The Anaemia of Malaria

GEOFFREY PASVOL

From the Tropical Medicine Unit, Nuffield Department of Clinical Medicine, John Radcliffe Hospital, Headington, Oxford OX3 9DU

Since red cells are the major target of the malarial parasite and as such are destined for premature destruction, should this not adequately explain the sometimes life-threatening fall in haemoglobin seen in this infection? Such an explanation is obviously inadequate, for the degree of anaemia is often far in excess of that accounted for by the removal of infected cells alone. These factors make the anaemia of malaria both an important clinical complication and a challenging biological problem in one of the most common infections of man.

In this issue of the Journal, Phillips, Warrell and co-workers in Thailand have made another important contribution to our clinical understanding of malaria due to Plasmodium falciparum and the aetiology of the anaemia caused by it [1]. Their extensive study including 169 patients with well-defined cerebral malaria has highlighted the frequency of this complication since almost all (94 per cent) of their cerebral cases were anaemic (haematocrit <35 per cent). Furthermore at least 30 per cent required blood transfusion to sustain a haematocrit greater than 21 per cent. Anaemia was most severe in patients with bacterial infection; a remarkable 40 per cent of those with cerebral malaria had a urinary tract infection, pneumonia or septicaemia. Could immunosuppression induced by malaria and sometimes manifested by a relative neutropenia be responsible for these superinfections?

It would appear that both increased destruction and decreased production of red cells play a role in the anaemia of acute malaria. Mechanisms of haemolysis over and above disruption of the red cell by the parasite remain an area of much controversy. However, a fundamental question remains unanswered; namely whether the prime defect lies intrinsic or extrinsic to the red cell. This will only be answered in man with survival studies of labelled autologous and heterologous cross-matched cells from uninfected donors given to infected patients. Immune mediated mechanisms of cell lysis have often been proposed, sometimes with supportive data [2, 3], but the paradox remains that seldom do the most anaemic patients have a positive Coomb's test [4]. It has recently been found that immune serum contains an antibody to a 175 kiloDalton parasite protein, a protein which in culture is released into the supernatant medium and specifically binds to the major red cell sialoglycoprotein, glycophorin [5], an essential component for the invasion of human red cells by P. falciparum [6]. This may provide a mechanism whereby antigen–antibody complexes could specifically adsorb to the surface of red cells in vivo and mediate the removal of both infected and uninfected cells. The reticuloendothelial system may yet prove to be more adept than our diagnostic assays at detecting sensitized cells.

Non-immune mediated haemolysis of uninfected cells has been proposed in a monkey model of malaria, where gross changes in the lipid bilayer observed in both infected and uninfected red cells...
cells could favour mechanical lysis in organs such as the spleen [7]. The paper of Phillips et al. does not address these two aspects of haemolysis, but provides good evidence against another pathway of red cell destruction, namely disseminated intravascular coagulation. Although 46 of 116 patients had raised fibrin degradation products, in only 13 was this associated with hypofibrinogenaemia. On the contrary there was a significant increase in plasma fibrinogen in patients with cerebral malaria when compared to controls. Bleeding was uncommon.

In the face of extensive haemolysis and in the absence of haematinic deficiency, it is surprising that the marrow appearances in acute malaria are often of normal or decreased haemopoiesis. However, recent evidence with malaria in mice would indicate that the decrease in marrow activity even precedes any change in haematocrit [8]. In addition dyserythropoiesis, previously seen in longstanding malarial infections [9] has now been documented by Phillips et al. in these rather acute cases. This ineffective erythropoiesis can only further contribute to the anaemia. Dyserythropoiesis is found in a wide variety of conditions such as megaloblastic anaemias, haemoglobinopathies, severe iron deficiency, neoplastic disorders and now malaria must be added to this list. The challenge of dyserythropoiesis is twofold. Firstly the basis of the marrow abnormality and how the parasite brings it about needs to be established. Does the parasite for example, produce a specific product toxic to erythroid precursors? Secondly, the specificity of these changes for malaria compared with that of acute infection remains unknown. These are exciting avenues yet to be explored.

Iron metabolism is equally interesting in malaria. Both this study [1] and another [9] have shown a fall in serum iron and transferrin, but once again how specific they are for malaria and whether they contribute to the anaemia, or are merely a byproduct of the infection, are unanswered questions. A dramatic rise in serum ferritin was documented in the present study in uncomplicated cases. Whilst this may represent part of the acute phase response it might equally reflect haemolysis, hepatocyte damage or reticuloendothelial system blockade. Whatever the mechanism, the raised ferritin levels in the face of a reduced proportion of iron-containing erythroblasts in the marrow points to a mechanism which might be rate limiting for erythropoiesis. This ‘sequestration’ of iron could present a two-edged sword, for if it is implicated in an inadequate marrow response, it might possibly be equally harmful to developing parasites which are said, not without controversy [10], to require extracellular iron [11].

Despite the controversial aspects of the subject of anaemia in malaria, in one all are agreed; namely that the mechanisms are both multifactorial and complex. Only a selected few have been discussed here.

REFERENCES