RECENT ADVANCES IN

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TROPICAL MEDICINE

Edited by

H. M. Gilles

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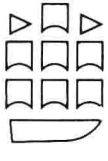

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To Mejra

Preface

It is over 20 years since the last issue of 'Recent Advances in Tropical Medicine', but no attempt has been made in this volume to span this long period. Rather, we have concentrated on advances in the last decade and especially in the previous five years. The impetus provided by the WHO/World Bank Special Programme for Research and Training in Tropical Diseases is reflected in the choice of diseases selected for review and no pretence is made to cover *all* the advances in *all* of the tropical diseases. The special WHO programme for control of the diarrhoeal diseases made a review of this important cause of morbidity and mortality in the Third World imperative.

The importance of basic research is reflected in the inclusion of an account of the 'experimental aspects' for some of the diseases while the application of modern technological advances to the better understanding of tropical disease is covered in some of the general chapters. For reasons of length, references have been provided selectively and the emphasis has been laid on more recent references, particularly in chapters 1, 4, 5, 8, 13 and 14. It is hoped that subjects not included in this volume will be dealt with in subsequent ones which, hopefully, will not be overdue.

H. M. GILLES

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INTRODUCTION

There has been a significant increase of malaria in recent years, of a particularly serious nature in South East Asia (Sharma & Mehrotra, 1982) and to a lesser extent in Central America; while the situation in tropical Africa has remained virtually unchanged. The development of multidrug resistant falciparum malaria poses a threat to the lives of millions of people. The number of cases of malaria reported to WHO is on the increase and are certainly an underestimate. The global malaria situation is shown in Figure 1.1. Hundreds of millions of people are still living in malarious areas (Wyler, 1983). The global morbidity and mortality is impossible to accurately assess; it is estimated that in tropical Africa alone more than one million malaria-related deaths occur annually (Editorial Lancet, 1975). Statistical demographic data from the Garki project in Northern Nigeria showed that the variation in the infant mortality rate between years and between seasons was associated with the infants' exposure to *P. falciparum* (Molyneux & Gramiccia, 1980). Despite the recession, air as well as all other forms of travel are on the increase. Cases of 'imported malaria' are regularly reported from Europe, Australia and the USA (Black, 1981; Nemirovskaya et al, 1981; Bruce-Chwatt, 1982 a and b; Morbidity and Mortality Weekly Report, 1982; Walker & Brodie, 1982). In 1982, 1471 cases were reported in the United Kingdom. Instances of unusual malaria transmission in individuals who had not travelled abroad have occurred in England, Belgium, France, Holland and Switzerland (Holvoet et al, 1982; C.D.R., 1983) when infected mosquitoes from malaria endemic areas were transported on incoming aircraft inadequately sprayed with knock-down insecticides. In non-endemic areas unnecessary deaths from malaria — there were 12 in the UK in 1982 — continue to occur because some practitioners still refuse to take a *geographical history*, or ignore it when it is provided; preferring to rely on their clinical judgement rather than carry out blood examinations to rule out the possibility, or giving the patient the benefit of any doubt by providing 'presumptive' antimalarial therapy. A limited survey of hospital pharmacies in England and Wales revealed that only a quarter of them stocked parenteral antimalarial drugs (Kapila et al, 1982), a far from satisfactory situation.

(a) Clinical aspects

H. M. Gilles T. Harinasuta D. Bunnag

In attempting to emphasize some of the advances in the clinical field we have only sought to highlight certain features which either seemed to have attracted special or

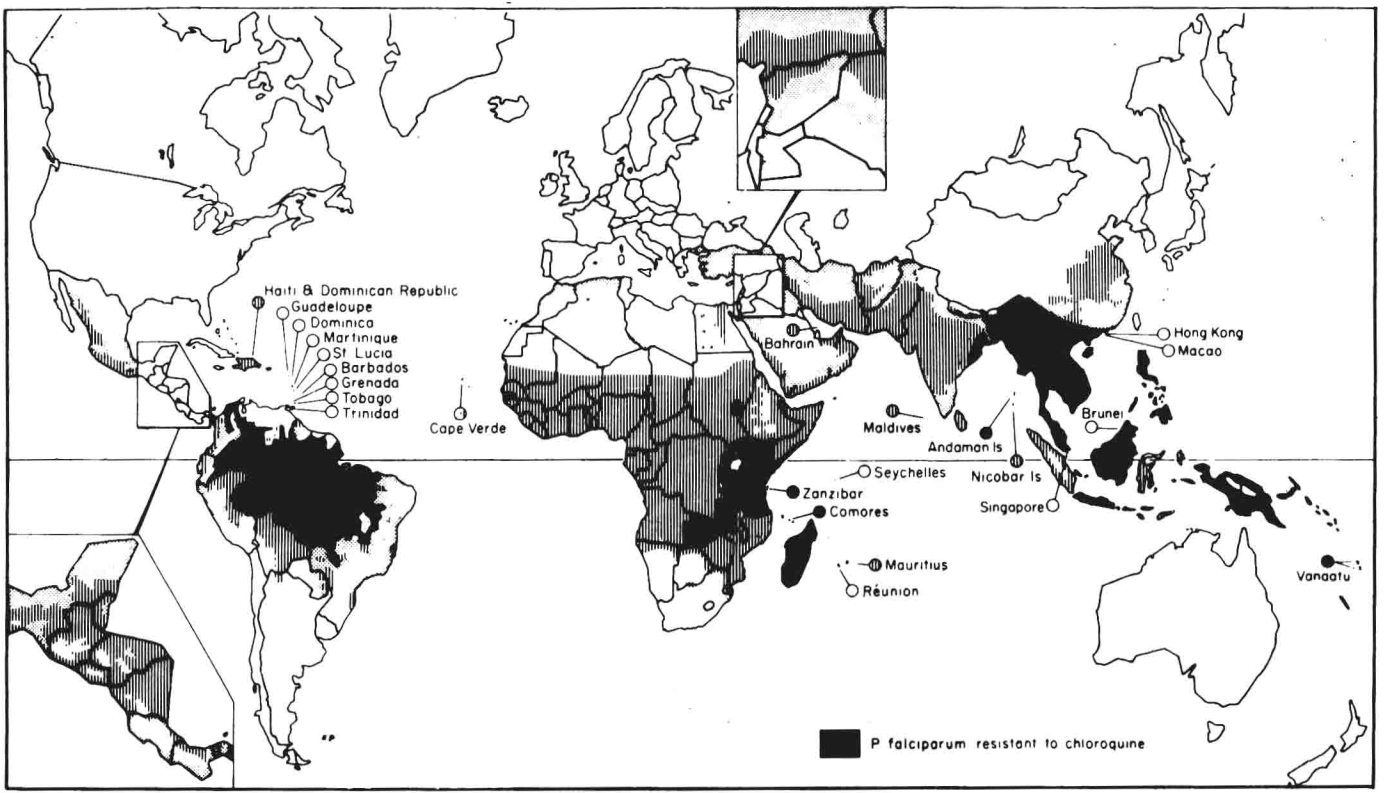

Fig. 1.1 Epidemiological assessment of status of malaria, June 1982

renewed attention or as in the case of chemoprophylaxis and chemotherapy have become controversial and complex.

Clinical features

a. *Plasmodium falciparum*

Some relatively mundane aspects of falciparum malaria are in need of re-emphasis. Firstly, that none of the symptoms and signs of malignant tertian malaria is specific; that malaria is a great mimic of other diseases (Senanayake & Wimalawanga, 1981; Buck et al, 1983), in particular of influenza and viral hepatitis; that in a comatose patient all other causes of encephalopathy must be excluded; that although in most patients cerebral malaria is associated with hyperparasitaemia in some this is not the case. This is due either to previous but inadequate treatment — and in this context it is important to remember that self-medication with antimalarials is increasingly occurring in the tropics — or to the sequestration of parasites in the deep capillaries. In a recent outbreak of *P. falciparum* malaria among military recruits in Ethiopia (350 cases), the most common clinical signs were enlargement of the spleen and liver. Jaundice was present in 9% and 4% had cerebral manifestations (Habte-Gabr et al, 1981).

A series of meticulously carried out clinical studies on severe falciparum malaria in Thailand has resulted in providing new and important observations on the varied and serious manifestations of this disease, as well as on their management (Warrell et al, 1982; Looareesvwan et al, 1983; White et al, 1983a). Some of the clinical observations are worthy of special mention; (1) *retinal haemorrhages* are common, (2) CSF opening pressure is usually normal, (3) *cerebral oedema* may occur in cerebral malaria but is not a consistent feature — it occurred in only two out of ten cases (5 fatal) studied by computerised tomography (4) *hypoglycaemia* may occur on the second day of treatment and when the parasitaemia is declining (Migasena, 1983). Two groups of patients with falciparum malaria seem to be at particular risk for the development of hypoglycaemia which may be profound and *recurrent* — (a) patients with severe malaria, (b) pregnant women. The diagnosis should be considered in any malaria patient but especially in those with severe disease if there is a change in the level of consciousness; deepening coma; abnormal behaviour; fits or any other sudden unexplained deterioration in the clinical condition of the patient. Recurrent hypoglycaemia despite administration of intravenous dextrose presents a major management problem. The pathogenesis is complex involving (a) quinine-induced hyperinsulinaemia, (b) the glucose requirements of the malaria parasites, and (c) possibly endotoxaemia (Tubbs, 1980; White et al, 1983a). (5) *septicaemia* with clinical manifestations varying from none to the extremes of endotoxic shock require prompt and appropriate antibiotic therapy — persistent fever and shock may indicate bacterial superinfection (Bygberg & Lanng, 1982), (6) the importance of DIC has been exaggerated, less than 5% of patients with cerebral malaria have overt DIC with bleeding and the best treatment for DIC with bleeding in malaria is transfusion of fresh blood *not* anticoagulants, (7) *thrombocytopaenia* is common and recovers spontaneously when the malaria is treated, (8) neurological features include dysconjugate ocular deviation; recoverable decerebrate rigidity, ataxic respiration and extrapyramidal signs (Jayaweera et al, 1977), (9) rapid complete recovery from deep coma

is the rule, (10) acute renal insufficiency is an important complication (Bourdais et al, 1980), (11) because of the plethora of complications that can occur in cerebral malaria, patients should ideally be nursed in an intensive care ward.

The use of *steroids* in cerebral malaria, although widely adopted in the past (including by us) never had a sound scientific basis. It was based on the assumption now proved largely incorrect — that there was *commonly* oedema of the brain in these cases and in the belief — now proved erroneous — that even if it did not do much good, it did no harm. In one of the most beautiful and exacting pieces of clinical research done in tropical medicine in recent years Warrell and his colleagues conclusively confirmed that steroids should no longer be used in cerebral malaria. As might have been expected, a few voices were raised in dissent while most people (including us) have accepted the result unreservedly (Bell, 1981; Hall, 1982; Warrell et al, 1982; Rees, 1982; Warrell et al, 1983b).

Delay in starting treatment, a high parasitaemia, impairment of renal function pulmonary oedema, metabolic acidosis and hypoglycaemia are some of the factors affecting prognosis in falciparum malaria (Ebisawa et al, 1980).

b. *Plasmodium vivax*

In a study from Madang in New Guinea the commonest clinical presentation in children was fever and cough (Darlow et al, 1981). A new subspecies *P. vivax multinucleatum* seems common in north and central China. It has a long incubation period 312–323 days, and relapses occurred in all three volunteers 66–69 days after primary infection (Jiang et al, 1982).

An unusual and peculiar presentation of *P. vivax* infection with fever, oedema of the face, hypotension and high IgE values (8000 IU : normal 594 ± 378) was recorded from India (Sharma et al, 1979).

As might have been expected fansidar was less effective for the treatment of *P. vivax* malaria in children in Papua New Guinea than chloroquine. Fever resolution as well as parasite clearance were slower and longer respectively (Darlow et al, 1982a).

A comparative trial of oral chloroquine and oral cotrimoxazole in children aged 6 months to 12 years, with vivax malaria in India showed that cotrimoxazole was acceptable for the treatment of vivax malaria in children because the drug caused less vomiting than chloroquine and all patients responded. Asymptomatic sulphonamide crystalluria was seen in 48 of 98 children given cotrimoxazole (Lal, 1982).

Malarial anaemia

Anaemia is one of the most important complications of malaria, especially in children. It has long been maintained that *P. falciparum* invades red cells indiscriminately, yet recent in vivo and in vitro studies have demonstrated that the rate of parasite invasion was higher in young than in old red cell populations (Pasvol et al, 1980) — a situation not dissimilar to *P. vivax* and *P. ovale* infections. An excellent review of the subject has recently been published (Weatherall & Abdalla, 1982). The pathophysiology of malarial anaemia is still far from clear, not only are the mechanisms multifactorial reflecting an extremely complex series of interactions involving parasite red cell destruction; erythrophagocytosis; inhibition of reticulocyte release; depression or ineffective erythropoeisis, immune mechanisms and dyserythropoeisis, but that the

predominant mechanisms may differ in acute infections with high parasitaemias from chronic *P. falciparum* malaria with low parasitaemias (Abdalla et al, 1980; Facer, 1980).

Exchange transfusion may be a life-saving measure if 25% or more of the red cells are parasitised (Kramer, 1983).

Malaria and pregnancy

Malaria, especially *P. falciparum*, is more hazardous during pregnancy with a mortality in severe disease which is 10 times higher than that of other patients (Warrell et al, 1982). Both prevalence and density of infection are higher particularly in primiparae, and a severe haemolytic anaemia develops in the second trimester (Bray, 1981; Bah et al, 1982). In a recent study from Zambia, more anaemia and malaria frequency was found in primigravidae than in multigravidae (Van Dongen & Van't Hof, 1983). Hypoglycaemia occurs more frequently in pregnant patients (White et al, 1983).

Acute malaria in a pregnant woman requires prompt treatment since it presents a great danger to both mother and foetus. In Zimbabwe, malaria was regarded as a cause of hyperpyrexia and abortion in the first trimester, while in the third trimester it was responsible for premature labour and the perinatal death of one infant in every six born (Heid & Jordan, 1981). McGregor et al (1983) in their Gambian studies found 20% of placentas to be malarious, the figure rising to 47% in rural primiparous women. No increase in stillbirths related to placental infection was found but as in previous studies the birthweight of infants was reduced by about 170 g. The prevalence and intensity of malaria were not uniformly distributed among parturient women, but affected primigravidae to a significantly greater extent than multigravidae. Microscopic observations on the human placenta in malaria infection in Nigeria confirmed previous findings.

Fear that quinine — in the dosages normally used for therapy — may cause abortion is exaggerated, especially as a suggested alternative of Fansidar with a folinic acid supplement is hardly acceptable for the severely ill patient. Chemoprophylaxis throughout pregnancy while in an endemic malarious area is imperative. There is no evidence of teratogenic effects of chloroquine, or proguanil, and any one of these two drugs can be used in areas where strains are sensitive to chloroquine (Editorial Lancet, 1983). For *chloroquine resistant areas* the problem is more complex and difficult. There is no evidence of any teratogenic effects when Maloprim (pyrimethamine with dapsone) is given at the recommended adult dose of one tablet a week (Bruce-Chwatt, 1983), the makers, however, do not recommend its use in the first 3 months of pregnancy. Current opinion does not advocate the use of fansidar in pregnancy although this policy has recently been challenged and it has been proposed, on the basis of available evidence, that the injunction against its use during pregnancy should be lifted in areas where there is good reason for its deployment (Editorial Lancet, 1983).

The practice of one of us (HMG) is to advise proguanil 200 mg daily, together with chloroquine 300 mg base once weekly for the first three months, and then continue with one tablet of maloprim once weekly + proguanil 200 mg daily or maloprim one tablet + chloroquine 300 mg base once weekly for the rest of the pregnancy. The time honoured methods of protection from mosquito bites are emphasised and folic acid

supplements are also given during the gestation period. *Prompt* treatment of a malaria breakthrough is urged.

Congenital malaria

Congenital malaria is increasingly being reported from various parts of the world.

A 6-week-old breast fed infant of an Indian mother was admitted in a hospital in California with fever, hepatomegaly splenomegaly. Blood films revealed a double infection of *P. vivax* and *P. malariae*. The mother had lived in the USA for the previous year (MacLeod et al, 1982). Four more cases were reported in infants born of Laotian and Vietnamese mothers. Between January 1980 and July 1981 no less than 13 cases of congenital malaria were reported in the USA (Quinn et al, 1982). Other cases have been reported from Sweden, Sri Lanka, Thailand, and Malaysia.

Anti-sporozoite antibodies were found in 18/20 Gambian mothers and 17/20 of their newborn infants $1\frac{1}{2}$ months after birth. High titre mothers had high titre infants but by $7\frac{1}{2}$ months only one infant was positive. No infant showed a parasitaemia at $1\frac{1}{2}$ months (Nardin et al, 1981).

Primaquine is not required in the treatment of congenital malaria because there are no 'hypnozoites'.

Nutrition and malaria

Clinical observations as well as autopsy records from Nigeria indicate that severely malnourished children are less prone to the more serious consequences of infection with *P. falciparum* than well nourished children (Hendrickse et al, 1971; Edington & Gilles, 1976). In this context Targett (1981) demonstrated that rats fed on a high protein diet were highly susceptible to infection; as the protein content of the diet was reduced levels of parasitaemia decreased until, on a protein free diet, only a transient patent infection occurred. Similarly, rats which were chronically undernourished developed only a low-grade parasitaemia. An interesting relationship between riboflavin status and malaria in infants in Papua New Guinea suggesting that riboflavin deficiency in infants may be protective has been reported (Thurnham et al, 1983).

In a critical assessment of the nutritional implications of malaria McGregor (1982) expresses the view that, although deficiencies of some dietary factors may potentiate the resistance to malaria conferred by some genetic traits, there is as yet little convincing evidence that malnutritional states in humans materially enhance the severity or lethality of plasmodial infections.

Brabin (1982) hypothesises on the importance of folacin in influencing susceptibility to malarial infection in infants. Children between 12 and 23 months in the Sau Valley of New Guinea which is malarious, showed a much higher proportion of stunting than those of the same age group in the 'malaria free' Lagarp Valley. Both communities share a common cultural tradition, language and staple diet (Sharp & Harvey, 1980).

Malarial nephrosis

While the basis of the nephrotic syndrome has been clarified to some extent in West and East Africa by epidemiological, clinical and immunopathological studies (Hendrickse, 1980), studies from Papua New Guinea indicated that *P. malariae* was

unlikely to be the common cause in this area. Studies on *P. malariae* antigenaemia and elution studies looking for *P. malariae* antibody within glomeruli and perhaps also *P. malariae* antigen could provide more conclusive proof for or against *P. malariae* being the aetiological factor in this area (Duggin, 1981). Whatever the outcome of further investigations, it would seem likely that in the tropics other chronic viral, bacterial, parasitic infections or intoxications could create immune complexes which are potentially damaging to the renal glomerulus and thus, there may be many factors other than *P. malariae* leading to the nephrotic syndrome, e.g. Schistosoma mansoni.

It is unwise to extrapolate findings from one country to another or even from one area of a country to another area with different ecological features. The association with *P. malariae* was not found in Accra nor in Abidjan (Ivory Coast) or Dakar (Senegal). On the other hand none of these hospital based studies took into consideration the increase in self antimalarial medication that has occurred in these cities in recent years, nor whether antimalarials were given at the outpatient clinic prior to referral. In an earlier study in Ibadan (Nigeria) no association could be found between *P. malariae* and nephrosis until it transpired that all the children were first seen at the outpatient department and given chloroquine prior to being referred to the renal specialists clinic!

In Accra, the histopathological lesion designated 'quartan malarial nephropathy' was not found (Adu et al, 1981).

Tropical splenomegaly syndrome (TSS)

It is now generally accepted that malaria is intimately involved in the aetiology and pathogenesis of TSS but contrary to earlier belief, it is not any one particular species of malaria that is involved. Among the important diagnostic criteria which differentiate TSS from the many other causes of splenomegaly in the tropics can be listed the following—(1) gross splenomegaly > 10 cm below the coastal margin and anaemia, (2) high titres of malarial antibodies, (3) serum IgM at least two standard deviations above the local mean, (4) reduction in spleen size; significant lowering of IgM and fluorescent malarial antibody titres within 3 months of continuous antimalarial prophylaxis, (5) hepatic sinusoidal lymphocytosis is found in most patients, (6) normal cellular and humoral immune responses to antigenic challenge, (7) a normal phytohaemagglutinatin (PHA) response, (8) hypersplenism occurs only in some cases and may be related to the extent of the splenomegaly, (9) there may be peripheral lymphocytosis and infiltration of the bone marrow by mature lymphocytes, (10) there is a plasma volume expansion due at least in part to increased albumin and IgG turnover. All the evidence points to overproduction of IgM resulting from stimulation of B lymphocytes by a malaria antigen or mitogen, as being the basis for the development of TSS (Greenwood & Fakunle, 1979). Splenectomy is associated with a high operative mortality and reduces the resistance of the patient to infections such as pneumonococcal septicaemia, malaria and babesiosis (Tsuchida et al, 1982).

Two excellent reviews of the subject have recently appeared (Crane, 1981; Fakunle, 1981).

Red cell factors and malaria protection

Evidence for and against protection from malaria by inherited red cell factors has been gleaned over the years from epidemiological, clinical and autopsy evidence (Luzzatto, 1979) and more recently at the cellular level from short-term and continuous

cultivation of *P. falciparum*. A recent review by Pasvol & Wilson (1982) has emphasized that experimental results from in vitro cultivation should be interpreted with caution since protective mechanisms in humans are likely to be multifactorial rather than single.

The wealth of available evidence is in favour of the hypothesis that Haemoglobin S heterozygotes are protected against the *lethal* effects of falciparum malaria. Metabolic as well as physical mechanisms — decrease in intracellular pH and deoxygenating haemoglobin; leakage of potassium ions from A S cells upon deoxygenation; and increased membrane rigidity — may prevent the multiplication of malaria parasites in A S cells.

Clinical studies on Haemoglobin C heterozygotes have rarely shown a protective effect and in vitro studies have also been inconclusive.

Parasite growth is retarded in the presence of HbF in cord-blood cells; in Hb-F containing cells obtained from infants and in cells obtained from adults with hereditary persistence of fetal haemoglobin (Pasvol et al, 1977). High HbF may play a part (in combination with maternal IgG) in the protection of new-born infants from severe malaria in endemic areas and in the protection of B thalassaemia heterozygotes.

Recent studies from Liberia (Willcox et al, 1983) have demonstrated a protective effect from falciparum malaria in B thalassaemia heterozygotes who had significantly lower densities of parasites than controls as well as lower malarial antibody titres consistent with less antigenic stimulation. Moreover, Beta thalassaemia heterozygotes suffered less morbidity and had relatively fewer pernicious *P. falciparum* infections than normal children. These findings are positive evidence for the malaria/beta thalassaemia hypothesis. Under oxidant stress Friedman (1979) was able to demonstrate a reduction in the number of parasites when they were grown in thalassaemic cells.

Epidemiological and clinical studies in Thailand where Haemoglobin E is common, carried out many years ago indicated that the HbAE heterozygote is not protected against the lethal effects of falciparum malaria, the numbers involved were, however, small and these important studies have not been repeated. In vitro experiments have produced conflicting results. Santiyanout & Wilariat (1981) found a marked reduction in parasite multiplication in EE cells.

Ovalocytosis which has a dominant inheritance, is a common red cell abnormality in the malarious coastal regions of New Guinea and these red cells are resistant to penetration by *P. falciparum* (Castellino et al, 1981; Kidson et al, 1981).

The position regarding G-6-PD deficiency and the malaria hypothesis is confusing. Significantly lower parasitaemia was found only in heterozygous females with genotype Gd^{A-}/Gd^{B}, (Bienzle, 1981); on the other hand severe *P. falciparum* infections were found in G-6-PD deficient individuals (Martin et al, 1979). Friedman (1978) demonstrated that parasites in G-6-PD deficient cells are more readily damaged by the effects of oxidants than they are in non-deficient cells yet Pasvol & Wilson (1982) were unable to detect reduced invasion or growth when *P. falciparum* was cultivated in cells from individuals with the African form of G-6-PD deficiency in the absence of oxidant stress. To complicate the issue even further, a G-6-PD of parasite origin has now been identified in cells infected with *P. falciparum* (Hempelmann & Wilson, 1981).

No association has been found between malaria infection and the A B O blood