Malaria, Microscopy and Marmosets: the Saga of Tropical Nephrotic Syndrome

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Is there a distinct renal glomerular pathology which is diagnostic of quartan malarial nephropathy? Workers in Nigeria who have studied children with the nephrotic syndrome have long maintained that there is [1]. In this issue of the Journal, Abdurrahman et al. present their analysis of 100 consecutive cases studied from 1977 to 1981, and they also accept this claim. However, they present no new proof: *Plasmodium malariae* parasitaemia rates were just as high (40 per cent) in their membranoproliferative glomerulonephritis patients in those diagnosed as quartan malarial nephropathy.

The role of *P. malariae* in the aetiology of human glomerulonephritis is based on circumstantial clinical and epidemiological evidence, and on experimental work [3]. *P. malariae* appears to be the most important single aetiological factor in nephritis in both West Africa [2] and East Africa [4], however, it is not easy to sustain an argument that it is the sole factor in individual cases. Parasitaemia and malarial antibodies are found in association with a wide variety of glomerular appearances and in patients without renal disease. Furthermore, experimental pathology has provided little support for the concept of simple cause and effect due to a single agent. While it is relatively easy to produce mild proteinuria and immunoglobulin deposition in rodents [5], chronic disease similar to human glomerulonephritis has been recorded only occasionally in primates [6].

The glomerulus has a limited repertoire of response patterns to injury and care should be taken before specific aetiologies are assigned to particular appearances [7], in addition, when diseases become chronic these patterns may be difficult to distinguish. In our view classifying glomerular lesions partly on the basis of morphology and partly on aetiology perpetuates confusion. To refer to a patient as having post-streptococcal glomerulonephritis when the data are no more than the clinical features of an acute nephritic syndrome is unscientific; likewise to label glomerular appearances as quartan malarial nephropathy may lead to error and inappropriate treatment. We would prefer to restate classical clinical descriptions of renal disease—the nephrotic syndrome, the acute nephritic syndrome and chronic renal failure—each of which is regularly encountered in Africa, and to use descriptive morphological terms to classify the histological appearances. The two levels of diagnosis, clinical and morphological, should not be mixed and epidemiological evidence should not be used to interpret individual cases encountered in the clinic.
We do, however, find ourselves in sympathy with the suggestion of Abdurrahman et al. [2], that susceptibility to *P. malariae* may be modified by other sources of exogenous antigen. Children in the tropics are subject to various infectious agents, amongst which beta-haemolytic streptococci [8], hepatitis B virus [9] and *Schistosoma* [10] all carry antigens capable of causing immune complex glomerulonephritis and the nephrotic syndrome. Some infections may also have an effect on the immune response to other organisms: the immunosuppressive effect of malaria is well known [11]. Epstein–Barr virus, which is ubiquitous in tropical Africa, also has an effect on immune responses [12]. In the common marmoset, *Callithrix jacchus*, concurrent experimental infections with this virus and *P. brasilianum* (a strain related to *P. malariae*) resulted in more severe glomerular disease than that seen in *P. brasilianum* infection alone [13]. The quartan malaria nephropathy story was unfolding at the time that the classic work on immune complex disease was being reported by Germuth, Dixon and others. The two phenomena were not unreasonably connected and the idea of quartan malarial nephropathy as an immune complex disease took root. Evidence for this has recently been reviewed by Houba [11]. A simple chronic serum sickness type mechanism does not seem likely, however, and the profound effect of malaria on the monocyte–macrophage system must be considered among the possible moderating factors. Malaria has been shown to result in release of tumour necrosis factor from macrophages [14], and it would not be surprising if this or other macrophage derived cytokines were shown to affect glomerular disease.

A complex picture resulting from the interplay of various possible aetiological factors thus emerges. In addition, the balance between these factors and the immunocompetence of the human host is continually changing. As the population of today's London differs from that in which Richard Bright studied his 100 cases [15], so the children of Africa of the 1990s may have changed in comparison to those of the 1960s. Abdurrahman et al. [2] note differences between their patients in Northern Nigeria and those reported by Gilles and Hendrickse in Ibadan [1], amongst whom a higher *P. malariae* parasitaemia rate was observed. They attribute this difference to geography but is it also possible that in the intervening years improved nutrition and hygiene and the more general prescription of antimalarials could have affected the pattern.

We should remember that the most significant epidemiological observation in the saga of tropical nephrotic syndrome is the change in incidence of renal disease following eradication of malaria in British Guiana [16]. Unfortunately, renal histological descriptions are not available to correlate with this observation. The linkage of such a dramatic epidemiological change to the elimination of a specific glomerular pathology would provide the proof that our Nigerian colleagues deserve for all their painstaking studies.

REFERENCES