ABSTRACT. Severe falciparum malaria is one of the most lethal parasitic infections in the world and is responsible for more than one million deaths in African children per year. Changes to management over the last 40 years have not improved survival. A reduction in the mortality and morbidity may only come about by a better understanding of the pathophysiological processes that are responsible for severe disease and that determine the outcome before antimalarials have had time to work. This review discusses potential adjunctive therapies for severe malaria that are under development following such detailed clinical and pathophysiological studies. 

KEY WORDS. Falciparum malaria, pathophysiology, children, adjunct therapy.

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1. INTRODUCTION

Malaria is one of the most common and important parasitic diseases worldwide. About 40% of the world’s population lives in malaria-endemic areas (Sturchler, 1990), and malaria is responsible for up to 500 million episodes of clinical infection and 2.7 million deaths every year (World Health Organisation, 1993). Plasmodium falciparum is the principal cause of severe disease, since the other species of malaria rarely cause death or persistent sequelae. P. falciparum may infect humans at any time from conception to adulthood. Malarial infection probably results in 3.5 million low birth-weight infants every year (Steketee et al., 1996), since an estimated 24 million pregnant women live in malaria-endemic areas. Children living in sub-Saharan Africa bear the brunt of the disease, as they are exposed to malaria frequently after birth, and either die from complications or experience clinical episodes of infection for many years until the slow and capricious development of antimalarial immunity (Edington, 1967). This balance between acquisition of immunity and development of severe disease has continued for thousands of years.

Since the first description of malarial parasites in a sufferer by Laveran in Constantine, Algeria in 1880, there have been considerable advances in the understanding of disease mechanisms in malaria (Laveran, 1880; White and Ho, 1992). These advances have resulted from detailed studies in patients, animal models of infection, biochemical, cellular, and molecular investigations. These studies have illuminated our understanding of disease processes, although none have succeeded so far in reducing mortality from severe infection. Mortality from treated severe malaria in children is between 5 and 15% (Waller et al., 1995; Marsh et al., 1995), and the current management of severe malaria has changed surprisingly little, in spite of rapid scientific advances in malariology.

Measures to eradicate malaria have been ineffective (World Health Organisation, 1993). After the initial successes in the 1960s, insecticides have failed to curb transmission by anopheline mosquitoes (World Health Organisation, 1993). Insecticide-impregnated bednets have reduced mortality and morbidity in malarial areas (Nevill et al., 1996; D’Alessandro et al., 1995c), but their efficacy may not be sustainable (D’Alessandro et al., 1995b; Greenwood, 1997). Results of recent trials with the current generation of malaria vaccines have been unimpressive (D’Alessandro et al., 1995a; Alonso et al., 1994), although newer prototypes are under continuous investigation (Stoute et al., 1997; Targett, 1995). Therefore, it probably will require a concerted combination of measures, including antimalarials, vaccines, and vector control, before a reduction in infection and mortality can be maintained. Furthermore, reducing the transmission of malaria in an endemic area runs the concomitant risk of reducing the development of antimalarial immunity in the population. This reduction in “herd immunity” eventually may result in the rapid spread of severe infection if control measures fail, so that longer-term study of preventive interventions will be crucial to assessment of their true and sustainable worth. The goal of effective prevention is not yet achievable, and consequently, we will still need to manage cases of severe malaria in the foreseeable future.

The early effective treatment of falciparum infection is critical in preventing the progression to severe, life-threatening disease. Falciparum malaria has become increasingly refractory to chloroquine, the cheapest and most widely available antimalarial (Krishna and White, 1996; Zucker et al., 1996). In Southeast Asia, multidrug resistance is rapidly spreading (Pukrittayakamee et al., 1994a; White, 1992), increasing the likelihood of severe disease. In Africa, widespread chloroquine resistance has increased the incidence of some complications such as anaemia (because of inability to cure infections) (Lackritz et al., 1992), and other related problems are anticipated to worsen as higher-grade resistance becomes entrenched.
Newer antimalarial treatment regimens testing, for example, the efficacy of artesether against quinine in children with severe malaria, have not confirmed any advantage for artesether in terms of survival (van Hensbroek et al., 1996a). Yet, in vitro, the artemisinin derivatives are some of the most rapidly parasiticidal drugs, with the broadest stage-specificity of action (Murphy et al., 1995b; ter Kuile et al., 1993), and indeed, in vivo, they clear circulating parasites much faster than other antimalarials (Hien and White, 1993). This observation, that the use of more rapidly parasiticidal drugs may not affect mortality, points to alternative directions for further research designed to reduce mortality in children with malaria. These alternative approaches are based on detailed studies of the pathophysiology of infection (White and Ho, 1992), and are aimed at reversing or ameliorating those disease processes that may contribute directly to a fatal outcome, in spite of the rapid administration of effective antimalarials to the patient. These adjunctive therapies are designed to support severely ill children until the underlying disease can be reversed by the antimalarial treatment. This review focuses on key pathophysiological observations made in children with severe malaria that may guide the eventual development of such adjunctive therapies.

2. DEVELOPMENT OF INFECTION
Clinical symptoms and signs of malaria occur when *P. falciparum*-infected erythrocytes multiply asexually (Marchiafava and Bignami, 1894). The hepatic stages and gametocytes are asymptomatic. The cause of *P. falciparum*’s virulence in comparison with other human parasites is unknown, but its multiplicative capacity and ability to sequester in the deep vascular beds are thought to contribute.

### 2.1. Multiplicative Capacity
The median number of falciparum sporozoites initiating infection is 8–15, but this may reach up to 100 sporozoites (White and Ho, 1992). In comparison with other malaria parasites, *P. falciparum* has a shorter pre-erythrocytic stage (5–7 days), prepatent period (interval between infection and the appearance of parasites in the erythrocytes), and incubation period (interval between infection and onset of symptoms). It also produces more merozoites from liver schizonts and after erythrocytic merogony.

Each infecting exo-erythrocytic merozoite can yield up to 36 daughter meronts once the erythrocytic stage of infection is initiated from the liver. Untrammelled multiplication rates in this stage of infection can exceed 10 per cycle, logarithmically expanding the parasite burden in an individual. Within a few days, a few thousand parasites liberated from the liver can progress to a total parasite burden of >10^12 parasites in adults (Fig. 1) (White et al., 1992a; White and Krishna, 1989). The threshold of microscopic detection is reached after 3–4 asexual cycles, and a lethal parasite burden may be reached in another 3–4 cycles. Young children will begin the asexual phase of parasite development at a higher parasitaemia, as they have a smaller blood volume in which to dilute the merozoites liberated by hepatic merogony (White and Krishna, 1989). Thus, in a
young child with a blood volume of 500 mL, a lethal parasitaemia could develop in 8 days from hepatic merogony (White et al., 1992a). *P. falciparum* can invade red cells of any age, and since more than one merozoite can infect a single erythrocyte, multiply infected erythrocytes are common in falciparum malaria.

### 2.2. Sequestration of Parasitised Red Blood Cells

During the first half (24 hr) of the parasite’s life cycle, the parasitised red blood cell (PRBC) is metabolically quiescent. There is a modest increase in parasite size and the expression of some parasite antigens on the surface of the infected erythrocyte. These PRBCs continue to circulate and are visible by microscopic examination of a patient’s blood. By contrast, the remaining 24 hr of development are characterised by intense synthetic and metabolic activity (Sherman, 1979). The PRBCs express molecules on the erythrocyte surface, which allows the cells to sequester in vascular beds. These include the expression of a recently identified family of parasite-encoded genes (the var genes), which are primarily responsible for increasing the adhesiveness of PRBCs to host ligands expressed on capillary and post-capillary venules (Su et al., 1995). The adhesion of cells infected with mature stages of parasites to capillary beds removes most of them from the circulation, thereby preventing their destruction by the spleen. It also allows asexual growth of the parasite and division to occur in a favourable hypoxic environment, and perhaps allows more efficient invasion of erythrocytes after schizogony (Marsh et al., 1988).

Observations on the age distribution of different stages of parasite development on admission blood films suggest that a preponderance of more mature forms (>20% trophozoites or schizonts, for example) is a prognostic indicator for fatal-ity (Silamut and White, 1993). These circulating mature forms easily can be quantitated on peripheral blood films and probably represent a fraction of the total sequestered parasite burden.

At this later developmental stage, there is a surge in the uptake of essential synthetic precursors, such as glucose (up to 25- to 50-fold increase compared with uninfected erythrocytes), amino acids, and nucleosides (Elford et al., 1995). The uptake of these metabolites and the disposal of lactate, the principal waste product resulting from the parasite’s anaerobic glycolysis, are mediated through poorly understood transport processes (Elford et al., 1995; Kanaani and Ginsburg, 1991). These biochemical changes are associated with a rapid increase in parasite size, the visible deposition of haemozoin in the PRBC, and subsequently syncytial nuclear division, which produces daughter merozoites (Leete and Rubin, 1996). The factors that signal cell rupture when multiplication is complete are also not understood, but subsequent invasion of red cells takes place within a few minutes, and the developmental cycle is re-initiated.

Sequestration of PRBCs is thought to give rise to the complications of falciparum malaria (White and Ho, 1992), which define severe disease. A consequence of sequestra-

### 3. PATHOLOGY

The finding of relatively mature parasites within the deep vascular bed at post mortem was made soon after the discovery of the parasite (Marchiafava and Bignami, 1894), and gave rise to the “mechanical” hypothesis for the pathogenesis of severe malaria. This hypothesis has dominated the thinking of severe malaria during this century. We will first discuss the pathological basis of this theory, describing the pathology of severe malaria, after which we will further discuss the mechanistic theory and other theories of the pathogenesis.

#### 3.1. Pathology of Infection

One of the difficulties of interpreting pathological findings has been heterogeneity in the clinical features of malaria (discussed in Section 6), particularly age-dependent and geographical disparities. The lack of clinical definition in most pathological studies has particularly hampered interpretation. This review focuses on pathological findings observed in CM as a clinically identifiable syndrome of severe disease. Clinico-pathological correlates in severe non-CM (NCM) still require further detailed studies, which should be guided by validated clinical definitions.

Most pathologists have defined cerebral involvement as the presence of sequestered parasites in the brain (Turner et al., 1994; Aikawa et al., 1980; Edington and Gilles, 1976; Thomas, 1971; Lemercier et al., 1966; Spitz, 1946). However, patients who die of noncerebral complications, e.g., renal failure, without clinical evidence of cerebral involvement, may also have cerebral sequestration (MacPherson et al., 1985). Resolving these apparent discrepancies requires careful quantitative comparisons of parasite density in cerebral and other tissues obtained from patients with meticulously documented clinical histories. These studies are now in progress and will be valuable in further establishing the validity of the mechanical model for malaria (Turner, 1997).

Alternatively, a method of quantitating the total parasite burden in an individual with malaria would also allow a direct test of the mechanical hypothesis, but this has not proved possible by simple methods (Davis et al., 1990a).
Most post-mortem studies [reviewed by Turner (1997)] have been conducted on adults, and in those series that include children, differences between adults and children have not been highlighted. The original autopsy studies in children were from Africa (Lemercier et al., 1966; Thomas, 1971; Edington and Gilles, 1976), and few have been performed elsewhere.

3.2. Macroscopic Appearances

In CM, brains packed with PRBC have a slate-grey discolouration, which is evident on the cut surfaces of the brain in both adults (Toro and Roman, 1978; Schmid, 1974; Khan and Durham, 1945; Dhayagude and Purandare, 1943; Thomson and Annecke, 1926; Aikawa et al., 1980) and children (Thomas, 1971; Lemercier et al., 1966; Edington and Gilles, 1976). The colour reflects the presence of malarial pigment (haemazoin). Meningeal vessels are often congested, with surrounding haemorrhage and some infiltration of leucocytes (Spitz, 1946; Khan and Durham, 1945; Dhayagude and Purandare, 1943; Boonpucknavig and Boonpucknavig, 1988; Thomson and Annecke, 1926). Haemorrhages, described as “punctiform” or “ring haemorrhages,” are a common pathological feature of CM and are distributed throughout the brain (including the brainstem). They are more common in children who have had convulsions associated with CM than in other children (Thomas, 1971).

A recent controversy has been the frequency with which cerebral oedema complicates CM, and how this swelling may contribute to mortality. The macroscopic features of oedema, such as increase in brain weight and compression of cerebrospinal fluid (CSF) spaces (e.g., gyri, ventricles, and pericisternal spaces), are observed in CM. The brains of African children (Walker et al., 1992; Edington and Gilles, 1976) and adults (Janota and Doshi, 1979; Rigdon and Fletcher, 1945) dying with CM frequently appeared swollen with flattened gyri. Thomas reported macroscopic oedema and an increase in brain weight by more than 10% in 10/13 (77%) Ugandan children with CM (all of whom were less than 5 years old), with white matter oedema more marked in the heavier brains (Thomas, 1971). However, in a Nigerian study, only one child had a heavy brain (Walker et al., 1992), although severe oedema was observed in 5/7 (71%) children with CM. Ventricular compression (without accompanying oedema) was seen in 79% of children with P. falciparum sequestered in their brains (Lucas et al., 1996), although these children may not have had CM since clinical details were lacking. Another study reported the incidence of cerebral oedema as similar in adult patients dying of CM and those dying without cerebral disease (Riganti et al., 1990), suggesting that it did not contribute to cerebral disease.

It has often proved difficult to distinguish oedematous changes seen at post-mortem from those occurring in life, or those arising in the agonal state. Cerebral swelling may also occur because of increased blood volume in cerebral tissues (Newton et al., 1991a) due to sequestration and microvascular obstruction. These changes can cause ventricular compression without associated tissue oedema. In view of the potential therapeutic implications, the presence of cerebral oedema and the delineation of its role in causing death from CM is an important area for future pathological studies in African children. Studies are in progress to address some of these issues (T. Taylor, web site: http://www.niaid.gov./ictdr/Blantyre.htm).

3.3. Microscopic Appearances

The earliest microscopic observations have dictated much of the current thinking about the pathogenesis of severe falciparum malaria. In 1949, Clark observed:

There is intense congestion of the vessels throughout the brain and spinal cord with special prominence in the cortical layer of both the cerebrum and cerebellum. These capillaries contain both parasitised and non-parasitised erythrocytes, depending on the terminal degree of parasitaemia and localisation. Frequently one area of the cortex will show scattered parasites while other areas will reveal almost complete parasitisation of the erythrocytes and no satisfactory explanation for this phenomenon is available (Clark and Tomlinson, 1949).

As discussed in Section 5, molecular explanations for this phenomenon have emerged recently.

3.3.1. Vascular congestion. Cerebral capillaries and venules distended with PRBCs are the microscopic hallmark of severe falciparum malaria (Fig. 2). In contrast to the peripheral blood, all mature stages of the parasite are seen within these vessels, both in adults (Spitz, 1946; MacPherson et al., 1985; Cropper, 1908; Aikawa et al., 1980), as well as in African children (Lemercier et al., 1966). The distended venules are more prominent in the gray matter, where they appear evenly distributed. Arteriolar dilatation has been noted (Dudgeon and Clarke, 1917), although arteriolar constriction was also described in one study (Polder et al., 1991).

3.3.2. Ring haemorrhages and granuloma formation. Ring haemorrhages contain a blocked central capillary, with an agglutinated mass of PRBCs surrounded by brain tissue that is necrotic and contains demyelinated fibres (Spitz, 1946; Boonpucknavig and Boonpucknavig, 1988) or a glial reaction. More recently, it has been suggested that the “haemorrhages” are a specific response to blockage of a vessel by PRBCs and reperfusion, resulting in the concentric pattern of haemorrhage surrounding a necrosed vessel (Turner, 1997), and are, therefore, different from petechial haemorrhages seen after a variety of hypoxic insults, e.g., typhus fever (Viete, 1978). Small malarial granulomata (Dürck’s nodules) are a distinctive pathological feature of malaria (Dhayagude and Purandare, 1943; Thomson and...
Annecke, 1926) associated with ring haemorrhages. They are not found in patients who die shortly after the onset of symptoms (Dhayagude and Purandare, 1943), and probably represent a more advanced stage of repair following haemorrhage in which necrotic tissue has been replaced by neuroglial cells and microglial tissue (Spitz, 1946; Edington and Gilles, 1976; Dhayagude and Purandare, 1943).

The presence of thrombotic lesions in CM is controversial. Some authors have described thrombi in the white and gray matter (Dudgeon and Clarke, 1917; Aikawa et al., 1980), often associated with ring haemorrhages or granuloma, although they do not contain PRBC (Spitz, 1946). In contrast, other pathologists have commented on the lack of evidence for organising thrombi in adult brains (Janota and Doshi, 1979) or in children (Edington and Gilles, 1976). These haemorrhagic deposits do not contain platelets (MacPherson et al., 1985) or fibrin (Dudgeon and Clarke, 1917). Since there is no evidence of fibrinolysis in most cases of severe malaria (Warrell, 1987), these lesions are unlikely to be true thrombi.

3.3.3. Cellular elements. Capillary endothelial cells are described as swollen (Sein et al., 1993; Pongponratn et al., 1991; Fitz-Hugh, 1944), necrotic, or desquamated (Aikawa et al., 1980). These changes appear only in samples taken more than 5 hr after death (Oo et al., 1987), suggesting that these features are post-mortem artefacts. The ultrastructure of capillaries appears well preserved, with only a few vessels showing patchy degenerative changes (MacPherson et al., 1985). Most pathologists have commented on the lack of inflammatory cells both in adults (MacPherson et al., 1985; Fitz-Hugh, 1944; Dudgeon and Clarke, 1917) and African children (Thomas, 1971). However, an accumulation of macrophages (with active phagocytosis of PRBCs and pigment), neutrophils, and plasma cells has been seen in areas of extravasated PRBCs (Boonpucknavig and Boonpucknavig, 1988), and has been interpreted as evidence of inflammation. Some immunofluorescence studies have shown the deposition of falciparum antigens and anti-falciparum antibody on the cerebral vessels (Aikawa, 1988), often associated with haemorrhages in the white matter (Oo et al., 1987; Nagatake et al., 1992; Boonpucknavig and Boonpucknavig, 1988), although other studies have not found evidence of such deposition (Turner et al., 1994; MacPherson et al., 1985). An increase in leukocytes in the cerebrum was reported in a single case of CM, but the patient also had acquired immunodeficiency syndrome (Porta et al., 1993), which complicates interpretation of these findings.

3.3.4. Pigment. Malarial pigment or crystalline haemoglobin is present in all erythrocytes that contain mature stages of parasites. Pigment accumulates in monocytes and macrophages in those tissues where there is significant parasitaemia, including in the peripheral circulation where its presence is a prognostic indicator (Metzger et al., 1995; Phu et al., 1995). In a rodent model of infection, the longer the preceding malarial infection, the more pigment is seen in the reticuloendothelial system (Sullivan and Meshnick, 1996). The presence of pigment in the brain of patients with CM when PRBCs are no longer present implies that coma was prolonged, and death ensued even after tissue parasitaemia had begun to clear.

Pigment is composed of sheets of β-haematin, which derive from haem polymerisation after haemoglobin breakdown by parasites. Most of the metabolised haemoglobin in the cell contributes to pigment formation (Morrison and Jeskey, 1948). Chloroquine, and perhaps other antimalarials, were thought to interfere with the process of haem polymerisation by inhibiting a purported enzyme (Slater and Cerami, 1992). More recently it has been shown that polymerisation can proceed without protein present (Dorn et al., 1995), although parasite histidine-rich protein II accelerates the process of haemoglobin formation (Sullivan et al., 1996). Pigment was believed to be relatively inert and nontoxic, but it can clearly modulate important biological activities. The quantitation of pigment in human tissues eventually may prove to be as interesting as the quantitation of parasites.

3.4. Relationship between Sequestration and Cerebral Disease

The degree and distribution of sequestered parasites varies according to the species of malaria parasite and host. For
example, in the night monkey (Aotus trivirgatus), P. falciparum sequestration affects in descending order myocardium, adipose tissue, and skeletal muscle, with no parasites visible in the brain (Miller, 1969). This difference in sequestration in animal models and humans is one of the key factors that complicates the extrapolation of findings in animal models to understanding of human disease.

The first semiquantitative assessment provided light and electron-microscopic comparisons of samples obtained from Thai adults dying with strictly defined CM (n = 7) and those with multi-organ involvement without predominant cerebral symptoms (n = 6) (MacPherson et al., 1985). An advantage of this study was early collection of specimens (~90 min after death), although only needle biopsies were obtainable, which may have caused a sampling bias in the results. Nevertheless, statistically significant differences were observed between clinical groups. Patients with CM had more PRBCs and more vessels affected than NCM patients. The degree of sequestration was greatest in the brain, followed by the heart and then the liver, lung, and kidney, all of which contained larger numbers of PRBCs than the blood. There was little evidence for haemorrhagic or inflammatory exudation in tissues, immune complex deposition, or widespread thrombosis. Knobs on PRBCs appeared to be the site of attachment to endothelial cells, some of which were swollen.

A subsequent study also carried out in Thailand of 39 adults confirmed that the percentage of PRBCs in organs was higher in CM patients than in NCM patients (Pongponratn et al., 1991). Again in the CM group, the sequestration of PRBCs in the brain was significantly higher than in other organs, and there was a strong correlation between peripheral parasitaemia and PRBC sequestration in brain (r = 0.7031). This organ difference was not seen in the NCM group, although some degree of PRBC sequestration was visible in 50% of the NCM cases. Interestingly in this study, lung tissue contained mononuclear cells rather than parasites.

In another study (Turner et al., 1994), based upon experimental observations on in vitro models of cytoadherence, a detailed quantitative analysis of expression of endothelial cell markers in tissues from adult patients (n = 9) with fatal CM were compared with control patients (n = 9). There was increased expression of intercellular adhesion molecule-1 (ICAM-1) and endothelial selectin (E-selectin) on cerebral vessels from malaria patients compared with controls. CD36 and thrombospondin staining was sparse in all cerebral tissue. Parasites co-localised to areas expressing ICAM-1, CD36, and E-selectin, supporting the notion that these molecules may be important vascular ligands in vivo. There was additional evidence of endothelial cell activation in malaria with increased expression of other markers such as human leucocyte antigen Class II antigens, but these changes were not accompanied by increased local accumulation of inflammatory cells. The most marked sequestration of parasites was in the brain, confirming findings from previous studies. There were also large accumulations of parasites and pigment in the spleen and liver. The observed increase in expression of receptors in severe malaria may be related to induction by high levels of so-called pro-inflammatory cytokines (see Section 4.3), which are found in severe, particularly cerebral disease. These findings begin to provide a mechanistic explanation for the development of severe malaria, as well as linking the mechanical hypothesis with the cytokine hypothesis. A more recent larger post-mortem study of 50 Vietnamese adults dying of severe and cerebral disease (Turner, 1997), found heterogeneity of distribution of parasites within cerebral tissue. Patients dying later in the course of infection did not show sequestration, although pigment was detectable. Some observers have reported that vessels congested with parasites are more prominent in gray rather than white matter, and also that the cerebellum is affected more than other parts of the CNS (Sein et al., 1993).

4. PATHOGENESIS—HOST FACTORS

4.1. Mechanical Hypothesis

The mechanical hypothesis assumes that organs will be affected in proportion to the overall number of PRBCs sequestered in tissues, as well as their relative proportions within different tissue capillary beds. Thus, CM arises because of sequestration of PRBCs in cerebral capillaries and postcapillary venules, whereas patients who may have similar numbers of sequestered parasites in other tissues, but not the brain, would not be expected to develop a full-blown cerebral syndrome. Patients, of course, may have other signs of severe disease, as many other organs, particularly the liver and spleen are frequently congested with PRBCs.

The mechanical hypothesis has been questioned by a number of investigators. The two main objections have been the lack of sequestration in some patients with cerebral symptoms associated with falciparum malaria, and the fact that most patients with CM recover without evidence of ischaemic damage.

The lack of massive intracerebral sequestration of parasites in some patients with CM can be rationalised in a number of ways (Sections 4.3–4.8) (Berendt et al., 1994). Since CM is a diagnosis of exclusion (Section 6.2), other diagnoses (e.g., encephalitis) (White et al., 1992b) may not have been excluded, and the coexistence of factors such as hypoglycaemia may also cause impairment of consciousness. Furthermore, the mechanical hypothesis may be unable to explain why all patients with malaria die. In some treated cases of malaria and coma, patients have died without any parasites visualised on histological examination, although changes in host tissues may be similar to those seen in patients dying with parasite-engorged capillaries (Dudgeon and Clarke, 1917). An obvious explanation for these findings is that parasites have responded successfully to treatment, but that pathophysiological processes have progressed to an irreversible stage, and resulted in a fatal outcome. There are, however, additional hypotheses that attempt to explain severe malaria and more particularly CM, and these are discussed below.
4.2. Toxin Hypothesis

Gaskell and Miller (1920) were the first to propose that patients with malaria died from an overwhelming toxaemia. The kallikrein-kinin system was shown to be important in murine and simian models of Plasmodium infection (Mae-grath and Fletcher, 1972), but similar evidence in humans is lacking (Warrell, 1987). Clark suggested alternative toxins were responsible for the clinical features of severe malaria, initially suggesting endotoxins (Clark, 1978), then reactive oxygen species (ROS) (Clark et al., 1986), cytokines (Clark et al., 1987), and nitric oxide (NO) (Clark et al., 1992). Although endotoxins are detectable in patients with falciparum malaria, they are associated with parasitaemia and leucocytosis, but not specifically with severe disease, including CM (Usawattanakul et al., 1985; Aung-Kyaw-Zaw et al., 1988). ROS are discussed in Section 4.6. More recent studies are attempting to isolate and characterise malarial material, possibly a glycosylphosphatidylinositol moiety associated with malarial antigens, which can cause release of cytokines from host cells (Schofield and Hackett, 1993) and up-regulate adhesion ligands (Schofield et al., 1996) and NO (Tachado et al., 1996) (Section 4.5).

4.3. Cytokine Hypothesis

Clark and co-workers suggested that cytokines caused CM (Clark et al., 1991; reviewed in Clark and Rockett, 1994). They suggested that the host overproduction of “pro-inflammatory” cytokines, such as tumour necrosis factor (TNF) and interleukin (IL)-1, is capable of inducing cerebral syndromes in patients with malaria. Localisation of parasites to certain tissues by sequestration would result in higher local synthesis and release of these potent mediators, and cause more marked local derangements in function and metabolism of tissues than elevations in circulating cytokines. Clearly, in those patients in whom there is no significant sequestration, but cerebral symptoms are still present, other mechanisms would have to be invoked to explain coma. These have not been defined further in the cytokine hypothesis.

P. falciparum-infected erythrocytes produce pyrogenic material that triggers the release of TNF (and other cytokines) from host mononuclear cells (Kwiatkowski et al., 1989). Merogony (soon after which parasite material is liberated in largest quantities into the circulation in vivo) provokes the largest pulses of TNF release in vitro (Kwiatkowski, 1989). Elevations of TNF result in pyrexia in both falciparum (Kwiatkowski et al., 1989) and vivax malaria (Karunaweera et al., 1992). A monoclonal antibody against TNF attenuates fever in children with CM, confirming the importance of TNF in causing fever (Kwiatkowski et al., 1993). In the relatively benign vivax malaria (without cerebral symptoms), very high (up to 3000 pg/mL) TNF levels have been measured transiently in serum (Karunaweera et al., 1992), suggesting that such high systemic levels do not themselves cause serious disease. Furthermore, elevations in TNF can exert antiparasitic effects by inhibiting parasite multiplication and synergising with other factors to produce gametocidal effects (de Naotunne et al., 1993).

Parasite-derived material is responsible for TNF release from host cells (Bate and Kwiatkowski, 1994), and in one study, parasites varied in their ability to induce TNF release (Allan et al., 1993). This variation correlated with the source of the parasites; those obtained from patients with cerebral disease induced more TNF release ex vivo than those from patients with uncomplicated disease (Allan et al., 1995). There was considerable overlap in TNF releasing activity between disease groups, and ~60% of parasites isolated from patients grew sufficiently to allow assay (Allan et al., 1995). It is possible that TNF may also be an effector arm of some parasite virulence factors if it has a central role in the pathophysiology of severe malaria.

The consensus that has emerged from a vast literature on experimental studies on the role of cytokines in malaria is that the timing and amounts of different cytokines that are released, particularly TNF, may be important determinants of subsequent pathophysiological events and perhaps mortality. Thus, increased production of TNF early in malarial infection may be protective, whereas prolonged, high TNF levels may be detrimental. This temporal relationship has been difficult to identify in humans. Furthermore, one of the difficulties in interpreting immunologically measured elevations in cytokines, particularly when receptor binding can influence the unbound concentrations, is that the biologically active moieties (either circulating or local) may not be represented in these measurements. Thus, bioassays of circulating cytokines may be more relevant, but are more laborious to perform.

In African children, circulating cytokines (particularly TNF) are much higher in severe malaria than controls (Krishna et al., 1994b; Nyakundi et al., 1994; Shaffer et al., 1991; Kwiatkowski et al., 1990; Kern et al., 1989; Grau et al., 1989; Scuderi et al., 1986). In some studies, TNF levels are correlated with parasitaemia (Nyakundi et al., 1994; Shaffer et al., 1991), but most studies detected higher levels in children with CM rather than NCM. Based on this cytokine theory, studies have focused on TNF in CM to substantiate if elevations in TNF are deleterious. These elevations in TNF may exacerbate the tendency to sequestration by the up-regulation of host ligand molecules responsible for cytoadherence of parasites, especially ICAM-1, vascular cell adhesion molecule-1 (VCAM-1), and E-selectin (see Section 5.1), increasing mechanical obstruction of cerebral or other blood vessels. As localised TNF production may not be detected by plasma assays, but nevertheless may have important pathophysiological consequences, TNF measurements have been carried out on CSF specimens from patients with CM, but the results from large series are lacking. Increased TNF may also have consequences on the metabolic status of patients (see Section 7.7) or in the pathophysiology of anaemia (Section 7.8).

Host factors are also important in determining the TNF released in response to infection. A TNF-α promoter polymorphism has been shown to be associated with disease se-
verity in Gambian children (McGuire et al., 1994), with a homozygous polymorphism at −308 bp relative to the start of TNF transcription associated with a 7.7-fold increase in the relative risk of death or neurological sequelae in CM. Other TNF promoter polymorphisms are now the subject of detailed assessments in case control studies in malaria, as well as other diseases. For example, in meningococcal disease, relatively low TNF production assessed ex vivo in first-degree relatives of patients was associated with a 10-fold increased risk of fatal outcome (Westendorp et al., 1997). Interestingly, this variation in TNF production was unrelated to polymorphisms at −308 bp and −238 bp in the promoter. A further risk factor in meningococcal disease was increased production of IL-10, which synergised with the effects of low TNF production, and this was associated with a 20-fold increase in the risk of fatality. There is increased IL-10 production in severe malaria associated with elevations in TNF levels (Anstey et al., 1996), which may contribute to severe disease.

An important test of the central role of TNF, therefore, was undertaken using anti-TNF monoclonal antibodies as adjunctive therapy to either quinine or artemether (in a factorial design) in children with CM, and assessing mortality and neurological sequelae as endpoints (van Hensbroek et al., 1996b). In this largest double-blind placebo controlled study of severe malaria in African children, 302 children were assigned to receive a mouse monoclonal anti-TNF antibody (B-C7) and 308 received placebo. Mortality was similar in the two groups (19.9% vs. 20.8%), adjusted odds ratio 0.9 (95% CI 0.57–1.42). However, residual neurological sequelae (assessed at 6 months) were detected in 15 (6.8%) survivors in the study group, compared with 5 (2.2%) of those receiving placebo, adjusted odds ratio 3.35 (95% CI 1.08–10.4). The biological effectiveness of the anti-TNF antibody was confirmed in this study group by the more rapid decline in rectal temperature in the treatment compared with the placebo group. Four hours after treatment, mean fall in temperature was 0.6°C in the BC-7 group compared with 0.2°C in placebo (P = 0.02). Thus, in this rigorous test designed to establish a causal role in mortality due to increased TNF production, neutralisation of circulating TNF did not reduce mortality, but did produce an appropriate antipyretic effect.

The simplest explanation for these findings is that increased circulating TNF associated with CM is an epiphenomenon in the complex array of pathophysiological processes and does not itself increase mortality. Indeed, interfering with elevated TNF levels may be harmful. Alternative explanations have been suggested, including the possibility that antibody prolonged the action of TNF on endothelium by retaining it within the circulation. It may also be that the antibody was administered too late in the disease process, when secondary cascades of mediators had already begun exerting their biological effects. In any case, the increased incidence of neurological sequelae after anti-TNF antibody administration suggests that future studies designed to investigate this aspect of pathophysiology must first overcome the simplest interpretation of these findings that increased TNF production is an appropriate response to malaria infection, and abrogation of this response, therefore, may be harmful. This interpretation is consistent also with the genetic studies reported on meningococcal disease (see above).

### 4.4. Other Cytokines and Markers of Endothelial Cell Activation

TNF is recognised as being one of the most important of the pro-inflammatory cytokines, and elevations in TNF concentrations trigger many secondary cytokine cascades in severe malaria. There are associated increases in IL-1 and interferon-γ concentrations, as well as increases in circulating TNF receptors in acute infection. Circulating IL-6 (Molyneux et al., 1991) and IL-8 levels (Friedland et al., 1993) are increased in falciparum infection. Interestingly, in relatively uncomplicated infections, IL-8 levels remained elevated for up to 4 weeks after the acute infection had been cured (Friedland et al., 1993).

Both falciparum and vivax infections are associated with increases in circulating markers of endothelial cell activation (serum ICAM-1, serum VCAM-1, and serum ELAM-1), and these markers were significantly higher in Gambian children with severe falciparum malaria compared with uncomplicated infections (Jakobsen et al., 1994). These markers were also elevated in nonimmune subjects, suggesting that elevations are a consequence of cytokine activation by TNF. However, in a recent study in Gambian children, malaria was associated with elevations in circulating ICAM-1 levels (which correlated with TNF and IL-1α levels), but elevations were not related to disease severity (McGuire et al., 1996). Thrombomodulin, another marker of endothelial cell damage, was also significantly higher in nonimmune adults with severe malaria compared with those with uncomplicated infections (Hemmer et al., 1994), and elevations were positively correlated with peripheral parasitaemia and TNF-α levels.

### 4.5. Nitric Oxide

Since the cytokine hypothesis was first elaborated, NO has been identified as a potential mediator for TNF action. NO is a short-lived, highly reactive molecule that has a wide spectrum of biological activities. NO is involved in defence by killing intracellular microorganisms (Vouldoukis et al., 1995; Wei et al., 1995), in maintaining circulatory status by its action on endothelial cells, and in neurotransmission (Vallance and Collier, 1994). It is produced both constitutively in certain tissues and in response to inflammatory stimuli through the action of cytokines that up-regulate the synthesis of inducible NO synthase (iNOS or NOS2).

Clark et al. (1992) proposed that TNF increased NO production, which caused the coma of CM. This NO is thought to be produced in cerebral endothelial cells and to diffuse into brain tissue, interfering with neurotransmission (Clark et al., 1992). It may also cause neurological damage...
and sequelae by forming peroxynitrite (Lipton et al., 1993), although this was not part of the original hypothesis. An alternative suggestion for the role of NO in malaria is that it may be important in host defence, particularly in intracellular killing of parasites. This dual pathogenic or protective role for NO is reminiscent of similar roles suggested for cytokines, and neither is mutually exclusive. However, testing these hypotheses is challenging because of the evanescent nature of NO and the inapplicability of results from many animal studies to human infection. Instead, indirect measures of increased NO synthesis have been used as markers for the activity of iNOS. NO is metabolised to nitrate and nitrite, and since these products are stable in plasma and urine, they may be used as endpoints that reflect increased iNOS activity. The effects of diet and renal impairment on nitrate levels have to be taken into account when these indirect measures are employed (Al Yaman et al., 1997; Prada and Kremsner, 1997; Anstey et al., 1996). The evidence for an important role of reactive nitrogen intermediates in severe and CM varies with the populations that have been examined.

In the largest study to date (Anstey et al., 1996), decreased NO synthesis was noted in Tanzanian children with CM compared with patients with uncomplicated or subclinical infections. Changes in plasma TNF profiles were consistent with previous reports that progressively higher levels were associated with increasing disease severity with highest levels in fatal cases. Levels of the anti-inflammatory cytokine IL-10 were also increased in more severe disease, suggesting a mechanism by which NO synthesis could be suppressed in the patients with CM. In this study, increased NO synthesis was interpreted as being protective of the development of cerebral and fatal disease, and, therefore, important in defence rather than as a contributor to cerebral pathology. Some support for this suggestion comes from work with desferrioxamine in children with CM, where NO synthesis was increased in desferrioxamine recipients compared with placebo recipients (Thuma et al., 1996).

In contrast, a study from Papua New Guinea noted elevations in reactive nitrogen intermediates in children with CM compared with conscious patients and higher levels in fatal cases compared with survivors (Al Yaman et al., 1996). Other smaller studies have also noted an association between elevated levels of circulating nitrogen oxides and severe malaria. However, African studies have failed to detect such an association (Agbenyega et al., 1997; Cot et al., 1994). In Ghanaian children, hyperlactataemia, a metabolic marker of disease severity, was not correlated with plasma nitrogen oxide levels, although it was clearly a prognostic marker for a fatal outcome and was correlated with depth of coma (Agbenyega et al., 1997). These findings are illustrated in Fig. 3. In order to assess the intracerebral synthesis of nitrogen oxides, which may arise through local diffusion of NO if it is produced by cerebral endothelial cells, CSF measurements were performed in a subset of patients with CM. Again, no elevations in nitrogen oxides were observed, suggesting that coma in malaria may not be due to derangements in NO metabolism.

Clearly, further studies are warranted to establish the importance of changes in NO metabolism in malaria. However, the balance of evidence suggests that changes associated with severe disease will be harder to establish than they have been with cytokines, and the role of NO in pathophysiology and defence is more subtle than results from plasma and CSF measurements can disentangle.

### 4.6. Reactive Oxygen Species

Clark et al. (1983) proposed that ROS may play a role in the pathogenesis of severe malaria. They based this hypothesis on experimental studies in which they showed that the ROS were produced during malaria infections of mice (Stocker et al., 1984). They also showed that antioxidants prevent cerebral involvement (Thumwood et al., 1989), including the breakdown of the blood-brain barrier (BBB) (Thumwood et al., 1988), and attenuated the fall in hae-
moglobin in mice (Clark and Hunt, 1983). Clark et al. (1986) suggested that extravasated erythrocytes may lead to ROS generation, causing coma and damage to local tissues, including the brain.

In humans, there is some evidence that ROS play a role in the pathogenesis. Monocyte generation of ROS was increased in adults with falciparum malaria, especially those with severe disease (Descamps Latscha et al., 1987; Dubey et al., 1991). In Indian children with CM, products of lipid peroxidation were found in the CSF (Das et al., 1991), but the lack of assessment of the BBB made this interpretation difficult. In African children, desferrioxamine, an ROS scavenger, appears to reduce the duration of deep coma (Gordeuk et al., 1992), although it has not been shown to improve the outcome or decrease the incidence of neurological sequelae. Desferrioxamine may act by other mechanisms (Section 9.7). Thus, ROS appear to be generated in acute malarial infections, but their role in the pathogenesis of complications is unclear.

4.7. The Permeability Hypothesis

In the 1960s, Maegraith and colleagues proposed that CM was caused by the stasis of blood secondary to an inflammatory state (Maegraith and Fletcher, 1972). They suggested that kinins increase the permeability of the BBB, causing an efflux of plasma out of the vessels, thereby concentrating the red blood cells within the cerebral vasculature and ultimately producing stasis of the blood. They based their hypothesis on the cerebral oedema found at post mortem in humans and studies of animals infected with malaria.

4.7.1. Experimental evidence. In the Rhesus monkey (Macaca mulatta), Maegraith and colleagues showed an efflux of albumin from the blood into the CSF (Migasena and Maegraith, 1968b), and since albumin is the protein responsible for 75% of the oncotic pressure, they suggested that the efflux of protein would draw water into the brain interstitium, causing cerebral oedema. However, they did not find a significant increase in CSF albumin, but showed that the protein was transported back into the blood at an almost equally fast rate (Migasena and Maegraith, 1968a). The increase in albumin transport did not appear to be associated with a raised intracranial pressure (ICP), although the pressure was not measured. Furthermore, they showed that chloroquine and hydrocortisone reduced the flow of protein in both directions in the monkeys (Migasena and Maegraith, 1968b; Maegraith and Fletcher, 1972), suggesting that the breakdown of the BBB was caused by inflammation. These experiments led to the widespread use of steroids in human CM (Rees, 1982; Woodruff and Dickinson, 1968), an intervention subsequently shown to be inappropriate (Warrell et al., 1982b).

There are important differences between monkeys dying of knowlesi malaria and humans with CM. *P. knowlesi* sequesters preferentially within the liver and the small intesti-
4.8. The Immunological Hypothesis

In the 1950s, immunological mechanisms were invoked to explain the low incidence of CM in malnourished African children since it was thought that they were immunodeficient (Edington, 1967). The effectiveness of chloroquine in treating CM was also partly attributed to its anti-inflammatory nature (Maegraith, 1969). Furthermore, immunological mechanisms have been invoked to explain the relatively late peak incidence of CM in children living in endemic areas, despite the fact that these children have been exposed to malaria prior to the development of this complication.

4.8.1. Experimental evidence. Experimental work in the 1960s demonstrated that golden hamsters that had a neonatal thymectomy (Wright, 1968) or those that were given antithymocyte serum were resistant to P. berghei infections (Wright et al., 1971). During the last decade, Grau and colleagues (1989) have developed a murine model of CNS involvement using P. berghei ANKA in genetically susceptible mice. Initially, they showed that CD4+ T-cells were essential for the development of neurovascular lesions (Grau et al., 1986) and then went on to demonstrate that T-cell-dependent macrophage activation led to the release of cytokines, including TNF, which meditated the development of these lesions (Grau et al., 1987a). Also, they showed that cyclosporin prevented the development of neurological complications in mice (Grau et al., 1987b). There are fundamental differences between rodent models of CNS involvement and humans with CM. In rodents, monocytes are the principal cells that adhere to the endothelium, with little sequestration of PRBC. Igs are consistently deposited on the cerebral endothelium in mice, but not in humans. Coma is not a prominent feature of murine malaria; rather, the neurological manifestations are limb paralysis, deviation of the head, ataxia, and convulsions (Grau et al., 1989).

4.8.2. Clinical studies. Although immunological mechanisms are favoured mainly by experimentalists, they have also been proposed by some investigators studying human CM. Malaria infections induce cellular and humoral immune responses in humans, and proliferative glomerulonephritis, a manifestation of immunological disease, has been reported in falciparum malaria (Boonpucknavig and Boonpucknavig, 1988). Based upon pathologic specimens of adults dying in South America, Toro and Roman (1978) suggested that CM is a form of disseminated vasculomyelinopathy resulting from a CNS hyperergic reaction to a massive antigenic challenge during a falciparum infection. The perivascular inflammatory response, however, is not a feature of CM, and the other features of a disseminated vasculomyelinopathy that are commonly seen in CM are not specific and could also arise from terminal hypoxia (Warrell, 1987). The more specific features of disseminated vasculomyelinopathy were not found in all patients. An increase in circulating immune complexes and the depletion of complement occurs in severe falciparum malaria, and in some studies, is more common in CM than NCM (Warrell, 1987). As mentioned in Section 3.3.3, immune complex disposition on the cerebral vessels is not a consistent feature of CM (Boonpucknavig and Boonpucknavig, 1988; MacPherson et al., 1985). Anti-inflammatory agents, such as steroids (Hoffman et al., 1988; Warrell et al., 1982a), Ig (Taylor et al., 1992), or the immunosuppressive agent cyclosporin A (Warrell et al., 1990), have not been shown to be beneficial in humans with CM.

5. PATHOGENESIS—PARASITE FACTORS

The macroscopic consequences of falciparum infection have been recognised for over a century, but the cellular and molecular mechanisms that give rise to the fundamental pathophysiological process of sequestration have only begun to unravel in the past few years. Infection with P. falciparum changes the host red cell in many and profound ways. One of these is by altering the surface property of infected cells to make it “sticky.” This increased adhesiveness manifests itself in ways that can be studied in laboratory models designed to represent the in vivo microenvironment of the PRBC. However, there is considerable functional redundancy in the parasite and host-encoded factors that mediate the attachment of PRBCs to other cells, making study of such mechanisms not straightforward. Parasites can be selected to exhibit increased (or decreased) rosetting and cytoadherence phenotypes relatively easily in vitro, suggesting that similar phenotypic plasticity may be important during the few cycles of multiplication necessary to produce a severe infection in an individual. Furthermore, demonstrating a potential pathogenic mechanism in vitro is only the first step in assessing its eventual in vivo importance. The principal mechanisms that are responsible for parasite virulence, the capacity to harm the host, are discussed in the following sections.

5.1. Cytoadherence

Understanding of the mechanisms of cytoadherence of PRBCs to endothelial cells has grown from observations made at post-mortem in malaria patients to the development of in vitro models that have helped to identify host ligands, and eventually to the characterisation of responsible parasite genes that are expressed at the erythrocyte surface. These more recent studies have reconciled the phenomenon of antigenic variation with the heterogeneity of parasite-encoded adhesion molecules expressed in asexual stages of development, and now allow for more detailed studies on their roles in pathogenesis of disease.

Cytoadherence describes the property of PRBCs to stick to nonerythrocytic cells or cell lines, and is the key pathophysiological process that distinguishes falciparum from other human malarias. Cytoadherence depends on a high molecular mass family of proteins encoded by var genes in P. falciparum. These var-encoded proteins [the P. falciparum
erythrocyte membrane protein-1 (Pfemp-1 family) are expressed on the surface of the infected erythrocyte and vary in molecular mass (between 200,000 and 350,000 M) (Smith, J. D. et al., 1995; Baruch et al., 1995) in parallel with parasite strain-specific antigenic variation. They are also responsible for agglutination of infected cells when exposed to strain-specific antibodies. These immunological properties helped to confirm the relationship between the var gene family identified during the hunt for the chloroquine-resistance gene and the properties of culture-adapted parasite clones varying in their cytoadherence and rosetting phenotypes, as well as in their variant surface antigens (Smith, J. D. et al., 1995).

Interestingly, sequence analysis of var genes shows a 2-exon structure (with an approximately 1-kb intron), which, when translated, contains degenerately homologous domains, with similarity to previously identified proteins implicated in the invasion of erythrocytes (Adams et al., 1992). These regions of the var genes contain cysteine-rich motifs similar to the Duffy-binding protein of P. vivax responsible for red cell invasion and, therefore, have been called "Duffy binding like" regions (Su et al., 1995). Thus, entry into red cells, antigenic variation, and evasion of host clearance by cytoadherence are probably all properties mediated by similar primary sequences. Antigenic variation in a cloned parasite line is detectable at a rate of ~2.4% per asexual generation (Roberts et al., 1992). It has been estimated that there are up to ~150 copies of the var gene family in the haploid genome of falciparum, accounting for between 2 and 6% of the whole parasite genome underlying the potential functional redundancy and significance of these gene products for the parasite.

Pfemp-1 is localised primarily to parasite-induced "knobs" on the surface of red cells. These knobs are small (60–100 nm in diameter) electron-dense structures consisting of submembranous accretions of parasite proteins, such as histidine-rich protein-1 and the mature parasite-infected erythrocyte surface antigen protein (Howard et al., 1990). Knobs form the supramolecular structures that allow apposition to host ligands on endothelial cells, and fine "processes" are visible on electron microscopy that span these putative attachment sites. However, not all natural infections are associated with knobs, and parasite clones isolated in vitro can still bind without knobs, suggesting that knobs contribute to, but are not essential for, the process of cytoadherence (Petersen et al., 1989). PRBCs can bind to a variety of host cells, such as monocytes, neutrophils, and platelets, confirming the phenotypic heterogeneity of cytoadherence. A number of studies have attempted to identify the host ligands both in in vitro models of cytoadherence and in vivo by immunocytochemical techniques.

Initially studies used endothelial cells and subsequently, the amelanotic C32 melanoma cell line as an in vitro model for cytoadherence (Sharma, 1991). Studies using monoclonal antibodies to a variety of ligands established that CD36 (formally platelet glycoprotein 4) was a potential endothelial cell ligand for PRBC. Subsequently, a variety of other host molecules were also identified as potential ligands, including ICAM-1, VCAM, and E-selectin (Section 4.4) (Turner, 1997). Some of these molecules have been assayed in heterologous expression systems and confer upon expressing cells the ability specifically to attach to PRBCs. Many of these potential ligands are inducible or are up-regulated when endothelial cells are exposed to appropriate cytokine stimuli (Section 4.3). The important ligands in vivo in severe infection have only been studied in a small number of cases, primarily in adult patients, so the key mediators of cytoadherence in African children dying of severe malaria have yet to be identified.

5.2. Rosetting

Rosetting is the phenomenon observed when PRBCs containing relatively mature stages of parasites (those with pigment visible with light microscopy) become surrounded and bound to non-PRBCs (NPRBCs) (Udomsangpetch et al., 1989). Rosettes commonly consist of up to 10 NPRBCs, but may be much larger ("giant rosettes"). At first sight, the formation of rosettes is puzzling because it may compete with the process of cytoadherence, which sequesters parasites from the circulation (indeed, in laboratory studies, it is necessary to disrupt rosettes to measure binding to cell lines). However, rosetting can also be viewed as a mechanism for increasing the chances of parasites multiplying by surrounding them with NPRBCs for reinvasion in the next replicative cycle (Wahlgren et al., 1991). This view is not shared by all investigators (Pasvol et al., 1995).

Rosetting has many features in common with cytoadherence, such as the parasite-stage specificity of expression of the phenotype, dependency on divalent cations, and sensitivity to trypsin. There are, however, also important differences, such as disruption of rosettes (but not of cytoadherence) by heparin and antibodies from patients with malaria and the lack of positive correlation between the two adhesive properties in parasitised erythrocytes obtained from patients (Ho et al., 1991). Certain blood groups (A/AB or B/AB) favour rosetting over others (blood group O), and this observation has been used to explain the relative protection of patients with blood group O from CM. The dogma that only sequestering species of malaria (P. falciparum, P. fragile, and P. chabaudi) form rosettes recently has been challenged by the observations that P. vivax and P. ovale can also form rosettes (Angus et al., 1996; Udomsangpetch et al., 1995). Thus, the rosetting phenotype may be necessary, but is not sufficient, to cause severe malaria, and relationship of this phenotype to cytoadherence is not clear.

In ex vivo assays, the mean number of parasites that formed rosettes was significantly higher in isolates from Gambian children with CM (n = 48, 31.7%) compared with those from uncomplicated malaria (11.4%, P < 0.00000001), and the rosettes were much larger in the cerebral group (Treutiger et al., 1992). Rosetting was not related to parasite density. Autologous (and some heterologous) testing of sera suggested that disruption of rosettes by sera from CM patients was less efficient than sera from uncomplicated cases. In a smaller subset of isolates, no correlation was observed
between disease severity and capacity to bind to melanoma cells in vitro. Studies on adults in Thailand (Ho et al., 1991) and children in Papua New Guinea have not found similar relationships between rosetting and disease severity (Al Yaman et al., 1995). The Thai study observed an inverse correlation between rosetting frequency and cytoadherence to C32 melanoma cell lines, but may have been too small to detect a difference in rosetting between groups of differing disease severity. In Papua New Guinea, although there was no association with disease severity or inhibition of rosetting by autologous sera in uncomplicated cases, an association between blood group AB and rosetting was observed (Al Yaman et al., 1995). Another study from Kenya has confirmed that increased rosetting is a feature of severe malaria and is underrepresented in patients with blood group O (Rowe et al., 1995). Haemoglobinopathies, such as sickle cell disease and thalassaemia, may also impair rosetting ability, the latter because of microcytosis (Carlson et al., 1994). A variety of sulphated glycoconjugates disrupt rosettes with varying degrees of effectiveness dependent on the parasite isolates tested (Rogerson et al., 1994). Rosetting is resistant to metabolic inhibitors (Carlson, 1993). The identification of parasite-encoded molecules responsible for rosetting, following the recent successes with the isolation of the var gene family, undoubtedly will help to clarify the sometimes conflicting experimental observations on this phenomenon. Both rosetting and cytoadherence alter the rheological characteristics of PRBC in laboratory models of flow (Kaul et al., 1991). These alterations are discussed in the next section.

5.3. Rheology

Early studies of P. knowlesi PRBCs showed infection increased resistance to flow through 5-µ polycarbonate sieves, and obstructed pores at high parasitaemia. Infection was also associated with a decrease in red cell deformability, and these changes were suggested to contribute to the development of microcirculatory obstruction (Miller et al., 1971). Subsequently, more sophisticated studies have confirmed that there is a stage-dependent decrease in the deformability of red cells as P. falciparum matures (Nash et al., 1989), and that mature parasites require correspondingly larger pressures (4- to 6-fold, compared with controls) to allow entry of PRBCs into small (3 µ) capillaries. These changes could reduce the circulatory flow in downstream (postcapillary) venules, and contribute to other pathophysiologically important processes such as cytoadherence. The molecular basis for adhesion at physiological flow rates has also been studied in cultured cell receptors (Wick and Louis, 1991; Nash et al., 1992), but relating changes ex vivo to patient’s clinical status is not straightforward (Cooke et al., 1993, 1995). Recently, reduction in red cell deformability assessed using ektacytometry has been shown to be strongly associated with a fatal outcome in severe malaria (Dondorp et al., 1997).

6. CLINICAL DEFINITIONS AND PRESENTATIONS

6.1. Severe Malaria

The parasite and host features that determine why a child who has been living in a malaria-endemic area and who is likely to have had extensive previous exposure to infection progresses to develop severe disease are still largely undefined. The clinical manifestations of severe malaria are determined by the degree of immunity in the affected child, as well as genotypic predispositions. African children growing up in endemic areas are exposed to malaria from infancy, and in some areas, may receive up to 100 infected bites per year (Mbogo et al., 1993). However, the relationship between malaria transmission and severe disease is complex, and the manifestations of severe disease vary with region (Snow et al., 1997). Initially, the children are protected by maternal factors (e.g., transplacental acquisition of maternal antibodies) and intrinsic factors (e.g., foetal haemoglobin). The protective effect of these factors, however, begins to wane during the first 6 months, so that severe disease leading to death is maximal between the ages of 1 and 4 years and is more likely in younger children. Thereafter, the children acquire immunity, so that adults who have lived continuously in endemic areas rarely develop severe disease. In contrast, children and adults who have not been exposed to malaria previously can rapidly develop severe disease after exposure.

Severe malaria is a spectrum of clinical syndromes unified by the single causative organism P. falciparum. It can be operationally defined as any malaria syndrome that is associated with a high mortality (>5%), even after appropriate hospital treatment. The clinical spectrum of severe malaria is different in African children growing up in malaria-endemic areas compared with nonimmune adults (Table 1). The reasons for these differences are not clear, although they appear to be related to exposure to malaria rather than age, since nonimmune children have similar features to nonimmune adults. The clinical picture, however, is changing, as in Southeast Asia jaundice is seen less frequently (Lalloo et al., 1996). This review largely concentrates on the clinical picture of African children since most of the recent work has been conducted on this group, who bear the brunt of the disease worldwide. Two studies have reported the admission of children to units in North America, but the number of children with severe disease was too small to make meaningful comparisons (McCaslin et al., 1994; Lynk and Gold, 1989).

In African children, the commonest presenting syndromes associated with significant mortality are CM; recurrent convulsions; metabolic dysfunction, which manifests itself as hypoglycaemia or lactic acidosis; or symptomatic anaemia. Children with the greatest risk of mortality can be identified as those with impaired consciousness or respiratory distress. Although severe anaemia is a common cause of admission, if blood transfusions are given quickly to those with cardiorespiratory distress, the mortality is low (Fig. 4). The age distribution of these syndromes is differ-
ent, so that severe anaemia affects younger children than CM, with respiratory distress overlapping both syndromes (Fig. 5). These syndromes are discussed in greater detail in Sections 6.2–6.4.

Children who present with severe malaria often have relatively short histories of illness, emphasising the rapidity with which illness may progress. Parents accompanying their children to hospital typically report fever beginning 1–3 days prior to admission, with neurological manifestations often beginning within 12 hr of admission (Musoke, 1966; Schmutzhard and Gerstenbrand, 1984; Waller et al., 1995; Gordeuk et al., 1992; Molyneux et al., 1989b). Children with severe anaemia may present with longer histories, although acute decompensation, manifesting as respiratory distress, often precipitates admission to hospital. Most deaths from severe malaria occur within 24 hr of starting treatment (Waller et al., 1995; Krishna et al., 1994b; Walker et al., 1992; Newton et al., 1991a; Marsh et al., 1995; Molyneux et al., 1989b) (Fig. 6), and most of those who survive make full recoveries within 48 hr of starting treatment (Krishna et al., 1994b; Waller et al., 1995; Walker et al., 1992; Gordeuk et al., 1992; Molyneux et al., 1989b).

The syndrome of CM is clinically discrete and relatively easily identified and, therefore, has been the subject of most of the published studies on severe malaria. However, it is important to appreciate that CM is one of the commonest manifestations of severe disease, but that severe malaria is not synonymous with CM. It is only within the past few years that metabolic derangements have been identified and subsequently incorporated into the definition of severe disease. Clinical syndromes of severe malaria exhibit significant overlap (Fig. 4), and CM is frequently complicated by lactic acidosis and/or hypoglycaemia. In cases where lactate levels or acid-base status cannot be assessed, clinical signs of respiratory distress suggest severe disease and are often associated with underlying acidosis. These clinical corre-

### TABLE 1. WHO Criteria for Severe Falciparum Malaria: Comparison of African Children and Papua New Guinean Adults Admitted to Hospital

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<th>African children (Marsh et al., 1995)</th>
<th>Nonimmune adults (Lalloo et al., 1996)</th>
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<td></td>
<td>Prevalence</td>
<td>Mortality</td>
</tr>
<tr>
<td>Defining criteria</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coma</td>
<td>10.0</td>
<td>16.8</td>
</tr>
<tr>
<td>Severe anaemia</td>
<td>17.6</td>
<td>4.7</td>
</tr>
<tr>
<td>Respiratory distress</td>
<td>13.7</td>
<td>13.9</td>
</tr>
<tr>
<td>Hypoglycaemia</td>
<td>13.2</td>
<td>21.7</td>
</tr>
<tr>
<td>Circulatory collapse</td>
<td>0.4</td>
<td>71.4</td>
</tr>
<tr>
<td>Renal failure</td>
<td>0.1</td>
<td>0</td>
</tr>
<tr>
<td>Spontaneous bleeding</td>
<td>0.1</td>
<td>0</td>
</tr>
<tr>
<td>Haemoglobinuria</td>
<td>0.1</td>
<td>50.0</td>
</tr>
<tr>
<td>Acidosis</td>
<td>63.6</td>
<td>21.4</td>
</tr>
<tr>
<td>Repeated convulsions</td>
<td>18.3</td>
<td>6.8</td>
</tr>
<tr>
<td>Supporting criteria</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Impaired consciousness</td>
<td>8.2</td>
<td>6.0</td>
</tr>
<tr>
<td>Jaundice</td>
<td>4.7</td>
<td>11.9</td>
</tr>
<tr>
<td>Prostration</td>
<td>12.2</td>
<td>5.2</td>
</tr>
<tr>
<td>Hyperpyrexia</td>
<td>10.6</td>
<td>1.6</td>
</tr>
<tr>
<td>Hyperparasitaemia</td>
<td>8.9</td>
<td>4.3</td>
</tr>
</tbody>
</table>

NA, not applicable.
lates of severe malaria have been recognised for decades (Guignon, 1965), although they have been more formally assessed recently (Waller et al., 1995; Marsh et al., 1995).

Multi-organ involvement is relatively uncommon in children compared with adults with severe disease. In our experience, none have required renal replacement therapy for significant impairment, and severe jaundice is uncommon unless it is associated with haemolysis. Pulmonary involvement has not been studied in detail in children, and the distinction between secondary infection and oedema requires more detailed examination. In a study of 180 children, 25 of whom died of severe malaria, the principal clinical causes of death were identified and summarised in Fig. 7.

Recognition of severe malaria is, therefore, of paramount importance in determining subsequent management decisions such as the use of a loading dose of quinine and the frequency of post-admission monitoring for complications such as hypoglycaemia. Whilst there is no single clinical or laboratory marker that adequately identifies all patients with severe disease, most high-risk patients are identified using a combination of clinical and laboratory criteria. These criteria are summarised in the following sections.

6.2. Cerebral Malaria

CM is a syndrome of impairment of consciousness associated with a falciparum malaria infection. Impairment of consciousness caused by other species of malaria have been described, but in these case reports, other causes of an encephalopathy have not been excluded and rigorous post-mortem studies are lacking.

6.2.1. Definition of cerebral malaria. There are no pathognomonic pathological features that differentiate CM from

FIGURE 5. Ages of 1844 Kenyan children admitted with CM, respiratory distress, and severe anaemia to Kilifi District Hospital, Kenya. Data from Marsh et al. (1995).

FIGURE 6. Cumulative percentage survival of 2155 children admitted to three African hospitals with severe falciparum malaria (Molyneux et al., 1989b; Marsh et al., 1995; Waller et al., 1995).
NCM (Section 3). Furthermore, consciousness can be depressed by a variety of pathophysiological processes, including seizures [either nonconvulsive status or post-ictal states (Crawley et al., 1996; Kirkham, 1991)], metabolic derangements [e.g., severe acidosis (Allen et al., 1996a)], and by the systemic effects of the infection [e.g., fever or hypotension (Arieff and Griggs, 1994)]. To exclude systemic causes of impaired consciousness and make studies of CM comparable, Warrell and colleagues (1982a) originally proposed a strict definition of CM based upon the response to a painful stimulus. This definition, slightly modified by a panel of experts at the World Health Organisation (WHO) (Warrell et al., 1990), is now widely accepted.

CM exists in a patient who:
- is unable to localise a painful stimulus
- has peripheral asexual falciparum parasitaemia
- has no other causes of an encephalopathy

The inability to localise a painful stimulus was chosen for two reasons. First, because it is associated with sufficiently deep coma as to exclude systemic effects of infection, and second, because it is a sign that can be reliably elicited (Newton et al., 1997a). Lesser degrees of CNS dysfunction (confusion, stupor) are frequently caused by falciparum infection and should also be managed as severe malaria. To exclude patients with uncomplicated falciparum infection and a complicating febrile seizure who are unrousable post-ictally, the child should be reassessed at least 30 min after a seizure. Warrell and colleagues originally stipulated that this assessment period should be after 6 hr, based on experience with adults, but this has now been shortened to 30 min since children often regain consciousness after febrile seizures within this time (Warrell, 1989). Our own observations also suggest that recovery 30 min following a febrile seizure is common, but children with malaria often have a prolonged post-ictal state after long or multiple seizures (Crawley et al., 1996). More than one seizure in a child with falciparum infection is indicative of significant cerebral involvement, as these children frequently progress to coma.

Asexual falciparum parasitaemia is a sine qua non of severe infection, since the liver stages and gametocytes do not contribute to symptoms. However, this definition does not include cases of blood slide-negative CM (Walker et al., 1992; Gopinathan and Subramanian, 1986; Edington and Gilles, 1976), i.e., malaria patients who have profound CNS disturbance, without asexual parasites detectable in the peripheral blood, but sequestered parasites found in the brain at post-mortem. The commonest cause of slide-negative falciparum malaria is pretreatment with antimalarials (White et al., 1992b), which remove circulating evidence of infection, but not the parasites sequestered in tissues. In these cases, the diagnosis may be suspected by rapid response to continuing antimalarial therapy, although this is relatively imprecise, or confirmed by finding sequestered parasites in the brain at post-mortem. It is likely that as the use of artemisinin derivatives becomes more widespread, slide-negative malaria will be observed more commonly, since this class of antimalarial clears circulating parasites rapidly.

Since a considerable proportion (up to 90%) of children living in endemic areas are infected with P. falciparum, but are asymptomatic, children admitted with other encephalopathies, which require exclusion (e.g., encephalitis or Rey's syndrome), may have a concomitant peripheral parasitaemia and thus, be misdiagnosed as having CM. This has led to inclusion of quantitative assessment of parasitaemia to establish the probability of malaria as a cause of symptoms in a patient. The parasitaemia cutoffs that have been used range from 2000 to 20,000/μL, depending on the geographical area and the criteria used for establishing positive predictive values for infection. However, most of these studies are community-based case-control studies and, therefore, are inapplicable to children who present to hospital with signs of moderate or severe malaria (as opposed to children presenting with uncomplicated infection). This may be particularly important in complicated falciparum malaria when a low peripheral parasite count may not reflect the parasites sequestered in the deep vascular beds. Thus, the absolute parasitaemia per se is not particularly useful in discriminating severe from uncomplicated or moderate malaria, and any patient who presents with symptoms of severe disease and the presence of asexual P. falciparum parasitaemia, therefore, must be managed as a case of severe malaria. The stages of parasite development on a peripheral blood film may be a more important parameter to assess in severe infections (Cropper, 1988). The importance of detecting these mature stages recently has been emphasised by studies that show that >20% mature stages in the presence of a high parasitaemia (pigmented trophozoites or later) is associated with a significantly higher mortality than patients who do not have such a high proportion of late stages (Silamut and White, 1993).

![FIGURE 7. Causes of death in 25 Gambian children with severe malaria. The causes of death were classified according to the following criteria: CM, highest BCS ≤2, no biochemical evidence of lactic acidosis, pulmonary complications, or sepsis; lactic acidosis, plasma lactate ≥5 mmol/L, BCS >2 after admission, and no evidence of pulmonary complications or sepsis; pulmonary complications, chest examination revealed signs compatible with infection or oedema; sepsis, proven by blood culture. Reproduced from Waller et al. (1995), with permission of the copyright holder, University of Chicago Press, Chicago.](image-url)
The exclusion of other causes of coma is determined by a careful history and by the available investigative facilities. In most hospitals in malaria-endemic areas, this entails the exclusion of other CNS infections (by obtaining clear and culture-negative CSF) and hypoglycaemia (either by performing a blood glucose estimation or observing the clinical response to glucose administration). The CSF needs to be examined in all children presenting with CM, since this condition cannot be differentiated clinically from bacterial meningitis (Wright et al., 1993), but the timing of the lumbar puncture is controversial (Greenwood, 1991; White, 1991; Kirkham et al., 1991; Kwiatkowski et al., 1991; Coulter, 1991). If examination is delayed or not possible, then children should empirically be managed with both antimalarial and antibacterial therapy (to cover the possibility of meningitis) and the diagnosis confirmed when permissible. Drug toxicity may confuse the clinical picture of CM, but clearly the presence of parasites dictates immediate antimalarial treatment. Other causes of encephalopathy, e.g., encephalitis without a pleocytosis or Reye’s syndrome, cannot be confidently excluded.

6.2.2. Coma scores. The inability to localise a painful stimulus identifies patients who are deeply unconscious, but not those with more subtle neurological impairments. A summated Glasgow coma score less than 8 (Table 2) has been proposed as part of the definition of CM, instead of the inability to localise pain (Leaver et al., 1990). However, this criterion is not applicable to children since children do not have the same range of summated scores (Newton et al., 1990) and thus, it has not been widely accepted. Molyneux and Taylor developed the Blantyre coma score (BCS) for the assessment of young Malawian children with CM (Molyneux et al., 1989b). The BCS is based upon the Glasgow coma scale (Table 2), but measures different responses. In particular, the eye responses do not take into consideration that some children may be blind and that directed eye responses can be caused by primitive subcortical reflexes (Plum and Posner, 1980) or seizures (Crawley et al., 1996). Likewise, withdrawal from a painful stimulus may be a spinal reflex requiring little cortical involvement and thus, is not a useful sign in assessing the depth of coma. Furthermore, there are considerable differences between clinicians in assessing this scale, particularly the verbal component, which will limit its use (Newton et al., 1997a). Despite these reservations, however, this scale appears to assess the overall degree of compromise due to falciparum malaria, and can be used to predict mortality, rather than the neurological complications (Newton et al., 1997a). The BCS is used by many researchers who define CM in children as a summated score of 2 or less: a total that is mostly derived from a motor and verbal score of 1 each and thus, is equivalent to the strict WHO definition. Other researchers include children with scores of 4 or less to define CM; however, this score would not exclude systemic effects and is not directly comparable with the strict WHO definition.

These definitions do not account for the fact that very young children may not have acquired the ability to localise pain and thus, may not satisfy the formal definition for coma, but nonetheless may be comatose. Thus, the definition of CM should be restricted to children over 8 months, until more appropriate criteria are found for younger children (Newton et al., 1997a). Overall, the WHO criteria offer a pragmatic definition that can be used for research and in the management of children older than 8 months. Coma scores may be useful in categorising the severity of CM, but their use as a criterion for diagnosis needs to be considered carefully.

6.2.3. Clinical presentation of cerebral malaria in African children. The clinical presentation of CM has features of a diffuse metabolic encephalopathy, as described by Plum and Posner (1980). The pathological basis of this picture has been discussed in Section 3 and its pathophysiology is discussed in Section 7.

<table>
<thead>
<tr>
<th>Blantyre coma scale</th>
<th>Glasgow coma scale</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Molyneux et al., 1989a)</td>
<td>(Teasdale and Jennett, 1974)</td>
</tr>
<tr>
<td><strong>Verbal</strong></td>
<td></td>
</tr>
<tr>
<td>2. Appropriate cry</td>
<td>5. Able to give name and age</td>
</tr>
<tr>
<td>1. Inappropriate cry or moan</td>
<td>4. Recognisable and relevant words</td>
</tr>
<tr>
<td>0. No cry</td>
<td>3. Incomprehensible, but complex vocalisation</td>
</tr>
<tr>
<td><strong>Motor</strong></td>
<td></td>
</tr>
<tr>
<td>2. Localises pain</td>
<td>6. Obey commands</td>
</tr>
<tr>
<td>1. Withdrawal from pain</td>
<td>5. Localises pain</td>
</tr>
<tr>
<td>0. Nonspecific or no response to pain</td>
<td>4. Withdrawal from pain</td>
</tr>
<tr>
<td></td>
<td>3. Flexes to pain</td>
</tr>
<tr>
<td></td>
<td>2. Extends to pain</td>
</tr>
<tr>
<td></td>
<td>1. No response</td>
</tr>
<tr>
<td><strong>Eye</strong></td>
<td></td>
</tr>
<tr>
<td>1. Directed eye movements</td>
<td>4. Spontaneous eye opening</td>
</tr>
<tr>
<td>0. Not directed</td>
<td>3. Opens eyes to voice</td>
</tr>
<tr>
<td></td>
<td>2. Opens eyes to pain</td>
</tr>
<tr>
<td></td>
<td>1. No eye opening</td>
</tr>
</tbody>
</table>
African children usually present in coma with an almost invariable 2- to 3-day history of fever (Rey et al., 1966; Molyneux et al., 1989b; Maguire, 1983; Ipatt et al., 1990; Conmey et al., 1980). Alterations in conscious level range from drowsiness and/or convulsions to deep coma and brainstem abnormalities (Musoke, 1966; Schmutz and Gerstenbrand, 1984; Waller et al., 1995; Newton et al., 1991a; Walker et al., 1992; Molyneux et al., 1989b). Fifty to 80% of children have a history of convulsions (Schmutzhard and Gerstenbrand, 1984; Molyneux et al., 1989b; Maguire, 1983; Ipatt et al., 1990; Conmey et al., 1980), one of which often precipitates coma (White and Looareesuwan, 1987; Warrell et al., 1990; Edington and Gilles, 1976). Seizures are witnessed at presentation in up to 50–80% of African children with CM (Table 3). If seizures persist after admission and particularly if they are prolonged or resistant to anticonvulsants, they are associated with the development of neurological sequelae (Bondi, 1992) or death (Kirkham et al., 1994; Brewster et al., 1990; Molyneux et al., 1989b). Occasionally, we have also observed both children and adults presenting with bizarre behavioural disturbances, such as confusion, clouding of consciousness, and stereotyped behaviour, such as tongue protrusion. Often, these symptoms progress rapidly to coma, soon after the initiation of antimalarial therapy.

Children with CM frequently develop abnormal postures (decorticate rigidity, decerebrate rigidity, opisthotonos), pupillary changes, absent corneal reflexes, abnormal respiratory rhythms (Kussmaul, Cheyne-Stokes, periodic apnoea), and gaze abnormalities (eyes wide open, conjugate gaze deviation, nystagmus) (Newton et al., 1998). Signs of frontal lobe release are often seen. Other brainstem signs, including dysconjugate and conjugate eye signs, and decerebrate posturing movements (all of which may represent seizure activity), occur in about one-third of children (Schmutzhard and Gerstenbrand, 1984; Molyneux et al., 1989b; Gelfand, 1973). Retinal haemorrhages are present in 6–36% of African children during admission (Newton et al., 1991b; Molyneux et al., 1989b; Kayembe et al., 1980). Haemorrhages are associated with a high mortality in adults (Looareesuwan et al., 1983), but in children, they do not appear to have prognostic significance (Kayembe et al., 1980). In both groups, they resolve without long-term visual defects (Kayembe et al., 1980; Bell et al., 1976). Papilloedema is present in between 2 and 12.5% of children (Newton et al., 1991a; Molyneux et al., 1989a; Kayembe et al., 1980), and was associated with increased opening pressures on CSF examination (Lewallen et al., 1993). Papilloedema and retinal oedema outside the vascular arcades were both independent indicators of fatal outcome in children.

CSF examination is useful not only in excluding infections that may mimic CM, but also in providing measurements of CSF lactate concentrations, which are one of the best independent prognostic indicators of fatality (Krishna et al., 1994b; White et al., 1985, 1987a). In children, CSF lactate (and glucose) concentrations are correlated with plasma levels, are not associated with a history of convulsions, and concentrations of lactate >4.5 mmol/L predict a particularly high mortality. In comparison with acute bacterial meningitis, the CSF glucose concentration is higher and the protein lower (Table 4). The CSF in CM should be clear (no more than 100 lymphocytes/mm³) and 25% have elevated protein levels. There are no elevations in CSF creatinine phosphokinase levels in cerebral disease (Miller et al., 1989b). These findings are discussed more fully in Section 4.5.

In African research settings, the mortality rate for strictly defined CM is 18.6% (95% CI 16.3–21.0) (see Table 3). There are no series large enough to give a true estimate of mortality in children treated in developed countries.

6.2.4. Neurological sequelae. Neurological damage has only been recently recognised as a common sequela of CM in African children (Brewster et al., 1990). In nonimmune adults, neurological sequelae are uncommon, although a variety of postmalarial syndromes have been described (Newton and Warrell, 1998). Although most neurological sequelae follow an episode of CM, neurological deficits can be found in children with seizures without sustained loss of consciousness (C. R. J. C. Newton, personal observation). The studies of neurological sequelae are often difficult to interpret since the definition of the severe falciparum malaria, the thoroughness of the examinations, and the extent of follow-up varies considerably, so that the incidence also varies considerably (Table 5). Recent studies of African children with CM (van Hensbroek et al., 1996a; Marsh et al., 1995; Bondi, 1992; Brewster et al., 1990; Molyneux et al., 1989a), which used similar criteria for the definition of CM, report an incidence of neurological sequelae rate to be 10.9% (95% CI 8.3–13.5% of survivors).

6.2.4.1. Factors predisposing to sequelae. In African children, the development of sequelae is associated with protracted seizures (van Hensbroek et al., 1996a; Brewster et al., 1990; Bondi, 1992), deep coma (van Hensbroek et al., 1997), prolonged coma (Sainokho et al., 1968; Brewster et al., 1990; Bondi, 1992; van Hensbroek et al., 1997), and anaemia in some studies (Brewster et al., 1990), but not in others (Bondi, 1992). Other smaller studies have shown an association between the development of sequelae and pathophysiological processes such as raised ICP (Newton et al., 1997b). Most of these factors are also associated with death, and may simply reflect the severity of the underlying insult, rather than a specific neuropathogenic process. The diverse pattern of neurological damage detected clinically and by CT suggests that there are likely to be a variety, probably interacting, of mechanisms responsible for neurological damage.

6.2.4.2. Patterns of sequelae. In the studies of African children, there is a difference between the sequelae found on discharge and those that persist (Table 5). About 50–84% of children recovered completely, usually within the first 6 months after discharge, and 9–55% had recovered 18 months after discharge, although this may be an overesti-
TABLE 3. Summary of Features of CM in Children

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Country</th>
<th>Number of cases</th>
<th>Mean age (years)</th>
<th>Hypoglycaemia (%)</th>
<th>Parasite count (/μL)</th>
<th>Seizures (%)</th>
<th>Treatment</th>
<th>Mean duration of coma (hr)</th>
<th>Neurological sequelae (%)</th>
<th>Mortality (%)</th>
<th>Mortality &lt;24 hr (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rothe, 1956</td>
<td>Kenya</td>
<td>97</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Q; C</td>
<td>22</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Armengaud et al., 1962</td>
<td>Senegal</td>
<td>88</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Q or C</td>
<td>14, 25</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Guignard, 1965</td>
<td>Madagascar</td>
<td>60</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>C</td>
<td>0, 38</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rey et al., 1966</td>
<td>Senegal</td>
<td>227</td>
<td>4.3</td>
<td></td>
<td></td>
<td></td>
<td>Q</td>
<td>31</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Musoke, 1966</td>
<td>Uganda</td>
<td>20</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>C</td>
<td>34, 5, 30</td>
<td>83</td>
<td></td>
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</tr>
<tr>
<td>Sanohko et al., 1968</td>
<td>Senegal</td>
<td>34</td>
<td>3</td>
<td></td>
<td></td>
<td></td>
<td>Q/C</td>
<td>21, 9</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lemercier et al., 1969</td>
<td>Senegal</td>
<td>235</td>
<td>3</td>
<td></td>
<td></td>
<td></td>
<td>Q/C</td>
<td>5, 9</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Berner, 1975</td>
<td>Malawi</td>
<td>39</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>C</td>
<td>3, 28</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Omanga et al., 1977</td>
<td>Zaire</td>
<td>121</td>
<td>3.7</td>
<td></td>
<td></td>
<td></td>
<td>C+Q</td>
<td>3, 4, 40</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Comney et al., 1980</td>
<td>Ghana</td>
<td>43</td>
<td>4.5</td>
<td></td>
<td></td>
<td></td>
<td>C</td>
<td>36, 5, 5</td>
<td></td>
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<tr>
<td>Stace et al., 1982</td>
<td>PNG</td>
<td>68</td>
<td>5.1</td>
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<td>Q</td>
<td>4, 6</td>
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<td>Tanzania</td>
<td>66</td>
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<td></td>
<td>C</td>
<td>17, 18</td>
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<tr>
<td>Ahmad and River, 1986</td>
<td>India</td>
<td>30</td>
<td>7</td>
<td></td>
<td></td>
<td></td>
<td>C</td>
<td>&lt;24, 3</td>
<td>20</td>
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<tr>
<td>Bernadino et al., 1986</td>
<td>Angola</td>
<td>254</td>
<td>3</td>
<td></td>
<td></td>
<td></td>
<td>Q/C</td>
<td>27</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Trape et al., 1987</td>
<td>Congo</td>
<td>140</td>
<td></td>
<td></td>
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<td>C</td>
<td>28, 64</td>
<td></td>
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<td>Thapa et al., 1988</td>
<td>India</td>
<td>40</td>
<td></td>
<td></td>
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<td>Q+C</td>
<td>0, 33</td>
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<tr>
<td>Taylor et al., 1988</td>
<td>Malawi</td>
<td>95</td>
<td>3.3</td>
<td>20</td>
<td></td>
<td></td>
<td>Q</td>
<td>11, 11</td>
<td></td>
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<tr>
<td>Molyneux et al., 1989b</td>
<td>Malawi</td>
<td>131</td>
<td>3.6</td>
<td>37</td>
<td>147,910–229,087</td>
<td></td>
<td>Q</td>
<td>9, 15</td>
<td>70</td>
<td></td>
<td></td>
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<tr>
<td>Grau et al., 1989</td>
<td>Malawi</td>
<td>55</td>
<td>5.3</td>
<td>18</td>
<td>273,400</td>
<td></td>
<td>Q</td>
<td>4, 18</td>
<td></td>
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</tr>
<tr>
<td>Brewer et al., 1990</td>
<td>The Gambia</td>
<td>377</td>
<td></td>
<td></td>
<td></td>
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<td>C</td>
<td>15, 9</td>
<td></td>
<td></td>
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<tr>
<td>Ikpatt et al., 1990</td>
<td>Nigeria</td>
<td>75</td>
<td>4.8</td>
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<td></td>
<td>C</td>
<td>9, 16</td>
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<td>Kawo et al., 1990</td>
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<td>110</td>
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<td>Carlsson et al., 1990</td>
<td>The Gambia</td>
<td>36</td>
<td>1.8</td>
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<td>Quinine (n)</td>
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<td>21</td>
<td>20.5</td>
<td>~70</td>
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\[1\] Geometric mean.

\[2\] \( P = 0.046. \)

Calculations of weighted means and confidence intervals were carried out in STATA without including ranges.

C, chloroquine; Q, quinine; AM, artemether; PNG, Papua New Guinea; RD, respiratory distress; NRD, no respiratory distress; P, pentoxifylline.

Modified from Waller et al. (1995).
mate, since the follow-up was incomplete in some of these studies and children with severe sequelae often die at home from an intercurrent illness. Other sequelae, e.g., epilepsy or behavioural difficulties, may develop after discharge and persist. However, some children with major sequelae showed dramatic resolution, particularly if they had cortical blindness.

Ataxia, common on discharge, rapidly improves over a period of weeks. The cause of the ataxia is not clear, since most children do not have the features of cerebellar involvement. It may be caused by muscle weakness following damage by cytokines, depletion of glycogen, or even parasite sequestration in the muscles (Miller et al., 1989b).

Although clearly definable neurological deficits are now well recognised, the importance of more subtle defects, manifesting as speech and behavioural difficulties, is becoming increasingly recognised. Psychoses with visual and auditory hallucinations have been reported in some African children (Sowunmi, 1993). The incidence of cognitive impairments is also not known. A case control study of 36 Gambian children who recovered from CM without any neurological deficits showed that cases may have had impaired balance, but there were no significant impairments of memory, perception, reasoning, learning, visiomotor coordination, dexterity, or manual speed (Muntendam et al., 1996). This study, however, only compared the results of single test scores that have a large standard deviation and thus, are unlikely to detect significant differences (and, therefore, subject to Type II error). Furthermore, there were no tests of long-term memory, and language was not adequately measured. Recent studies from Kenya suggest that children have difficulties in attention, expressive language, and behaviour following CM.

The pattern of neurological sequelae in adults is different from children (Newton and Warrell, 1998). There are no studies of nonimmune children, but they may have similar

| TABLE 5. Incidence and Pattern of Neurological Sequelae Following CM |
|------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|
|                        | Malawi (Molyneux et al., 1989b) | Gambia (Brewster et al., 1990) | Nigeria (Bondi, 1992)          | Kenya (Murphy et al., 1996)¹    | Gambia (van Hensbroek, 1997)²   | Total                           |
| Number studied         | 131                             | 308                             | 72                              | 160                             | 624                             | 1295                            |
| Survivors              | 111                             | 265                             | 62                              | 134                             | 490                             | 1062                            |
| Sequelea/number followed up (%) | 12 (11%)                        | 35 (13%)                        | 11 (18%)                        | 7 (6%)                          | 13 (10%)                        | 114 (24%)                       |
| Sequelea detected 1 month after discharge | 7 (6%)                          | —                               | 13 (10%)                        | NR                              | 20/452                          | 25/1000                         |
| Persistent sequelae    | NR                              | 11/23                           | NR                              | 18 months                       | NR                              | 25/1000                         |
| Duration of follow-up  | NR                              | 6 months                        | 12–16 months                    | NR                              | 18 months                       |                                  |

¹Examined 7 days after discharge.
²Sequelae assessed 1 month after discharge.
³Two patients were re-admitted (with convulsions and parasitaemia) within 48 hr of initial discharge.
⁴NR, not reported; [ ], persistent sequelae.
patterns of damage as the adults. In adults, sequelae are not confined to CM, but are often associated with laboratory evidence of severe disease. The major deficits are isolated cranial nerve lesions, mononeuritis multiplex, polynuropathy, extrapyramidal tremor, and other cerebellar signs (de Silva et al., 1992; White and Looareesuwan, 1987). Some adults have transient psychosis or delirium during recovery, whilst others develop focal epilepsy, sometimes associated with transient tomographic opacities in the brain (Looareesuwan et al., 1983). More recently, a postmalarial syndrome, consisting of confusion, convulsions, and tremor, associated strongly with mefloquine treatment in Southeast Asia has been described (Nguyen et al., 1996).

6.3. Metabolic Abnormalities in Severe Malaria

Hypoglycaemia and lactic acidosis both frequently co-exist and are also complications of CM (Krishna et al., 1994b). There are few clinical features that distinguish hypoglycaemia from other manifestations of malaria, since conventional signs, such as decreased consciousness level, sweating, pupillary dilatation, tachycardia, and seizures, are common to both CM and hypoglycaemia. Hypoglycaemia (defined as blood or plasma glucose <2.2 mmol/L), therefore, should be suspected in all patients who look severely ill, and rapidly excluded using bedside tests such as the BM-stix™ (a colorimetric assay for blood glucose that relies on glucose oxidase). Unfortunately, BMstix™ are not always available and are relatively expensive (although their cost-effectiveness can be enhanced by longitudinally cutting them into 2 or 3 strips). If diagnosis of hypoglycaemia is unconfirmed or likely to be delayed more than a few minutes, then empirical administration of hypotonic glucose (1 mL/kg, 50% glucose) is indicated. The majority of patients will not improve dramatically after correction of hypoglycaemia, indicating that hypoglycaemia is not the main cause of symptoms such as coma.

Lactic acidosis (defined as blood or plasma lactate ≥5 mmol/L) may be equally difficult to recognise clinically. It should be suspected in any severely ill patient who has markedly abnormal respiratory patterns, such as tachypnoea (>50 respirations/min in children), deep gasping respirations, or the use of secondary muscles of respiration (Marsh et al., 1995; Krishna et al., 1994b). In Kenyan children, “respiratory distress” was defined asalar flaring, chest recession (intercostal or subcostal), the use of accessory muscles of respiration, or abnormally deep (acidotic) breathing, whilst “severe respiratory distress” was used for children with chest recession or abnormally deep breathing (Marsh et al., 1995). In this study, respiratory distress was observed in 7% of 1844 children admitted with malaria to a district hospital. Half were fully conscious, 19% died (13.9% died with any symptom of respiratory distress and 24.8% with severe respiratory distress). In the children with respiratory distress in whom plasma bicarbonate was measured, 81% were severely acidic (plasma bicarbonate concentration <15 mmol/L). Respiratory distress was not associated with abnormal pul-

monary auscultatory or chest X-ray findings and thus, is probably a manifestation of a systemic acidosis. Similar conclusions also apply to Gambian children with hyperpnea, where acidosis is an underlying identifiable cause in ~70% (van Hensbroek, 1996). A study of 24 Nigerian children also identified respiratory distress as a poor prognostic indicator, but a high proportion of children (37.5%) had coarse crepitations on auscultation (Olluminate et al., 1995).

In nonimmune adults with uncomplicated falciparum malaria, pulmonary involvement, which is mild and asymptomatic, is frequent and disappears when the malaria is treated (Gozal, 1992). Community-based studies have shown that malaria may be associated with interstitial shadowing on a chest X-ray, independent of lower respiratory tract infections (Byass et al., 1991), although oxygen desaturation is not a feature of severe malaria in hospitalised children with respiratory symptoms (Taylor et al., 1988). The clinical differentiation of pneumonia- and malaria-associated respiratory abnormalities can be difficult (O'Dempsey et al., 1993). Also, the nomenclature of the “respiratory syndrome” is debatable, as respiratory distress suggests a primary pulmonary pathology, rather than the underlying acidosis. Hyperpnoea (defined as an increase in depth and rate of breathing) may be more appropriate as it does not presuppose the underlying cause(s) (Newton et al., 1998).

There are no rapid simple laboratory methods to confirm lactic acidosis when it is suspected on clinical grounds, and diagnosis currently relies on dedicated equipment that is expensive. However, manufacturers are developing simpler methods equivalent to the BMstix™ for glucose estimations, and these will prove particularly useful in the identification of patients at risk of death with severe malaria. Of a variety of admission clinical and laboratory parameters assessed by logistic regression analysis in a Gambian study of 115 children with severe malaria, deep coma and the lactate/glucose ratio were independently found to be predictive of mortality. Figure 8 shows the relationship among hypoglycaemia, hyperlactataemia, and mortality in these patients.

When all clinical and laboratory variables were examined together in a regression model, sustained hyperlactataemia (≥5 mmol/L 4 hr after admission) proved to be the single most sensitive indicator of a fatal outcome, followed by the BCS at 4 hr and presence of hypoglycaemia on admission (Krishna et al., 1994b). In many children, hyperlactataemia resolves soon after admission, resuscitation, and the start of antimalarial treatment. In a proportion of children, hyperlactataemia remains even after vigorous attempts at resuscitation, correction of electrolyte abnormalities, and hypoglycaemia (English et al., 1996c; Krishna et al., 1994b). The severity of lactic acidosis in this latter group is clearly much greater than in children who recover quickly. This is reflected in blood gas measurements made in Malawian children who presented with severe malaria (Taylor et al., 1993). Sustained acidemia was the most specific indicator of a poor prognosis in this group of children, again suggesting that the buffering capacity of the patient could
not cope with an increased acid load. Approximately 42% (25/60) of children with CM were acidemic (capillary blood pH < 7.3) compared with 5% (4/81) with uncomplicated disease (P < 0.0001), and some had inadequate respiratory compensation for the metabolic acidosis. The relative risk of a fatal outcome for acidemic patients with CM was 8.5 (95% CI 1.1–64). Acidaemia, attributable to a lactic acidosis, was associated with hypoglycaemia, elevated white cell count, and witnessed convulsions. Although lactate levels were lower in uncompensated metabolic acidosis than in those who had partially compensated, this finding probably represents the inability of some patients with CM to mount an effective ventilatory response to acidosis.

6.4. Severe Malarial Anaemia, Jaundice, and Haemolysis

The incidence of severe malarial anaemia has increased with the spread of chloroquine-resistant *P. falciparum* parasites across the world (Zucker et al., 1996). Patients may improve symptomatically following chloroquine treatment, but unless the parasites are cleared completely, the haemoglobin is lowered and the patient becomes increasingly vulnerable to a life-threatening anaemia (Bloland et al., 1993). Destruction of PRBCs is an inevitable consequence of *P. falciparum* infection and usually produces a fall in haemoglobin. The WHO defines severe malarial anaemia as a haemoglobin concentration < 50 g/L (or a haematocrit < 15%) in a patient with a *P. falciparum* parasitaemia in excess of 10,000 trophozoites/mm³ (Warrell et al., 1990), with normocytic indices. However, this definition may not be appropriate in malarial-endemic areas, since anaemia is common, caused mainly by iron and folate deficiency or haemoglobinopathies (Newton et al., 1997d), and children often adjust physiologically to the low haemoglobin concentrations. Life-threatening anaemia is determined more by the rate of decrease in haemoglobin than the absolute level of haemoglobin, but children with chronic anaemia may decompensate rapidly when challenged with a febrile illness.

The symptoms and signs of life-threatening severe malarial anaemia are those of respiratory distress and hyperdynamic circulation, which may be caused by the underlying acidosis from inadequate oxygenation (English et al., 1997) or impairment of cardiac function. The contribution of impaired cardiac function to respiratory distress is not determined. However, most African children with severe falciparum malaria are fluid depleted, and respond well to rapidly administered blood transfusions (English et al., 1996c).

Malaria is the most common cause of severe anaemia in children admitted to hospitals in Africa and is responsible for many blood transfusions (Newton et al., 1997d; Slutsker et al., 1994; Greenberg et al., 1989). In children with CM, the lowest haematocrit is reached within the first 24 hr after treatment (Molyneux et al., 1989b) and 23% of the children required blood transfusions during the first 24 hr (Molyneux et al., 1989b). In some studies, African children with CM who also have severe anaemia (haemoglobin < 50 g/L) are less likely to die (Marsh et al., 1995), but in others are more likely to die or survive with sequelae (Brewster et al., 1990). They may take longer to recover consciousness (Molyneux et al., 1989b). Whether severe anaemia contributes directly to impaired metabolism (by reducing oxygen delivery) or simply is a marker of severe disease is unclear.

6.5. The Commonest Modes of Presentation of Severe Malaria in Children

Identifying children with malaria who are at high risk of a fatal outcome depends on recognition of clinical signs, as well as access to laboratory variables. When only simple clinical criteria and bedside tests are available, children who are deeply unconscious, hyperpnoeic, and hypoglycaemic represent the most severely ill group of patients. If lactate measurements or blood gas data are available, then the additional presence of lactic acidosis (lactate ≥ 5 mmol/L) or acidaemia (pH < 7.3, or base excess < 15 mmol/L) identifies the majority of severely ill children (~80% of whom will die if they have 3 risk factors) (Taylor et al., 1993). However, the largest experience with these prognostic variables is from Africa, and there may be considerable geographic variation in their relative importance. In Papua New Guinea, depth of coma was surprisingly not an important discriminant of a fatal outcome, whereas lactic acidosis was in one study (Allen et al., 1996b), but in another study, deep coma, anaemia, and leucocytosis were associated with death (Genton et al., 1997). In our experience with African children, parasitaemia is not a useful prognostic variable (for reasons discussed in Section 2). The distribution of stages of development on a peripheral blood film may prove to be an additional simple bedside marker of severe disease, as in Southeast Asia (Silamut and White, 1993), but further studies are needed to confirm the utility of this test in African children. Likewise, the pres-
ence of pigment in leucocytes was found to be a useful prognostic index in Vietnamese adults (Nguyen et al., 1995), and was associated with severe malaria in Gabonese children (Metzger et al., 1995), but its usefulness remains to be established in other areas. Detailed consideration of the pathophysiology of these clinical syndromes is discussed in Section 7 and their management in Section 9.

6.6. Moderate Malaria

Moderate malaria is a disease category that identifies children who require parenteral treatment, but are unlikely (<10%) to progress to severe disease once appropriate antimalarial treatment has begun. Patients with moderate malaria have none of the defining features of severe disease (no hypoglycaemia, lactic acidosis, coma, or recurrent seizures), but have other features that suggest the requirement for parenteral treatment:

- a history of frequent and/or recent vomiting
- drowsiness
- obtundation, i.e., an apathetic response to painful stimuli such as capillary blood sampling or venepuncture
- prostration, i.e., difficulty or inability to suckle, sit up, stand up, or walk unaided according to the child's age

Moderate malaria, like severe malaria, does not have a predictable relationship with the level of peripheral asexual parasitaemia or vital signs in individual cases (Sowunmi et al., 1992). Whilst the majority of children with moderate disease improve rapidly with treatment and are discharged from hospital within 1–2 days, deterioration in clinical status can occur within a few hours. Apart from the requirement for parenteral therapy, this potential for rapid disease progression necessitates admission and close observation. However, in-hospital mortality in this category of patients is by definition low (<3%).

Uncomplicated malaria is infection not associated with any of the features of moderate or severe disease. It most commonly presents with fever, and the child is able to tolerate oral antimalarial medication and can be treated as an outpatient with an appropriate antimalarial. Mortality is not anticipated in uncomplicated malaria, providing appropriate antimalarials have been administered.

7. PATHOPHYSIOLOGY

7.1. Fever

Fever is a characteristic feature of falciparum malaria, although parasitisation is not inevitably associated with fever. In malaria-endemic areas, many children are afebrile despite being parasitaemic, even with relatively high parasitaemias. There is, however, a broad relationship between the level of parasitaemia and fever in these areas, so that it is possible to determine a threshold of parasitaemia (usually 2000–20,000 parasites/μL) that has an optimum sensitivity and specificity for the definition of a clinical episode of malaria (Greenwood, 1996; Smith et al., 1995). The relationship is complicated by the fact that the threshold at which fever occurs appears to be influenced by age (Greenwood, 1996). Thus, recent studies confirmed older findings that the parasitaemic threshold for fever varied by a factor of 5 with age and the threshold was highest in 1- to 2-year-old children (Rogier et al., 1996).

The rise in temperature during malaria infections is thought to be mediated by TNF (Kwiatkowski et al., 1989). TNF is an endogenous pyrogen, acting on the hypothalamus to reset the set-point for temperature homeostasis. The ablation of fever in children administered anti-TNF monoclonals supports the importance of TNF as the cause of fever (Kwiatkowski et al., 1993), although the fact that not all fevers are associated with elevations in TNF suggests that other mechanisms may also be involved.

The role of fever in the pathophysiology of severe malaria is undetermined. Fever may synchronise the stages of parasites (Kwiatkowski, 1989), promoting the survival of parasites. In Gambian children with uncomplicated malaria, the increased resting energy expenditure is 37% higher compared with when they have recovered, and this is associated with a doubling of whole body protein turnover assessed by stable isotope techniques (Berclez et al., 1996). Elevations in body temperature are important in increasing energy expenditure (by between 8.5 and 13.2%/°C), but are not the only mechanism causing these rises. There is a negative protein balance during acute infection, which is reversed 15 days after the infection has been treated. Similar studies are lacking in children with severe malaria, but even greater perturbations of energy expenditure are likely during the acute phases of infection. The role of fever on cerebral metabolism is not known and is unlikely to be predicted from whole body metabolism in unconscious children (Matthews et al., 1995). The effect of temperature on the brain is potentially important because increases in temperature promote ischaemic damage to neurons and may contribute to the development of neurological sequelae in children with CM.

7.2. Coma

The cause of the depressed level of consciousness in falciparum malaria is unknown. Any theory of causation needs to explain why coma develops relatively late in the illness in adults, compared with children; the fact that most patients recover without any evidence of neurological sequelae; and that coma is caused by more than one mechanism. Part of the difficulty has been the definition of impairment of consciousness, since some of the “coma” scales used may not measure the depth of coma (Newton et al., 1997a).

Consciousness may be impaired by depression of the reticular activating system within the brainstem or a diffuse process affecting the cerebrum (Plum and Posner, 1980). Sequestration of PRBC within the cerebral venules, particularly within the brainstem, is the most widely accepted mechanism. The patchy involvement of blood vessels in the brain may explain why most patients with CM develop a completely reversible coma. The impaired delivery of nutrients to certain areas of the brain may be compensated for
by normal or increased delivery to microscopically adjacent regions (luxury perfusion), preserving the integrity and function of the brain as a whole, in spite of coma. Global cerebral blood flow is not decreased in adults or children with CM (Newton et al., 1996a; Warrell et al., 1988), but whether it is appropriate for metabolic demands is unknown. The sequestered parasites may also produce toxins, either directly or stimulate host cells to produce substances that interfere with neuronal metabolism.

The common occurrence of seizures may contribute to the impairment of consciousness, although the contribution is difficult to determine. Subtle seizures and nonconvulsive status have been documented in Kenyan children (Crawley et al., 1996; Kirkham et al., 1994). In the later study, only half of the children with subtle seizures (i.e., 7.5% of children with CM) appeared to regain consciousness within 6 hr of the termination of the electrical activity with diazepam. Prolonged post-ictal states may also contribute to the impairment of consciousness in other children (Crawley et al., 1996), but there are no specific EEG features that differentiate a post-ictal state from a rapidly improving encephalopathy. The inappropriate administration of benzodiazepines (intramuscular administration of high doses) may also contribute to impaired consciousness and apparently prolonged post-ictal states.

In a few children with hypoglycaemia, the conscious level improves with the administration of glucose, although most do not (Taylor et al., 1988). Other metabolic derangements [e.g., severe acidosis (Allen et al., 1996a)] are associated with coma, but whether they are directly responsible for coma is unclear. Systemic effects of the infection [e.g., fever or hyponatraemia (Arieff and Griggs, 1994)] may also contribute, although they are unlikely to be responsible for deep coma. The role of toxins in the pathogenesis of coma requires further investigation. NO may impair neurotransmission, but there is little evidence to support this as a mediator in CM (see Section 4.5). Desferrioxamine, a ROS scavenger, appears to reduce the duration of deep coma (Goettein et al., 1991), although the mechanism is unclear. More recently, excitotoxins have been implicated (Dobinie et al., 1997), particularly to explain the incidence of seizures.

Thus, it is likely that the impairment of consciousness produced by falciparum malaria is caused by a number of interacting mechanisms (Newton et al., 1994) that cannot be easily differentiated from each other, and the contribution of each mechanism cannot be easily determined. Further light on these mechanisms may be shed by specific interventions.

7.3. Seizures

Seizures, particularly those witnessed after admission in children with CM, are associated with death (Waller et al., 1986; Molyneux et al., 1988b), and prolonged and multiple seizures are associated with neurological sequelae. The relationship may not be causal, since seizures may be a marker of neurological damage rather than the cause. In other encephalopathies, seizures often herald the onset of neurological damage, particularly if they are focal in nature. Distinguishing cause from effect clearly has important ramifications, since anticonvulsant prophylaxis may prevent seizures, but not neurological damage. Seizures may cause death by aggravating intracranial hypertension (IH) (Newton et al., 1991a), may cause neuronal loss, and may precipitate aspiration of the gastric contents into the lungs (Waller et al., 1995).

The cause of the seizures in CM is unclear. Intracranial sequestration of metabolically active parasites is a potential mechanism, but difficult to investigate. The seizures are unlikely to be simply febrile convulsions (Akpede et al., 1993), since 54% of seizures occurred when the rectal temperatures were less than 38.0°C, 48% were partial, and over 70% were repetitive (Waruiru et al., 1996). Seizures may be caused by hypoglycaemia and hyponatraemia, although studies of Malawian and Kenyan children have not identified these mechanisms as clinically important in malaria (Crawley et al., 1996; Waruiru et al., 1996; Molyneux et al., 1989b). Other potential mechanisms include toxins, e.g., NO, excitotoxins, as discussed in Section 7.5.2.

7.4. Raised Intracranial Pressure

Raised ICP is an important cause of poor outcome in paediatric encephalopathies, particularly in CNS infections (Goitein et al., 1983). It can cause death by transtentorial herniation or a reduction in cerebral perfusion pressure (CPP), where CPP = mean arterial pressure − ICP. Raised ICP was thought not to be important in adults with CM, since over 80% of opening CSF pressures were in the normal range, there was no difference in the CSF pressures between those who died and survived (Warrell et al., 1986), and cerebral oedema was probably an agonal event (Looaeeswun et al., 1983, 1995). However, opening CSF pressures do not predict the maximum ICP when studied in other encephalopathies, and raised ICP may be caused by an increase in cerebral blood volume (Newton et al., 1991a) rather than cerebral oedema. Opening CSF pressures are raised in most African children with CM (Lawall et al., 1993; Waller et al., 1991; Newton et al., 1991a). The CSF pressures are similar to those found in adults with malaria, but are above the normal range for children. Most Kenyan children dying with CM have clinical signs compatible with transtentorial herniation (Newton et al., 1991a), although these signs may be caused by other mechanisms (Kwiatkowski et al., 1991; Kirkham et al., 1991a; Newton et al., 1991a). ICP monitoring confirmed that children deeply unconscious from CM all had raised ICP (with maximum ICP higher than the upper limit of adults) and that opening ICP did not predict maximum ICP (Fig. 9) (Newton et al., 1997b). Furthermore, all children who developed severe IH (maximum ICP >40 mm Hg, minimum CPP <40 mm Hg) either died or survived with severe neurological sequelae. One child, who developed an ICP of 158 mm Hg, died with signs of transtentorial herniation. In another study, transcranial Doppler studies showed that about one-half of the children dying from
CM had sonographic features of progressive IH, whilst the remainder had sonographic features similar to children who died of NCM (Newton et al., 1996a).

Transtentorial herniation occurs when there is an ICP gradient established between the contents of the skull and the spinal cord (Plum and Posner, 1980). This may not apply in CM, where there may be a uniform increase in pressure in the neuraxis due to swelling and, therefore, displacement of cerebral structures is less likely to occur until ICPs become grossly elevated. The pathological features of tentorial herniation, despite being described in the 1930s, have been reported infrequently in CM until recently (Section 3.2).

The most likely cause of raised ICP in CM is an increase in cerebral blood volume (Newton et al., 1991a) aggravated by cytotoxic oedema in those who develop severe neurological sequelae (Newton et al., 1994). In a CT of Kenyan children recovering from CM, the scans were normal in most children, but transient brain swelling occurred in children with intermediate IH, and tomographic features of cytotoxic oedema were seen in children who developed severe IH (Newton et al., 1994). There was no evidence of vasogenic oedema or acute hydrocephalus in any of these children. These findings are consistent with observations made in a magnetic resonance imaging study in adults with CM (Loa-reesuwan et al., 1995). Cerebral blood volume could be increased by the sequestration of PRBC in the vascular compartment, either acting as a diffuse space occupying lesion or obstructing venous outflow. Other features of CM, such as seizures, anaemia, and hyperthermia, would also increase cerebral blood flow and thus, increase cerebral blood volume.

Thus, raised ICP appears to be a feature of CM in African children, and severe IH, when it occurs, is associated with a poor outcome. Whether IH is a primary pathophysiological process remains to be established. Mannitol was effective in lowering the ICP in Kenyan children (Newton et al., 1997b) and may have prevented children with mild degrees of IH from dying or developing neurological sequelae, but it did not prevent the development of intractable IH in those children with a poor outcome (Newton et al., 1997b). Further post-mortem studies examining the importance of herniation, and clinical studies to test the effectiveness of substances to reduce ICP in children with CM, are needed before treatment recommendations can be made.

7.5. Causes of Neurological Sequelae

The pathogenesis of neurological damage is likely to be different from the mechanisms that cause death, since the risk factors are different (Newton, 1995). Death of neuronal tissues may be caused by necrosis or apoptosis, with similar or differing pathophysiological processes that lead to these mechanisms (Table 6). In Kenyan children with neurological sequelae, CT scans demonstrate a variety of patterns of damage, suggesting that a number of mechanisms may be responsible.

7.5.1. Ischaemia. Necrosis is caused by a critical reduction in blood supply (ischaemia) or damage by toxins, such as ROS, NO, or excitotoxins. Reduction of cerebral blood flow has not been associated with diffuse neurological damage in either children (Newton et al., 1996a) or adults (Warrell et al., 1988), although these intermittent measurements may have missed critical periods of reduced perfusion. Reduced CPP, however, is strongly associated with severe neurological sequelae (Newton et al., 1997b), and if cerebral autoregulation is impaired, cerebral blood flow will be determined by CPP. Some children with neurological sequelae have evidence of borderzone infarction (Fig. 10), providing further evidence of reduced cerebral perfusion (Newton et al., 1994), although this is not a consistent feature. Seizures, either prolonged or repetitive, may promote ischaemic damage, although as yet the evidence is lacking (Newton et al., 1997c).

7.5.2. Reactive oxygen species. ROS are generated during and after hypoxia-ischaemia. These species damage tissues by interacting with the polyunsaturated fatty acids of cellular membranes, damaging proteins and DNA (Siesjo et al., 1989). ROS initiate a vicious cycle of lipid peroxidation, which is promoted by the presence of iron and lactic acidosis. This mechanism appears to be important during reperfusion, particularly after a period of reduced microcirculatory flow (Hurn et al., 1996) rather than complete ischaemia, as may occur during the clearance of parasites. These species also promote the formation of NO and may enhance the damage caused by excitotoxins.

7.5.3. Excitotoxins. Excitotoxins are endogenously produced amino acids, which, under normal conditions, act as ex-
citatory neurotransmitters, but when overproduced, become toxic to the neuronal cells. The release of excitatory amino acids is stimulated by hypoxia-ischaemia, hypoglycaemia, and seizures; the latter two are associated with the development of neurological sequelae in CM. There is no direct evidence that the above toxins cause neurological damage in CM, although these substances are difficult to measure, particularly in the brain. The studies that have been conducted demonstrate the raised concentrations of quinolinic acid, an excitotoxin in the CSF in children with sequelae (Dobbie et al., 1997). These results need to be interpreted within the light of a possible breakdown in the BBB (Section 4.7.2).

7.5.4. Apoptosis. Apoptosis is the process of programmed cell death that occurs in vertebrates. The cell activates an intrinsic suicide mechanism that leads to characteristic morphological changes (Fraser and Evan, 1996). It is induced by many factors, including TNF, ROS (Baier-Bitterlich et al., 1995), and proteases. The role of apoptosis in neuronal death remains controversial, and as yet, there is no evidence to suggest apoptosis is responsible for neurological damage in CM, although this mechanism is difficult to investigate noninvasively.

7.5.5. Hemiparesis. Hemiparesis is one of the most common and uniform neurological sequelae, but the cause is unknown. In studies of 10 West African children with hemiparesis who did not have clearly defined CM (i.e., other causes of an encephalopathy were not excluded), angiography demonstrated stenosis abnormalities in 5 children (Omanga et al., 1983; Collomb et al., 1967). Cerebral artery occlusion was found in 4 children and segmental narrowing of the internal carotid in a further child; 5 children had completely normal angiograms. In Kenyan children with strictly defined CM, over one-half had a marked asymmetry of blood flow velocity in the middle cerebral artery, as detected by transcranial Doppler sonography (Newton et al., 1996a). In 2 out of 7 children with hemiparesis, no flow could be detected in the contralateral middle cerebral artery.

In a CT scan study of 12 children who had a residual hemiparesis 3–40 months following CM, 4 had unilateral atrophy, 5 asymmetrical atrophy, and 3 diffuse atrophy (Newton et al., 1996b). All the children with unilateral atrophy had partial motor seizures and tomographic features similar to those seen in hemiconvulsion-hemiplegia syndrome after prolonged febrile convulsions (Kataoka et al., 1988). A child with multiple seizure types had severe asymmetrical atrophy. The atrophy was more severe in the parieto-occipital regions in 8 children. In none of these scans was the damage confined to a single basal cranial artery territory. Furthermore, in an electroencephalographic study of CM, 66% of seizures were partial, often localised over parieto-temporal regions (Crawley et al., 1996), regions that are not typically borderzone areas. These findings suggest that hemiparesis in CM may be caused by convulsions, possibly as part of the hemiconvulsive-hemiparesis syndrome. The occlusion of middle cerebral artery found in some children still requires an explanation since large vessel thrombosis is not a recognised feature of CM. Underlying anatomical abnormalities, disturbances of clotting, or severe vasospasm may contribute.

7.5.6. Visual impairment. Cortical visual impairment, defined as visual impairment with intact pupillary responses and normal fundi, is common following CM (Brewster et al., 1990). Although it can occur in isolation following CM, it is usually associated with evidence of more diffuse damage (Lafaix et al., 1970). Blindness tends to improve, although most children do not recover completely. The cause of blindness is not clear, although it is often associated with seizures (Olurin, 1970). The occipital area is vulnerable to hypoxic-ischaemic insults in other encephalopathies [e.g., meningitis (Thun-Hohenstein et al., 1992)]. This area is particularly prone to damage following a reduction in cerebral perfusion, possibly because of a difference in the

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autoregulation of the blood flow in the posterior circulation, making it more vulnerable to changes in perfusion pressure. Damage to the thalamic radiations and other extrastriate structures may also occur.

7.6. Hypoglycaemia

Early studies noted that hypoglycaemia was a common complication of malaria infection in humans (Fitz-Hugh, 1944) and animals (Mercado and von Brand, 1954). More recently, there have been studies of the mechanisms of hypoglycaemia in animal models of malaria, but findings may not be directly applicable to human disease processes.

Observations were occasionally made in patients with severe disease (Migasena, 1983; Fisher, 1983), but the first prospective series that identified hypoglycaemia and lactic acidosis in malaria and studied its pathophysiological mechanisms was published from Thailand in 1983 (White et al., 1983). Twelve of 151 (8%) adult patients with CM experienced hypoglycaemia, although 17 patients were studied overall, including 3 women with otherwise uncomplicated infection who were pregnant or who had delivered recently. The mortality in the hypoglycaemic group was significantly higher than in patients without hypoglycaemia [8/14 (57%) vs. 27/139 (19.4%), respectively; \( P = 0.004 \)], and hypoglycaemic patients had higher parasitaemias and more severe multi-organ involvement than the remainder. A striking observation was that plasma insulin and C peptide levels were inappropriately high during episodes of hypoglycaemia. In all but one patient, plasma quinine was detectable during the episode of hypoglycaemia, and quinine and insulin concentrations were correlated at the first hypoglycaemic episode. There was an unpredictable clinical response to glucagon or glucose treatment in these patients, although glucagon increased plasma glucose in all patients.

When quinine was infused in normal volunteers, there was a significant increase in plasma insulin concentrations and a corresponding fall in fasting plasma glucose concentrations. These observations confirmed that quinine was responsible for most episodes of hypoglycaemia in these patients, through its capacity to induce hyperinsulinemia. Pregnancy was identified as a major risk factor for the development of hypoglycaemia.

These studies in adults subsequently led to an examination of the incidence and mechanisms of hypoglycaemia in African children with severe malaria (White et al., 1987b), after 2 index cases presented with hypoglycaemia during the course of pharmacokinetic studies on chloroquine. In Gambian children who had \( P. falciparum \) parasitaemia and required parenteral chloroquine treatment, the incidence of hypoglycaemia was 15/47 (32%), and its presence was predictive of subsequent mortality (White et al., 1987b,c). Hypoglycaemia was significantly associated with CM (52% had hypoglycaemia in this subgroup), a higher peripheral parasite count, and abnormal liver function tests. In contrast to Thai adults, insulin levels were appropriately low in hypoglycaemic children, and patients were appropriately ketotic. A later Sudanese study also found that pregnant women were prone to hypoglycaemia without associated hyperinsulinaemia (Saeed et al., 1990). These observations are consistent with the rapidity with which starved children (or pregnant women, or rarely other adults) are prone to deplete glycogen reserves and the inability of chloroquine to provoke hyperinsulinemia. They suggest important differences in the pathogenesis of hypoglycaemia between Southeast Asian adults and patients in Africa.

Since the first reports on hypoglycaemia, many prospective studies have confirmed that children are particularly prone to develop this complication (Tables 1 and 3), but few have examined its pathophysiology in detail. In

**FIGURE 10.** CT scan of child with CM. (A) acute scan showing diffuse brain swelling with extensive hypodensity of the superficial watershed areas (arrows) and the basal ganglia. (B) convalescent scan showing contrast enhancement of the border zone (arrows) between the left middle and posterior cerebral artery areas. Reproduced from Newton et al. (1994), with permission of the copyright holder, BMJ Publishing Group, London.
Malawi, blood glucose was negatively correlated with the plasma concentrations of the gluconeogenic substrates lactate and alanine, but interestingly, not with the length of time that patients had symptoms or had been fasting (Taylor et al., 1988). In this study, quinine was infused with dextrose solution, and patients who were normoglycaemic on admission did not develop hypoglycaemia. Pretreatment hypoglycaemia was associated with higher mortality and recurrent episodes of postadmission hypoglycaemia in some children, and a proportion of this group had inappropriate elevations in plasma insulin levels. In survivors, hypoglycaemia was associated with a higher incidence of neurological sequelae. There is likely to be depletion of glycogen reserves in the livers of children with severe malaria, but the biochemical basis of gluconeogenic defects has not been identified. Growth hormone concentrations are elevated in hypoglycaemic children, and there is no deficiency in plasma cortisol levels, suggesting appropriate counter-regulatory homeostatic responses.

In adults with severe malaria, the conversion of galactose (Pukrittayakamee et al., 1991b) or glycerol (Pukrittayakamee et al., 1994b,c) to glucose are not significantly impaired when compared with similar rates measured in convalescence, arguing against gluconeogenic impairment affecting the enzymes responsible for these relatively proximal synthetic pathways. Similar studies have been completed with the most distal metabolite alanine, and this study will provide a more comprehensive assessment of gluconeogenesis in severe malaria (S. Pukrittayakamee, S. Krishna and N. J. White, unpublished observations). Glucose kinetics measured in pregnancy (Davis et al., 1994) and in adults with uncomplicated (Davis et al., 1990b) and severe infection (Davis et al., 1993) demonstrate increased consumption of glucose in acute infection. In the latter study, a primed infusion of $[^3H]$glucose was given to 18 normoglycaemic glucose in acute infection. In the latter study, a primed in-

plasma glucose production (Dekker et al., 1996), and did not increase with the infusion of alanine (Dekker et al., 1997). Thus, in this group of children, it appears that endogenous glucose production is an important determinant of plasma glucose, in contrast to the findings in adults.

This increased demand for glucose in falciparum malaria results from many stresses, including the effects of fever and increased anaerobic glycolysis (which utilises glucose much less efficiently to produce ATP) by both host tissues and parasitised erythrocytes. Anaerobic glycolysis is discussed in the following section.

### 7.7. Lactic Acidosis

Systemic lactic acidosis, like hypoglycaemia, is a metabolic endpoint of many potential causes in severe malaria. The relative importance of these causes may vary from patient to patient, and broadly reflect both increases in lactate production and inadequate lactate clearance by normal homeostatic mechanisms (Mordes et al., 1996). Lactic acidosis is one of the best markers of disease severity and mortality in malaria (Krishna et al., 1994b). In normal individuals, gross elevations in plasma lactate occur transiently in response to anaerobic strenuous exercise. These elevations are a short-term solution to the demand for ATP generated in skeletal muscle, and lactate is rapidly metabolised from peaks of up to 20 mM to basal levels of ~1 mM when oxygen becomes available to tissues. The production of lactate under anaerobic conditions allows glycolysis to continue by maintaining a supply of NAD$^+$, without which glycolysis will cease. Utilisation of lactate takes place in the liver, kidney, skeletal muscle, and CNS by metabolism via pyruvate. Most pyruvate enters Krebs’ cycle, where it is oxidised to CO$_2$ and water, utilising both the accumulated lactate anion and the accompanying acidic proton. Without this resolution of lactic acidosis, the buffering capacity of the blood and tissues is exceeded, and lactic acidemia supervenes on lactic acidosis (Stacpoole, 1997). The levels of lactic acid where acidemia is likely to supervene are $\geq$5 mM, although there may be significant metabolic dysfunction in patients with lactate levels below this value. Sustained elevations in plasma lactate, therefore, can be viewed as a marker for inadequate mitochondrial metabolism of pyruvate, as this is the principal route whereby lactic acid is cleared in health (Stacpoole, 1997). In severe malaria, it is unlikely that alternative routes of lactate utilisation via pyruvate through synthetic routes (by conversion to oxaloacetate or acetyl coenzyme A) will be quantitatively important.

Increased lactate production in severe infection can result from many causes. Fever and anaemia themselves increase metabolic rates (Stettler et al., 1992). Generalised seizures cause brief, large bursts of anaerobic glycolysis in muscle tissue, and can produce severe, if transient, lactic acidosis in otherwise normal adults (Orringer et al., 1977). Their effects are likely to be more severe in malaria where there are other derangements in glycolytic pathways, and some host tissues (such as the brain and muscle) are already
net exporters of lactic acid to the blood. While muscle tissue damage is well documented in severe malaria in children (Miller et al., 1989b) and a higher proportion of children with abnormal creatine kinase values [12/16 (75%)] have a history of seizures when compared with those whose creatine kinase values are in the normal range [21/21 (50%); \( P = 0.076 \), Fisher’s exact test], there are no studies that have prospectively evaluated the contribution of seizures to lactic acidosis in malaria in children.

Infected erythrocytes generate 20- to 50-fold lactate (and consume correspondingly large quantities of glucose) compared with NPRBCs (Warrell, 1989). This increased glycolysis may not be sufficient to perturb homeostasis in a normal individual, but it may be more important in severe malaria where the PRBC are localised to capillaries, and local metabolic diversion may be more severe. Severe anaemia decreases the oxygen-carrying capacity of blood, although compensatory mechanisms can restore oxygen delivery to tissues. If anaemia develops over a period of days rather than hours, then there may also be changes in the oxygen-dissociation curve (Jones and McGregor, 1954) induced by increased glycolysis which can increase blood flow to tissues. Anaemia also decreases viscosity, which can increase blood flow to tissues, although the increase in cerebral blood flow following a drop in haemoglobin is caused by a decrease in oxygen-carrying capacity (Brown and Marshall, 1985). These physiological adaptations have not yet been examined in severe malaria in humans, although a study in an animal model of severe malaria where the PRBC are localised to capillaries, and local metabolic diversion may be more severe. Severe anaemia decreases viscosity, which can increase blood flow to tissues, although the increase in cerebral blood flow following a drop in haemoglobin is caused by a decrease in oxygen-carrying capacity (Brown and Marshall, 1985). These physiological adaptations have not yet been examined in severe malaria in humans, although a study in an animal model of severe malaria, 31P-NMR studies demonstrated adequate cerebral stores of phosphocreatine, ATP, and pH, in spite of severe anaemia and lactic acidosis (Krishna et al., 1983).

In adults with severe malaria, adrenaline use, in contrast to dopamine, was associated with a worsening of lactic acidosis complicating severe malaria (Day et al., 1996). In children, inotropic support is infrequently required in management, but dopamine would be the preferred inotrope. Chronic salicylate toxicity has been identified in Kenya as a potential cause of lactic acidosis and hypoglycaemia in some children presenting with clinical features of severe malaria (English et al., 1996a). Geographical variations in accessibility to aspirin and local prescribing habits may alert clinicians to this possible cause, although in Ghana, salicylates are not used and children presenting with lactic acidosis do not have detectable plasma levels (T. Aghenye, T. Planche and S. Krishna, personal observations).

In Thai adults (n = 8) with malaria and moderate metabolic derangement (mean arterial lactate concentrations of 3.44 mmol/L and pH values >7.3), lactate kinetics and skeletal muscle lactate metabolism were examined using a lactate infusion labelled with a stable isotope (Davis et al., 1996). Quinine treatment did not affect the plasma lactate, pyruvate, or alanine concentrations or arteriovenous differences in these metabolites measured across forearm muscle. Lactate turnover did not change significantly during acute infection (both before and after quinine treatment) and in convalescence, although metabolic clearance of lactate was significantly lower in acute infection. Lactate turnover in acute infection was correlated with simultaneous arterial plasma lactate concentrations, but no such correlation was observed with lactate clearance rates. Lactate release from skeletal muscle was significantly greater following quinine, and this was much higher than that observed in convalescence. The observed reduction in lactate clearance in these patients accords with observations made in severe malaria, where there is diminished liver blood flow. This reduction in liver blood flow may limit lactate delivery to the liver (Molyneux et al., 1989a), although this is less likely in patients with moderately severe disease (Pukrittayakamee et al., 1994b). Additionally, the liver may have an impaired intrinsic capability to clear lactate in acute infection.

Many of these earlier observations made on lactic acidosis and malaria have been repeated in a recent Kenyan study (English et al., 1997). In this study, a high anion gap (>11) remained in most patients with severe malaria, even after accounting for hyperlactataemia, and alternative causes for this were suggested. Renal impairment was not severe (as estimated by plasma creatinine values) and was associated with acidosis, but could not account for the increase in anion gap, as organic acids retained by the kidney result in a relatively slowly developing lactic acidosis, usually when renal impairment is severe. It is likely that other anions, such as β-hydroxybutyrate (not picked up by dipstick analysis of urine) or phosphate or urate, could have contributed to the anion gap, although these were not investigated in this study. In summary, lactic acidosis is an important complication in severe malaria that is difficult to manage, and may contribute directly to a fatal outcome.

7.8. Anaemia and Thrombocytopenia

Destruction of PRBC with a fall in haemoglobin is almost an inevitable consequence of falciparum malaria. Severe anaemia can be one of the life-threatening complications of P. falciparum infections, although in African children, it is associated with a relatively low mortality on its own (Fig. 4), but much higher when associated with CM or acidosis (Marsh et al., 1995).

The anaemia could be caused by many interacting mechanisms. Removal of erythrocytes by the spleen is an important mechanism in adults with splenomegaly, in whom the spleen is the major site of erythrocyte destruction after the institution of therapy (Loosareewarawat et al., 1987). In non-immune adults without CM, using a simple mathematical model, the fall in haematocrit could be described by a three-term equation (Davis et al., 1990a). The initial fall in haematocrit (during the first few hours) is caused by plasma volume expansion; a zero-order fall with a mean half-life of 25 hr occurred with the fall in parasitaemia and another fall with a half-life of 43 days is associated with a loss of NPRBC. However, this model relies on some tenuous assumptions, e.g., that the number of PRBC that sequester af-
ter treatment is small, although it is unlikely that quinine used in this study affected sequestration during the initial phases (Watkins et al., 1993). This model has not been verified in adults or children with CM.

Impaired red cell production, manifesting as dyserythropoiesis in chronic malarial infections (Abdalla et al., 1980), is thought to play a role in the production of severe anaemia in malaria. Dyserythropoiesis is a feature of chronic anaemia caused by *P. falciparum* in Gambian children (Fig. 11), but is not a significant factor in the fall of haemoglobin in acute infections (Abdalla et al., 1980). It is not confined to children with malaria since it is also found in children with iron deficiency and sickle cell disease (Newton et al., 1997d). In Gambian children and adults with uncomplicated malaria, the degree of dyserythropoiesis correlates with the severity of iron deficiency (Abdalla, 1990; Phillips et al., 1986), but in children with severe anaemia, no such relationship was found (Newton et al., 1997d). The cause of dyserythropoiesis in these children is not clear. TNF may lead to dyserythropoiesis (Clark and Chaudhri, 1988), although there is no clinical evidence to support this assertion in Kenyan children (Newton et al., 1997d). In African children with severe malarial anaemia, erythropoietin levels were appropriately raised for the haemoglobin concentration (Burchard et al., 1995; Newton et al., 1997d), unlike Thai adults, in whom erythropoietin levels were inappropriately low (Burgmann et al., 1996).

As documented by a positive direct antiglobulin test (DAT), autoimmune haemolysis has been suggested as an important component of severe malarial anaemia (Facer et al., 1979). Several studies have not found a consistent association between a positive DAT and parasitaemia (Newton et al., 1997d; Merry et al., 1986; Abdalla et al., 1983; Abdalla and Weatherall, 1982; Greenwood et al., 1978), although in one study, a positive DAT was associated with clinical malaria (Abdalla et al., 1983) and in others, it was associated with anaemia (Jeje et al., 1983; Facer et al., 1979). One possible mechanism is the production of autoantibodies to triose phosphate isomerase (TPI), a glycolytic enzyme. These antibodies are associated with haemolytic anaemia in Epstein-Barr virus infection (Ritter et al., 1990), and the hereditary deficiency of this erythrocyte enzyme is associated with a neurological syndrome and increased susceptibility to infections. In *P. vivax* infection, no anti-TPI antibodies were detected in 5 patients. However, in 4 of 10 nonimmune patients with *P. falciparum* infection, who had biochemical manifestations of haemolysis (lactate dehydrogenase >200 U/L and anaemia) continuing for weeks after parasitaemia had cleared, there was a correlation between anti-TPI antibody titres and severity of anaemia (Ritter et al., 1993). Reactivation of Epstein-Barr virus infection was only detectable in 1 of these 4 patients with anti-TPI antibodies, suggesting that reactivation is not necessary for this mechanism of autoimmune haemolysis to operate in malaria. The exact mechanism of red cell damage is still unclear, and the significance of anti-TPI antibodies in the anaemia of malaria in African children is unknown, but worth exploring.

Thrombocytopenia commonly accompanies both falciparum and vivax malaria, and is due to increased consumption of platelets during the acute infection with adequate numbers of megakaryocytes in the bone marrow (Srithaikul et al., 1988; Looareesuwan et al., 1992). Thrombocytopenia was associated with elevations in macrophage colony-stimulating factor, which may mediate the increased destruction (Lee et al., 1997). In some adults, it is associated with a specific IgG attached to platelet-bound malaria antigen (Kelton et al., 1983). It was more profound in severe disease and was associated with increases in plasma P-selectin levels (a marker of endothelial cell activation) (Lee et al., 1997). Although thrombocytopenia is common and may be associated with biochemical markers of disseminated intravascular coagulation, a haemorrhagic diathesis in severe malaria in children is rare. The degree of thrombocytopenia is frequently mild to moderate (>50 × 10⁹/L), and in African children, is probably unrelated to disease severity. Changes in platelet aggregability also accompany thrombocytopenia (Srithaikul et al., 1988).

### 7.9. Electrolyte Abnormalities and Fluid Balance

Hyponatraemia (Na⁺ <135 mmol/L) occurs in over half of the patients with severe malaria, particularly CM (English et al., 1996b). The cause of the hyponatraemia is controversial. English and colleagues argued that hyponatraemia results from an inappropriate hormonal response to the loss of electrolyte and fluid in sweat and stool. Yet, the children with most severe hyponatraemia were less dehydrated (lower urea and less weight gain after treatment). A more recent study has shown that some Kenyan children appear to have inappropriate urinary sodium loss for the plasma sodium level (Sowunmi, 1996a), although osmolality was not measured. Furthermore, at least one child had features of cerebral salt wasting syndrome, and in both of these studies, urinary sodi ums are often inappropriately high. Thus, it is

![Figure 11](image-url)
likely that hyponatraemia results from a combination of mechanisms that include lack of sodium intake, loss of sodium in body fluids, including sweat and gastrointestinal losses, and inappropriate arginine vasopressin secretion. Whatever the mechanisms, hyponatraemia does not appear to be associated with seizures, neurological damage, or death, and consequently, is of little direct clinical significance. Hypernatraemic dehydration occasionally occurs in death, and consequently, is of little direct clinical significance. Hypernatraemic dehydration occasionally occurs in African children and is often associated with a poor outcome (C. R. J. C. Newton, personal observations), although not studied in detail.

Hypokalaemia ($K^+ < 3.5 \text{ mmol/L}$) was present in 14% on the day of admission in survivors, but this increased to 39% the following day. There was speculation that hypokalaemia may contribute to a variety of complications, such as cardiac dysrhythmias and late respiratory arrest. However, dysrhythmias are not important complications of malaria in children (Bethell et al., 1996), although supraventricular ectopic beats can be observed frequently in some children with severe disease, and a prolonged Q-T interval is seen in acute infections (von Seidlein et al., 1997). Respiratory arrest most commonly follows a neurological pattern (with progressive brainstem signs) rather than a metabolic one. Hyperkalaemia is uncommon in severe childhood malaria, and if it occurs, it is often associated with severe haemolysis or renal impairment.

Other electrolyte abnormalities have been detected, e.g., hypophosphataemia (i.e., $<0.8 \text{ mmol/L}$ phosphate in 43% adult patients and $<0.3 \text{ mmol/L}$ in 11/14 severely ill patients) (Davis et al., 1991) and less commonly hyperphosphataemia, but their significance in the pathophysiology of infection is unknown. Mildly abnormal plasma calcium (corrected) levels and magnesium levels were commonly observed, but are unlikely to contribute significantly to pathophysiology (Davis et al., 1991). By contrast, in children with severe malaria, serum calcium, potassium, urate, and phosphate concentrations were significantly elevated in fatal cases compared with survivors (Waller et al., 1995). Whilst mean serum calcium and potassium concentrations were still within the normal range in fatal cases, mean phosphate and urate concentrations were increased above normal.

Electrolyte abnormalities can assist in choice of intravenous fluid in the initial management of children with severe malaria, but accurate assessment of the circulating intravascular volume is necessary to estimate the amounts of fluid needed. Intravascular volume is notoriously difficult to assess clinically in children and in severe malaria, especially in hypotensive children. Central venous pressure (CVP) measurements are probably the most accurate way to estimate fluid requirements. Where possible, these measurements should be interpreted in conjunction with plasma electrolytes to determine the nature and rate of fluid replacement in severely ill children.

### 7.10. Renal Impairment and Blackwater Fever

Acute renal failure and pulmonary oedema are common complications of falciparum malaria and a major cause of death in adults (Warrell, 1987; Tran et al., 1996a; Mate Kole et al., 1996; Trang et al., 1992), but are rarely seen in African children (Waller et al., 1995; Marsh et al., 1995; Molyneux et al., 1989b). Elevation in plasma creatinine, however, is common in childhood CM (Sowunmi, 1996b), and although it is associated with death (Waller et al., 1995), none of the children die from renal failure. A disproportionate increase in urea suggests that the elevated creatinine is probably caused by hypovolaemia (English et al., 1996b) and aggressive intravascular volume repletion may be required in some children (English et al., 1996c). There have been no clinical trials to determine if rate of rehydration and type of intravenous fluid therapy influence outcome in severe disease. There is little evidence that such aggressive fluid therapy is detrimental to the brain in children with CM. Whole blood transfusion, for example, improves the perfusion pressure, with a mild increase in ICP (Newton et al., 1994). Renal impairment can also be caused by a glomerulonephritis from the circulating immune complexes, intravascular haemolysis manifesting as blackwater fever. The glomerulonephritis is seen in nonimmune patients (Anonymous, 1976; Boonpucknavig and Boonpucknavig, 1988), but rarely documented in African children.

Blackwater fever was often associated with malaria infections in the past, but the incidence appears to have fallen (Mate Kole et al., 1996). It is more frequently seen in nonimmune patients (Warrell, 1987), particularly in Southeast Asia (Tran et al., 1996a), where the outcome is better than earlier reports from Africa. In Africa, it is occasionally seen in children with severe malaria, but is often caused by other infections or haemoglobinopathies (Delacollette et al., 1995).

### 7.11. Secondary Infections

Superimposed bacterial infections (pneumonia, septicaemia, and urinary tract infections) can complicate malaria in nonimmune adults (Phillips et al., 1986) and may be detected in African children and contribute to mortality. Non-typhi Salmonella septicaemia was found in Gambian children with malarial parasitaemia (Mabey et al., 1987), but septicaemia was rarely found in African children with CM in one study (Molyneux et al., 1989b).

### 8. Antimalarial Treatment

#### 8.1. Introduction

This article focuses on supportive care, but would be incomplete without a brief description of the main groups of antimalarial drugs. Often antimalarial treatment is unavailable at the primary health care level when parents present with their sick child, frequently after delays induced by arduous travel, the need to care for the remaining children in the family, consultation with traditional healers, and the lack of money. In this context, a simple (nonparenteral) method of administering antimalarials could make the difference between progression of infection to severe disease and death, or
survival. Intrarectal formulations of antimalarials currently are being developed to examine this interventional strategy in the near future (Barennes et al., 1996; Hien, 1994).

In essence, modern management of severe malaria consists of the rapid administration of an appropriate antimalarial and the treatment of complications, such as hypoglycaemia, anaemia, intravascular volume depletion, and convulsions. Administration of a rapidly acting parasiticidal antimalarial is, therefore, one of the immediate aims of management. Which antimalarial and by what dose and route are questions that have to be answered individually for particular geographic areas. All antimalarials require time in which to exert their maximum antimalarial effects. These effects, and their speed of inhibition, vary between antimalarials and have been studied in detail (Watkins et al., 1993; ter Kuile et al., 1993). Thus, parasite killing, inhibition of parasite metabolism (glycolysis, nucleic acid synthesis, and protein synthesis), and of virulence factors (such as rosetting ability and cytoadherence characteristics) are all endpoints that have potential relevance to pathophysiology of severe disease, as well as variability in their responsiveness to different classes of antimalarials (Udomsangpetch et al., 1996; Kwiatkowski and Bate, 1995). The artemisinin derivatives as a class are undisputedly the most rapidly acting of antimalarials (Hien and White, 1993). Additionally, they have the broadest stage specificity of antimalarial effect. These in vitro (or ex vivo) observations are clearly translated into significantly faster parasite clearance estimates in vivo compared with other antimalarials, in patients with both severe and uncomplicated malaria (Hien and White, 1993). However, in studies designed to answer the crucial question of improved survival when artemisinin derivatives are compared with quinine, there is no clear benefit for artemether over quinine in African children (van Hensbroek et al., 1996a) or Vietnamese adults (Tran et al., 1996b). Indeed, clinical measures of recovery from disease (rather than parasitological ones) favoured the use of quinine over artemether (shorter duration of coma and hospitalisation time, and significantly fewer seizures) (van Hensbroek et al., 1996a). These findings highlight a number of important general points about antimalarials.

Relying on parasite clearance estimates as an endpoint in severe malaria is misleading. Apparent benefits such as speed of parasiticidal activity in vitro do not necessarily mean benefits in vivo, and there may be unsuspected disadvantages of artemether use (such as seizures) in children. There is little doubt that if and when quinine becomes ineffective as an antimalarial for severe infections, then the next line of treatment will rely on one of the artemisinin derivatives for which there is a growing experience in parenteral formulations. Once the toxicity of these compounds has been defined better, their availability and usage are, therefore, likely to increase. However, for the moment, the drug of choice for severe malaria in most of sub-Saharan Africa, where there is established chloroquine resistance in parasites, is quinine. The pharmacokinetics of the cinchona alkaloids and the aminoquinolines, and their clinical applications, recently have been reviewed (Krishna et al., 1996) and their usage is briefly covered in the following sections.

8.2. Cinchona Alkaloids

Quinine is the preferred antimalarial for the treatment of severe malaria in both children and adults. In some countries such as the United States, quinine has been unavailable since 1991, and quinidine, the diastereomer of quinine, is the alternative (Miller et al., 1989a; Phillips et al., 1985). Unfortunately, with the introduction of newer antiarrhythmic agents, even quinidine availability is becoming increasingly and worryingly limited in the United States (Rosenthal et al., 1996).

Recent debate on quinine use has focused on the question of applicability of a loading dose in severe malaria, and the exact recommended dose. In patients who have not received previous quinine treatment, we favour the use of a loading dose to ensure a rapid increase in plasma concentrations in children with severe disease. In centres that lack intensive care facilities, quinine can be given by the intramuscular rather than the intravenous route, and at a 12-hourly rather than an 8-hourly maintenance regimen in children for a number of reasons. First, it is simpler, with fewer doses required overall. Second, in many settings, intravenous infusions may not be monitored as closely as necessary to prevent excessively rapid quinine administration and attendant cardiotoxicity. Third, it may be cheaper as there is less requirement for sterile disposables. Fourth, intravenous access is not a prerequisite, as antimalarial treatment can begin without delay and intravenous access can be established later. Finally, there are no important pharmacokinetic differences in profiles and behaviour of intramuscular compared with intravenous quinine, even in patients who are severely ill (Pasvol et al., 1991). A potential disadvantage of intramuscular quinine is local toxicity, but this can be minimised if the quinine is diluted 1:1 (v:v) with either water for injection or sterile normal saline. The loading dose is then administered divided equally into both thighs, and maintenance doses are carefully alternated between thighs. Tetanus is a rare complication, which should be avoidable by scrupulous adherence to sterile technique (Yen et al., 1994). Quinine can cause hypoglycaemia by stimulating insulin release (Section 7.6). This complication is much more common in adults (particularly in pregnancy), but hypoglycaemia should be also excluded in children wherever possible by regular monitoring. Children receiving glucose supplementation rarely develop refractory hypoglycaemia (Taylor et al., 1988).

The doses and frequency of administration of different regimens of quinine are summarised in Table 7. Quinine should be given for 7 days when used as a single antimalarial agent. Shorter regimens (e.g., 5 days) can be completed with pyrimethamine-sulfadoxine. A recent report of intramuscular quinine in children with global malnutrition (not kwashiorkor) and malaria suggests that an 8-hourly maintenance regimen may be preferred because of in-
creased quinine clearance in the malnourished group compared with controls who were not undernourished (Treluyer et al., 1996). The rectal route for quinine administration was once considered too toxic, but recently, preparations of cinchona alkaloids (>95% quinine in Quinimax™) have been successfully used after dilution in water for uncomplicated malaria (Barennes et al., 1996). This route has not been studied in severe malaria. Quinidine is used in lower doses than quinine because of its greater potential for cardiotoxicity. Optimal dosing regimens have been debated recently (Krisha et al., 1996).

8.3. 4-Aminoquinolines

Chloroquine (and its structural relative amodiaquine) should only be used to treat severe malaria when there is confidence that parasites still retain responsiveness to the drug. In areas of emerging resistance, the acute infection may be managed with chloroquine, but cure may no longer be achievable. The choice of when to change from chloroquine to quinine is particularly difficult under these circumstances. Quinine is the preferred antimalarial, but the financial implications of a change in policy can be devastating in some sub-Saharan countries.

Chloroquine’s pharmacokinetics dictate that small frequent dosing is preferable to larger, less frequent dosing, as chloroquine has a small central compartment relative to its volume of distribution. Higher doses of chloroquine, therefore, can give dangerously high peak concentrations. Chloroquine can be administered by a variety of routes in severe malaria (subcutaneously, intramuscularly, intravenously, or even via nasogastric tube) and is absorbed rapidly from parenteral sites. Our preferred regimen is via the intramuscular or subcutaneous route (3.5 mg base/kg, given every 6 hr to a total dose of 25 mg/kg. Amodiaquine is a produg for desethylamodiaquine, which has similar (though not identical) pharmacokinetic properties to chloroquine.

8.4. Artemisinin Derivatives

The artemisinin derivatives, like quinine, are plant extracts that have had a long-standing role in the treatment of malaria in China, but are now much more widely available. There are a variety of formulations of the artemisinin derivatives, which are principally distinguished by their solubility in oil or water. These formulations (e.g., artesunate or arte- misinin, which are oil soluble, and artesunate, which is water soluble) have been administered via oral, rectal, intravenous, and intramuscular routes. In severe malaria, a number of recent large prospective studies in African children and Southeast Asian adults have compared intramuscular artesunate with quinine. Artemether is similar in efficacy to quinine for the treatment of severe malaria and is conveniently administered. Concerns about toxicity have led to caution in recommendations for use. Currently, toxicological aspects of artemisinin derivatives are being investigated intensively.

The availability and usage of artemisinin derivatives eventually will be determined by drug regulatory bodies and the WHO, but currently they are not licensed for use in Western Europe or the United States. They are, however, widely available in sub-Saharan Africa, but generally are more expensive than chloroquine or quinine. Pharmacokinetic studies on these compounds have been hampered by technical difficulties with assays that only recently have been overcome, so that dosing regimens have been based primarily on studies of drug efficacy. In children, artesunate can be given in a loading dose (3.2 mg/kg, intramuscularly) followed by a maintenance dose of 1.6 mg/kg daily for a minimum of 5 days. Artesunate can be given intravenously or intramuscularly in severe malaria (loading dose of 2.4 mg/kg, followed after 12 hr by 1.2 mg/kg, then at 24 hr by 1.2 mg/kg, and 1.2 mg/kg every 24 hr for 7 days). Artesunate tablets can be substituted when tolerated. These regimens may be modified as pharmacological and toxicological experience accumulates.

9. ADJUNCTIVE MEASURES

Good nursing care is crucial to the management of children with severe malaria (Murphy et al., 1995a; Krishna and White, 1989). Children should be transferred to a dedicated (intensive care type) unit wherever possible and cared for by experienced nurses. Those children who develop signs of deepening coma or abnormal brainstem signs should be considered for assisted ventilation, if facilities exist for this supportive measure. These children should not be made normocapnic, since this may precipitate transtentorial herniation (Looaereseawun et al., 1995). Children should be monitored regularly for vital signs and the complications of hypoglycaemia and seizures. A nasogastric tube should be inserted in those with impaired consciousness or those at risk of aspiration pneumonitis, and eye care and oral hygiene measures should be instituted.

9.1. Antipyretics

Reasons to treat fever in malaria include making the patient more comfortable, minimising metabolic stresses of

### TABLE 7. Dose Regimen of Quinine Dihydrochloride in Severe Falciparum Malaria

<table>
<thead>
<tr>
<th>Reference</th>
<th>Route</th>
<th>Loading dose</th>
<th>Maintenance dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Winstanley et al., 1993</td>
<td>Intravenous</td>
<td>7.5 mg/kg in 30 min, then 7.5 mg/kg over 1.5 hr</td>
<td>10 mg/kg over 2 hr every 12 hr</td>
</tr>
<tr>
<td>Winstanley et al., 1994</td>
<td>Intravenous</td>
<td>15 mg/kg over 2 hr</td>
<td>10 mg/kg over 2 hr every 12 hr</td>
</tr>
<tr>
<td>Waller et al., 1990</td>
<td>Intramuscular</td>
<td>20 mg/kg (2-site injection)</td>
<td>10 mg/kg every 8 hr</td>
</tr>
<tr>
<td>Pasvol et al., 1991</td>
<td>Intramuscular</td>
<td>20 mg/kg (2-site injection)</td>
<td>10 mg/kg every 12 hr</td>
</tr>
</tbody>
</table>
infection, and perhaps reducing the risk of convulsions and neurological sequelae in children. There are no studies in malaria that have shown an improvement in these parameters in parallel with a reduction in fever, although nonimmune adults with uncomplicated malaria reported an improvement in headaches following the use of ibuprofen (Krishna et al., 1995b). It is not clear if a reduction in core temperature benefits cerebral consequences of severe malaria.

Whenever they have been studied, antimalarials, such as chloroquine and quinine, have not been found to have useful antipyretic properties (Krishna et al., 1995b; Vannjanonta et al., 1996) contrary to dogma. Specific antipyretic treatment is often used as an adjunct to antimalarial treatment. In most developing countries, although aspirin is frequently used, paracetamol is the antipyretic of choice. In suppository formulation, paracetamol is convenient to administer. Recently, however, paracetamol has been shown to prolong parasite clearance in Gabonese children with non-severe malaria, possibly from a decreased production of TNF-α and ROS (Brandts et al., 1997). In this study, it offered no benefit over mechanical antipyresis. However, oral paracetamol reduces fever in Thai adults with uncomplicated malaria (Krishna et al., 1995b), and ibuprofen (10 mg/kg), a nonsteroidal anti-inflammatory drug, is significantly more effective (Krishna et al., 1995b). Indomethacin is also superior to paracetamol in adults with uncomplicated infection. Fever begins to recur 3–4 hr after paracetamol (15 mg/kg), so the dosing frequency may have to be up to 4 hourly until the underlying pyretic tendency subsides. Ibuprofen has a more sustained antipyretic action and, therefore, can be given less frequently (6–8 hourly).

Although salicylates are not recommended in children because of the danger of provoking Reye’s syndrome, in many countries aspirin is still used as an antipyretic. Additionally, aspirin may aggravate or even cause metabolic acidosis (English et al., 1996a) or, rarely, precipitate a bleeding tendency (Warrell et al., 1990). Parenteral antipyretics, e.g., dipyrone, are not widely used because of a significant risk of fatal agranulocytosis (Warrell et al., 1990). Monoclonal antibodies against TNF reduce the temperature in Gambian children, but are unlikely to gain currency as an antipyretic (Krishna et al., 1996b). Contrary to dogma, specific antipyretic treatment was often used as an adjunct to antimalarial treatment. In most developing countries, although aspirin is frequently used, paracetamol is the antipyretic of choice.

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### 9.2. Anticonvulsants

It is prudent to prevent or terminate seizures since they are associated with a poor outcome in CM and cause neuronal damage in other encephalopathies, as well as in experimental models (Wasterlain and Shirasaka, 1994). In the prevention of malaria-associated seizures, phenobarbitone is the only drug that has been studied in any detail. In a randomised double-blind study of 48 nonimmune Thai adults with CM, phenobarbitone (3.5 mg/kg, intramuscular) reduced the incidence of seizures after admission from 54 to 12.5% (White et al., 1988). This effect was surprising since this dose is not usually associated with anticonvulsant effects (Shorvon, 1994), although plasma phenobarbitone concentrations were not measured in this study. A slightly higher dose (5 mg/kg, intramuscular) administered to Gambian children with CM did not cause a deterioration in level of consciousness, and subsequently, studies using 7 mg/kg of phenobarbitone showed it was clinically well tolerated, even when other anticonvulsants had to be added (S. Krishna, personal observation).

A small study of Southeast Asian children with severe falciparum malaria demonstrated that phenobarbitone (also used at 7 mg/kg, intramuscular) was well absorbed, reaching a peak (7 mg/L) within 4 hr, but failing to reach concentrations above 15 mg/L (ter Kuile et al., 1992), the level thought to prevent febrile seizures (Faero et al., 1972). This dose was associated with depression of consciousness level in some patients. In 12 Kenyan children with severe malaria, a higher dose (10 mg/kg, intramuscular) only achieved maximal concentrations above 15 mg/L in 4 patients, and did not appear to reduce the incidence of seizures or affect the duration and depth of coma (Winstanley et al., 1992). Currently, a larger prophylactic dose is undergoing clinical trials.

Seizures in severe malaria may abort spontaneously, but data from other encephalopathies suggests that seizures lasting longer than 5 min should be actively terminated. Diazepam and paraldehyde are effective drugs for the termination of seizures, although there have been no studies conducted on their relative efficacy in children with malaria. In many hospitals, these drugs, particularly diazepam, may be given in inappropriate doses by intramuscular injection or too rapidly by the intravenous route, with the attendant risk of respiratory depression. Diazepam-induced respiratory depression is rapidly reversed by flumazenil, but this drug is expensive and not widely available. If diazepam overdose is suspected, children, therefore, should be ventilated by bag and mask or endotracheal tube until spontaneous respirations return. Paraldehyde is well absorbed from intramuscular injections and rectal administration (Shorvon, 1994). It is generally safe (C. R. J. C. Newton, personal observations), although it causes sedation and may prolong coma following the post-ictal phase. Other side effects are rare and include hypotension, metabolic acidosis, and pulmonary oedema (Shorvon, 1994). The rectal administration of an outdated drug has caused severe proctitis, excoriating rash, and large-bowel perforation. The chemical interaction of paraldehyde with plastic syringes has limited the drug’s use, but if paraldehyde is quickly administered after being drawn up, there appear to be no adverse effects.

The treatment of repeated or continuous seizures not controlled with diazepam or paraldehyde should follow the standard treatment of status epilepticus. This may require...
access to facilities for assisted ventilation. Phenobarbitone and phenytoin have both been used successfully, although not directly compared in malaria. Phenobarbitone can be given in a loading dose of 15–20 mg/kg (preferably intravenously, but may also be given intramuscularly), followed by 5 mg/kg 12 hr later. Toxic effects of phenobarbitone include decreasing the level of consciousness, respiratory depression, and hypotension (reputedly after diazepam); although these effects are rarely seen in status epilepticus (Shorvon, 1994). Phenytoin (20 mg/kg) should be infused over 20 min into a line that does not contain dextrose (to prevent precipitation), preferably with the patient’s ECG monitored for excessive QTc prolongation, which predisposes to ventricular arrhythmias. Phenytoin has relatively little respiratory and cerebral depression, although it may potentiate the effects of benzodiazepines and barbiturates. If seizure control is not achieved with the use of one of these drugs, the second should be added, although not in a solution containing other drugs, as precipitation may occur. Other measures (e.g., thiopentone, hypothermia) may occasionally be necessary.

9.3. Measures to Reduce Raised Intracranial Pressure

Of the many modalities for reducing ICP, osmotic diuretics are the only agents that have been tested in malaria. Mannitol and glycerol are thought to reduce ICP by creating an osmotic gradient across the BBB, thereby causing extracellular fluid to be drawn into the intravascular space (Go, 1991). The BBB must be relatively impermeable to the agent for the gradient to develop. The decrease in ICP is correlated with the increase in plasma osmolality that these agents achieve, although the changes in ICP do not parallel the changes in osmolality (Heinemeyer, 1987). Thus, these agents may act by other mechanisms. For example, Muizelaar et al. (1984) have suggested that mannitol causes vasoconstriction by reducing blood viscosity, if autoregulation is intact. The vasoconstriction reduces cerebral blood volume and thus, ICP. In general, the reduction of ICP following the administration of osmotic agents depends upon the ICP level at which the treatment is instituted, the rate of change in the osmolality, and the degree of hyperosmolality induced (McGraw et al., 1978).

Osmotic diuretics are used in children with head injury (Muizelaar et al., 1984; Marshall et al., 1978) and Reye’s syndrome. In Reye’s syndrome, mannitol, in doses as low as 0.25 g/kg, reduces ICP (Brown et al., 1978), although repeated doses are often required (Marshall et al., 1978), and some clinicians have used continuous infusions of mannitol to control raised ICP (Berman et al., 1975). Mannitol can make the BBB more permeable and may cause a rebound phenomenon in which the ICP rapidly rises after an initial fall. This is thought to occur because the mannitol passes into the interstitial space of the brain, drawing fluid from the intravascular space (Go, 1991).

Osmotic agents may also have other effects that contribute to a reduction in ICP. Mannitol scavenges ROS, which in experimental models have been shown to be associated with raised ICP. Also, PRBC are particularly susceptible to lysis with osmotic agents (K. Silamut, N. J. White and S. Krishna, unpublished observations), although the concentrations required for lysis are significantly higher than can be achieved with the safe administration of these agents in humans. Osmotic diuretics have been used in African children with CM, but their efficacy is difficult to assess since randomised control trials have not been conducted. Kingston (1971) reported an improved outcome in Liberian children who were given 30% urea in 10% invert sugar after the children had deteriorated or were in prolonged coma. Commey et al. (1980) thought that mannitol (1 g/kg every 8 hr) improved the level of consciousness and perhaps outcome in Ghanaian children (Commey, 1984). In Kenyan children, mannitol (0.5–1.0 g/kg) reduced ICP and improved CPP in all cases, although in children with severe IH, this caused only transient improvements and did not prevent the development of intractable IH. A major question to arise from this study was whether osmotherapy contributed to the outcome in the group with intermediate IH. In 74% of children, the ICP was greater than 20 mm Hg for more than 15 min, a level that would be actively treated in most intensive care units. All of these children except one were given mannitol, and 70% had a good outcome. It was not possible to determine if severe IH was a consequence of untreated intermediate IH or whether severe IH reflects the development of widespread cerebral damage secondary to other concurrent pathogenic processes. At present, there are not enough data to recommend an empirical regimen for control of ICP.

The effectiveness of other modalities that can be used to reduce ICP has not been tested in CM. Two controlled trials of steroids have been conducted in Asian adults (Hoffman, S. L. et al., 1988; Warrell et al., 1982a), but the effect on ICP was not monitored, and steroids did not reduce mortality. Hyperventilation has not been studied in CM since most patients are not ventilated. Indeed, spontaneous hyperventilation, secondary to metabolic acidosis, may reduce the ICP and, therefore, increasing the PaCO2 in ventilated patients may increase the blood volume and precipitate transtentorial herniation in adults (Looureesuwan et al., 1995).

9.4. Correction of Hypoglycaemia

Theoretically, correcting hypoglycaemia in the presence of tissue hypoxia can worsen tissue acidosis, as original studies by Siesjo and colleagues in animal models clearly demonstrated (Siesjo, 1978). However, similar studies monitoring tissue pH responses to correction of hypoglycaemia have not been carried out in patients with CM, and would be technically and ethically challenging. Consequently, indirect measurements monitoring, for example, plasma lactate concentrations after administration of hypertonic glucose in adult patients with severe malaria suggest this procedure is not associated with major adverse systemic effects (Pukrittayakamee et al., 1991a).
The correction of hypoglycaemia (blood sugar <2.2 mmol/L) or incipient hypoglycaemia (blood sugar >2.2–3.3 mmol/L) requires hypertonic glucose (1 mL/kg of 50% dextrose or 2 mL/kg of 25% dextrose). The maintenance requirements of glucose in children with severe malaria are much higher than for uninfected children. In uncomplicated infection in Kenyan children, the rate of glucose utilisation was 5.0 (4.1–8.4) mg/kg/min (Dekker et al., 1996). Guidelines from studies carried out in adults suggest glucose should be replaced at ~3 mg/kg/min, and are presently a reasonable basis for determining glucose infusion rates (Davis et al., 1993).

Other options have been suggested for correction of hypoglycaemia in severe malaria, but none are appropriate for African children presenting with this complication. Thus, in Thai patients with hyperinsulinaemic hypoglycaemia due to quinine, Sandostatin (SMS 201-995, a long-acting somatostatin analogue) given with glucagon boluses effectively restored plasma glucose levels and reduced circulating insulin concentrations (Phillips et al., 1993). However, the treatments are expensive and have not been studied in African children, where the natural history of postadmission hypoglycaemic episodes is somewhat different. Similarly, galactose infusions in adults are readily converted to glucose, but similar studies are not available in African children (Pukrittayakamee et al., 1991b).

9.5. Acidosis

No human studies have demonstrated an improvement in mortality when lactic acidosis is treated with adjunctive therapies (Stacpoole et al., 1992). The initial management of patients with lactic acidosis from any cause, therefore, relies on the effective treatment of the underlying disease, as well as measures designed to optimise oxygen delivery to tissues and to improve tissue perfusion (Stacpoole et al., 1994). In severe malaria, this involves the rapid administration of antimalarials, correction of intravascular volume depletion and severe anaemia, anticonvulsant therapy if indicated, and general measures such as reduction in high temperature. However, in a significant proportion of patients, severe lactic acidosis still persists. In this group, an important unresolved question is whether lactic acidosis per se can contribute directly to mortality from severe disease. This question can only be adequately resolved by studying lactate metabolism in severe malaria, and then by intervening with a specific therapy to assess its impact on mortality.

Dichloroacetate (DCA) acts specifically to stimulate the rate-limiting enzyme complex pyruvate dehydrogenase, which regulates the entry of pyruvate into Krebs’ cycle (Stacpoole, 1989). Its mechanism of action is shown in Fig. 12. DCA maintains pyruvate dehydrogenase kinase in its active dephosphorylated state, allowing greater utilisation of pyruvate by aerobic metabolism, concomitantly reducing acid (i.e., free protons), as well as the lactate anion. The pharmacokinetics and pharmacodynamics of DCA have been studied in great detail in animal models and a variety of disease states in humans, and its safety in severe disease is established (Krishna et al., 1995a; Stacpoole, 1989).

DCA was first examined in malaria in a P. berghei young rat model of severe metabolic dysfunction, where it attenuated rapidly rising lactate levels when given with quinine (Holloway et al., 1991). Subsequent studies established that DCA could ameliorate malaria-associated lactic acidosis significantly more rapidly in both adults and children (Krishna et al., 1995a).
et al., 1994a, 1995a). These studies also examined the pharmacokinetics of DCA in severe disease, as well as its efficacy. In order to justify further studies in patients, a large prospective single-blind mortality study was carried out in the rodent model of severe malaria (Holloway et al., 1995). Rats with lactic acidosis due to P. berghei infections (n = 183 with lactate ≥ 5 mM) were randomised to receive either a loading dose of quinine (and saline placebo, n = 84) or quinine with DCA (n = 99). Mortality was monitored for 2 parasite life cycles (50 hr). DCA treatment significantly reduced mortality (by 33%, odds ratio > 2.2, P < 0.021) compared with placebo. These findings confirmed that DCA as an adjunct therapy with quinine in severe malaria has the potential to reduce mortality in patients. Furthermore, the previous studies in patients have already established that in spite of lactic acidosis, aerobic metabolism of lactic acid can be augmented by the addition of DCA, implying that oxygen delivery to tissues may not be the limiting factor in allowing aerobic metabolism in some patients. In order to test this hypothesis further and to assess the relevance of DCA in severe malaria, a large placebo-controlled, double-blind mortality study of DCA is now underway in Ghanaian children.

Sodium bicarbonate has been considered useful in the past in the management of lactic acidosis complicating severe disease states. However, its use may be harmful because of the dangers of volume overload and paradoxical tissue acidification (Stacpoole, 1986). We do not recommend its use in malaria-associated lactic acidosis or, indeed, in lactic acidosis complicating any severe disease. Other agents such as carbicarb have not been studied in malaria.

9.6. Anaemia and Exchange Transfusion

The role of blood transfusions in the treatment of severe malaria remains controversial. Blood transfusions are expensive and potentially dangerous in many malaria-endemic areas, since a high proportion of blood donors are hepatitis B surface antigen and human immunodeficiency virus-seropositive, and screening for these pathogens is not always possible. Other viruses (such as hepatitis C) are also common, but not routinely tested for in blood banks. For these reasons, most clinicians prefer to restrict blood transfusions to individuals with clear signs of cardio-respiratory compromise, hyperparasitaemia, or CM and associated anaemia (English et al., 1996c; Newton, 1992; Lackritz et al., 1992).

In a study of 24 Kenyan children, metabolic acidosis was attributed to anaemia in 80% of the patients (English et al., 1996b). In many children, the acidosis responded to aggressive intravascular volume repletion, although ~20% of the children continued to have sustained hyperlactataemia 4 hr after CVP guided treatment was begun, and unfortunately, the study lacked a control comparison group. Blood (20 mL/kg) was transfused if haemoglobin was 5 g/dL or below. These findings independently confirm that in the majority of survivors with metabolic acidosis due to malaria, simple resuscitative measures are sufficient to rapidly reverse metab-
antimalarial properties in its own right (Whitehead and Peto, 1990), probably by withholding iron from the parasite (Peto and Thompson, 1986; Hershko and Peto, 1988). Recently, a third mechanism has been proposed, i.e., desferrioxamine enhances interferon-γ activity and macrophage activation, and those effects promote the destruction of parasites through NO (Weiss et al., 1997). This may lead to enhancement of T1-cell-mediated immunity and possibly to impaired T2-cell responses (Thuma et al., 1996).

These observations encouraged the trial of desferrioxamine in uncomplicated infections, and more recently as an adjunctive therapy in Zambian children with CM (Gordeuk et al., 1992). In adults with mild or moderate malaria, desferrioxamine (100 mg/kg/day) enhanced the clearance of asexual parasites in the absence of other antimalarials (Mabeza et al., 1996), although recrudescences were common. In a controlled trial as an adjuvant treatment to quinine in Zambian children with CM, it appeared to reduce the duration of deep coma, and perhaps hasten the clearance of parasitaemia, although the study did not show any difference in outcome or neurological sequelae (Gordeuk et al., 1992). Gordeuk and colleagues also showed that the duration of coma was inversely proportional to the transferrin levels (Weiss et al., 1997). The significance of these clinical findings is not entirely clear, particularly because children did not receive a loading dose of quinine and control patients had unusually prolonged coma recovery times. Desferrioxamine has been combined safely with artesunate in the treatment of patients with uncomplicated malaria (Looaeesuwon et al., 1996), and further trials in CM are in progress. Indeed, a recent report on 352 children with CM concluded that desferrioxamine given as an adjunct therapy to a loading dose of quinine did not reduce mortality when compared with placebo (Thurma et al., 1998).

9.8. Anti-Inflammatory Agents

9.8.1. Corticosteroids. Steroids have long been advocated for the treatment of CM, but two controlled trials in Southeast Asian adults have shown no benefit (Hoffman, S. L. et al., 1988; Warrell et al., 1982a). The earlier trial concluded that dexamethasone (1–2 mg/kg over 48 hr) was deleterious because it prolonged coma in survivors and there was an increased incidence of side effects, such as pneumonia and gastrointestinal bleeding (Warrell et al., 1982a). The other study used larger doses (11.4 mg/kg dexamethasone over 48 hr), but was smaller and included patients who were not strictly defined as having CM. No studies have been reported in African children.

9.9. Agents that Improve Microcirculatory Flow

9.9.1. Pentoxifylline. Pentoxifylline (or oxpentifylline) is a methylxanthine derivative that has many effects of potential benefit in the management of severe malaria. It is a vasodilator that reduces red cell deformability and blood viscosity, decreasing systemic vascular resistance, and impairs platelet aggregation, thus improving microcirculatory flow. It has been shown to be useful in animal models of ischaemia, particularly during reperfusion. It is useful in the management of peripheral vascular disease, but studies in human cerebrovascular disease have been unconvincing. It prevents the neurological signs in mice infected with P. berghei, possibly by inhibiting the release of TNF (Kremsner et al., 1991). Furthermore, it inhibits rosette formation and promotes red blood cell detachment from rosettes in blood taken from Gambone children with nonsevere malaria (Lehman et al., 1997). It has been studied prospectively in a trial of African children with CM, where it appeared to reduce the duration of coma (Di Perri et al., 1995), but this study was too small to study effects on mortality with confidence. A study in nonimmune adults was abandoned because patients had more gastrointestinal complaints and there was no effect on inflammatory markers (Hemmer et al., 1997).

9.9.2. Miscellaneous agents. Heparin and dextran have been suggested as agents that may improve microcirculatory flow by reducing the viscosity of blood. No large controlled studies have been conducted. In one study, heparin (300 IU/kg intramuscularly/day) given to 21 Indonesian children with CM, as adjunct therapy to quinine did not significantly improve the outcome compared with controls or those given dexamethasone (Rampengan, 1991). It is unclear if these children were adequately heparinised, but it is unlikely that a significant difference would be found in this study (Type II error). Similarly, there is no evidence that dextran improves outcome in CM, although again, proper controlled studies have not been conducted.

9.10. Other Agents

Prostacyclin, an inhibitor of platelet aggregation, has been described in a single case report (Weston et al., 1982), but it is impossible to assess the effect on the outcome of the patient.

10. DISCUSSION AND FUTURE STUDIES

Many potentially important pathophysiological events have been identified in severe malarial infection, but the testing of appropriate interventions to reverse them still remains one of the most challenging tasks for investigators. In order to test adjunctive therapies rigorously, very large clinical trials are needed, and the infrastructure and expertise to implement such studies, even if funding were to be made available, is frequently lacking. Thus, to demonstrate a reduction in mortality with an adjunctive intervention effective at reducing mortality by 20% in severe disease where the underlying mortality is ~25%, >1000 patients will need to be enrolled. Recent studies have shown that many of the surrogate markers that have been considered useful in monitoring response to therapy in severe malaria may not correlate with the most important outcome measure, mortality. Thus, duration of coma, estimates of parasite clearance
time, and even perhaps seizures, although significantly different between treatment groups in one large study, were not associated with any difference in mortality (Tran et al., 1996b). It is, therefore, inappropriate to generalise from improvements in surrogate markers of infection (including peripheral parasitaemia) and to anticipate corresponding improvements in survival. Therefore, interventional studies on severe malaria designed to assess usefulness in management (as opposed to answering pathophysiological questions or pilot Phase II studies), perforce, will have to be sufficiently large as to assess mortality, or they should not be conducted at all.

Much of what has been learned about disease mechanisms and management of severe malaria has been derived from studies carried out in adults in Southeast Asia. As emphasised in this review, there are important differences between patterns of disease in African children compared with adults. Such differences may reflect age, genotypic variations, and patterns of transmission, as well as immunological responses. In order to optimise the treatment of severe malaria in children, more studies are necessary in this population. These studies should be designed to examine the pathophysiological basis of severe disease, as well as newer treatment regimens, particularly adjunctive therapies, and are urgently needed. Many prognostic indicators, both laboratory and clinical, are now available to identify children at risk of dying from severe infection. In assessing potentially new indicators that may then point to future interventional studies, it is important to relate these indicators to those that already have been identified. This approach of assimilating new correlates of severe disease into what is already known about infection relies on more difficult statistical techniques. It may be more statistically demanding, but it is also potentially more valuable in assessing a new prognostic indicator’s true value.

The recent advances in understanding the molecular basis of many of the central pathophysiological events in severe malaria suggest interventions that are directed at reversing these processes. We know that antimalarial drugs kill parasites, but require hours before they can exert their maximum effects. During this time, it may be advantageous to employ interventions that can immediately reverse, for example, the cytoadherence of PRBCs from capillary beds in the brains of patients with CM. Such approaches have been attempted in the past (the use of hyperimmunoglobulin in one example), and a hope for the future is that more specific therapies guided by current molecular understanding may fare better. Before such approaches can be implemented at the bedside, however, the importance of many new and exciting laboratory observations needs to be examined in geographically different patient populations.

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