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Malaria

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IN THIS COMMUNICATION I intend to review, discuss and critically evaluate certain aspects of malaria which have exercised me for some years and which I hope will be of interest to an audience of physicians. I shall deal with the following topics –

1. Misconceptions in clinical malaria.
2. Controversial aspects in the treatment of cerebral malaria.
3. Treatment and prophylaxis of chloroquine resistant malaria.
4. Genetics and malaria.
5. Malaria; anaemia and pregnancy.
6. Quartan malarial nephrosis of childhood.

The geographical distribution of malaria still covers a very considerable area of the world and in some Asian countries – India, Pakistan and Bangladesh, the incidence of malaria has recently shown a considerable rise not only in rural but also in urban areas (Bruce-Chwatt, 1974). Over the past five years there has been a striking increase of malaria imported into the United Kingdom from Asia (Brit. med. J. 1974) and consequently in 1974 *P. vivax* represented 66% of all infections (Bruce-Chwatt, 1975); fortunately vivax malaria is not a directly fatal disease. On the other hand, fatal cases of malaria in visitors, especially to Africa, have averaged 6.5% of reported infections due to *Plasmodium falciparum* (Bruce-Chwatt *et al.*, 1974).

Misconceptions in Clinical Malaria

The three most common misconceptions relating to the clinical picture of falciparum malaria as it presents in Britain are – 1) the pattern of the fever, 2) the appearance of jaundice, and 3) an appreciation of the time interval between treatment and clinical and parasitic response. The *fever* in *P. falciparum* malaria, especially in primary attacks, is irregular rather than tertian; its pattern is in fact unpredictable with a daily swinging fever not uncommon, which may or may not be accompanied by rigors and profuse sweating.

Jaundice frequently occurs in severe attacks. The diagnosis that is often made, even when a history of travel to the tropics has been elicited, is infectious hepatitis. Although the latter is a very common disease, *falciparum malaria* should always be excluded first. Moreover, in infectious hepatitis the fever usually subsides with the appearance of jaundice while in *P. falciparum* infections the temperature remains elevated (Gilles, 1974).

After a successful therapeutic course of antimalarial drugs the average time interval between the onset of treatment and the clearance of fever is about 62 hours, while the average parasite clearance time is around 77 hours (Hall *et al.*, 1975). Unless this is recognised, premature condemnation of a perfectly effective and adequate therapy is made. Careful monitoring of parasitaemia is a mandatory concomitant investigation when assessing treatment.

In severe falciparum malaria, mental confusion is a very important prognostic sign necessitating emergency treatment while careful daily assessment

of renal function is mandatory to anticipate impending renal failure and institute prompt dyalisis.

Controversial Aspects in the Treatment of Cerebral Malaria

Punyagupta *et al.,* (1974) reported on 12 patients with severe falciparum malaria, all of whom had received heparin as well as other drugs. Haemoptysis was observed in 4 patients, severe gastrointestinal bleeding in 8; 9 out of 12 patients died – a staggering mortality by any standard! Neither severe gastrointestinal bleeding nor haemoptysis are common complications of acute *P. falciparum* malaria; yet the authors concluded their paper as follows – "We feel strongly that in addition to effective antimalarial drugs, adequate doses of heparin, steroids and low molecular weight dextran should be given at the earliest moment to patients with acute *P. falciparum* who present with one or more severe clinical complications, or with early laboratory evidence suggesting D.I.C., whether or no coagulopathy is evident".

Although severe falciparum malaria may be associated with intravascular coagulation, its pathogenic significance remains uncertain and it could even be a protective reaction (Reid and Nkrumah, 1972); moreover, therapeutic defibrination by ancroid ('Arvin') benefited neither patients with cerebral malaria (Reid and Nkrumah, 1972) nor monkeys with knowlesi malaria (Reid and Sucharit, 1972). In human falciparum malaria heparin has caused haemorrhage which may well have contributed to death (Borochovitz *et al.,* 1970; Smitskamp and Wolthuis, 1971). Like Reid (1975) I feel that heparin is unlikely to benefit patients with cerebral and other forms of severe malaria. In this context, it is interesting to record the findings of Elmes (1975) in Belfast who reported that heparin headed the list of iatrogenic admissions to hospital due to drugs.

Clinical or pathological evidence in favour of cerebral oedema in cerebral malaria is unconvincing yet it has been claimed that steroids benefit such patients by relieving this oedema. Since a short course of dexamethasone (or any other steroid preparation) is unlikely to harm the patient and may possibly give some benefit, I think it is justifiable to give steroids, as adjuvant treatment in cerebral malaria on empirical grounds. I have certainly witnessed a few African children recover from a 3 day coma due to *P. falciparum* when parenteral chloroquine alone was administered; nor should one ignore the fact that both quinine and chloroquine have well known anti-inflammatory properties.

Genetics and Malaria

At least two genes affecting red cells confer relative resistance against *P. falciparum;* the autosomal gene for haemoglobin S and the sex linked gene for the glucose-6-phosphate-dehydrogenase variant named A^-. Whereas for these genes malaria selection can be regarded as established, it is still a hypothesis for some other polymorphic traits of red cells (Allison, 1954; Allison and Clyde, 1961; Gilles *et al.,* 1967; Edington and Gilles, 1975).

Intracellular parasitism brings about an extreme degree of contact between two completely different genomes. Therefore, it is not surprising if sometimes unusual features arise. A case in point is that of malaria infection of G-6-PD-normal and G-6-PD-deficient red cells. Here it is found that, in heterozygous females who have in their blood a mixture of these two cell types, the G-6-PD-normal cells are infected preferentially (Luzzatto *et al.,* 1969), and these persons enjoy relative protection against *P. falciparum* (Bienzle *et al.,* 1972). However, in homozygous males having only G-6-PD-deficient cells no protection is apparent. These findings have led to the suggestion that adaptation of the parasite to a particular cell type may place it at a disadvantage when confronted alternatively with two different types of erythrocytes (Luzzatto, 1972).

Allison (1957) suggested that the increased levels of fetal haemoglobin (HbF) which are associated with some form of thalassaemia might protect against malaria, and there is data to suggest that falciparum malaria infection correlates inversely with the level of HbF in infants during the first 3 months of life (Gilles, 1957). We have approached this problem in two ways. First, we have examined the red cells of infants with *P. falciparum* infection to see if there is any difference in the distribution of parasites between cells carrying predominantly HbA as compared with HbF; secondly, we have looked at the relative degree of parasitization of fetal and adult cells in tissue culture. The preliminary results indicate clear-cut differences in both distribution and degree of parasitization of fetal as compared with adult haemoglobin-containing cells (Pasvol *et al.* 1976).

Miller *et al.* (1975) have recently suggested that Duffy blood groups determinants (Fy^a or Fy^b) may be erythrocyte receptors for *P. vivax,* and that this phenomenon may explain the insusceptibility of West Africans to vivax malaria, since Duffy negative erythrocytes occur in high frequency in West Africa.

Treatment and Prophylaxis of Chloroquine-resistant Malaria

Chloroquine-resistant *Plasmodium falciparum* strains are known to occur in various parts of South America, e.g. Brazil, Colombia, Venezuela and in Southeast Asia, e.g. Thailand, Vietnam, Laos, Cambodia, Malaysia, Indonesia, West Irian and the Philippines. Any patient who has contracted falciparum malaria in these areas should be considered for practical purposes as having been infected by a chloroquine resistant strain and treated as such whether seriously or moderately ill. Until recently, 16 different regimens involving 12 drugs administered over 1 to 14 days were recommended (WHO. 1973). A recent paper by Hall *et al.,* (1975) has improved matters considerably and has rendered the treatment of chloroquine-resistant malaria simple and effective. It consists of quinine (at least four doses given at intervals of 8 to 12 hours) followed by a single dose of sulfadoxine-pyrimethamine (Fansidar). A slight modification of this regimen for adults who are not severely ill is given below –

Day 1. Quinine sulphate (orally) 540 mg. base (2 tablets) 12 hourly.

Day 2. Quinine sulphate (orally) 540 mg. base (2 tablets) 12 hourly.

Day 3. Quinine sulphate (orally) 540 mg. base (2 tablets) 12 hourly.

Day 4. Pyrimethamine 75 mg. + Sulfadoxine 1500 mg. (Fansidar: 3 tablets)

The reasons why I advocate 3 days of quinine instead of 2 are as follows – a) in 82% of Hall's series at least one dose of quinine was given by intravenous infusion thus ensuring optimal absorption which cannot be guaranteed with oral therapy, especially in the first days of malarial illness when gastrointestinal disturbances are not uncommon, b) in Hall's own series the *average* course of quinine was 3 days. The dose of Fansidar can also be given on Day 1.

For severely ill patients, parenteral quinine given by slow intravenous infusion is mandatory and will have to be continued until oral therapy (as above) is possible. The progress of the parasitaemia should be monitored twice daily.

Malaria. Anaemia and Pregnancy

In areas where falciparum malaria presents a 'stable' pattern, adults usually suffer little overt disease because of their acquired immunity. However, during pregnancy, and especially in primiparae there is a temporary loss of this immunity manifested by certain specific features. Firstly, there is a dramatic increase in both parasite rates and densities (Kortman, 1971). Secondly, a very marked haemolytic anaemia occurs which bears little relation to the density of the falciparum parasitaemia and it is thought that the effect might be immunologically mediated. However, there is no doubt that malaria is implicated, since prophylactic antimalarial treatment results in a dramatic fall in the incidence of anaemia of pregnancy in primiparae (Gilles *et al.,* 1969).

The mechanisms involved in this loss of immunity to falciparum malaria in pregnancy are not known, although Cohen and McGregor (1963), found that turnover rates of IgG were much lower in pregnant women than in other adult Gambians. A baffling feature of this temporary loss of immunity is that it seems to be selective to the haemopoietic system, since the other severe manifestations of malaria, e.g. cerebral, are not usually seen.

Quartan Malarial Nephrosis of Childhood

The tropical medical literature contained many references regarding some association between quartan malaria on the one hand and nephrosis on the other (Atkinson, 1884; Giglioli, 1930). Unfortunately, many of the early workers often made free and interchangeable use of terms such as 'nephritis' and 'nephrosis', and differentiation between the nephrotic syndrome in children and in adults was frequently ignored; moreover, the epidemiological evidence produced for the association was not devoid of flaws. Thus, in the first edition of the texbook 'Diseases of Children in the Tropics and Subtropics' (Trowell and Jelliffe, 1958) the following paragraph appears – "there is considerable disagreement in the literature concerning the incidence and nature of nephrosis in malaria ..... the question of an association must, therefore, still be considered unproven".

Irrefutable proof of this association came from the studies of Gilles and Hendrickse (1963) who found that almost all of their West African children with nephrosis also had demonstrable *P. malariae* infection. In contrast, in only a small minority of the non-nephrotic children could quartan malaria be detected. In both groups, however, the prevalence of *P. falciparum* was not significantly different (Fig. 1.). Hendrickse and Gilles (1963) first advanced the suggestion that the nephrotic syndrome might be due to glomerular damage caused by the deposition of immune complexes. There is now much evidence to support this point of view (Ward and Conran, 1969; Allison *et. al.,* 1969; Houba *et al.,* 1971; Voller *et al.,* 1971).

Conclusion

Malaria still remains the most important of the acute imported diseases into the United Kingdom and the dictum first pronounced by Maegraith in 1963 'Unde Venis' – where have you come from – remains as pertinent as ever.

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