A patient with proved or suspected falciparum malaria who loses consciousness is in urgent need of antimalarial drugs (given by intravenous infusion), close observation, and, if possible intensive care [1]. Use of the term cerebral malaria emphasizes the gravity of the situation, but for the purposes of clinical research and to make reports from different geographical areas comparable, a more rigorous definition is required. Cerebral malaria is an encephalopathy associated with the sequestration of parasitized erythrocytes in cerebral venules and capillaries [2,3]. It must be distinguished from the effects of high fever per se, such as minor disturbances of consciousness (drowsiness, obtundation, confusion, irritability), and the transient post-ictal coma which follows febrile convulsions in children. The wide range of neurological signs, sequelae and case mortality rates reported in the literature before 1980 suggested imprecision in the definition and diagnosis of cerebral malaria. In Thailand, we attempted to overcome this problem by defining the level of unconsciousness using the Glasgow Coma Scale [4], by requiring proof of acute P. falciparum infection by finding asexual forms of the parasite, and by excluding other locally important encephalopathies such as viral, bacterial and fungal meningoencephalitides, eclampsia, cerebrovascular accident and intoxications [5]. To exclude transient post-ictal coma, this definition required a persistence of coma for at least 6 h after a generalized convulsion. This did not, of course, imply that treatment should be delayed until this criterion had been fulfilled [6]. Level of consciousness was assessed by observing motor and focal responses to painful stimuli. For a diagnosis of cerebral malaria, we stipulated a best motor response to noxious stimuli that was ‘non-localizing’, and a best vocal response which was considered ‘inappropriate’ [4]. This level of unconsciousness was chosen because the distinction between obtundation or drowsiness and unrousable coma is clear cut, whereas minor degrees of unconsciousness are difficult or impossible to separate from the effects of fever alone. In Thailand, we chose to study patients who were more than five years old, so avoiding the difficulties of assessing the level of consciousness in younger children and of distinguishing febrile convulsions from those attributable to cerebral malaria. However, cerebral malaria in holo-endemic areas is essentially a disease of young children (aged six months to five years) and it was essential that the definition should be adapted for use in this age group.

There have been a number of clinical studies of cerebral malaria in children, but the study reported by Molyneux and his colleagues in this issue of the Quarterly Journal of Medicine is outstanding in several respects. They have been able to study a large group of Malawian children, both clinically and with detailed laboratory measurements, they have employed a strict definition of cerebral malaria and they have derived a prognostic index from their clinical and laboratory data. Their definition retains the three main criteria used in Thailand,
but they have redefined unrousable coma so that it can be diagnosed in children who are not yet able to talk. Most children recover consciousness quickly after a febrile convulsion and those with cerebral malaria recover from coma more quickly than adults, sometimes within 6 h of starting treatment. It was, therefore, decided that persistence of unrousable coma for more than 30 min after a convulsion would be accepted as evidence of cerebral malaria. Molyneux and his colleagues have modified the Glasgow Coma Scale by scoring the best motor and vocal responses to a painful stimulus. They observed whether the child’s eyes moved to watch or follow the mother’s face rather than recording eye-opening responses. This coma scale is simple and proved effective in young children with cerebral malaria in Malawi. However, the scheme is open to criticism. Attentiveness was inferred if the child’s eyes seemed to follow the mother’s face, but this could have been achieved through primitive ocular following reflexes at a subcortical level, as in some patients with the persistent vegetative state [7]. Other more complicated techniques for assessing coma in young children are the Adelaide Score [8] which is closer to the original Glasgow Coma Scale and the Seattle Coma Scale [9] which assesses both cortical and brain-stem functions. A criticism of these scales, and the system used by Molyneux and his colleagues, is that the allocation of numerical weighting for different levels of response is arbitrary and its numerical precision questionable and possibly misleading. In the case of the original Glasgow Coma Scale, the summation of the three responses assumes their equal significance and the sum conveys less information than description of the three separate responses [10].

In the Malawi study, the diagnosis of falciparum malaria was confirmed in every case but since autopsies were not possible, the definition of cerebral malaria lacks the final confirmation of finding classical histopathological appearances in the 20 fatal cases. Lumbar punctures were performed to exclude meningitis. Measurement of CSF opening pressure is not reported. In only 12 of the 131 children were convalescent serum samples tested for antibodies to a range of African arboviruses, and so this important differential diagnosis was not excluded in the remainder.

The paper contains many points of interest. The Malawian children differed in major respects from the older patients studied in Thailand [5]. Evolution of coma and recovery were more rapid; half of the children had regained consciousness within 24 h of starting hospital treatment. Convulsions were more common in the Malawian children: 82 per cent had a history of convulsions, 31 out of 131 had convulsions within 3 h of admission and in 29 they occurred later in the clinical course. Convulsions were associated with delayed recovery of consciousness and an increased risk of neurological sequelae and death. These data surely argue for the routine prophylactic use of an anticonvulsant in patients with cerebral malaria [11]. Extensor posturing, as described in Thailand [5,12] was common and, although a recognized neurological manifestation of hypoglycaemia [13], was equally common in hypoglycaemic and normoglycaemic children. Twenty-three per cent of the children were given blood transfusions, an important but increasingly difficult aspect of the treatment of severe falciparum malaria in areas of high HIV prevalence. Criteria are not fully discussed: transfusion was given ‘when the degree of anaemia was judged to be life-threatening’. The high incidence of neurological sequelae (12 of 111 survivors) was partly attributable to hypoglycaemia rather than cerebral malaria. Five cases had been hypoglycaemic (whole blood glucose less than 2.2 mmol/l) on admission, and in one of them hypoglycaemia recurred. Four of the children were hemiparetic after recovery and of these, two had been hypoglycaemic on admission. The frequent mention of hemiparesis and hemiplegia as sequels of cerebral malaria in children, especially in Francophone Africa, is intriguing and unexplained [14]. Prolonged hypoglycaemia could be a cause. The evidence for vascular occlusion, resulting perhaps from cytoadherence of parasited erythrocytes and other mechanisms, has been contradictory.
The authors' arguments for the use of a prognostic index are somewhat unconvincing. They admit that the index should not be allowed to influence the urgency or enthusiasm of treatment in this potentially fatal condition. For testing comparability of treatment groups in controlled therapeutic trials and patient populations in different studies, direct comparison of clinical observations or laboratory measurements is preferable to the use of indices.

For those practising medicine in the temperate zone, this excellent paper will be a useful reminder of the existence and importance of severe falciparum malaria. From 1977 to 1988, the annual mortality in Britain ranged from two to 12 (case mortality of *P. falciparum* cases 0.5 to 2.8 per cent) [15] whereas in West Germany case mortality from 1973 to 1977 was 9.3 per cent and in the United States from 1966 to 1984 it was 4.2 per cent. There have been two recent fatalities in England. Physicians should always consider severe falciparum malaria in patients with fever, impaired consciousness, gastrointestinal symptoms and any of the other typical manifestations and should avoid the common misdiagnoses of influenza, viral encephalitis, viral hepatitis and ‘travellers’ diarrhoea’.

REFERENCES