immunoelectrophoresis special studies were made for Gm blood groups and hepatitis-B antigen (HBAG) by Dr. Rivat (Rouen). Anti-*P. falciparum* and anti-*P. malariae* antibodies were studied in London by A.G.S. Estimation of C3 was done in all cases by immune diffusion, as were latex tests for rheumatoid factor (all of which gave negative results). Also, but without success, antiglomerular basement membrane, antitubular, and antinuclear antibodies were sought by indirect immunofluorescence on normal human kidney and (for antinuclear factor) rat kidney.

Except for those in hospital it was difficult to determine the exact treatment given to many patients. Some had received steroids, some cyclophosphamide alone or in combination with steroids, and many had been given chloroquine at some time. In five cases twice biopsied treatment after the first biopsy included a low-salt diet and the administration of diuretics and antibiotics.

The six adult patients were included in the study with a view to comparing the syndrome in infants and children with that in adults.

Renal biopsy specimens (containing at least eight glomeruli) were in part treated with Dubosq-Brazil fixative (Morel-Maroger *et al.*, 1972) and in part transferred to dry ice (after being snap-frozen) for immediate transport to Paris. Immunofluorescence (Berger *et al.*, 1967) studies were carried out with antisera to IgG, IgA, IgM, C3, C4, C1q, properdin, glycine-rich β -glycoprotein (GBG; C3 pro-activator), fibrinogen, and albumin. In addition a human serum with a high titre of antibody against *P. falciparum* was labelled with fluorescein isothiocyanate and applied without positive result to six specimens (cases 4 (ii), 5 (ii), 6 (ii), 10 (ii), 19 (ii), and 20 (ii)). No similar antibody against *P. malariae* was available.

Material for electron microscopy was fixed in 6.25% glutaraldehyde in cacodylate buffer and postfixed in Millonig's phosphate-buffered 1% osmium tetroxide. Biopsy specimens were immediately conveyed at 4°C in 70% acetone to England, where they were rinsed in 1% uranyl acetate and embedded in Durcupan resin (Fluka), the sections being stained with Reynold's lead citrate.

Results

Of the 30 cases investigated 16 were examples of tropical nephropathy and five examples of tropical extramembranous glomerulonephritis (see table). Five showed a diffuse proliferative glomerulonephritis, while in the remaining four (adult) cases various other renal lesions encountered in non-tropical areas were seen. Serum and biopsy specimens were taken on two occasions in seven cases, designated (i) (first) and (ii) (second).

TROPICAL NEPHROPATHY

In all cases evidence of the nephrotic syndrome was obtained. The glomerular lesions (figs. 1-4) in every case were a segmental or diffuse splitting or flaking of the glomerular capillary walls and the intrusion of basement-membrane-like material into the capillary lumen, best seen in silver preparations using Wilder's technique. In the five mild cases (cases 1-5) these changes were focal and segmental; in the three moderate cases (cases 6-8) they were diffuse and associated with capillary coalescence and areas of hyalinization—that is, eosinophilic areas in which the structure was unrecognizable; in the eight severe cases (cases 9-16) the changes were more advanced.

Mild Lesions, cases 1-5.—All five patients had a normal blood urea nitrogen level, and the blood pressures were normal except in case 2 (160/90 mm Hg). The serum C3 level was raised in case 5 (i). Ascaris, *S. haematobium*, and hookworms were found in case 3, and the last two in case 4 (i). In all these patients the distribution of Gm blood groups was normal with respect to the ethnic groups studied. Apart from the changes listed in the table small focal and segmental deposits of IgA and IgG in occasional glomeruli were found in case 1 and a diffuse linear parietal deposition of albumin alone in case 2. Electron microscopy of the glomeruli showed fusion of podocyte foot processes, slight irregularity and thickening of the basement membrane, and intrusion of split basement membranes into capillary lumina. Small localized electron-dense deposits, in part extramembranous, were noted in case 1, and a second, small intramembranous deposit was noted in the first but not the second biopsy specimen from case 4. No lacunae were found in basement membranes.

Moderate Lesions, cases 6-8.—Serum complement was raised in case 8, and all the blood pressures were normal except in case 7 (160/90 mm Hg). The serum was HBAG-positive in case 6 (i). *Giardia lamblia* and trichuris were present in the faeces in case 7. In these cases and also in the severe group (see below), with the exception of case 14, the distribution of Gm groups was abnormal—that is, IgG₄ was absent or grossly diminished. Light microscopy showed similar glomerular changes to those seen in mild lesions but there were also capsular adhesions and segmental coalescence of capillaries. In case 6 the segmental hyalinization became more conspicuous on second

Clinical Features of Patients with Nephropathy of Unknown Aetiology and Results of Investigations

Case No.	Sex and Age (Years)	Months between Clinical Presentation and First Biopsy	Serum antibody titres against:		Immunofluorescence			Electron Microscopy		
			<i>P. falciparum</i>	<i>P. malariae</i>	IgM	C3	C1q, C4	Irregular Thickening and Splitting of Basement Membrane	Lacunae	Deposit
Tropical Nephropathy										
1	M/14	27	—	1/64	(+)	—	—	+	—	(E.I.S.)
2	M/15	36	—	1/64	—	—	—	+	No glomeruli	—
3	M/17	24	—	—	—	—	—	+	—	(I)
4(i)	M/15	1	1/256	1/16	—	No glomeruli	—	+	—	—
5(i)	M/11	1	1/4096	—	—	—	—	+	Not done	(I)
6(i)	M/4	8	1/256	1/16	—	—	—	++	(+)	(S)
7	M/15	2	1/1024	—	(+)	—	—	++	—	—
8	M/10	0.5	1/256	—	(+)	—	(+) (C1q)	++	Not done	—
9	M/49	12	Not done	—	(+)	—	—	++	—	—
10(i)	F/7	8	—	—	(+)	—	—	++	—	—
11	F/13	12	—	—	(+)	(+)	(C1q)	++	(+)	(M)
12	F/8	1	—	—	(+)	—	—	++	—	—
13	F/10	2	1/1024	1/256	(+)	—	(+)	++	(+)	—
14	M/6	1	—	—	(+)	—	(C4)	(+)	—	—
15	M/9	1	1/256	1/256	+	—	+	+	No glomeruli	—
16	F/6	1	1/4096	1/256	(+)	(+)	(+)	+	++	—
Tropical Extramembranous Glomerulonephritis										
17	M/44	4	Not done	—	++	+++	—	+	—	I. E. ++
18(i)	M/4	3	—	—	—	++	++	+	Not done	—
19(i)	M/12	12	1/256	1/64	—	+++	++	+	Not done	—
20(i)	M/5	3	1/16	—	—	No glomeruli	++	+	Not done	—
21	F/5	3	—	1/64	—	+++	—	—	—	I. E. ++

E. = Extramembranous. I = Intramembranous. M = Mesangial. S = Subendothelial. () = Occasional focal and segmental deposits.

FIG. 1—Case 6 (i), tropical nephropathy. Renal biopsy specimen from moderate lesion showing flaking of basement membrane. (Wilder's silver stain. $\times 757$.)

FIG. 2—Case 14, tropical nephropathy. Renal biopsy specimen from severe lesion showing segmental area of loss of pattern in glomerulus ("sclerotic lesion") together with irregular thickening elsewhere in capillary basement membrane. (Mallory's trichromic stain. $\times 303$.)

biopsy. Immunofluorescence showed segmental deposits of immunoglobulin and complement components only in occasional glomeruli in cases 6, 7, and 8. On electron microscopy similar but more numerous lesions were seen. There was some endothelial cell swelling and occasional collapse of the capillary wall. In some foci it was not possible to establish whether the swollen cytoplasm adjacent to basement membrane intrusions was of endothelial or mesangial origin. One electron-dense subendothelial deposit (1200 $\times$ 600 nm) was identified in case 6 (i) (in which HBAG was found in the serum). Near the endothelial aspect of this deposit was a lacuna (diameter 200 nm) containing an electron-dense oval fleck (diameter 150 nm).

Severe Lesions, cases 9-16.—Blood pressures were all normal except in cases 9 (170/20 mm Hg), 10 (i) and (ii) (140/100 mm Hg), and 11 (150/100 mm Hg). In all cases the serum complement level was normal. Ascaris was found in the faeces in cases 9, 10, 13, and 14. *P. malariae* was found in blood smears in case 15, the only one of the 30 cases to be thus affected. Light microscopy showed the glomerular lesions to be widespread and severe and to include segmental areas of hyalinosis and sclerosis with occasional foam cells. Capsular adhesions were more conspicuous than in the mild group. The arteriolar media showed chronic hyaline degeneration. In most instances interstitial fibrosis with foci of lymphocytes and histiocytes with areas of tubular atrophy were found. Immunofluorescence studies showed small focal and segmental deposits but only in case 15 were these diffuse and granular; in cases 9 and 13 the focal deposits listed were accompanied by IgG and properdin respectively. Electron microscopy of the glomeruli showed changes similar to those seen in moderate lesions. Endothelial cell swelling was conspicuous. Electron-

FIG. 3—Case 3, tropical nephropathy. Electronmicroscopical appearances of renal biopsy specimen from mild lesion. Note irregularity of thickening of capillary basement membrane (top right) and intrusion of basement-membrane-like material into lumen of capillary (arrowed); smudging of foot processes of podocytes is present on upper aspect of this capillary. (Uranyl acetate: Reynold's lead citrate. $\times 4060$.)

FIG. 4—Case 6 (i), tropical nephropathy. Electronmicroscopical section of renal biopsy specimen showing conspicuous intrusion of basement-membrane-like material into capillary lumen and swelling of cell cytoplasm. Several lacunae are present in capillary basement membrane containing single electron-dense flecks. Lumina in other capillaries in this glomerulus were patent. (Uranyl acetate: Reynold's lead citrate. $\times 5586$.)

dense deposits were exceptional. Eosinophil leucocytes were found in the glomerular capillaries in case 9, and intracapillary platelets in case 12. Occasional lacunae with electron-dense central flecks were seen in the basement membrane in cases 11 and 13. Many lacunae were observed in case 16 (in which the highest titre against *P. falciparum* was observed). These were similar in size to those noted in case 6 (i).

Sequential biopsy and serum studies were performed at intervals of four to seven months in cases 4, 5, 6, and 10. In case 4 (ii) the *P. falciparum* titre fell to 1/16, in case 5 (ii) the *P. malariae* titre rose to 1/256, in case 6 (ii) both titres rose to 1/1024, and in case 10 no antibodies were found. A progression in the glomerulosclerosis was evident only in case 10. Thus in contrast to the initial findings in this case occasional segmental deposits of IgM and C3 were found in the glomeruli and occasional mesangial deposits were shown by electron microscopy. In case 4 (ii) immunofluorescence studies showed no deposits, nor were any found in electronmicrographs. Ultrastructural changes in cases 4 (ii) and 5 (ii) resembled those noted in case 3 (see table). In cases 3 (ii) and 6 (ii) occasional segmental

immunofluorescent deposits of IgM and C3 were found and occasional electron-dense deposits were seen in electronmicrographs.

COMMENTS

There was no increase in blood urea and hypertension was infrequent and slight. This was so irrespective of age, of time elapsing between clinical presentation and biopsy, and of the grading of the light-microscopical changes. It was remarkable, however, that all cases of mild lesions were male while of the rest many were female and except in case 14 the distribution of Gm groups was abnormal.

Though intramembranous lacunae containing electron-dense material were noted in the glomeruli in four of the 16 cases (one adult) they were particularly evident in case 16. In this case and in case 13 the presence of lacunae was associated with a high anti-*P. falciparum* titre (1/1024 or more); but in three other similar cases (5, 6 (ii), and 7) no such lacunae were found. The relevance of these lesions to plasmodial infection is thus dubious. Remarkably in a malarial area, in five of the 15 cases analysed in this manner no plasmodial antibodies were found. In keeping with the greater prevalence of falciparum infection, in only two of the 10 cases with malarial antibodies was the titre against *P. malariae* higher than that against *P. falciparum*.

Except in case 15, the immunofluorescent deposits were focal and segmental and affected only occasional areas in the glomeruli. Such isolated deposits thus differed from the diffuse, granular, linear, or fine deposits seen by Hendrickse *et al.* (1972) in Q.M.N. Electron-dense deposits in relation to the capillary basement membrane were similarly infrequent. Case 15 was somewhat different, firstly, in that *P. malariae* was found in a blood smear and, secondly, in that diffuse deposits of IgM, C1q, and C4 were found in mesangial areas and along capillary loops.

TROPICAL EXTRAMEMBRANOUS GLOMERULONEPHRITIS (Figs. 5 and 6)

Hypertension and raised blood urea nitrogen levels were found in case 17, and cases 17, 18, and 19 showed haematuria. Serum C3 and C4 values were low in cases in which they were measured (cases 18, 19, 20, and 21), reverting to normal over a period of five months in one (case 20 (ii)). *Ascaris* was found in the faeces in case 17.

In these cases extramembranous glomerulonephritis was severe and unusual in that in the four children in this group there was a conspicuous nuclear proliferation which on electron microscopy was shown to affect endothelial and mesangial nuclei. Chronic arteriolar changes were present only in the adult patient, and in this case patches of interstitial fibrosis and lymphocytic and histiocytic infiltration associated with tubular atrophy were evident.

Immunofluorescence studies showed IgG in every instance diffusely distributed in granular form along the peripheral capillary loops; this was accompanied by IgA in the adult case (case 17) and by properdin in the remainder. C1q and C4 were found in three of the patients in whom it was sought (cases 18 (i) and (ii), 19 (i) and (ii), and 20 (ii)).

Electron microscopy showed diffuse, conspicuous extramembranous and intramembranous deposits in all five cases. No lacunae were noted though there was evidence of some splitting and intrusion of the thickened basement membrane into the capillary lumina in cases 17, 18 (ii), 19, and 20 (ii) but not in case 21. In case 20 (ii) a cluster (280 × 460 nm) of electron-dense haloed particles (each 30 × 45 nm) was found in the capillary basement membrane.

Sequential biopsy and serum studies were performed at intervals of four to six months in three cases. The *P. falciparum* titre had fallen to 1/64 in case 19 (ii) and to zero in case 20 (ii). Electronmicrographs in all cases showed the changes seen in

FIG. 5—Case 18, tropical extramembranous glomerulonephritis. Immunofluorescence study showing diffuse granular deposits along capillary walls. (Fluorescein-labelled antihuman C1q. × 350.)

FIG. 6—Case 17, tropical extramembranous glomerulonephritis. Large electron-dense deposits are present on epithelial aspect of basement membrane with fusion of overlying foot processes. (Uranyl acetate: Reynold's lead citrate. × 9424.)

case 17. Immunofluorescence findings in case 18 (ii) were as in case 18 (i), and in case 20 (ii) as in for example, case 19 (i); in case 19 (ii) deposits of C3 and properdin were lacking but GBG was present.

COMMENTS

In non-tropical areas cases of extramembranous glomerulonephritis show a hypocomplementaemia only in patients with systemic lupus erythematosus (Gewurz *et al.*, 1968), of which in our cases there was no evidence. In the Senegal cases, moreover, the histological features were unusual—firstly, because there was glomerular nuclear proliferation, which is not a feature of this form of nephritis, and, secondly, because there were deposits not only of C3, which is well recognized in extramembranous glomerulonephritis, but also of C1q, C4, and properdin. The reason for their presence is obscure though they are seen in

systemic lupus erythematosus (Andres *et al.*, 1970; Rothfield *et al.*, 1972). Their presence perhaps indicates a particularly active immune disturbance. No single aetiological factor was identified, but it is of interest that in one patient (case 20 (ii)) virus-like particles were found in the glomerulus. A high titre of antibody against *P. falciparum* was found in case 19 but neither in this case nor in case 20 could its antigens be shown by immunofluorescence in the glomeruli. One of the cases tested showed no malaria antibodies.

DIFFUSE PROLIFERATIVE GLOMERULONEPHRITIS

Out of five patients with diffuse proliferative glomerulonephritis (cases 22, 23, 24, 25, and 26; ages 7, 3, 14, 3, and 13 years respectively) all but one (case 26) were male. All were seen within three months of the onset of symptoms.

Antistreptolysin O titres were 1/960 (case 22), 1/240 (case 23), 1/960 (case 25), and 1/480 (case 26) and *Streptococcus viridans* was cultured from the blood in case 24. Serum complement was low in this case. Antibody titres of 1/64, 1/256, 1/4096, and 1/64 against *P. falciparum* (cases 22, 23, 24 and 25) and of 1/256 and 1/16 against *P. malariae* (cases 24 and 26) were noted.

Light microscopy showed a conspicuous and diffuse nuclear proliferation in the glomeruli in cases 22, 25, and 26 whereas in case 23 this proliferation was segmental. Eosinophil "humps" were present in cases 22 and 25. In case 24 there were numerous crescents and areas of segmental glomerular necrosis, changes consistent with the subacute bacterial endocarditis found in this patient.

Immunologically there were diffuse deposits of C3 in case 22, diffuse deposits of IgG, IgM, C3, C1q, and C4 and focal deposits of fibrinogen in case 24, diffuse deposits of properdin in case 25, and diffuse deposits of C3, properdin, and IgG in case 26.

Electron microscopy of the glomeruli showed conspicuous electron-dense inclusions which were mesangial in cases 22 and 23. There were extramembranous humps in case 22. In case 24 electron-dense deposits were mesangial, intramembranous, and subendothelial. In cases 22 and 23 haloed electron-dense inclusions within the basement membrane, about 50 nm in diameter, were seen. These might have been viral in origin but the preparations did not allow adequate study at high magnification. In these cases no intrusion of basement membrane material into the capillary lumen was seen and there were no lacunae.

COMMENT

These cases exemplify "acute" diffuse proliferative glomerulonephritis seen in other tropical areas (see Edington and Mainwaring, 1966; Wing *et al.*, 1971) characterized by high antistreptolysin O titres, resolving in case 23 and associated with bacteraemia in case 24. Serological evidence of plasmodial infection was present in all five.

HETEROGENEOUS CASES

Four patients (cases 27, 28, 29, and 30; ages 31, 58, 52, and 31 years respectively) were heterogeneous cases. One (case 28) was a woman. All presented with the nephrotic syndrome. Case 27 had interstitial inflammation of the kidney with many obsolescent glomeruli. Case 28 presented with diabetes mellitus and glomerulosclerosis, changes confirmed by electron microscopy. Case 29 had nephrosclerosis characterized by severe arteriosclerosis, numerous obsolescent glomeruli, and widespread tubular atrophy. Electron microscopy showed, apart from foot-process fusion, irregular thickening of basement membranes, which occasionally appeared to intrude into the capillary lumen.

One patient (case 30) suffered from lepromatous leprosy, and there was ultrastructural evidence of amyloidosis. Immunofluorescence findings in the glomeruli were negative in cases 27 and 29, deposits of IgM being found in the glomeruli in case 28. Cryostat preparations lacked glomeruli in case 30.

Discussion

These renal biopsy specimens from nephrotic children in Senegal showed a number of unusual features. Thus by contrast with findings in temperate climates (Churg *et al.*, 1970; Habib *et al.*, 1971) in none of the specimens were the light-microscopical appearances normal. Furthermore, in 19 children two forms of nephropathy were found which are not seen in temperate areas. Four had an unusual extramembranous glomerulonephritis, and 15 had a form of "tropical nephropathy" also seen in one of the six adult patients studied. Of the latter four others suffered from forms of nephropathy commonly encountered in temperate climates and one from an extramembranous glomerulonephritis. The latter was seen in an unusual form in four children in that the serum complement level was low, an association hitherto noted only in systemic lupus erythematosus. The renal lesion also was remarkable both because of the presence of cell proliferation in the glomerular tuft and because of the wide variety of complement components shown along the capillary basement membrane by immunofluorescence.

The cases of tropical nephropathy seen were characterized by a progressive segmental and focal glomerulosclerosis in which the glomerular capillary walls showed a fibrillary appearance and tended to coalesce. This lesion has been reported in Nigeria, where it has been attributed to quartan malaria (Hendrickse *et al.*, 1972), and the Ivory Coast (Habib, 1973) but is not seen in children in temperate climates. With one exception (case 15), however, the cases seen in Senegal lacked the diffuse deposition of immune complexes seen in Nigeria; indeed, such complexes, when found, involved at most occasional glomeruli, so that it seems unlikely that this nephropathy, unlike the extramembranous glomerulonephritis seen in Senegal, was due to circulating immune complexes.

Moreover, though malaria is endemic in Senegal a third of the childhood cases of tropical nephropathy lacked serological evidence of infection. Equally, though the remaining cases showed such evidence titres against *P. falciparum* were higher than those against *P. malariae* in all but three instances. Despite, therefore, the cross-reactivity between human malaria parasites it was unlikely that quartan malaria had a major nephropathic role in Senegal. Nor again was it possible to demonstrate *P. falciparum* antigen in the glomeruli of six cases in which it was sought. Furthermore, in no case did glomeruli show the widespread mesangial immune deposits which Voller *et al.* (1973) found in the kidneys of a single monkey (which developed the nephrotic syndrome) after experimental infection with *P. malariae*; nor did any biopsy specimen show the essentially mesangial immune deposits and subendothelial electron-dense deposits reported by Bhamarapravati *et al.* (1973) in the glomeruli of (non-nephrotic) patients acutely infected with *P. falciparum*.

In two respects, however, there were striking similarities between many of our cases and those described as examples of Q.M.N. Thus in terms of the diffuse granular pattern of immunofluorescence found in the glomeruli and of the conspicuous electron-dense subepithelial deposits seen in electron-micrographs the renal lesion we saw in *extramembranous glomerulonephritis* closely resembled some cases of Q.M.N. analysed by Allison *et al.* (1971). This immunofluorescence pattern appears, indeed, to be the dominant type seen in Q.M.N., though some cases of Q.M.N. are described as showing a "diffuse or mixed" pattern characterized by fine fluorescent granules in the glomerular capillary wall. In such cases Allison

et al. (1971) noted that electron-dense deposits in electron-micrographs were usually on the "endothelial surface of the glomerular capillary wall." Such lesions were clearly not among those we saw.

With regard to the relationship between Q.M.N. and the tropical nephropathy seen in Senegal the similarities lie in the histological features rather than in the immunofluorescence findings. Thus in both conditions a fibrillary change in the capillary wall leads to focal and segmental glomerulosclerosis. Moreover, electronmicrographs show intrusion of basement-membrane-like material into the capillary lumen, which was one of the lesions that White (1973) stressed in Q.M.N. He also reported the presence of curious lacunar areas of basement membrane resorption, at the centre of which were electron-dense flecks. These were not noted in the study of Q.M.N. made by Allison *et al.* (1971), though they described conspicuous electron-dense deposits within the glomerular basement membrane in 12 out of 14 cases, deposits which were not seen by White.

In short, the two unusual nephropathies we observed in Senegal differed, despite some similarities, from others hitherto reported in West Africa. One was a form of extramembranous glomerulonephritis characterized by hypocomplementaemia in the absence of evidence of systemic lupus erythematosus. No cause could be found for this nephropathy though it appeared to have an immune basis. In this respect it differed from the second and commoner condition which we term tropical nephropathy. No single cause of this condition was apparent, and, in particular, evidence of malaria was lacking in many instances; yet it had morphological features similar to those seen in cases described in Nigeria as Q.M.N. The most obvious morphological change common to Q.M.N. and tropical nephropathy was the curious fibrillary thickening and narrowing of the glomerular capillaries. Possibly this change is a primary abnormality in African children, an abnormality capable in various circumstances of trapping circulating micro-organisms, parasites, and immune complexes.

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Addendum

Dr. D. Wright, of the Department of Microbiology, Charing Cross Hospital Medical School, has provided serological evidence of treponemal infection—for example, Yaws or Syphilis—in two cases of tropical nephropathy (nos. 12 and 13) and in one of extramembranous glomerulonephritis (case 20 (ii)) but not in nine others tested (cases 4, 5 (ii), 10, 14, 15, 18 (ii), 19 (ii), 21, and 26). Thus in cases 12, 13, and 20 (ii) the treponemal haemagglutination test gave a positive result, as did the V.D.R.L. (modified Wassermann) agglutination test at titres of 1/32, 1/8, and 1/1. The fluorescent treponemal antibody test was positive in case 13. None of the 12 sera reacted with the indirect immunofluorescent technique against cercariae of *S. haematobium*.

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Serum Ferritin Assay and Iron Status in Chronic Renal Failure and Haemodialysis

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Summary

Forty-four patients with chronic renal failure on haemodialysis for four months to eight years were studied. All received intravenous iron dextran 100 mg on alternate

weeks. Serum ferritin concentrations correlated well with body iron stores estimated by grading the bone marrow stainable iron. Altogether 34 patients showed increased bone marrow iron stores and serum ferritin concentrations greater than controls; four patients showed absence of iron in the marrow, and three of these had subnormal serum ferritin concentrations. Serum ferritin assay represents the best method of repeatedly monitoring the exact amount of iron therapy needed by patients with chronic renal failure, particularly those on regular haemodialysis.

Introduction

A sensitive immunoradiometric assay of serum ferritin has been described (Addison *et al.*, 1972) and a good correlation found

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