The Six Diseases of WHO

Malaria

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The global situation of malaria does not provide cause for complacency as may be seen from the map (fig 1) and the number of cases of malaria reported to WHO in 1979 (table).

Number of cases of malaria reported to WHO in 1979

Africa south of the Sahara	5·80 million (31 countries)
India	3·1 million
Bangladesh	50 000
Pakistan	12 000
China	2·4 million
Thailand	303 000

In 1980, 1670 cases were recorded in Britain with seven deaths due to *Plasmodium falciparum* malaria, while the mid-year figure for 1981 was 584. As in recent years, *P vivax* was the predominant species of parasite, and the main categories of patients were: (*a*) immigrants after visiting their relatives in the tropics, predominantly the Indian subcontinent, (*b*) businessmen and technologists on contract work in malarious areas, (*c*) holidaymakers, and (*d*) recently arrived immigrants.

Clinical features

The incubation period of malaria (the time between the infection and the first appearance of clinical signs) is shortest for *P falciparum* (12 days) and longest for *P malariae* (average 28 days). The average for *P vivax* is 13-17 days, but some strains show much longer incubation periods of up to nine months. The relapses in *P vivax* and *P ovale* are now thought to be due to the presence of latent cryptozoites—"hypnozoites."[1] For all types of malaria fever is the most common presenting sign.

FALCIPARUM MALARIA

In non-immune people there is little that is typical about falciparum malaria, and its many and various symptoms can be very misleading. The periodicity of the fever is irregular, especially in first attacks, and often of daily occurrence. Headache, malaise, nausea, vomiting, and generalised joint pains may be the only additional presenting symptoms of an uncomplicated attack. On physical examination the liver and spleen may be enlarged, depending on how long the infection has been present, and there may be a variable degree of anaemia.

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This rather undramatic clinical picture can deteriorate suddenly into one with severe manifestations where treatment may be hopeless. Abdominal presentations resembling appendicitis and acute abdomen have been described. Among the "pernicious" manifestations of malaria, the commonest are cerebral malaria, renal failure, hepatic failure, and severe anaemia with or without haemoglobinuria. Confusion is a warning sign that cerebral complications are imminent, and in more advanced stages the patient presents with convulsions, or coma, or both, hyperpyrexia, and localised neurological signs. Oliguria followed by acute renal failure may also occur, and urinary output and blood urea should be monitored regularly to detect the early onset of oliguria and acute renal failure for which haemodialysis or peritoneal dialysis is often life-saving. Jaundice with or without hepatic failure is a manifestation that is often misdiagnosed as infectious hepatitis. Heart failure as well as haemoglobinuria may accompany the severe anaemia. Other less common complications are diarrhoea (occasionally with very watery stools as seen in cholera), electrolytic changes, pulmonary oedema, and shock.

In *semi-immune people* malaria produces little clinical disturbance except in pregnancy; in immunosuppressed patients, especially those taking steroids; or in individuals who have undergone splenectomy. In semi-immune people falciparum malaria causes a mild fever and general malaise lasting for a few days, but the severe complications of malaria do not develop. Symptomless parasitaemia is not uncommon.

VIVAX MALARIA

Fever is the most constant sign of vivax malaria. After a brief period of remittent fever the pattern of intermittent fever occurring every other day becomes established. The classic features of the attack—cold stage, hot stage, sweating stage—are unusual in infants and children. General symptoms similar to those described for *P falciparum* infection may occur but are usually milder. The spleen enlarges early in the disease, some degree of anaemia may be present, and there is often mild leucopenia. Pernicious complications are rare, but if fever is high convulsions may occur in children. Vivax malaria per se is rarely lethal.

Diagnosis

The only certain proof of the infection is the finding of malarial parasites in the peripheral blood, and this examination should never be neglected. In patients with severe clinical symptoms the diagnosis is usually clear after looking at only a few fields with an oil immersion lens. In most cases the seriousness of the infection is proportional to the density of parasitaemia, but difficulty arises in the patient who has taken a small dose

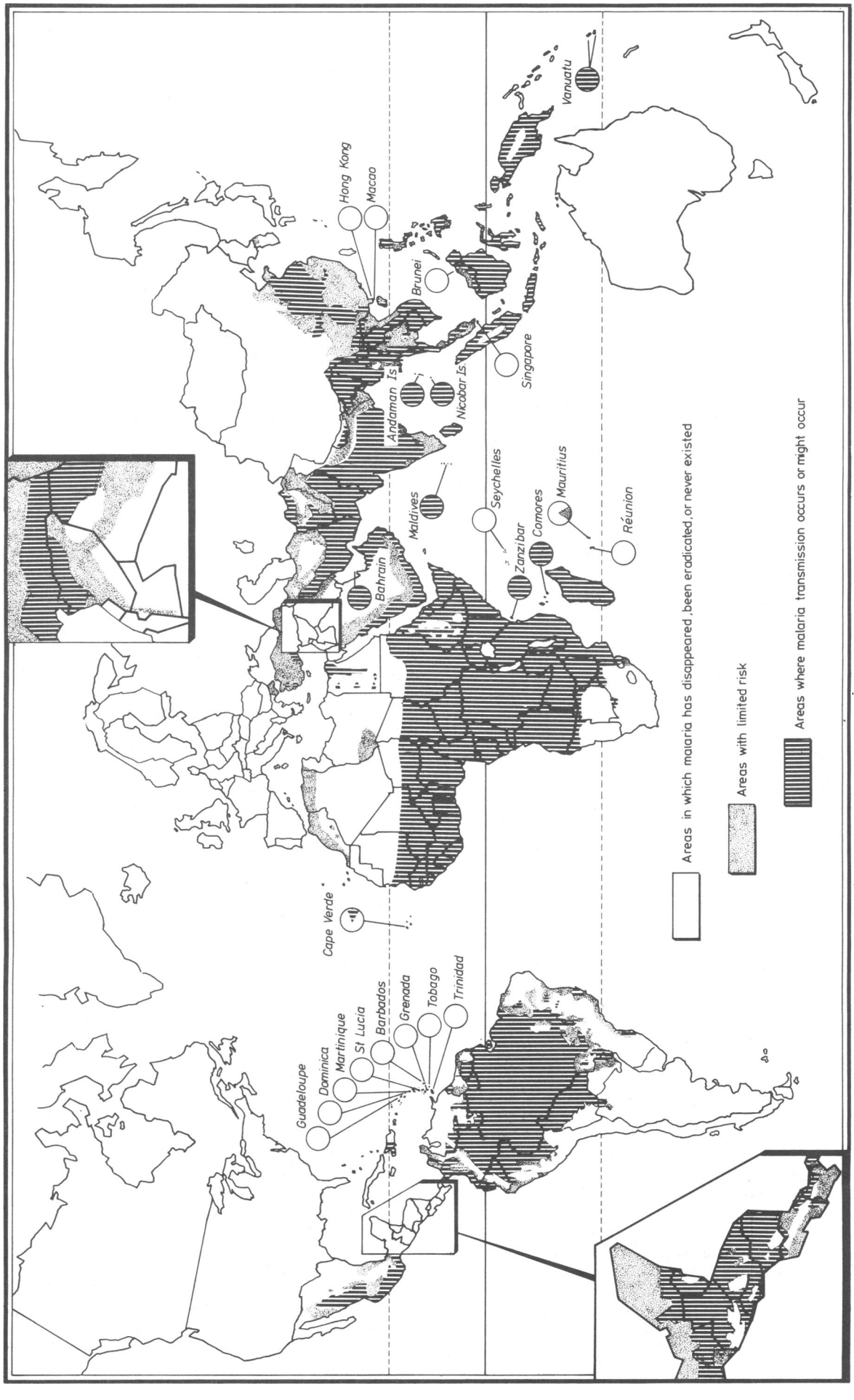

FIG 1—Epidemiological assessment of status of malaria, December 1979. (*Weekly Epidemiological Record* No 27, 10 July 1981.)

of an antimalarial drug, which is sufficient to clear most of the parasites from the peripheral blood but not to cure the infection.

The thick film gives better results in the hands of an experienced worker, but for the inexperienced the thin film is preferable. Some indication of density should be given since this is also useful as a measure of response to treatment. If rapid examination of blood films is not possible and the probability of malaria exists adequate treatment must be started at once after taking the blood sample, without waiting for its result.

Treatment

The treatment of *P falciparum* and *P vivax* malaria is readily available in various standard textbooks and up-to-date regimens have been published.[2 4]

Prophylaxis

The whole subject of malaria prevention in travellers from the United Kingdom was exhaustively covered at recent meetings convened by the Ross Institute.[5]

The following basic points will be re-emphasised.

(1) It must never be assumed that chemoprophylaxis, even when taken regularly, will always protect against malaria—*protection is relative*. Thus every non-immune person residing temporarily or for longer periods in a malarious area must be warned that, if he feels ill, malaria must still be excluded as a possible diagnosis. This is particularly relevant because of the spread of resistance to many antimalarial drugs and the absence of accurate and comprehensive maps of the distribution of resistance to the antimalarials in current use. Evidence of resistance based on "clinical" experience often without concomitant and competent microscopic diagnosis of malaria has aggravated an already complex situation.

(2) Reports that any potentially malarious area is free from risk should be accepted only with the greatest scepticism. Anecdotes that in West Africa, for example, cities are free from malaria are quite inaccurate.

(3) Malaria can be acquired at relatively short stops on a journey—for example, while refuelling the aeroplane.

(4) It is important to have adequate blood concentrations of antimalarials by the time a person is at risk. This may be achieved by taking a dose the day before departure. Despite this, it is considered wise to begin antimalarials one week before travelling to get used to the habit and to detect rare cases of idiosyncrasy.

(5) Antimalarial chemoprophylaxis must be continued for four weeks after returning from an endemic area, and the need to continue must be emphasised.

(6) It is important to remember that *P falciparum* can recrudesce for one year. Any fever occurring during this period should be suspected to be malaria until the contrary is proved, irrespective of whether the person has been on chemoprophylaxis, or even if he has been treated.

The practical implication of this recommendation is to detect as early as possible a recrudescence of falciparum malaria resulting from a chloroquine-resistant infection type I (RI).

(7) Young children are as liable to get malaria as anyone.

Chemoprophylaxis for Kenya needs reassessment in the light of the following observations: (*a*) there is a high prevalence of pyrimethamine resistance, (*b*) there is no evidence to date of chloroquine resistance among the indigenous semi-immune population, (*c*) only isolated cases of RI resistance in visitors (despite thousands of tourists) have been reported, and (*d*) low and ineffective serum concentrations should be ruled out before chloroquine resistance is confirmed.[6] It seems premature in the circumstances not to continue recommending chloroquine prophylaxis for Kenya, especially if the advice given in (6) above is followed.

Chloroquine-resistant malaria

The present state of chloroquine-resistant malaria is shown in figure 2. Autochthonous infections have been reported from 21 American and Asian countries, and a bridgehead seems to have been established in East Africa.

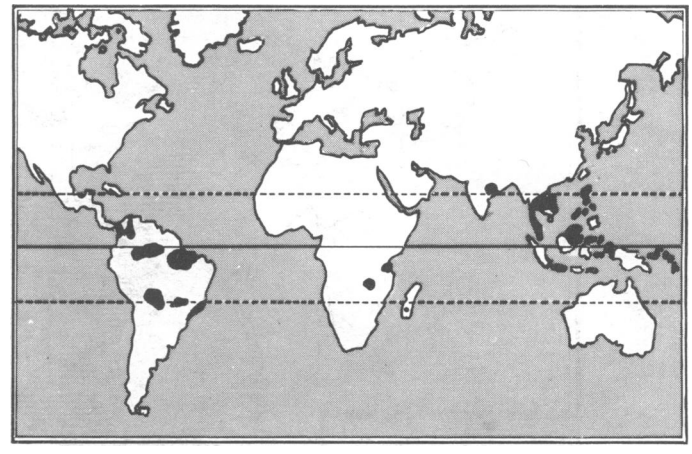

FIG 2—Present state of chloroquine-resistant malaria. (Map redrawn from W Peters and H M Gilles. *A colour atlas of tropical medicine and parasitology*. London: Wolfe Medical Publications, 1981.)

Retreat

In 1955 and 1956 the 8th and 9th World Health Assemblies adopted a policy of malaria eradication. In 1968 Sri Lanka experienced an epidemic of *P vivax* malaria affecting 1·5 million people. In 1969 the 22nd World Health Assembly adopted a revised strategy of malaria eradication and control. By 1981 the policy had changed to one of containment and control aimed at reducing the morbidity and mortality of malaria, which still affects directly some 200 million people every year and kills around one million infants and children. The annual labour losses due to malaria were estimated to be 10 million work days in Thailand and 171 million work days in the agricultural population of India.[7] Why has the disease made a remarkable comeback, especially in Asia and some parts of Central and South America, and why has the impact been so minimal in tropical Africa from the very start?

In tropical Africa where malaria is predominantly stable and endemicity high none of the economically feasible methods of vector control or drug administration, or both, permitted a major reduction of malaria transmission, let alone interruption. The high vectorial efficiency of *Anopheles gambiae*, the interaction of climatic and hydrological factors, an inadequate development of health services and health manpower, financial constraints, and lack of government commitment are some of the reasons for the dismal failure in this area. Because of the high level of immunity among the adult populations of the "stable" malaria areas of Africa some health administrators are unconvinced that the cost of malaria eradication is justified in their environment and readily divert their meagre resources to other health priorities.

Some of these factors are globally applicable; other important constraints militating against malaria eradication are: (*a*) widespread resistance of anopheline vectors to insecticides, (*b*) the exophilic behaviour of certain anopheline vectors, (*c*) impracticability and high cost of larval control, (*d*) rising costs of insecticides, (*e*) rising costs of motor vehicle operations, which are essential for antimalaria campaigns, (*f*) temporary inaccessibility of large population groups to control measures due to combined climatic and topographical factors, (*g*) population movements of migrant workers and nomadic tribes, and (*h*) lack

of community participation and indeed active opposition to spraying and other control measures in some areas. Finally, the widespread resistance of *P falciparum* to 4-aminoquinolines in countries of the American, South-east Asian, and western Pacific regions robbed the campaign of one of its essential thrusts. Even more disquieting are confirmed reports from Vietnam, Thailand, and Kampuchea of resistance to quinine and the sulfadoxine/pyrimethamine combination (Fansidar). A recent provocative article by Chapin and Wasserstrom[8] attributes the resurgence of malaria in Central America and India to intensified agriculture in these countries and the associated increased use of pesticides. Moreover, artificially created malaria from inadequate water management in irrigation schemes or dam sites is on the increase.

The future

By far the most important discovery in the past 30 years has been the development of a technique for the long-term cultivation of *P falciparum*.[9] Not only has this major advance created the prospect of a malaria vaccine, but it has stimulated activity in a wide variety of subjects—biochemical, genetic, pharmacological, as well as studies of the parasite/cell relationship at the molecular level. The whole issue of a vaccine against malaria was recently reviewed and evaluated.[10]

The WHO Special Programme for Research and Training in Tropical Diseases has reactivated interest in malaria research, which had waned so drastically soon after the Vietnam war. Important progress is being made in immunology with such advances as the recently introduced hybridoma technique, which should prove of value both for the identification of antigens and for providing monoclonal reference antibodies. Studies on the analysis and characterisation of antigens, particularly those responsible for the induction of protective immunity, are continuing.[11]

Chemotherapy has been given an added urgency as a result of the ominous spread of chloroquine-resistant and multidrug-resistant falciparum malaria.

The development of antimalarials with a minimum duration of effect of three months is being pursued, as are attempts at targeted chemotherapy using liposome-entrapped primaquine. The pharmacokinetics of this 8-aminoquinoline compound—the only currently available tissue schizonticidal—is actively being studied, and all the evidence suggests that the tissue schizonticidal activity of primaquine resides with one or several metabolites rather than in the parent drug.[12]

Mefloquine, a drug that is structurally related to quinine, has undergone extensive and successful clinical trials in Thailand and elsewhere and has been shown to be effective against multidrug-resistant strains of *P falciparum*. When the drug becomes commercially available caution in its use is advocated by Peters.[13]

The most exciting development, however, has been the re-examination by Chinese research workers of traditional herbal remedies for antimalarial activity. From a medicinal herb Qinghao, *Artemisia annua*, which has been used in China for at least 2000 years, they isolated a compound possessing antimalarial properties against parasites both sensitive to and resistant to *P falciparum*. The compound has been variously called Qinghaosu, artemisinine, and arteannum and represents an entirely new chemical class of antimalarial. Extensive clinical trials have shown that it clears parasitaemia more rapidly than chloroquine or quinine.[14]

Malaria control has received a serious setback but recent developments provide hope for the future.

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MATERIA NON MEDICA

The perks of the job

Travelling abroad for work is usually seen by friends and colleagues as additional holiday, confirmation that academics have few responsibilities and commitments but too many perks. I had never been to Nigeria before and was delighted to accept an invitation to give a series of seminars and lectures.

Road travel in Nigeria is a natural hazard that no one would insure you against. Coming from a large capital city, I thought myself familiar with traffic anarchy and congestion, but Lagos must be unbeatable. It was so bad that only those with even-numbered registration plates could enter the city on certain days and odd on the remaining others. This had no effect since everyone went out and bought second cars with an alternate registration to their first. Paradoxically people drive in Lagos and the surrounding countryside as if no other cars are to be seen, happily mending punctures, leaving abandoned cars in the middle of the road, and doing U turns on motorways. No visitor can be unaware of the high carcase count in cars since every roadside is littered with rusting or burnt-out crashed remains. And I can vouch that it is not all that difficult to join them. Driving along we were aware that two large lorry wheels, with an independent existence, were bouncing towards us followed by a swerving overloaded vehicle, sparks flying. We all missed each other but ended up in the ditch.

I was due to start work the next day but woke to a national strike, which meant no food and water on the university campus and no telephone communications for five days. The hospitals all closed so I was unable to see patients and had no audience for my lectures and seminars. I had always wanted to read Doris Lessing's *Golden Notebook* and spent the five days on my back rationing the number of pages, lest I run out, as well as the bowl of water per day to cope with the humidity and non-flushing toilets and bags of crisps and chicken legs, which seemed to be the only food available. My stay ended with the strike.

Within two hours of returning to work in London I developed a bilateral conjunctivitis and within 24 hours could not open my eyes, all caused by a Nigerian picorna virus. I spent a further five days on my back in a dark room wishing I could finish Doris Lessing. Still, it allowed me time to think about all those perks of the job.—MICHAEL ADLER (professor of genitourinary medicine, London).