PART 2

Major Tropical Infections

CHAPTER 9

Malaria

Importance and distribution

Malaria is the most important of all tropical parasitic diseases, causing many deaths and much morbidity. It is widely distributed in the tropical and subtropical zones. There are four parasite species that cause human malaria, all of which belong to the genus *Plasmodium*. In order of their prevalence worldwide these are *Plasmodium falciparum* (the cause of nearly all of the deaths caused by malaria), *P. vivax*, *P. malariae* and *P. ovale*.

A malarial infection can occasionally be transferred directly from one person to another by blood transfusion, accidental inoculation or across the placenta. However, transmission usually depends on an insect vector, in which the parasite spends several weeks undergoing the sexual part of its life cycle.

Life cycle (Fig. 9.1)

Malaria is usually transmitted by the bite of an infected female anopheline mosquito. The infecting agent is the sporozoite, a microscopic spindle-shaped cell which is in the mosquito's saliva. Thousands of sporozoites may be injected in a single bite. The sporozoites disappear from the blood within 8 h, and the successful ones enter liver cells. The process by which the malaria parasites multiply asexually is called schizogony, whether it takes place in a hepatocyte or in an erythrocyte.

Inside the liver cell, the sporozoite divides by asexual fission to form a cyst-like structure called a pre-erythrocytic (PE) schizont, which contains tens of thousands of merozoites. Each merozoite consists of a small mass of nuclear chromatin within a tiny sphere of cytoplasm. When the PE schizont is mature, it ruptures and liberates its contained merozoites. These now enter the bloodstream to penetrate red cells.

The time between the bite of the infecting mosquito and the appearance of parasites in the blood is the prepatent period. It is 7–30 days in *P. falciparum* (usually around 10 days), and longer in the other species. It may be very long; in the case of *P. vivax* and *P. ovale* many months or even more than a year. This dormant stage of the parasite is the hypnozoite.

Merozoites, released into the bloodstream from hepatic PE schizonts, attach themselves to red cells by means of surface receptors. The parasite then penetrates the red cell and resides in a vacuole with a lining derived from the red cell surface. Here it begins the process of blood schizogony. Schizogony occurs in the circulating blood in the cases of *P. vivax*, *P. ovale* and *P. malariae*, so in all these infections schizonts are

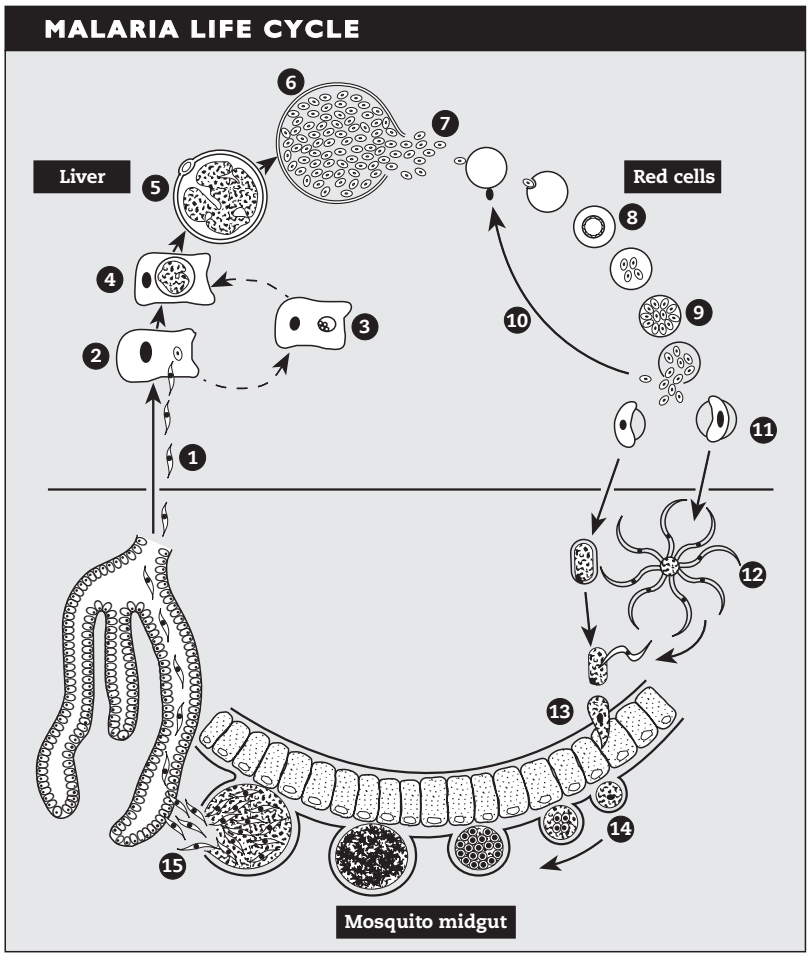

Fig. 9.1 Malaria life cycle. 1, Sporozoites, injected through the skin by female anopheline mosquito; 2, sporozoites infect hepatocytes; 3, some sporozoites develop into 'hypnozoites' (*Plasmodium vivax* and *P. ovale* only); 4, liver-stage parasite develops; 5–6, tissue schizogony; 7, merozoites are released into the circulation; 8, ring-stage trophozoites in red cells; 9, erythrocytic schizogony; 10, merozoites invade other red cells; 11, some parasites develop into female (macro-) or male (micro-) gametocytes, taken up by mosquito; 12, mature macrogametocyte and exflagellating microgametes; 13, ookinete penetrates gut wall; 14, development of oocyst; 15, sporozoites penetrate salivary glands. (Reproduced with permission from Zaman V. *Atlas of Medical Parasitology*. Balgawlah, NSW, Australia: ADIS Press, 1978.)

commonly seen in the peripheral blood films from infected patients. In *P. falciparum*, schizogony only occurs in capillaries deep within the body. At the stage of the maturing trophozoite, parasite antigens are expressed on the surface of the red cell. Some of these antigens are capable of linking to receptors expressed on the endothelial cells lining capillaries in various organs and tissues of the body. The resulting cytoadherence of parasitized erythrocytes to endothelial

surfaces leads to the gathering or sequestration of large numbers of mature parasites in deep tissues.

The periodicity of schizogony characteristically coincides with paroxysms of fever and this led to the traditional names of the different types of human malaria.

- *Tertian malaria*—fever every third day, if the first day is given the number 1: *P. vivax* and *P. ovale*.
- *Subtertian malaria*—fever slightly more often than every third day: *P. falciparum*.
- *Quartan malaria*—fever every fourth day if the first day is given the number 1: *P. malariae*.

Plasmodium falciparum malaria was sometimes called malignant tertian malaria, because of its much greater lethal potential than the other tertian malarias. These antique names for malaria are best avoided, not only because they can be confusing, but because the periodicity they imply often fails to develop. Many patients have lost their lives from *P. falciparum* malaria because they never developed the periodic fever that their doctors wrongly believed to be invariable.

Some of the merozoites entering red cells do not develop into schizonts, but develop more slowly into solid-looking parasites called gametocytes. These may persist in the circulation for many weeks without destroying the red cells containing them, and they are the forms infective to the mosquito. In each species of malaria, the gametocytes are differentiated into male and female. When the female mosquito swallows the male and female gametocytes in her blood meal, they develop further in her stomach. The male gametocytes rapidly develop to produce spermatozoon-like microgametes, and the female gametocyte becomes the egg-like macrogamete.

Clinical features

There are no recognized symptoms associated with the liver stage of malaria infections, or (as far as we know) with rupture of tissue schizonts. The development of a blood stage infection is necessary for malarial illness.

Infections with each of the four different malaria species have many clinical features in common. These result from the release, when red cell schizonts rupture, of 'malaria toxins' or pyrogens. The common features are as follows.

- *Fever*—often irregular. Fever is believed to be mediated by host cytokines, which are secreted by leucocytes and other cells in response to the released pyrogens. The pattern of regularly periodic fever often does not occur until the illness has continued for a week or more. It depends on synchronized schizogony. Why schizogony should ever become synchronized is unknown, but an intriguing explanation has been suggested. High temperatures slow the growth of mature more than of young parasites. Fever itself may therefore allow young parasites to 'catch up' with older ones, leading to increasing synchrony with successive cycles.
- *Anaemia*. This is caused by a combination of haemolysis and bone marrow suppression. Haemolysis is usually most severe in *P. falciparum* malaria because cells of all ages can be invaded in this infection.
- *Splenomegaly*. The spleen enlarges early in the acute attack in all types of malaria. When a patient has had many attacks, the spleen may be of enormous size and lead to secondary hypersplenism.
- *Jaundice*. A mild jaundice caused by haemolysis may occur in all types of malaria. Severe jaundice only occurs in *P. falciparum* infection, and results from specific liver involvement.

Classical stages of fever

In a paroxysm of malaria, the patient may notice the following stages.

1 *Cold stage*—the patient shivers or has a frank rigor; the temperature rises sharply.

2 *Hot stage*—the patient is flushed, has a rapid full pulse and a high temperature is sustained for a few hours.

3 *Sweating stage*—the patient sweats freely, or is even drenched, and the temperature falls rapidly.

These stages are most often recognized in *P. vivax* infection. For the clinician or epidemiologist, the important point is that an individual with a symptomatic malarial infection, or even with severe disease, may be afebrile at one particular time; a history of recent febrile symptoms and/or repeated measurements are important. In rare cases, a patient may be persistently afebrile in the presence of a very severe *P. falciparum* infection. Hyperpyrexia may complicate malaria, especially in attacks of *P. falciparum*.

Progress of the untreated attack

The natural history of untreated malaria differs with each species.

Plasmodium falciparum

Following a single exposure to infection, the patient will either die in the acute attack (a common event) or survive with the development of some immunity and residual anaemia. Attacks may recur over the course of the next year (a phenomenon called recrudescence, caused by the persistence of blood forms in small numbers between attacks) but then die out spontaneously in the absence of reinfection.

Plasmodium malariae

Following a single exposure to infection, and an incubation period that may extend to many weeks, the patient develops a recurrent fever that occurs at increasing intervals. There may be considerable anaemia, and enlargement of the liver and spleen. If no treatment is given to clear the blood forms of the parasite, recrudescences may occur from time to time for more than 30 years. The severity of the attacks tends to diminish as time goes by, until bouts of fever last only a few days.

Plasmodium vivax and *P. ovale*

Plasmodium vivax and *P. ovale* malaria cause very similar illnesses, with bouts of fever that relapse periodically but irregularly over a period of up to 5 years. These are true relapses and not simple recrudescences, because they may occur despite treatment with drugs that entirely eliminates the parasites from the blood. The relapses are caused by reinvasion of the blood by merozoites produced when hypnozoites awake from dormancy and develop into PE schizonts.

Peculiarities of *Plasmodium falciparum* infection

The important difference between *P. falciparum* and the other plasmodia that infect humans is the capacity of *P. falciparum* to cause severe (or complicated) disease. Nearly all of the million or more malaria deaths that occur each year result from *P. falciparum* infections. In endemic areas, most of the clinical impact of *P. falciparum* infection falls on young children. Nevertheless, the majority of infections cause only a self-limiting febrile illness or, as immunity increases, no illness at all. For reasons that are still not understood, some infections progress to severe disease, and some of these are fatal. In areas with limited or unstable transmission, adults (including tourists) with *P. falciparum* infection may develop severe or complicated disease, especially if diagnosis is neglected or delayed.

Complicated *P. falciparum* malaria, also known as 'severe' malaria, may take a number of clinical forms, which are listed in Table 9.1. In young children in endemic areas, who suffer the greatest malaria mortality, five clinical syndromes predominate: prostration, severe anaemia, cerebral malaria, acidosis and hypoglycaemia. A child may suffer from just one of these complications, or from any combination of them. Other complications seen in adults are unusual in children in endemic areas. Non-immune adults may develop any combination of these or of the other syndromes listed in Table 9.1.

Specific syndromes caused by *Plasmodium falciparum*

Altered consciousness and coma

In a patient with *P. falciparum* malaria and coma,

MICROCIRCULATORY ARREST

Organs most affected	Main symptoms or signs	Typical misdiagnosis
Stomach and intestines	Vomiting and diarrhoea	Gastric flu; cholera (diarrhoea is *not* bloody)
Brain	Delirium Disorientation Stupor Coma Convulsions Focal neurological signs	Encephalitis, meningoencephalitis (there may be misleading CSF abnormalities)
Kidneys	Renal failure, with or without oliguria or haemoglobinuria	Nephritis
Liver	Jaundice and fever	Hepatitis
Lungs	Pulmonary oedema	Pneumonia, heart failure

Table 9.1 Microcirculatory arrest in *P. falciparum* infection.

several possible causes of altered consciousness must be considered.

- A metabolic explanation, such as *hypoglycaemia* (especially in a young child or pregnant woman) or *acidosis*. Correction of either of these may restore consciousness.
- The patient may be having a *seizure*. This is sometimes manifested by only very minor twitching movements or none at all, but an anticonvulsant drug may restore consciousness.
- The patient may be *postictal* after a recent seizure, when recovery is likely within a few minutes or hours.
- *Very severe anaemia* may also impair consciousness.

If none of these complications accounts for the coma, or if coma persists despite finding and correcting these, then the patient may have 'cerebral malaria'. When a diagnosis of cerebral malaria is made, it is important not to overlook other possible explanations of the illness (e.g. meningitis, encephalitis, severe pneumonia or head injury) in an individual who happens to be parasitaemic.

Cerebral malaria

This common complication is one of the important causes of malaria deaths. It is a diffuse disturbance of cerebral function, characterized by altered consciousness, commonly accompanied by convulsions. The onset may be gradual or sudden, usually within hours or days of the first febrile symptoms of malaria. It is not uncommon for a child to become comatose without any preceding fever or other symptoms. Coma may be accompanied by flaccidity of limbs, or by any combination of hypertonicity, posturing and opisthotonos. Any repetitive muscular movement, even of a minor degree, may reflect underlying seizure activity.

Recently, a characteristic retinopathy has been observed in children and adults with cerebral malaria. A short-acting mydriatic can be used to dilate the pupils, and the retinopathy can then be seen with a direct ophthalmoscope and with practice. The changes consist of areas of whitening in the macula and extramacular optic fundus, with patchy whitening of small vessels. These features are sufficiently distinctive to be diagnostically helpful. Most children with cerebral malaria also have white-centred retinal haemorrhages, and about 10% have some

degree of papilloedema, neither of these being distinctive of malaria.

For research purposes, a strict definition of cerebral malaria requires that the parasitaemic patient be unable to localize a painful stimulus (Glasgow coma score ≤8; Blantyre coma score ≤2), that coma persists despite correction of metabolic defects and seizures, and that no other explanation for the coma can be found. If effective antimalarial drugs are given, together with supportive care, about 80% of patients with cerebral malaria recover. Coma usually persists for 1–3 days after the start of treatment, on average somewhat longer in adults than in children. If recovery does occur, a minority of patients (5–10%) are left with a neurological deficit, such as hemiparesis, cerebellar ataxia, amnesia, diffuse spasticity or epilepsy. Clinically obvious sequelae may resolve over a period of months, but some are permanent. We do not know how many individuals may suffer more subtle impairment (e.g. of memory or intelligence) after cerebral malaria.

The pathogenesis of cerebral malaria remains unclear. The usual histopathological finding in fatal cases is the presence of large numbers of erythrocytes containing mature parasites in the capillaries and venules of many organs, including the brain. Because irreversible brain damage is unusual in those who recover, it seems unlikely that the microcirculation is totally obstructed by these sequestered cells. The highly active, developing and dividing parasites may consume essential nutrients such as oxygen and glucose and release toxic products, including lactate, with detriment to surrounding tissues. As the schizont ruptures the red cell, substances are released that are known to stimulate the release of cytokines from host cells: these in excessive local concentrations may contribute to coma and other complications of *P. falciparum* malaria (Figs 9.2 & 9.3, see colour plate facing p. 146).

Perivascular 'ring haemorrhages' are commonly found in the brain at autopsy (Fig. 9.4, see colour plate facing p. 146). Their numbers correlate with the number of retinal haemorrhages visible by ophthalmoscopy during life, but their pathogenetic significance is not known. Raised intracranial pressure is usual in children with cerebral malaria, but there is no firm evidence that the raised pressure itself contributes to mortality. Factors contributing to raised intracranial pressure include cerebral oedema and, probably to a lesser extent, the mass of sequestered parasitized erythrocytes.

Severe anaemia

This complication is most common in children between 6 and 24 months of age in areas of intense transmission of *P. falciparum*. There is direct red cell destruction when schizonts rupture, and further haemolysis, both of parasitized and unparasitized erythrocytes, occurs through autoimmune mechanisms.

Red cell destruction is not, however, the whole story. One would expect a brisk reticulocytosis in a haemolytic anaemia, but this is often absent in acute malaria, reflecting impaired bone marrow function. Like fever, this is believed to be mediated by a host cytokine response to the infection. Marrow aspirates often show evidence of dyserythropoiesis, including phagocytosis of parasitized red cells by macrophages, and phagocytosis of apparently uninfected red cells.

Severe anaemia may be found by chance when a patient attends for some unrelated problem, or it may lead to breathlessness, weakness and, occasionally, impaired consciousness. Dyspnoea in a child with severe malarial anaemia is most commonly a manifestation of acidosis; occasionally, dyspnoea is a result of heart failure.

Acidosis

Tissue anoxia leads to anaerobic metabolism and the release of lactic acid. The resulting acidosis is initially compensated for by deep breathing, which eventually may be insufficient to prevent the arterial blood pH from falling. Factors contributing to tissue anoxia include: the sequestration of parasitized red cells, which may impair tissue perfusion; anaemia; hypovolaemia; and hypotension. Rapid fluid volume replacement, with whole blood if necessary, may be life-saving.

Hypoglycaemia

Hypoglycaemia is a common complication of untreated *P. falciparum* malaria in children, as it is of many other infections in children. Hypoglycaemia may also occur in adults with malaria and pregnant women are particularly susceptible. The principal mechanism of malarial hypoglycaemia is probably cytokine-induced impairment of hepatic gluconeogenesis, although the consumption of glucose by millions of parasites may also contribute. Hypoglycaemia sometimes develops as a complication of quinine or quinidine therapy, probably because these drugs stimulate the pancreas to secrete insulin; again, pregnant women are particularly susceptible.

'Blackwater fever'

This obsolete term used to be applied to the syndrome that sometimes occurs in *P. falciparum* malaria when severe intravascular haemolysis is associated with haemoglobinuria and renal failure. The syndrome still occurs, especially in non-immune adults with severe *P. falciparum* infection. In children in the endemic areas of sub-Saharan Africa, haemoglobinuria sometimes occurs in *P. falciparum* malaria, but it is rarely accompanied by renal failure. In some cases, haemoglobinuria is precipitated by a drug or dietary factor in an individual with glucose-6-phosphate dehydrogenase (G6PD) deficiency. Haemolysis in this condition usually only affects the older cells, so ceases when the haemoglobin has dropped to about 6 g/dL.

Bleeding disorder

A minor degree of disseminated intravascular coagulation (DIC) is common in *P. falciparum* malaria, and DIC severe enough to cause bleeding is an occasional complication in adults.

Malaria in pregnancy

All types of malarial infection can lead to abortion. In *P. falciparum* infection, even in women normally immune, pregnancy is associated with an increased likelihood of developing parasitaemia and with higher parasite densities, especially in the first pregnancy. Anaemia is a common consequence, and many women enter labour with a low haemoglobin concentration, making peripartum blood loss more dangerous. Organ complications such as coma and renal failure are rare in pregnant women living in endemic areas but, among the non-immune, pregnant women are liable to the same complications as other adults.

Plasmodium falciparum in endemic areas is an important cause of low birth weight, especially in first-pregnancy babies, who are then at increased risk of dying in infancy from any of a variety of causes. Low birth weight because of maternal malaria presumably results from the fact that the placenta becomes packed both with late-stage parasites and host mononuclear cells, especially in the first pregnancy.

In endemic areas, it is common to find malaria parasites in umbilical venous blood; it is less common to find them in the neonate's peripheral blood, and these usually disappear within the first 2 days of life. Illness brought about by congenital infection is rare in endemic areas, but may develop in infants born to non-immune mothers. *Plasmodium vivax* is a more common cause of congenital malaria than *P. falciparum*; the illness presents within a few days or weeks of birth with fever, haemolytic anaemia and failure to thrive.

Immunity in malaria

Immunity in malaria is most pronounced in *P. falciparum* infection. In areas of very high transmission, if a child survives to the age of 5 or 6 years, he or she is likely to have achieved a high degree of immunity to the lethal effects of the infection. This immunity has two main components: an ability to limit parasitaemia by the development of specific protective immunoglobulin (IgG) and cell-mediated immunity (antiparasitic immunity), and a physiological tolerance such that parasitaemia produces little or no fever or subjective illness (antitoxic immunity). In order to maintain this immunity, frequent re-exposure to infection is required. If re-

exposure does not occur, the immunity wanes over a period of a few years. Although West African students living in the UK gradually lose their protective antibodies over a 5-year period, they rapidly regain immunity on re-exposure to infection, but the price may well be two or more attacks of malaria on first returning home. The development of a high degree of immunity in an entire population exposed to high levels of *P. falciparum* infection has an extremely important effect on the epidemiology of the infection.

As the CD4 count falls, an individual with HIV infection becomes increasingly susceptible to *P. falciparum* infection, and is likely to develop a greater density of parasites in the peripheral blood than more immunocompetent people. It has not yet been shown that such individuals are susceptible to more severe malaria disease. HIV-positive pregnant women are more likely than others to have malaria in pregnancy and to fail to clear it with standard treatment. Conversely, malaria increases the plasma viral load in HIV-infected people, and there is suggestive evidence that placental malaria may enhance mother–child transmission of HIV.

Non-immune protective factors in malaria

There are several non-immune factors that affect susceptibility to malaria. *P. vivax* is unable to infect red cells lacking the Duffy blood-group antigen. This is believed to account for the natural resistance of those of pure Negro race to infection with this parasite.

Individuals whose haemoglobin genotype is AS are resistant to the lethal effects of *P. falciparum* infection, but no more resistant to infection itself than those with normal (AA) haemoglobin. This is because the sickle trait prevents the development of high parasitaemia, probably partly as a result of parasitized red cells sickling in the circulation and being removed by the spleen before they can develop into schizonts.

Evidence that G6PD deficiency has a similar protective effect does exist, but is less striking. Sickle-cell anaemia itself is not protective, for malarial infection is disastrous in such patients. There is now good evidence that the beta-thalassaemia trait confers protection against *P. falciparum*. Malnutrition was once thought to protect against the lethal effects of *P. falciparum* infection, but recent case–control studies have failed to confirm this.

Immune disorders in malaria

Some complications of malaria are related to immune effects. *Malarial nephrosis* is an occasional complication of *P. malariae* infection in children. Antigen–antibody complex is bound firmly to the glomerular basement membrane. An intractable nephrotic syndrome results, with non-selective proteinuria and a bad prognosis. Neither treatment with corticosteroids nor eradication of the malaria seems to influence the outcome. The intractability of the condition seems to be determined by the permanence of the complex-binding mechanism.

A more tractable condition is hyper-reactive malarial splenomegaly (formerly known as tropical splenomegaly syndrome), in which marked splenomegaly in *P. falciparum* infection is associated with infiltration of the hepatic sinusoids with lymphocytes, with or without features of secondary hypersplenism. Serum IgM levels are very high. This condition usually resolves within a few months if the patient is given continuous effective chemoprophylaxis.

There is good evidence that an acute attack of malaria has general immunosuppressive effects. The effects of chronic malaria are less well-defined. Interventions against malaria (e.g. bed-nets) have sometimes led to a fall in mortality from other causes, including respiratory infections, suggesting that malarial immunosuppression may increase susceptibility to other common pathogens. The immunosuppressive effects of malaria may account for the tendency of the Epstein–Barr virus to produce Burkitt's lymphoma in malaria-endemic areas.

Diagnosis

Direct diagnosis

The specific diagnosis of malaria is made by examining the blood, by making a film, drying and

staining it. The thin blood film shows the undistorted parasites within the red cells. It is of most use in the detailed study of parasite morphology and species identification. Its disadvantage is that it requires a very prolonged search to detect a low parasitaemia, so its sensitivity is low. A patient may have a fever resulting from *P. falciparum* and yet have no parasites detected by searching the thin film.

The thick film, in which cells are piled upon each other 10–20 deep and lysed and stained at the same time, allows far more red cells to be examined at a time, but it has the disadvantage that the parasites in the lysed cells are distorted. Although readily recognizable as malaria parasites, their specific features of identification may be ambiguous or entirely lost. However, in experienced hands, the thick film is the best method to use for answering the question, 'Does the patient have malaria?'

Serodiagnosis

Serodiagnosis of malaria is of no use for diagnosis of the acute attack. It depends on finding specific antibodies, and most methods in common use are incapable of distinguishing between antibodies to the different species of parasite. Antibodies may be detectable for several years after the last attack of malaria. The main use of serodiagnosis is in excluding malaria in a patient suffering from recurrent bouts of fever who does not present during a bout. Serology may also be used in surveys as an approximate measure of exposure of a population to malaria. The most frequently used serological technique is the indirect fluorescent antibody test (IFAT).

New methods of diagnosis

Many new techniques for identifying malaria parasites are being developed. The quantitative buffy coat (QBC) technique makes use of the fact that parasitized erythrocytes have a different specific gravity from unparasitized red cells and can therefore be looked for in a particular segment of the blood in a centrifuged capillary tube. Several dipstick methods are now available, by which parasite antigens are detected by placing a drop of blood on a dipstick impregnated with antibody. Polymerase chain reaction (PCR) can be used to detect parasite DNA. While these methods are useful in research studies, they have not replaced thick and thin films for routine clinical diagnosis.

Treatment

The treatment of a patient with malaria is supportive and specific. Supportive treatment may include the following.

1 Reducing the temperature if hyperpyrexia is present—especially common with *P. falciparum* infection. Oral or rectal paracetamol is the method of choice. If this is unavailable, tepid sponging and fanning offers temporary benefit.

2 Rehydration, especially when vomiting and diarrhoea have been prominent, and in the patient with deep breathing suggestive of acidosis.

3 Monitoring renal output and taking corrective measures if necessary (first, rapidly correct any hypovolaemia; if oliguria persists, maintain careful fluid balance).

4 Monitoring the need for blood tranfusion, which may be life-saving. However, blood should only be transfused when there are strong clinical indications; e.g. when the haemoglobin concentration is <4 g/dL (haematocrit $<12\%$) or when higher levels are accompanied by coma, acidosis or hyperparasitaemia. In most patients, the haemoglobin concentration rises rapidly when the attack has been terminated by specific chemotherapy.

5 Terminating convulsions with appropriate drugs—rectal diazepam or lorazepam, rectal or intramuscular paraldehyde, and intramuscular phenobarbital are some options. These should be used in a sequence, proceeding to the second or third option only when the others have failed.

6 Monitoring of blood glucose and correction of hypoglycaemia where necessary (10–40 mL of 50% dextrose diluted$\times 3$ with saline and infused over 5–10 min).

7 Reducing acidaemia. Rehydration, blood transfusion (when appropriate) and antimalarial therapy are usually sufficient for this purpose. The use of bicarbonate infusion is not of proven benefit, but may be attempted with care in severe acidosis.

8 Treating DIC if this complication is severe enough to cause bleeding; fresh whole blood, platelet-rich plasma and fresh frozen plasma may be given according to availability.

9 Giving antibiotics is likely to be helpful:

- if the diagnosis of malaria is in doubt;
- in an unconscious patient in whom lumbar puncture is deferred; or
- in patient groups known to have a high risk of bacteraemia accompanying severe malaria.

This may vary geographically: at-risk groups identified have been children with cerebral malaria in coastal Kenya, and young children with severe anaemia in southern Malawi.

Specific chemotherapy

Specific treatment is directed to terminating the parasitaemia as rapidly as possible. The drug of choice depends on national policy in the particular country, and on the likely place of origin of the patient's parasites. Drug resistance is an increasing problem throughout the world, and the picture changes with time. Many endemic countries now have a national programme that sets policy for first-line treatment of uncomplicated malaria, with other drugs for treatment of failures or of severe disease. In some countries, multidrug resistance threatens to make malaria untreatable, and new additions to the armamentarium of drugs are urgently needed. In general, national policy should be followed. Treat non-severe malaria with oral drugs if the patient can take them. Complicated *P. falciparum* malaria requires parenteral antimalarial drugs, at least until there is clinical improvement and the patient can swallow.

Drugs that prevent the development of the blood stages which are causing the illness are traditionally called schizonticides. Some of them also act against the gametocytes of some species, but this has no relevance to the clinical situation. Some of the schizonticides also have useful anti-inflammatory effects. The most widely used schizonticide has until recently been chloroquine, but the spread of parasite chloroquine resistance has limited the use of this drug in recent years. Chloroquine remains the first-line treatment for non-severe *P. falciparum* malaria in some semi-immune populations in parts of Africa, and it is the drug of choice for all non-*falciparum* malarias (*P. vivax* resistance to chloroquine is increasingly common but, as the disease is not life-threatening, it is reasonable to try chloroquine first).

Chloroquine

This is a synthetic compound of the 4-aminoquinoline group. It is a bitter white powder. As a base, it forms salts with acids. Those in common use are diphosphates (Aralen, Resochin, Avloclor) and sulphate (Nivaquine). It is a powerful schizonticide; it also has anti-inflammatory action and so helps to reduce the non-specific symptoms of malaria (malaise, headache, myalgia).

Chloroquine is relatively non-toxic if properly administered in the correct dosage. The drug should be given orally when possible. Intravenous infusion must be over 2–4 h, and intramuscular or subcutaneous chloroquine should be divided into frequent small doses rather than given as a single large injection. The drug is taken up by the liver, so higher blood levels follow parenteral rather than oral administration, allowing larger, less frequent doses by mouth.

Main toxic effects include: gastrointestinal effects (nausea, vomiting, etc.); a fall in blood pressure; generalized itching (a common complaint in black-skinned people only); the hair may turn white with chronic overdosage; the vision may also be affected with prolonged use (acute effects, corneal crystal deposition; chronic effects, retinopathy).

Dosages are as follows, and all doses are expressed as dose of base as this is the active part of the drug.

- **Adults**

  Oral—600 mg initially, 300 mg 6 h later, then 300 mg/day for 2 days (total dosage 1.5 g).

  Intravenous—5 mg/kg (maximum 300 mg) infused over 3 h in saline, repeated every 8 h to total of 25 mg/kg.

  Intramuscular or subcutaneous—2.5 mg/kg (maximum 150 mg) every 4 h to total 25 mg/kg.

When giving chloroquine parenterally, change to oral treatment as soon as the patient can take it.

- **Children**

  Oral—The dose should be in proportion to the body weight (using the full dose at 60 kg).

Amodiaquine

This is a 4-aminoquinoline with a molecule that has some resemblance to chloroquine and some to quinine. Preparations include tablets of amodiaquine hydrochloride (Camoquin (PD)) containing 200 mg of base. The dose is the same (in terms of base) as for chloroquine. Toxic effects are also similar to chloroquine, but agranulocytosis has been reported.

Amodiaquine is effective against some strains of chloroquine-resistant *P. falciparum* both *in vivo* and *in vitro*; it is no longer recommended for prophylaxis because of the incidence of agranulocytosis when used for this purpose.

Quinine

The main use of quinine is for treatment of severe *P. falciparum* malaria in areas of chloroquine resistance. Its isomer, quinidine, is equally effective. Quinine is a natural alkaloid derived from cinchona bark, a bitter crystalline powder practically insoluble in water. It forms salts of varying solubility: the sulphate and bisulphate are used for oral preparations and the dihydrochloride or chloride for injection. It is a powerful schizonticide; it also has an anti-inflammatory action.

Toxic effects may vary. The symptom complex of tinnitus, deafness, dizziness, nausea and vomiting, which is known as cinchonism, is almost inevitable with normal doses of quinine; therapy does not need to be stopped or changed on account of such symptoms unless they are severe. Others include hypoglycaemia (especially in pregnancy); hypotension (if excessive dose or if given too fast intravenously); thrombocytopenia (a rare idiosyncratic reaction); and erythematous rash. Overdose of quinine can cause deafness, blindness and severe hypotension. Quinine has a stimulatory effect on uterine muscle, and overdose can cause abortion. However, this is not a reason to avoid quinine in pregnancy, because the benefit of curing malaria greatly outweighs the risk of uterine excitation from therapeutic doses of the drug.

Doses are given below, and are expressed as dose of salt.

- **Adults**

  Oral—600 mg 8-hourly for 7–14 days (usually as sulphate).

  Parenteral—The intravenous route is preferred. First (loading) dose of 20 mg/kg (maximum dose 1400 mg) quinine dihydrochloride infused over 4 h in an isotonic glucose–electrolyte fluid (e.g. half-strength Darrow's–5% dextrose); subsequent doses of 10 mg/kg similarly infused over 2 h, at 12-hourly intervals. Change to oral therapy as soon as the patient can take it.

  Intramuscular—Injection of quinine dihydrochloride may be given if intravenous infusion is impossible. It is usually well-tolerated if given deep, with aseptic precautions. The provided ampoule (300 mg/mL) should be diluted fivefold with sterile water to reduce the pain of the injection. As with intravenous infusion, the first dose should be a loading dose of 20 mg/kg: to reduce the volume of this large dose, it may be divided between the two thighs, and further divided by giving half at time zero and the remainder 4 h later.

Mefloquine

This is a 4-quinoline methanol drug chemically related to quinine. It is bound to plasma, has a half-life of 21 days and is effective as a single adult oral dose of 750–1250 mg. It has the major disadvantage that no parenteral preparation is available, and naturally occurring RI resistance has been reported. It is available in 250 mg tablets as Lariam. Minor toxic effects include headache, dizziness and disturbances of sleep. Occasional severe toxic effects are fits, psychomotor disturbances and psychoses. Individuals with a history of convulsions or neuropsychiatric disease are therefore advised not to use mefloquine. There have been many hundreds of well-observed cases in which the drug has been used in pregnancy without adverse

effect on mother or fetus; nevertheless it is wise if possible to avoid the use of mefloquine in pregnancy on general grounds. Patients on cardiosuppressant drugs or beta-blockers should not take mefloquine because of its additional effects on the myocardium.

Sulfadoxine–pyrimethamine (Fansidar)

The two components of this widely used therapy inhibit enzymes required by the parasite for folic acid synthesis. Sulfadoxine (like other sulphonamides) competitively inhibits the enzyme dihydropteroate synthetase (DHPS), while pyrimethamine (like the biguanide proguanil) inhibits dihydrofolate reductase (DHFR). Sulfadoxine–pyrimethamine (SP) has been widely used as an alternative to chloroquine in the treatment of uncomplicated *P. falciparum* malaria. It has two major benefits as a first-line treatment in impoverished countries: it is very cheap, and it is used as a single-dose treatment.

When introduced in South East Asia as therapy for malaria in the wake of chloroquine resistance, SP resistance rapidly appeared until SP was useless. Its use in Africa has had mixed effects, with increase of resistance being rapid in some areas and much slower in others. Resistance appears to be the result of mutations in the parasites' DHFR and DHPS genes, and the capacity to detect these mutations by PCR may provide a useful means of monitoring and predicting the spread of SP resistance in different populations.

Atovaquone–proguanil (Malarone)

This is a recently licensed combination therapy for the treatment of uncomplicated *P. falciparum* malaria. The standard regimen is four tablets daily for 3 days.

Halofantrine

This is an effective antimalarial that is used in some parts of Africa. However, it is cardiotoxic, prolonging the QT interval and leading to arrhythmias. It is therefore no longer recommended for the treatment of malaria.

The artemisinin drugs

These compounds are derived from the plant *Artemisia annua*, which has been used for thousands of years as a herbal remedy for fevers in China. The plant's active components, arteether, artemether and artesunate are highly effective antimalarials, active against chloroquine-resistant and multidrug-resistant *P. falciparum* and useful in the treatment of severe and complicated malaria as well as uncomplicated disease. Parasites are cleared from the circulation faster by artemisinins than by quinine or chloroquine. When used for severe disease, artemisinins are as effective as quinine, less toxic and more convenient to use, although their more rapid antiparasitic action has not yet been shown to translate into improved survival.

If used alone for treatment of *P. falciparum* infection, an artemisinin drug must be given for at least 5 and preferably 7 days; shorter courses are followed by recrudescence of parasites in over half of cases. Artemisinins are therefore usually used in combination with other antimalarial drugs.

Oral, intramuscular, intravenous and rectal formulations of various artemisinins are available.

- *Artesunate* is available as tablets, suppositories and a powder for preparing an intravenous solution. Rectal artesunate is being studied as a possible first-line drug for patients with severe malaria in remote areas where injections cannot be given, pending the patient's transfer to a hospital.
- *Artemether* is an oil-soluble derivative suitable for intramuscular injection. In several studies, artemether has proved as efficacious as quinine in the treatment of severe malaria in children, although absorption from the injection site appeared to be impaired in a few very ill, acidotic children.
- *Artemisinin* can be used orally or rectally.

No important human toxicity of artemisinins has been detected after thousands of treatments. Brainstem damage has been observed in animals given more than 10 times the usual human doses of arte-ether or artemether, but careful examination has failed to reveal any neu-

rotoxicity in clinical practice. Artemisinins reduce gametocyte production. This may in turn reduce the transmission of malaria locally, although probably not to an important degree in hyper- or holoendemic areas. The rapid killing of blood-stage asexual parasites is a property of artemisinin drugs that makes them particularly suitable for combination therapy.

Combination therapy

For many decades in the mid-20th century, chloroquine monotherapy was the standard treatment for malaria. Then *P. falciparum* resistant to chloroquine began to appear and to spread, followed by parasites resistant to many other first-line antimalarial drugs. We now, belatedly, recognize the importance of combining drugs with different modes of action, as is usual practice in the treatment of tuberculosis, leprosy, cancers and HIV infection, in order to delay the development of resistance.

Various combinations of antimalarial drugs are now being evaluated for their capacity to cure patients and to prevent the emergence of drug-resistant parasites. Artemisinin drugs lower asexual parasitaemia rapidly, leaving a much diminished parasite biomass; a second drug can then kill the remaining parasites, with a much reduced chance that a resistant mutation will occur and break through the treatment.

Combination therapies, many of which include an artemisinin drug, are currently being widely evaluated. It seems likely that combination therapy will become a standard first-line therapy for uncomplicated malaria in many countries. It remains to be seen whether the use of combination therapies, especially those containing an artemisinin drug, will reduce the advance of drug-resistant *P. falciparum*. There is emerging evidence that the addition of artemisinin will improve the efficacy of an existing antimalarial treatment that is failing because of increasing resistance.

Co-artem (artemether–lumefantrine)

This is the first commercially available artemesinin combination therapy. It is currently being evaluated by the World Health Organization (WHO) in a number of African sites. Standard adult doses are 1 tablet twice a day for 3 days. Absorption of the lumefantrine component is increased considerably by fat and therefore this drug should ideally be taken with food.

Classifying antimalarial drug resistance

Antimalarial drugs can be judged *in vivo* by their efficacy in patients with malaria. They can also be assessed *in vitro* by measuring their capacity to inhibit the growth of cultured *P. falciparum*. An *in vivo* assessment requires the identification of a number of individuals with malaria (fever, parasitaemia and no other cause of illness), who must be observed to take the correct dose of the drug being assessed. Parasitaemia is monitored on days 0, 1, 2, 3, 7 and 14. Further samples on days 21 and 28 may be included, especially if further exposure to malaria infection can be prevented.

Resistance (R) is divided into three grades:

RI. Parasites disappear from the blood by day 3 but reappear by day 14.

RII. Parasites fall to less than 25% of the day-0 density by day 2 or 3, but do not disappear, and are increased in density by day 7 or 14.

RIII. Parasitaemia never falls below 25% of the day-0 level, and may even increase after treatment.

A newer classification allows for the fact that a patient may be completely well, even though parasitaemic, after treatment. In this classification patients are described as having the following.

- *Early treatment failure (ETF)* — if they develop severe illness with parasitaemia during the first 4 days after treatment; or if they remain febrile and parasitaemic throughout those 4 days.
- *Late treatment failure (LTF)* — if, having improved clinically, both fever and parasitaemia recur by day 14.
- *Adequate clinical response (ACR)* — if there was neither ETF nor LTF, and the patient does not develop febrile parasitaemia by day 14; i.e. for an ACR, the patient may have either fever or parasitaemia by day 14, but not both.

The problem of relapse

Relapse in *P. vivax* or *P. ovale* malaria can usually be prevented by giving a course of primaquine, but some strains of *P. vivax* (e.g. from Papua New Guinea) are resistant to normal doses of the drug. Primaquine is a bitter white powder, a synthetic drug of the 8-aminoquinoline group. Tablets of 26.5 mg primaquine diphosphate contain 15 mg primaquine base (or tablets half this size). The dosage is usually expressed as the weight of the base. It is a weak schizonticide. There is action on hypnozoite forms of *P. vivax* and *P. ovale*, and it destroys gametocytes of all species. Side-effects include gastrointestinal disturbance, especially abdominal cramps. Acute haemolysis may occur in G6PD deficiency. Methaemoglobinaemia (cyanosis) is usually only seen with high doses.

For radical cure of relapsing forms of malaria, 15 mg base/day is given for 10–14 days. The dose may have to be doubled in some *P. vivax* strains. A single weekly dose of 45 mg base for 6 weeks is better tolerated by G6PD-deficient patients than is daily dosing with the lower dose. For clearing gametocytes of *P. falciparum*, 15 mg/day is given for 5 days. This use of primaquine does not benefit the individual: it has been advocated in order to reduce the transmission of *P. falciparum*. In highly endemic areas this is a waste of time, because most transmission occurs from individuals who are not even known to carry the parasite.

Chemoprophylaxis

Chemoprophylaxis of malaria involves the regular administration of drugs to prevent clinical symptoms. Drugs taken for this purpose act in two ways: as *schizonticides*, so that when the parasites enter the red cells they are destroyed; and *causal prophylactics*, which prevent the development of the PE schizonts in the liver, and may also have blood schizonticidal effects.

Neither the *in vitro* nor the *in vivo* method of assessing drug resistance gives any indication of causal prophylactic efficacy, which can only be assessed by large controlled trials using willing travellers or volunteer populations. In considering malaria prophylaxis, one is always concerned with balancing risk and benefit. It takes a long time for the real incidence of the toxic effects of a new drug to emerge, and just as long to find out how rapidly resistance develops to it. Currently, chemoprophylaxis is routinely advised only for non-immune travellers visiting endemic areas.

Something akin to chemoprophylaxis is recommended for pregnant women in endemic areas. It has been shown in some endemic communities that two or three doses of a drug such as SP, given during the second half of pregnancy (irrespective of maternal illness or parasitaemia), reduces placental malaria and low birth weight in first-born babies. This routine administration of antimalarials occasionally in pregnancy is more accurately termed intermittent presumptive therapy (IPT) rather than chemoprophylaxis. A similar approach to malaria in infancy is under evaluation.

Proguanil (Paludrine, Chlorguanide)

This is a synthetic biguanide. It is a bitter white powder available as hydrochloride. Tablets are 100 mg proguanil hydrochloride, as well as a paediatric 25 mg preparation. It is a slowly acting schizonticide and a causal prophylactic. When a mosquito takes up gametocytes from a patient receiving proguanil, their development in the mosquito is inhibited, so the mosquito fails to become infective.

Proguanil is the safest of all antimalarials: no deaths have ever been recorded from overdose (up to 14.5 g). Occasionally, it can cause heartburn or epigastric pain, but this is minimized by taking the drug after food. Mouth ulcers are an unpleasant side-effect in some people. Gross overdose may cause haematuria. It is safe in pregnancy in a normal dosage, but a folic acid supplement should be given.

It is used as a prophylactic only. The adult dose is 200 mg/day. It is well-tolerated by children, who can take 25 mg/day from infancy, 50 mg/day

from age 2, 75 mg/day from age 4 and 100 mg/day from age 6 years. It has been most widely used in combination with chloroquine as malaria prophylaxis for travellers to parts of the world with limited chloroquine resistance.

Chloroquine (for prophylaxis)

The normal adult dosage is 300 mg base/week. There is virtually no danger in taking this dosage of chloroquine for short periods (say, less than 3 years) but, as chloroquine binds firmly to melanin (including the pigment of the retina), there is a theoretical possibility that long-term dosage at this level may lead to retinal damage. This has been well-documented when chloroquine has been given in high dosage for the treatment of rheumatoid arthritis and related diseases. Total dosage (because of binding) may be more important in the genesis of retinotoxic effects than the mean daily dosage. We therefore do not recommend chloroquine for people who require chemoprophylaxis for more than 6 years on 300 mg base/week continuously. Chloroquine is most commonly used in combination with proguanil. However, increasing chloroquine resistance means that this combination is now no longer effective in most parts of the world and it is currently only recommended for parts of South Asia and South America.

Mefloquine (for prophylaxis)

As a result of the spread of chloroquine resistance around the world, mefloquine (alone) is now the prophylactic drug of choice for many areas. Initial anxieties about drug accumulation have diminished, and it is now acceptable to recommend an adult dose of 250 mg/week for periods of a year or more. Contraindications must be borne in mind.

Doxycycline

This long-acting tetracycline is an effective prophylactic against malaria in a dose of 100 mg/day. It is useful in areas where there is resistance to both chloroquine and mefloquine. It should not be used in pregnancy or lactation, nor in young children. An occasional toxic effect is a rash caused by photosensitization.

Atovaquone–proguanil

This recently licensed drug combination is effective against chloroquine-resistant *P. falciparum*. It is a causal prophylactic, preventing development of parasites in the liver and therefore only needs to be taken for a week after leaving the malarious area. The standard dose is one tablet daily. Serious adverse effects are rare.

Other drugs

Sulfadoxine–pyrimethamine (Fansidar) is not used for prophylaxis because of the risk of Stevens–Johnson syndrome. Amodiaquine should be avoided because of a risk of marrow aplasia. Pyrimethamine–dapsone (Maloprim) has been used for many years and is effective in areas of chloroquine resistance, but has largely been superseded by other drugs and is no longer being manufactured. It has been associated with agranulocytosis.

No prophylactic regimen described can be completely depended on to suppress *P. falciparum* malaria, especially in non-immune people. Patients should be warned of this and advised to have an alternative drug available for treatment in the case of failure. Similarly, a non-immune individual developing fever after return from an endemic area, even if he or she faithfully took prophylaxis, may have *P. falciparum* malaria. Nevertheless, if a patient develops malaria more than 4 weeks after leaving a malarious area, it is still most likely that it will be with one of the three non-*falciparum* species, all of which commonly have a long incubation period.

Recommendations for antimalarial prophylaxis in specific geographical locations are constantly changing. Authoritative up-to-date sources such as the WHO or UK guidelines are recommended (see Further reading).

Epidemiology

The epidemiology of malaria has been most studied in the case of *P. falciparum*. The two most important factors are:

1 intensity of transmission (the number of infective bites per year); and
2 the immune response of the host.

Measuring malaria in a community

Traditional methods

It has been customary in the past to characterize the epidemiological situation in a community by describing its malariometric indices. These are established by surveys that, by examining all age groups of the population, determine for each group:

1 *parasite rate*—the proportion of blood films that are positive; and
2 *spleen rate*—the proportion of the group with a palpable spleen.

Morbidity and mortality

It is now recognized that parasite and spleen rates are measures of malaria infection, reflecting the intensity of transmission, but they are not measures of the clinical impact of malaria on the community. It is the morbidity and mortality attributable to malaria that are important as the basis for designing a malaria control programme, and these indicators are equally important in monitoring the effectiveness of control.

Ways of estimating malaria-attributable mortality include hospital studies and 'verbal autopsies'. The latter technique makes use of tested questionnaires to inquire of mothers about the nature of the final illness in any children dying within a specified period before the survey. Unfortunately, the verbal autopsy technique cannot distinguish reliably between malaria and pneumonia or meningitis, and deaths caused by severe malarial anaemia may not be identified. Therefore only an approximate measure of malarial mortality can be obtained.

Stable malaria

Transmission occurs for at least 6 months in the year and is intense. Malarial infection is acquired repeatedly. Children suffer repeated attacks of malaria from the age of a few months onwards. Very young children are partly protected by passive immunity acquired by transplacental passage of protective maternal IgG. This may modify the severity of the first few attacks, so allowing them to develop some active immunity while still partly protected. Children reaching the age of 5 or 6 years have substantial immunity, but the price of this immunity is that some children will die of malaria before immunity develops. The proportion who do so is likely to depend on many factors, including the intensity of transmission, the availability of drugs and the prevalence of parasite drug resistance. Data on the actual death toll in different populations are still rarely available.

When immunity has been established, older patients may still suffer attacks of malaria, but these take the form only of mild or moderate flu-like episodes lasting a few days. Severe and complicated disease rarely occurs. Nevertheless, in areas of stable malaria, malaria illness episodes in adults may be sufficient to cause absenteeism from work and thus to have an impact on the economy. There is little variation in the incidence of malaria from year to year (hence the word 'stable'), but there may still be pronounced seasonal fluctuations in new cases seen in children. In such an area, there is often a marked rise in the number of children seen with cerebral malaria about 2 weeks after the rains begin.

Unstable malaria

This situation is the antithesis of stable malaria. There are wide changes in transmission, not only throughout each year but also from year to year. This results in the tendency for epidemics to occur (hence the term 'unstable'). The transmission season is typically short and the mosquito population fluctuates widely. Infection is usually so infrequent that no member of the population has the opportunity to develop a significant level of immunity. For this reason, when transmission does suddenly increase (usually because of freak environmental conditions leading to an explosion in the mosquito population), people of all ages are equally susceptible to infection. This results in serious disease or even death, regardless of age. The health of the working community may be disastrously

affected, and the economic effects of an epidemic can be dire.

Global malaria eradication

Attempts at global eradication of malaria have failed and local eradication has only succeeded in a few areas, mostly islands. The main causes of failure have been the following.

1 *Operational*—not all houses were sprayed. There are many causes for this, including lack of cooperation, poor mapping, accelerated destruction of thatched roofs (DDT kills caterpillars and their predators; caterpillars soon reappear but predators do not) and resentment of intrusion into privacy.

2 *Technical*—resistance of mosquitoes to insecticide; behavioural resistance in which mosquitoes fly straight out of the house after feeding, and so do not rest on the sprayed surface; resistance of the parasite to antimalarial drugs.

3 *Political* (not a cause recognized by the WHO)—failure of countries to cooperate; civil war and severe political unrest; lack of a suitable infrastructure on which to build the control programme; political and administrative incompetence.

4 Ill-advised and unpopular pilot schemes.

5 Failure to convince the people of the need for the programme.

Malaria control at present

Global eradication as an objective has been abandoned as unrealistic. Instead, the objective now is the control of disease and mortality that result from malaria. This objective requires:

1 the provision of diagnostic and treatment services as close as possible to where the people live;

2 simple, affordable and safe therapy for uncomplicated disease;

3 prompt recognition and treatment of severe disease, with systems of referral to hospital centres when necessary;

4 education of the population about the features and dangers of malaria;

5 drug prophylaxis or intermittent presumptive therapy for selected subgroups;

6 antivector measures and water clearance where achievable (and not elsewhere); and

7 the use of permethrin-impregnated bed-nets or curtains.

Several randomized controlled trials in endemic areas have demonstrated that widespread use of insecticide-treated nets in a community can reduce child mortality and malaria-related morbidity. How well this works in the context of a routine health service programme (in the absence of a research team) is less certain: some early observations have been discouraging, others have shown significant effectiveness of nets in a programme making use of social marketing to promote net usage.

Vaccines may in the near future be added to the list of effective interventions. Several candidate vaccines have been evaluated or are undergoing trials, but none has yet been found to be both efficacious and practicable.

Individual precautions

Because the anopheline vectors of malaria are night biters, a high degree of protection is given by:

1 covering up the exposed skin in the evenings (of limited value because most infective biting occurs between 10 p.m. and 2 a.m.);

2 the use of insect repellents such as dimethyl phthalate, dibutyl phthalate or diethyl toluamide; and

3 the use of an efficient mosquito net over the bed, preferably impregnated with a synthetic pyrethroid such as permethrin or deltamethrin.

Further reading

Breman JG, ed. The intolerable burden of malaria: a new look at the numbers. *Am J Trop Med Hyg* 2001; **64** (Suppl). [A supplement reviewing the world's malaria problem, with articles on disease burden in childhood and in pregnancy, drug resistance, economic impact and possible long-term sequelae of malaria.]

Gilles HM, Warrell DA, eds. *Bruce-Chwatt's Essential Malariology*. London: Edward Arnold, 2001. [A con-

venient and erudite volume covering malaria from the point of view of numerous disciplines including clinical medicine, pharmacology, therapeutics, epidemiology, parasitology, immunology, entomology and public health.]

http://www.hpa.org.uk/cdph/issues/CDPHvol4/No2/malaria_guidelinesp.pdf This source has also been published. Bradley DJ, Bannister B. Guidelines for malaria prevention in travellers from the United Kingdom for 2001. *Commun Dis Public Health* 2001; **4**: 84–101. [UK guidelines on prophylaxis.]

World Health Organization. Severe falciparum malaria. *Trans R Soc Trop Med Hyg* 2000; **94** (Suppl): 1–90. [A comprehensive review of clinical features, pathogenesis and management of severe falciparum malaria, with an extensive list of references.]

World Health Organization. *Management of Severe Malaria*. WHO booklet, 2000. [A slim attractive book giving essentials of diagnosis and treatment. Useful for reference—fits easily into a coat pocket—and helpful as text for training seminars or for under- and postgraduate teaching.]