

## Chapter 6

### PATHOLOGY OF MALARIA

H M Gilles

The pathological changes in malaria are related to the development of asexual parasites in the blood. In *P. falciparum* infections, the multifaceted nature of the interaction between the erythrocyte, the host immune system and the parasite is central to the pathogenesis of severe malaria and results in mechanical and rheological changes to the infected erythrocyte. These modifications lead to knob protrusions, cytoadherence and rosette formation. Parasitised erythrocytes bind to host molecules CD36, ICAM-1, thrombospondin, E-selectin, VCAM-1, chondroitin sulphate (Hommel 1993).

The release of malaria antigens, pigment and toxins gives rise to a cascade of pathological events. Among these the production of cytokines, particularly tumour necrosis factor (TNF), induced by the release of parasite products during schizont rupture, appears to play a central role; complemented by the effects of other circulating “endogenous pyrogens” such as interleukin-1 (IL-1) and IL-6. TNF or cachexin has been implicated as the cause of malarial fever. Although the nature of malarial toxin is still controversial, it is generally agreed that it is released at the time of schizont rupture. Excellent reviews on the pathogenesis of malaria have been published (Miller et al 1994; Pasvol et al 1995). The immunopathology of malaria is further considered in Chapter 6.

#### Pathology of the individual organs

In spite of the many forms of malignant tertian malaria that are known, death from *P. falciparum* in children living in areas of stable malaria is usually due either to cerebral malaria, malarial anaemia, metabolic acidosis, or a combination of these; whereas death in non-immunes are often associated with acute renal insufficiency, cerebral malaria, pulmonary oedema and disseminated intravascular coagulation. In any description of the pathological changes of malaria, two situations must be borne in mind namely (1) acute lesions responsible for death in the non-immunes (2) changes occurring in the organs of the partially immune child or adult who has died from other causes.

Parasitisation is greatest in descending order in the following organs: brain, heart, liver, lung, kidney and blood (Edington 1967; Edington & Gilles 1969; Francis & Warrell 1993).

#### Central nervous system

Although changes have been reported in the spinal cord and peripheral nerves, the most marked changes are seen in the brain itself. The major feature of cerebral malaria is the existence of cytoadherence of parasitized erythrocytes to the endothelium of cerebral capillaries and venules, resulting in the sequestration and tight packing of infected cells in these vessels.

The meninges are grossly congested, the smaller vessels being packed with parasitized cells. A perivascular lymphocytic infiltration has been described. The brain itself may show gross congestion only, but it is usually leaden in colour (Fig.1) - the smaller vessels of the grey matter being packed with red cells containing pigmented parasites in all stages of development. Gross congestion of the vessels is invariable, and in the majority of instances numerous petechial haemorrhages are evident in the white matter of the cerebrum, brain stem and cerebellum (Fig.2).

Haemorrhages are not usually seen in the grey matter although they can occur there; this lesser liability to haemorrhage is thought to be due to the greater number of capillaries and anastomatic channels in this area of the brain as compared with the white matter. Histologically the capillaries and arterioles are packed with parasitized cells, and ring haemorrhages are a striking feature. These consist of a central 'blocked' vessel (most frequently an arteriole), containing an agglutinated mass of parasitized erythrocytes surrounded by brain tissue, and then by a ring of extravasated red blood cells (Fig.3). Parasites are sometimes present at the periphery of these haemorrhages.

In older haemorrhages necrosis of the midzonal brain tissue occurs, and there is a peripheral reaction of small glial cells - the so-called malarial granuloma. Healing is said to cause subsequent scarring possibly with residual brain damage.

Death can occur in cerebral malaria with few parasites in the majority of the cerebral vessels. In these cases parasitized erythrocytes have been seen in the central vessels or in the erythrocytes in the ring haemorrhage, and a history of treatment prior to death has usually been obtained.

In deaths due to malarial anaemia there is pallor of the brain and its coverings, the vessels are empty and pigment has not been seen in the endolethial cells of the vessels.

### **Anaemia**

This is an inevitable consequence of erythrocyte parasitization but the mechanism is multifactorial and complex. The following points are established (1) parasitized and unparasitized cells are phagocytosed and destroyed; (2) anaemia is not necessarily related to the degree of parasitaemia; (3) transfused cells in a malarial patient may be destroyed more rapidly than in a normal recipient; (4) iron-sequestration and dyserythropoiesis occur; (5) erythropoiesis in the bone marrow is depressed. TNF stimulates erythrophagocytosis and bone marrow depression of erythropoiesis and is considered an important aggravating factor in the pathogenesis of anaemia.

In the acute stage there may be few changes in the morphology of the red cell other than those changes initiated by the parasite itself. In other instances, however, anaemia may be marked and the findings in the peripheral blood thus depend on the duration and stage of the infection. It must be remembered that malaria is a potent cause of severe anaemia in children from the age of 6 months to at least 2 years in areas of stable malaria and it can be sufficiently severe as to cause death.

The anaemia is haemolytic and in the acute attack there may be a sudden and dramatic fall in the haemoglobin values of the blood. It is usually normocytic and normochromic, or hypochromic but macrocytic if there is a marked reticulocytosis or if folic-acid deficiency eventuates - a not uncommon complication in tropical areas. The causes of folic acid deficiency in such patients are multiple: (1) inadequate dietary folate; (2) reduced absorption of folic acid; (3) increased utilisation due to haemolysis and fever of malaria. The peripheral blood film shows many parasites, polychromasia, anisocytosis, poikilocytosis, target cells, basophilic stippling and, in severe cases, Cabot's rings, Howel Jolly bodies, and nucleated red cells. A reticulocytosis may be present but this is more usual as a result of treatment.

Thrombocytopenia is common in both *falciparum* and *vivax* malaria; platelet survival is reduced; enhanced splenic uptake and sequestration occurs.

Mild leucopenia is usual in uncomplicated malarial infections but leucocytosis is an important abnormality in severe malaria and is associated with a bad prognosis.

Haemozoin (malarial pigment) is commonly present in the monocytes and may occur in the polymorphonuclear leukocytes as well. Haemosiderin, a dark yellow trivalent iron-containing pigment, is formed in the reticulo-endothelial system from the breakdown of haemoglobin contained in red cell debris liberated during schizogony, from senescent and parasitized cells, and from unparasitized cells haemolysed or phagocytosed during the acute attack. It is deposited mainly in the spleen, liver and marrow. This pigment can be differentiated from haemozoin in tissue in that it gives a positive Prussian blue reaction. The haemosiderin formed by the reticulo-endothelial system from the breakdown of haemoglobin is immediately available and is re-utilised in the synthesis of the large amounts of haemoglobin necessitated by the haemolytic process.

### **Bone marrow**

The bone marrow is greyish red, soft and hyperaemic and is increased in the long bones. In the acute stages its vessels are full of parasitized erythrocytes and haemozoin is present in the reticulo-endothelial cells and monocytes. There is a marked normoblastic hyperplasia even in the absence of a reticulocytosis in the peripheral blood and there is also myelocytic proliferation. Some authors, however, have demonstrated a temporary inhibition of the marrow during parasitaemia. Megaloblastic change may result if folic-acid deficiency occurs. Increased numbers of large abnormal-looking megakaryocytes are found in the marrow.

### **The spleen**

In the acute attack the spleen is enlarged, and tense, and the cut surface is slaty greyish red with the malpighian corpuscles prominent (Fig.4). The consistency may be soft if a terminal bronchopneumonia is present. Histologically the blood vessels, Billroth cords, and sinusoids are filled with parasitized red cells. Parasitized and unparasitized cells and haemozoin are seen in the pulp histiocytes and sinusoidal lining cells. Pigment may be found lying free in the pulp and sinusoids, and it can also be found in the germinal follicles. A splenic smear reveals developing forms of parasites and haemozoin lying free and contained in monocytes. Degeneration of the endothelial cells of splenic vessels may occur causing thrombosis, haemorrhage and infarction.

With increasing immunity the spleen becomes at first jet black with much pigment in the cords, but gradually the congestion decreases and the pigment disappears first from the sinusoids and last from the cords with parasitized cells becoming scanty. The spleen diminishes in size, the capsule becomes greyish, fibrotic, and wrinkled, perhaps with some evidence of old-standing perisplentitis, and some fibrosis is seen in the pulp.

Rupture of the spleen is a not uncommon complication of malaria and usually occurs through the hilar region. It should be emphasised that, if such an accident occurs and splenectomy is performed for this or any other reason in an immune individual living in an area of stable malaria, continuous suppressive antimalarial therapy must be considered to prevent the possible development of a severe malarial infection.

### **The liver**

The pathological changes in the liver vary according to the immunological status of the individual and the mode of death. In cerebral malaria the liver is enlarged and tense and its colour varies from dark red to slaty grey. If, however, anaemia has been gross the liver is enlarged and pale yellowish grey in colour.

Histologically the striking feature in the acute stage is the gross congestion of the sinusoids and centrilobular veins by parasitized erythrocytes. The Kupffer cells are hypertrophied and contain parasitized and unparasitized red blood cells, remnants of parasites and granules and masses of haemozoin, with haemosiderin inconstantly present. The parenchymal cells may contain haemosiderin but never haemozoin. One of the most striking and constantly reported features has been degeneration and necrosis in the centrilobular regions in the absence of heart failure (Fig.5). This feature was not noticeable in autopsies on children dying of cerebral malaria in West Africa (Edington 1967).

### **The kidneys**

In *falciparum* malaria an acute and transient self-limiting glomerulonephritis is common, whereas in *P. malariae* a chronic glomerulonephritis presents as nephrotic syndrome. In blackwater fever, large amounts of haemoglobin are cleared by the kidney following intravascular haemolysis. This may lead to oliguric or anuric renal failure. In severe malaria, there is gross congestion of the vessels (Fig.6) with parasitized erythrocytes, especially in the capillaries of the glomerular tuft. The histological changes are those of acute tubular necrosis due to reduced cortical perfusion.

Pigment has been described in vessels, free in the interstitial tissue, occasionally in the epithelial cells of the tubules, and within phagocytes in the capsular spaces. It has also been described in both the epithelial and endothelial cell of the glomeruli. Hyaline, epithelial, and granular casts may be present in the tubules. Scattered small haemorrhages may be seen in the cortex and medulla.

An association between the nephrotic syndrome in children and *P. malariae* infection has been established (Gilles & Hendrickse 1963).

*P. malariae* results in a nephropathy of immune complex origin with microscopical patterns ranging from minimal change to membranous, the latter referred to as "quartan malarial nephropathy" (Hendrickse et al 1972).

### **Adrenals**

Changes in the adrenals are variable. Degenerative and necrotic changes in the inner zone of the cortex with loss of lipid have been described. The more usual finding, however, is gross congestion and haemorrhage.

### **The lungs**

The smaller vessels are packed with parasitized erythrocytes and small haemorrhages may be present. Hyaline membrane formation, thickened alveolar septa and areas of alveolar haemorrhage have been described. The alveoli are congested with pigment-laden macrophages, plasma cells, neutrophils and parasitized erythrocytes.

In Spitz's autopsy series, pulmonary oedema was a universal finding; when not iatrogenically produced, it often resembles the picture seen in the adult respiratory distress syndrome (ARDS). The basic lesion appears to be injury to the capillaries of the lung with congestion and leakage of oedema fluid.

### **The cardiovascular system**

The usual picture is one of vessels congested with parasitised erythrocytes, pigment-laden macrophages, lymphocytes and plasma cells. There is little evidence of cytoadherence. Small subendocardial haemorrhages may occur.

Fatty degeneration of the myofibrils and brown atrophy have been described. In severe malarial anaemia in children the effects are those resulting from increase in blood volume and anoxia.

### **Gastro-intestinal tract**

Congestion with capillary stasis, necrosis, mucosal ulceration and haemorrhages can occur. Sequestration and cytoadherence have been seen, both in the small and large bowel, especially in the lamina propria capillaries. Malabsorption of amino-acids, sugars and fats have been described. Absorption of antimalarial drugs is generally adequate.

### **Placenta**

It is black or slaty grey and the sinusoids are packed with infected erythrocytes (Fig.7).

Developing trophozoites are numerous in the intervillous spaces and are found in the greatest numbers next to the trophoblast of the stratum spongiosum, and haemozoin may be seen within the fibrin masses, in some instances surrounding degenerate villi. It would appear that the 'stickier' parasitized cell tends to 'sludge' in the eddies of the slow-moving placental stream. Pigment is seen in the fibrin. This most probably favours fibrin deposition on the villi thus hastening the degenerative processes, interfering with the nutriment of the fetus and causing stillbirths and premature labour. There is an increase of cells - mainly histiocytes - in the maternal sinuses of the placenta. The maternal blood in the intervillous spaces is high in glucose content - favouring the development of the parasite. (WHO, 1996). The mechanism by which placental parasitisation affects foetal growth is not known.

### **References**

1. Edington G M (1967) Pathology of malaria in West Africa. Brit. Med. J. 1, 715-721
2. Edington G M, Gilles H M (1976) Pathology in the Tropics, 2nd Ed. Edward Arnold, London. Malaria p17-33
3. Francis N, Warrell D A (1993) Pathology and Pathophysiology of human malaria. In Bruce Schwatt's Essential Malariology 3rd Edition (Eds) Gilles H M and Warrell D A. Pp 50-59

4. Gilles H M, Hendrickse R G (1963) Nephrosis in Nigerian children. Role of plasmodium malariae and effect of antimalarial treatment. Brit, Med. J2, 27-31.
5. Hendrickse R G et al (1972) Quartan malarial nephrotic syndrome. Collaborative clinicopathological study in Nigerian children. Lancet 1, 1143-1148
6. Hommel M (1993) Amplification of cytoadherence in cerebral malaria: towards a more rational explanation of disease pathophysiology. Ann. Trop. Med. Parasit. 87, 627-635
7. Miller L H, Good M F, Milor G (1994) Malaria pathogenesis. Science. 264, 1878-1883
8. Pasvol G & Hogg A (1995) The pathogenesis of severe falciparum malaria. In "Bailliere's Clinical Infectious Diseases - Malaria". Ed. G Pasvol. Builliere Tindall, London. 249-270
9. WHO (1996) Severe and complicatd malaria, Trans. R. Soc. Trop. Med. Hyg. Supplement (in press)

### **LEGENDS TO FIGURES**

Fig. 1 Leaden appearance of brain in cerebral malria

Fig. 2 Cerebral malaria. Numerous petechialhaemorrhages are shown scattered throughout the white matter

Fig. 3 Ring haemorrhage in cerebral malaria

Fig. 4 Spleen - showing slaty greyish-red appearance

Fig. 5 Liver - centrilobular necrosis

Fig. 6 Kidney - Medullary congestion in severe malaria, resulting in acute tubular necrosis

Fig. 7 Placenta - Massive placental parasitisation in a primigravidae