

AD-A206 379

REPORT DOCUMENTATION PAGE

1a. REPORT SECURITY CLASSIFICATION Unclassified			1b. RESTRICTIVE MARKINGS		
2a. SECURITY CLASSIFICATION AUTHORITY DTIC FILE COPY			3. DISTRIBUTION / AVAILABILITY OF REPORT Approved for public release; distribution is unlimited		
2b. DECLASSIFICATION / DOWNGRADING SCHEDULE			5. MONITORING ORGANIZATION REPORT NUMBER(S)		
4. PERFORMING ORGANIZATION REPORT NUMBER(S) NMRI 86-115			7a. NAME OF MONITORING ORGANIZATION Naval Medical Command		
6a. NAME OF PERFORMING ORGANIZATION Naval Medical Research		6b. OFFICE SYMBOL (if applicable)	7b. ADDRESS (City, State, and ZIP Code) Department of the Navy Washington, D.C. 20372-5120		
6c. ADDRESS (City, State, and ZIP Code) Bethesda, Maryland 20814-5055		8a. NAME OF FUNDING / SPONSORING ORGANIZATION Naval Medical Research and Development Command			
8b. OFFICE SYMBOL (if applicable)		9. PROCUREMENT INSTRUMENT IDENTIFICATION NUMBER			
8c. ADDRESS (City, State, and ZIP Code) Bethesda, Maryland 20814-5055		10. SOURCE OF FUNDING NUMBERS			
		PROGRAM ELEMENT NO. N.A.	PROJECT NO.	TASK NO.	WORK UNIT ACCESSION NO.
11. TITLE (Include Security Classification) Treatment of malaria					
12. PERSONAL AUTHOR(S) Hoffman SL					
13a. TYPE OF REPORT journal article		13b. TIME COVERED FROM TO		14. DATE OF REPORT (Year, Month, Day) 1986	
15. PAGE COUNT 54					
16. SUPPLEMENTARY NOTATION Reprinted from: Clinics in Tropical Medicine and Communicable Diseases. Vol 1(1) April 1986 pp. 171-224					
17. COSATI CODES			18. SUBJECT TERMS (Continue on reverse if necessary and identify by block number)		
FIELD	GROUP	SUB-GROUP	Malaria Plasmodium...		
			Chemotherapy Drug resistance		
			Falciparum		
19. ABSTRACT (Continue on reverse if necessary and identify by block number)					
DTIC ELECTE S MAR 27 1989 D D C& D					
20. DISTRIBUTION / AVAILABILITY OF ABSTRACT ☒ UNCLASSIFIED/UNLIMITED ☐ SAME AS RPT. ☐ DTIC USERS			21. ABSTRACT SECURITY CLASSIFICATION Unclassified		
22a. NAME OF RESPONSIBLE INDIVIDUAL Phyllis Blum, Information Services Division			22b. TELEPHONE (Include Area Code) 202-295-2188		22c. OFFICE SYMBOL ISD/ADMIN/NMCI

6

Treatment of Malaria

STEPHEN L. HOFFMAN



Accession For	
NTIS CRA&I	☒
DTIC TAB	☐
Unannounced	☐
Justification	
By	
Distribution /	
Availability Codes	
Dist	Avail and/or Special
A-1	20

Almost all patients with malaria can be successfully treated by non-physician health care workers trained to select and administer antimalarials and antipyretics. These health care workers can also recognize patients who are at risk of developing, or who have developed, complicated malaria, but the treatment of patients with severe malaria requires all the skills and resources available to the modern physician. All malaria infections can be cured with available antimalarials if the patient receives a complete course of appropriate therapy.

The principles of malaria therapy are:

1. Recognize malaria infections as rapidly as possible.
2. Initiate effective antimalarial therapy to reduce and eliminate parasitaemia as rapidly as possible.
3. Anticipate and prevent complications.
4. Treat complications and prevent death.
5. Prevent recrudescence and relapse.
6. Recognize and treat recrudescence and relapse and prevent recurrence.
7. Reduce transmission.

MALARIA TERMINOLOGY

Some terms relevant to treatment of malaria are defined as follows. The *prepatent period* is the time from sporozoite inoculation by a mosquito until asexual parasites are detectable in the blood. The *incubation period* is the time from sporozoite inoculation until onset of clinical symptoms. *Recurrent parasitaemia* occurs when parasites reappear in the blood after they have been undetectable by standard methods. Recurrent parasitaemia may be due to either relapse or recrudescence. *Relapse* is the reappearance, after eradication of the original blood stage infection, of asexual parasitaemia resulting from delayed maturation of a hypnozoite (the slowly developing or dormant exoerythrocytic stage) in the liver. It only occurs with *Plasmodium vivax* and *P. ovale*. *Recrudescence* is the reappearance of detectable asexual parasitaemia due to persistence of asexual erythrocytic stages at undetectable (subpatent) levels. Subpatent parasitaemia can be documented only by subinoculation of blood into susceptible volunteers. In the absence of reinfection, recrudescence is responsible for all recurrences of *P. falciparum*.

and *P. malariae* infections. A *blood schizonticide* is a drug that destroys the asexual erythrocytic stages of the parasite. It is used for treating acute infections and recrudescences and for chemoprophylaxis as a *suppressive prophylactic*. A *tissue schizonticide* destroys the liver asexual stages including hypnozoites. It is used to prevent relapse and as a *casual prophylactic* to prevent blood stage infections. *Gametocytocidal* drugs destroy the sexual forms of the parasite and *sporonticidal* drugs inhibit the development of oocysts on the stomach wall of the mosquito. They are both used to reduce transmission. *Clinical cure* refers to relief of symptoms of malaria without complete elimination of the infection. *Radical cure* refers to complete elimination of malaria parasites from the body so that recrudescences and relapses cannot occur. A *semi-immune* individual is one who has had multiple malaria infections, has developed an acquired immune response to malaria, is relatively resistant to infection and, if infected, is unlikely to develop severe disease. A *non-immune* individual is one who has had little or no recent exposure to malaria and has no effective acquired immune response against malaria.

DRUG RESISTANCE

Drug resistance refers to the ability of a parasite strain to multiply or survive in the presence of concentrations of a drug that normally destroy or prevent multiplication of that species of parasite. Resistance may be *relative* (yielding to increased doses of the drug) or *complete* (withstanding the maximum tolerated doses of the drug).

Most drug resistance terminology refers to the response of *P. falciparum* to chloroquine and other 4-aminoquinolines. An in vivo grading system developed by the World Health Organization defines *P. falciparum* sensitivity to 4-aminoquinolines (World Health Organization, 1973; Lepes et al. 1980). Parasites are *sensitive* to the antimalarial if they are cleared from the bloodstream within seven days of initiation of therapy and do not return within 28 days. *R1* resistant organisms are cleared within seven days, but reappear (recrudesce) within 28 days. With *RII* resistant organisms, parasitaemia levels fall by more than 75% within 48 hours of initiation of therapy, but are not cleared within seven days. With *RIII* resistant organisms, parasitaemia levels fall by less than 75% within 48 hours and are not cleared within seven days. There is some controversy about the appropriateness of this system for classifying the response to longer acting antimalarials, such as mefloquine, but it is still generally used. In vitro correlates of in vivo resistance have been established for some antimalarials. In vitro tests are useful epidemiologically, but proof of drug resistance is dependent on demonstrating in vivo resistance in patients shown to have received and absorbed adequate amounts of antimalarials.

There has been little work on resistance of *P. vivax* to blood schizonticides because: (1) the parasite has remained highly sensitive to chloroquine, (2) it is extremely difficult to distinguish between recrudescence because of drug resistance and relapse, and (3) the parasite cannot be grown in culture.

However, some strains of *P. vivax* display relative resistance to primaquine, the most commonly used tissue schizonticide (Bruce-Chwatt, 1981).

The mechanisms of development and spread of drug resistance are poorly understood in human malaria. It is never clear whether initial resistant isolates are introduced to an area from outside or represent spontaneous mutations. It seems clear that continued drug pressure selects for resistant isolates which eventually become predominant. All investigations indicate that resistance to chloroquine, sulphonamides, and pyrimethamine is transferred by classical Mendelian inheritance during sexual reproduction of the parasite in the anopheline vector (Beale et al, 1978; Walliker, 1982; World Health Organization, 1984).

HISTORY OF ANTIMALARIALS

The first and, until the twentieth century, the only blood schizonticide known in the Americas and Europe was cinchona bark, which takes its name (given by Linnaeus in 1649) from the Countess of Chinchon, who may, or may not, have been cured of malarial fever in 1630 in Peru by an oral infusion of an extract of the bark (Wesselhoeft, 1914; Haggis, 1941). It was introduced to Europe from Peru in the 1630s or early 1640s by Jesuit priests and during the next 200 years the 'Jesuit's' or 'Peruvian' bark became increasingly more important for treating malarial fevers (agues). Quinine, the principal alkaloid of cinchona bark, was isolated from cinchona in 1820 and by the late nineteenth century quinine was widely used to treat malarial fevers which had been shown in 1880 to be caused by a protozoan. The first synthetic antimalarial, pamaquin, was introduced in the 1920s. Mepacrine and several 4-aminoquinolines were synthesized in the 1930s. Mepacrine (= atabrine = quinacrine) was the most commonly used antimalarial during World War II. The 4-aminoquinolines, chloroquine and amodiaquine, and the biguanide, proguanil, were developed during the war and the folic acid synthesis inhibitor, pyrimethamine, in 1951. By the early 1950s, chloroquine, which was easily administered in a short course and effective against all human malarias, was the drug of choice for treatment of malaria and the use of quinine fell out of favour. In the late 1950s and early 1960s, resistance of *P. falciparum* to chloroquine was documented in Colombia and Thailand (Harinasuta et al, 1962; Peters, 1970). Since then chloroquine resistance has spread to most of the malarious world. Although several excellent new antimalarials including mefloquine and halofantrine have been developed by the United States Army, in 1986 quinine is again the most important *P. falciparum* blood schizonticide outside of China. For nearly 2000 years *qing hao* (*Artemisia annua* L., sweet wormwood, annual wormwood) was used in China to treat fevers including malaria. In 1972 a sesquiterpene lactone constituent of *qing hao* was isolated and found to be active against malaria. It was named *qinghaosu* (active principle of *qing hao*) in Chinese and artemisinin in English. Reports from China indicate that it is an effective, rapidly acting blood schizonticide (Qinghaosu Antimalaria Coordinating Research Group, 1979; China Cooperative Research Group of Qinghaosu

and its Derivatives as Antimalarials, 1982; Guoqiao et al, 1982; Jiang et al, 1982a; Guoqiao, 1984; Li et al, 1984; Klayman, 1985).

DIAGNOSIS

Delay in treatment of malaria patients, especially those with *P. falciparum* infections, can be disastrous and has been responsible for many unnecessary deaths. Institution of antimalarial therapy requires rapid diagnosis. Individuals with a febrile illness who have been in a malarious area within the past 12 months should be evaluated for malaria infection regardless of whether or not they have taken malaria chemoprophylaxis. More than 95% of primary infections will become patent within four weeks of mosquito inoculation of sporozoites of *P. falciparum* and *P. ovale* and within six weeks of inoculation of *P. vivax* and *P. malariae* (Kitchen, 1949; Miller 1975). Delayed primary attacks of *P. vivax* more than six months after exposure have been described for Dutch, Korean, Pakistani, Chinese, and Hibernians (Russia) strains (Miller, 1975; Jiang et al, 1982b; G. Strickland, personal communication). Secondary or relapse infections with *P. vivax* and *P. ovale* can occur from several months to, occasionally, three years after infection. Untreated or incompletely treated *P. falciparum* infections are usually eliminated by host immune response within one year of infection, but may rarely persist for two to three years (Verdrager, 1964; Brooks and Barry, 1969). *P. malariae* persists longer than the others and has been responsible for transfusion malaria 46 years after last exposure (Miller, 1975).

Even when parasitaemia is extremely low, parasites can generally be found if a thick blood film is prepared, stained, and read properly (see Chapter 5). Thin films (peripheral smears) in which parasites are visualized within intact erythrocytes are used to distinguish between the four species of human plasmodia. It is often difficult to detect low levels of parasitaemia with a thin film. Parasites can sometimes be found in bone marrow aspirates or in intradermal fluid when not found in thick blood films (Guo et al, 1984). *P. vivax* schizonts have a buoyant density similar to that of leukocytes. Smears made from buffy coats or the mononuclear cell layer of ficoll-Hypaque gradients are more sensitive than thick blood films for detecting *P. vivax* infection (Bass and Johns, 1915; Le Bras and Payet, 1978). *P. falciparum* has a 48-hour life cycle. Merozoites which invade erythrocytes develop from early trophozoites to schizonts. The schizonts rupture and release merozoites which reinvade erythrocytes. Only the early trophozoites (rings) are generally seen in peripheral blood films. Late trophozoites and schizonts are sequestered in the capillaries and postcapillary venules of the deep organs. The rings are only present for 18–24 hours of the 48-hour life cycle. Thus, a patient with a synchronous high level infection (all parasites at same stage of development) could have a negative blood film when all parasites are sequestered and a heavy parasitaemia 6–24 hours later. If malaria is suspected and the thick blood film is negative, the smear should be repeated every 6–12 hours for 24–36 hours.

In recent years radioimmunoassays (Mackey et al, 1980; Avraham et al,

1982), enzyme-linked immunosorbent assays (Mackey et al. 1982) and DNA probes (Franzen et al. 1984; Pollack et al. 1985; Mucenski et al. 1986; Walker et al. 1986) for *P. falciparum* antigen detection in blood have been developed. None of these techniques have been validated or standardized for routine use. It is likely that they will prove useful for screening large numbers of individuals for parasitaemia, but not be particularly important for diagnosis in individual patients (Chapter 5).

ANTIMALARIAL DRUGS

Rapid reduction and clearing of parasitaemia require *blood schizonticidal drugs*, i.e. antimalarials which are effective against the erythrocytic, asexual, stage of the parasite. Treatment of *P. falciparum* infections from some areas of the world may require two blood schizonticides; the first to rapidly reduce parasitaemia and the second, a more slowly acting drug, to achieve radical cure.

Choice of blood schizonticide

The choice of antimalarial depends on the species of *Plasmodium* with which the patient is infected, the expected drug sensitivity pattern of the parasite, the clinical condition of the patient, the malaria immune status of the patient and the patient's tolerance of specific antimalarials. The route of administration is dictated by the patient's condition and the availability of intravenous fluids. In general, the physician treating an individual patient out of a malarious area should treat all patients with uncomplicated *P. vivax*, *P. malariae*, or *P. ovale* infections with oral chloroquine, all patients with uncomplicated *P. falciparum* infections with an antimalarial other than chloroquine (pyrimethamine-sulfadoxine, quinine, quinidine, mefloquine), and all patients with complicated malaria, regardless of the apparent species of *Plasmodium*, with intravenous quinine or quinidine. The physician in a malarious area who is confident of the response of local *P. falciparum* to chloroquine or amodiaquine may use one of these 4-aminoquinolines instead of the alternative drugs listed above.

Response to therapy is monitored by examining the patient and malaria blood films daily. If parasitaemia is not reduced by >75% within 48 hours, the clinician should suspect high grade drug resistance.

Classes of antimalarials

There are a number of classes of antimalarials, each of which may have an effect on a different stage of the parasite and different species:

1. Cinchona alkaloids (quinine, quinidine)
2. 4-Aminoquinolines (chloroquine, amodiaquine)
3. Diaminopyrimidines (pyrimethamine)
4. Sulphonamides and sulphones (sulfadoxine, sulfametopyrazine sulfalene), dapsona)

5. Tetracyclines (tetracycline, doxycycline, minocycline)
6. Quinoline methanols (mefloquine)
7. Sesquiterpene lactones (artemisinin = qinghaosu)
8. Phenanthrene methanols (halofantrine)
9. 8-Aminoquinolines (primaquine)
10. Biguanides (proguanil, chlorproguanil, cycloguanil)
11. Other antibiotics and antimalarials.

Cinchona alkaloids

Quinine and quinidine are the only cinchona alkaloids in frequent clinical use. They are both rapid-acting agents against the asexual stages of all four species of plasmodia that infect humans. More experience has been gained with quinine than with quinidine, and since the use of quinidine is associated with more frequent electrocardiographic abnormalities (White et al, 1983a) quinine, when available, is still the cinchona alkaloid of choice for the treatment of malaria. If quinine is not available, quinidine is an excellent substitute.

Quinine

Recommendations regarding the optimum dosage, route of administration and length of treatment with quinine are controversial. This has been due to incomplete pharmacokinetic studies, non-specific and non-uniform methods of measuring blood levels of the drug, the inability until recently to measure the in vitro inhibitory concentrations of quinine against *P. falciparum*, changing quinine sensitivity patterns of *P. falciparum*, lack of data establishing correlations between in vitro and in vivo parasite inhibitory concentrations of quinine and difficulty in distinguishing the hypotensive, life-threatening complications of *P. falciparum* infections from the serious side-effects of quinine.

In a series of well-designed studies carried out since 1980, investigators in Thailand have provided pharmacokinetic data for the rational use of quinine (White et al, 1982, 1983b) and quinidine (Phillips et al, 1985) in severe malaria. They have shown that, in severe malaria, high plasma levels of quinine are common, safe, and well tolerated and that severely ill patients treated with standard regimens often die before plasma levels of quinine adequate for in vitro parasite inhibition are achieved (White et al, 1982, 1983b). Their conclusions regarding the requirement for a loading dose of quinine or quinidine in order to rapidly achieve and maintain adequate drug concentrations are well substantiated from a pharmacological perspective and are suggestive from a clinical and parasitological perspective. There have been no studies which have adequately compared the clinical efficacies of intravenous loading dose, intravenous non-loading dose, and intramuscular quinine regimens for the treatment of severe malaria.

Antimalarial activity. Quinine is active against asexual erythrocytic stages of all four human malaria parasites. It has no effect on exoerythrocytic forms.

Immature gametocytes of *P. falciparum* and all gametocytes of the other species are sensitive to quinine. *P. vivax* infections may respond less rapidly than *P. falciparum* infections.

Absorption and disposition. Quinine is well absorbed after oral administration. Peak plasma concentrations occur within one to four hours after a single dose. It is generally given as quinine sulphate which in some studies was not as well absorbed as the dihydrochloride and bisulphate salts (Garnham et al, 1971). Plasma concentrations were 10–30% lower after tablets and intramuscular injection than after intravenous infusion in adults (Hall et al, 1973, 1975a). In children there was no difference between levels after tablets or intravenous infusion (Sabchareon et al, 1983). When 10 mg/kg quinine dihydrochloride (8.3 mg/kg base) was given by four-hour intravenous infusion every eight hours, steady state levels (10–15 mg/l) were not reached for 48–72 hours. When a loading dose of 20 mg/kg was given during four hours, levels of $93\% \pm 10$ of steady state peak and $75\% \pm 14$ of steady state trough were reached after the first dose (White et al, 1982, 1983b). Erythrocyte concentrations of quinine are directly correlated with the level of parasitaemia, but the ratio of red cells to plasma quinine levels rarely exceeds one (White et al, 1983c). Cord blood and breast milk concentrations of quinine are approximately one-third those of maternal plasma levels (White, 1985). Plasma protein binding is higher in cerebral malaria (93%) than in uncomplicated malaria (90%) or in convalescence (89%) (Silmaut et al, 1985). This may explain the lack of apparent quinine toxicity despite high plasma concentrations in severe falciparum malaria. Cerebrospinal fluid levels of quinine are 5–10% of plasma levels suggesting that quinine does not freely cross the blood–brain barrier (White et al, 1982; Silmaut et al, 1985).

Metabolism and elimination. Quinine is cleared primarily by hepatic metabolism and only 15–20% is excreted in the urine. Acidification of the urine increases excretion. There is little, if any, reduction in quinine clearance in patients with renal failure (White et al, 1982). Several studies have shown that plasma and erythrocyte levels of quinine are higher in patients with severe malaria than in those with uncomplicated malaria and higher in patients with acute malaria than in non-infected volunteers or convalescent malaria patients (Trenholme et al, 1976; White et al, 1982; Sabchareon et al, 1983; White et al, 1983c; White, 1985). In cerebral malaria patients given 10 mg/kg quinine dihydrochloride every eight hours, once steady state levels were reached, serum levels consistently exceeded 10 mg/l and in 60% of patients exceeded 15 mg/l (White et al, 1982). The increase in quinine levels with increasing severity is thought to be due to a decrease in the volume of distribution of the drug and a decrease in hepatic metabolism in patients with severe malaria, resulting in a decrease in clearance and a longer half-elimination time (White et al, 1982; White, 1985). The half-elimination time is approximately 10 hours, but becomes shorter during convalescence, and may be shorter in children than in adults. If the parasite requires a high concentration of quinine for inhibition, the quinine dose may

have to be increased on day 4–5 after initiation of therapy (Chongsuphajaisiddhi et al, 1981a). During the third trimester of pregnancy pharmacokinetics are similar to those in children; elimination half-life and volume of distribution decrease, but clearance is similar to other adults (Looareesuwan et al, 1985a; White, 1985). Quinine pharmacokinetics have been inadequately studied in patients with severe parenchymal liver disease. Quinine metabolites have less antimalarial activity than quinine.

Toxicity. Serious side-effects of quinine are infrequent, but minor side-effects are common (Powell and McNamara, 1972). Quinine has a bitter taste. Side-effects increase with increasing plasma levels of quinine. Headache and tinnitus are the most common side-effects. Cinchonism, which includes tinnitus, headache, nausea, vomiting, abdominal pain, blurred vision, transient loss of hearing, vertigo, and tremors, often occurs during the first two to three days of therapy, sometimes subsides spontaneously during therapy, but always subsides after discontinuation of the drug. It is more common in women than men and in adults than children, and is sometimes so unpleasant as to necessitate a change in therapy. Drug fever is sometimes confused with an inadequate response to therapy. Diarrhoea, constipation, pruritus, and nervousness have also been described. Rarely encountered serious reactions include urticaria, bronchospasm, angioedema of the face, mucous membranes and the lungs, deafness, blindness or amblyopia, haemolytic anaemia, and agranulocytosis. The deafness and amblyopia are occasionally irreversible. Overdose of quinine, usually caused by rapid injection of a large dose, may result in convulsions, hypotension, heart block, ventricular fibrillation, and death. Intravenous quinine given by slow infusion and oral quinine for acute malaria are associated with minor electrocardiographic changes (10% lengthening of QT interval and T wave flattening) with no other evidence of cardiotoxicity (White et al, 1983b). Quinine is a local irritant which occasionally causes nausea, vomiting, and midepigastria pain when given orally, thrombophlebitis with sclerosis of veins when given intravenously, and tissue necrosis and sterile abscesses when given intramuscularly. Many clinicians consider it to be an abortifacient inducing uterine contractions. A recent study in Thailand indicates that this is not the case (Looareesuwan et al, 1985a).

Measurement of quinine levels. High-performance liquid chromatography (HPLC) is the best method for measuring quinine levels (Edstein et al, 1983). The benzene extraction fluorescence technique (Cramer and Isaksson, 1963) does not distinguish between quinine and quinidine, and may measure metabolites (Edstein et al, 1983). A metaphosphoric acid precipitation method has been used to assess quinine metabolism (Trenholme et al, 1976).

Mechanism of antimalarial action. This is unknown, but the drug is thought to influence haemoglobin digestion by the parasite leading to development of a haemolytic complex that disrupts the parasite–host membranes. It is

apparently bound at a different site within the parasite than is chloroquine and leads to a modification of the ultrastructure of malarial pigment (Warhurst, 1981).

Resistance to quinine. It is believed that minimal inhibitory concentrations (MIC) of quinine must be maintained for four to seven days to effect radical cure of *P. falciparum* infections (Chongsuphajasiddhi et al, 1981a). Since it takes two to three days to achieve steady state plasma levels of quinine when 10 mg/kg are given every eight hours, quinine must be given for at least seven days and perhaps 10 days, depending on the parasite's MIC. Resistance of *P. falciparum* to quinine was described in Brazil in 1908 where as much as 25.5 g of quinine base given during 21 days was unable to cure all *P. falciparum* infections (Neiva, 1910; Nocht and Werner, 1910; Bruce-Chwatt, 1981). Relative resistance was also described in Italy, Parama, and New Guinea, but, in spite of widespread use of quinine before the introduction of synthetic antimalarials, *P. falciparum* has remained remarkably sensitive to quinine, especially in Africa (Bruce-Chwatt, 1981). In recent years *P. falciparum* infections resistant to quinine have been described in Vietnam (Hall, 1972), Thailand (Pinichpongse et al, 1982), Irian Jaya (Hoffman, unpublished data), and Tanzania (Mutabingwa et al, 1982). In Vietnam 14% of 36 adults treated with 10 days of intravenous quinine (1800 mg/day) were found to be resistant (Hall, 1972). In Thailand, 25% of 28 children who received quinine 30 mg/kg/day, 38.5% of 26 who received quinine plus a single curative dose of pyrimethamine-sulfadoxine, and 13% of 23 who received 30 mg/kg/day for four days and then 45 mg/kg for three days were found to be resistant (95% at RI level, one case RII) (Chongsuphajasiddhi et al, 1981a). Increasing the dosage at a time when quinine clearance was increasing (see above) appeared to be associated with an improved radical cure rate. The sensitivity of *P. falciparum* to quinine is now also being monitored by in vitro tests. In Thailand the MIC of quinine increased from a mean of 12.1 to 19.4 $\mu\text{mol/l}$ (3.9 to 6.3 mg/l) from 1978 to 1981. Some isolates required 32.0 μmol quinine/l (10.4 mg/l) for inhibition. Some isolates from Irian Jaya have been shown to produce schizonts in the presence of 51.2 $\mu\text{mol/l}$ (16.5 mg/l) of quinine (Hoffman, unpublished data). The World Health Organization now considers the production of schizonts in the presence of 51.2 $\mu\text{mol/l}$ (256 pmol) quinine to indicate in vitro resistance (D. Payne, personal communication). When seven days of tetracycline were given with quinine in Thailand, cure rates of 95% were obtained (Pinichpongse et al, 1982).

The way in which *P. falciparum* becomes resistant to quinine is unknown. It has been suggested that resistance to quinine develops more readily in areas where chloroquine resistance is widespread and is related to chloroquine resistance. However, in vitro resistance to quinine and mefloquine have been observed in *P. falciparum* infections shown to be sensitive in vivo and in vitro to chloroquine (Hoffman et al, 1986).

P. vivax infections respond less rapidly than *P. falciparum* infections to quinine. Neither *P. vivax*, *P. ovale*, nor *P. malariae* erythrocytic stages have ever been documented to be resistant to quinine. On the other hand,

clinicians anecdotally report the appearance of *P. vivax* parasitaemia four to five days after initiating appropriate therapy for *P. falciparum* infections.

Formulations. Quinine is available as tablets containing quinine sulphate (125–300 mg), quinine bisulphate (300 mg), quinine dihydrochloride (300 mg), and quinine hydrochloride (300 mg), capsules of quinine sulphate (125–300 mg), ampoules of quinine dihydrochloride (500–1000 mg), ampoules of quinine–antipyrine, and ampoules containing 385 mg of quinine–resorcinol bichlorhydrate, 10 mg of quinidine–resorcinol bichlorhydrate, 2.7 mg of cinchonine–resorcinol bichlorhydrate, and 2.7 mg of cinchonidine–resorcinol bichlorhydrate (Quinimax). In the United States quinine dihydrochloride for intravenous use can be obtained from the Center for Disease Control, Atlanta, Georgia.

Uses. Treatment of complicated malaria and multidrug resistant uncomplicated *P. falciparum* infections is shown in Table I.

Quinidine

Quinidine, a diastereoisomer of quinine, was found to be effective against *P. falciparum* over 100 years ago in India. Although shown to be as effective and perhaps more effective than quinine for the treatment of falciparum malaria, it was largely ignored as an antimalarial until recently (Sanders and Dawson, 1932; Sanders, 1935; Taggart et al, 1948). Studies in Thailand have suggested quinidine is as effective as quinine in complicated and uncomplicated falciparum malaria and shown quinidine to be effective in infections resistant to quinine (White et al, 1981; Phillips et al, 1985).

Antimalarial activity. This has not been as extensively tested, but is apparently similar to that of quinine. Quinidine has been shown to have a lower MIC for *P. falciparum* in Thailand than quinine and to be effective against quinine resistant strains (White et al, 1981).

Absorption and disposition. Few pharmacokinetic data are available on humans infected with malaria, but it appears that the pharmacokinetics are similar to quinine (White et al, 1981; Phillips et al, 1985). Mean plasma levels are slightly lower than with equivalent doses of quinine. Neonatal concentrations were 82% and breast milk concentrations 70% of maternal serum values in a woman with cardiovascular disease on long-term quinidine therapy; levels much higher than those observed for short-term quinine therapy (see above) (Hill and Malkasian, 1979).

Metabolism and elimination. This is primarily hepatic (60–85%), but renal clearance may be higher than for quinine (20–35%). Limited experience from Thailand suggests that total clearance of quinidine is not reduced in patients with renal failure any more than in other patients with severe malaria (Phillips et al, 1985). The elimination half-life is not prolonged in non-malarious patients with renal failure.

Toxicity. This is also similar to the toxicity of quinine. Prolongation of the QT interval (~24%) of the electrocardiogram was two to three times greater than with quinine (White et al, 1983a). Two of 11 patients with severe malaria developed hypotension during the loading dose infusion. Hypotension resolved with discontinuation of the infusion. Quinidine has been given throughout pregnancy without adverse effect to mother or infant (Hill and Malkasian, 1979).

Measurement of levels. The benzene extraction method does not distinguish between quinine and quinidine. Newer techniques, including HPLC, are likely to be more specific.

Mechanism of antimalarial action. This is unknown, but is probably the same as for quinine.

Resistance. Resistance patterns have not been extensively tested. Quinidine has been effective in treating quinine resistant infections. It may bind to the parasite's 'clumping site' more effectively than quinine. Resistance to quinidine can be expected to develop with increased use.

Children. No data are available on this for malaria patients.

Formulations. Quinidine sulphate, gluconate, and polygalacturonate are available as tablets and capsules containing 100–324 mg of the drug. Quinidine gluconate is available in 10 ml vials containing 80 mg/ml and quinidine sulphate is available in 1 ml ampoules containing 200 mg/ml.

Uses. Quinidine is used in the treatment of complicated malaria and multi-drug resistant uncomplicated *P. falciparum* infections when quinine is not available (Table 1).

4-Aminoquinolines

Chloroquine and amodiaquine are the only two 4-aminoquinolines in common use. Both are rapidly acting antimalarials.

Chloroquine

Chloroquine was the blood schizonticide of choice for treating all malaria infections from the late 1940s to the early 1970s. Chloroquine is inexpensive, safe and widely available and is still the drug of choice for treating *P. vivax*, *P. ovale* and *P. malariae* infections. However, due to the development of resistance by *P. falciparum* to this drug, in 1986 chloroquine can only be recommended for treating non-immunes with *P. falciparum* infections acquired in West Africa, Central America above Panama, Haiti and the Dominican Republic.

Antimalarial activity. Chloroquine is a rapidly acting blood schizonticide

Table 1. Treatment regimens for specific malaria infections.

Species	Disease severity	Choice of drug	Drug	Route of administration*	Initial dose (mg/kg)	Other doses (mg/kg)	Interval between doses (hours)	Length of therapy (days)	Comment
<i>P. falciparum</i>	Severe	Drug of choice	Quinine dihydrochloride	IV infusion (2-4h)	20	10	8	7-10	Dosage could be reduced in areas with more sensitive parasites
		Quinine not available	Quinidine gluconate	IV infusion (2-4h)	24	12	8	7-10	
		Certain of sensitivity to chloroquine	Chloroquine base	IV infusion (4h)	6.2	6.2	12	1-2.5	Children receive lower doses (see text)
<i>P. falciparum</i>	Uncomplicated chloroquine sensitive	Drug of choice	Chloroquine base	Oral	10	5-10	6-24	48	Total of 25mg/kg given during 48h (see text)
	Uncomplicated chloroquine resistant	Depends on sensitivity	SP	Oral	S = 25 P = 1.25	None		Single dose	
			Amodiaquine	Oral	10	5-10	6-24	Total of 25-50mg/kg during 48h	Not used in non-immune
			Quinine sulphate	Oral	10	10	8	7-10	More effective with tetracycline
			Mefloquine	Oral	15-25			Single dose	Children receive the higher dose

	MSP	Oral	M = 15 S = 25 P = 1.25	Single dose	Available in Thailand
<i>P. vivax</i> <i>P. ovale</i> <i>P. malariae</i>	Tetracycline	Oral	5-6	6	7
	Doxycycline	Oral	1.5-2	12	7
	Clindamycin	Oral	10	10	5
	Treatment is the same as for <i>P. falciparum</i> (see text), followed by radical cure of <i>P. vivax</i> and <i>P. ovale</i> with primaquine				
<i>P. malariae</i> <i>P. vivax</i> <i>P. ovale</i>	Chloroquine	Oral	Same regimen as for uncomplicated <i>P. falciparum</i>		
	Amodiaquine		Same regimen as for uncomplicated <i>P. falciparum</i>		
	Quinine		Same regimen as for uncomplicated <i>P. falciparum</i>		
	Mefloquine		Same regimen as for uncomplicated <i>P. falciparum</i>		
	SP		Same regimen as for uncomplicated <i>P. falciparum</i>		
	<i>P. vivax</i> and <i>P. ovale</i> require addition of primaquine for radical cure				
	Primaquine base	Oral	0.25	0.25	14
			0.75	or 0.75 weekly	6 weeks
					Some strains may require twice the dose (see text)

* IV = intravenous.

against *P. vivax*, *P. ovale*, and *P. malariae*, and sensitive strains of *P. falciparum*. It is not effective against exoerythrocytic (liver) stages, but has some gametocytocidal activity against gametocytes of *P. vivax*, *P. ovale*, and *P. malariae*, and immature gametocytes of *P. falciparum*.

Absorption and disposition. There have been few studies of the pharmacokinetics of chloroquine in malaria patients and no published studies in severe malaria. Most studies were done in non-infected volunteers and until recently used non-specific techniques for determination of levels of the drug in body fluids and tissues. In recent years studies in non-infected volunteers in Sweden (Gustafsson et al, 1983a,b) and in children with uncomplicated malaria in Nigeria have been carried out (Adelusi et al, 1982; Walker et al, 1983). In one study of 12 children with malaria who were treated with an initial oral dose of 10 mg/kg base and a total dosage of 25 mg/kg base during 48 hours, chloroquine levels were measured by HPLC. Average peak plasma concentrations of 144 µg/l were reached in one to eight hours and the terminal half-life after the last dose was 75 hours (Walker et al, 1983). The absorption was more variable than in non-infected volunteers. In another study in which a fluorometric technique was used for measuring drug levels, erythrocyte/plasma levels of chloroquine showed a progressive decrease from a peak of 21 shortly after starting therapy to a stable ratio of 5.3, 72 hours later (Adelusi et al, 1982). The decline in ratio correlated directly with the decline in parasitaemia, a finding consistent with the observation that parasitized erythrocytes concentrate chloroquine. Peak plasma and erythrocyte levels occur at the same time. Studies in healthy subjects have shown terminal half-lives to be longer and erythrocyte/plasma ratios to be lower than in infected subjects (Gustafsson et al, 1983a,b).

In healthy adults, peak plasma concentrations after intravenous injection of 300 mg of base have been shown to be 10 times higher than after oral administration of the same dose (0.83 µg/ml compared to 0.07 µg/ml) (Gustafsson et al, 1983a). The distribution phase is rapid and may be associated with potentially serious cardiovascular side-effects; it is not apparent with a four hour infusion of 10 mg/kg base. There is no information on absorption or distribution after intramuscular injection.

Animal studies indicate that chloroquine accumulates in the tissues: concentrations in spleen, kidney, lungs, heart, and liver were 300–500 times higher than those found in the plasma (World Health Organization, 1984). Other studies have shown extensive binding to granulocytes and platelets. In healthy subjects the volume of distribution has been as high as 1000 l/kg indicating extensive tissue distribution (Frisk-Holmberg et al, 1984). Binding to plasma proteins in healthy subjects is approximately 50%.

Metabolism and elimination. The drug is metabolized by side-chain de-ethylation in the liver leading successively to desethylchloroquine and then bisdesethylchloroquine, a primary amine. It can be further dealkylated to 7-chloro-4-aminoquinoline, but in man the primary metabolite is desethylchloroquine, which is biologically active. Plasma levels of the metabolite are

generally 25–40% of chloroquine levels and it has the same profile of distribution and tissue binding as the parent drug. Chloroquine is eliminated from the body slowly; after a single dose of 300 mg of base, the drug and its metabolites can be detected for up to 56 days in plasma. Because of extensive tissue binding and continuous redistribution from the tissues to the plasma, determination of true terminal half-life is difficult, and requires long studies and extremely sensitive methods. In healthy adults, renal clearance is approximately 50% of total clearance of chloroquine (mean 412 ml/min) (Gustafsson et al, 1983a). Approximately 50% of chloroquine is recovered unchanged in the urine. In a single study of the kinetics of elimination of a single oral dose of chloroquine in patients with renal failure, it was estimated that the elimination half-life of chloroquine would be longer in patients with renal failure (Salako et al, 1986). Chloroquine metabolism and elimination has not been studied in patients with severe liver disease.

Toxicity. Toxic manifestations are uncommon and mild with oral doses used for treatment of malaria (Weniger, 1979a). They include nausea and vomiting when the drug is taken on an empty stomach, dizziness, headache, blurred vision, fatigue, diarrhoea, and confusion. Symptoms disappear when the drug is discontinued. Pruritus, particularly of the scalp, palms, and soles, has been reported, mostly from Africa, and is associated with repeated treatment with chloroquine and higher than normal skin levels of chloroquine and lower than normal levels of desethylchloroquine.

Rapid intravenous administration of chloroquine has been associated with hypotension, acute circulatory failure and respiratory and cardiac arrest, particularly in infants and children. This has not been described with slow intravenous infusion, but has been reported after intramuscular administration.

There is no information on the disposition of chloroquine in pregnancy. No adverse effects on the fetus or mother have been reported. It is generally used as for non-pregnant adults.

Measurement of levels. HPLC is presently the most sensitive and specific method for determining chloroquine levels, which should be measured in plasma (Bergquist and Frisk-Holmberg, 1980). Whole blood levels are 3–10 times higher than plasma levels and serum levels are considerably higher than plasma levels (White, 1985). This is thought to be due to the fact that chloroquine and its major metabolite are extensively bound to granulocytes and platelets with up to 80% of total blood cell contents localized in these cells (Bergquist and Domeij-Nyberg, 1983). Serum levels are spuriously high because of release of chloroquine from platelets during clotting.

Mechanism of antimalarial action. Chloroquine is thought to influence haemoglobin digestion by the parasite. It binds to haematin (ferriprotoporphyrin IX), a transient breakdown product of haemoglobin, within the parasite to form a haemolytic complex which may disrupt parasite and host membranes, killing the plasmodium (Fitch, 1983; World Health Organization, 1984).

Resistance. No infections with *P. vivax*, *P. ovale*, or *P. malariae* have been documented to be resistant to chloroquine. However, many clinicians in endemic areas believe that they have treated chloroquine resistant vivax malaria. Documentation of resistant vivax infections is difficult because of the problem of distinguishing between relapse (not resistance) and recrudescence (resistance).

P. falciparum infections resistant to chloroquine were first suspected in Colombia and first documented in Thailand in the late 1950s (Harinasuta et al, 1962; Peters, 1970); they have now been documented from all parts of the malarious world, except Central America (north of the Panama Canal), the Caribbean islands and West Africa. It is likely that chloroquine resistance will soon spread to these areas. The prevalence and degree of resistance varies from that in Thailand and other countries of South-East Asia, where the drug is essentially useless for treating non-immunes with falciparum malaria, to that in parts of Africa where it is still highly effective for most infections. Production of schizonts in the presence of 1.14 $\mu\text{mol/l}$ of chloroquine in the *in vitro* test is considered evidence of resistance (Lepes et al, 1980).

There has been much work done on the mechanism of development of resistance, but there is still no clear explanation. Some hypothesize that resistant parasites may effectively isolate themselves from the drug by increasing their surface area, that they induce increased production of proteolytic enzymes which metabolize haemoglobin and decrease the quantity of haematin available for binding with chloroquine, and that they synthesize a protein that binds with haematin and segregates it in the form of the malaria pigment, haemozoin, making it unavailable for binding with chloroquine. Resistance is maintained throughout the life cycle and transferred to progeny (World Health Organization, 1984).

Renal failure. Elimination half-life may be prolonged in renal failure (Salako et al, 1986). However, if chloroquine is used to treat severe malaria with renal failure, the dosage need not be reduced.

Formulations. Chloroquine is available as tablets of chloroquine phosphate, diphosphate, and sulphate containing from 100 to 300 mg of chloroquine base, as a suspension, and as ampoules of chloroquine hydrochloride, diphosphate, or sulphate solution containing 40 mg of chloroquine base per ml.

Uses. Chloroquine is used in the treatment of all *P. vivax*, *P. malariae*, and *P. ovale* erythrocytic stage infections and sensitive *P. falciparum* infections (Table 1). It is also used in the chemoprophylaxis of malaria (see Chapter 7).

Amodiaquine

Amodiaquine has always been considered to be similar to chloroquine in pharmacokinetics, clinical efficacy and toxicity. The drug has recently received increased attention because of new observations regarding its

toxicity, pharmacokinetics (Pussard et al, 1985) and because it has been shown to be more effective than chloroquine for treating infections in Kenya and Thailand (Hall et al, 1975b; Watkins et al, 1984), effective at an increased dosage with erythromycin for clearing parasitaemia in multidrug resistant *P. falciparum* in Thailand (Looareesuwan et al, 1985b), and useful parenterally for clearing parasitaemia in moderately ill falciparum patients in Thailand (Looareesuwan et al, 1985b).

The pharmacokinetic findings indicate that amodiaquine undergoes rapid first-pass biotransformation in the liver and that monodesethylamodiaquine is the principal metabolite with antimalarial activity (Pussard et al, 1985). The metabolite may be the more appropriate compound for in vitro drug sensitivity testing.

Several studies in Kenya have shown that amodiaquine is slightly more effective than chloroquine in achieving radical cure of infections; cure rates of approximately 80–97% as compared to 50–75% have been found (Watkins et al, 1984; Brandling-Bennett et al, 1985). In Thailand 41 mg/kg amodiaquine base given during three days in combination with five days of erythromycin led to initial clearing of parasitaemia in 94% of cases, but subsequent recrudescence in 52% (Looareesuwan et al, 1985b). Also in Thailand, 10 mg/kg base given over four hours by intravenous infusion followed by three doses of 5 mg/kg at 24-hour intervals (total dosage 25 mg/kg) to patients with moderately severe falciparum disease led to clearing of parasitaemia and a clinical response similar to that expected with quinine infusion; 55% had subsequent recrudescences (Looareesuwan et al, 1985b).

The enthusiasm for amodiaquine has been tempered by the results of studies from the Philippines where 25 mg/kg amodiaquine base was less effective than chloroquine (Watt et al, 1985), and from Pakistan where they were equally ineffective (Khaliq et al, 1986); 20 mg/kg amodiaquine base was used in Pakistan.

Formulations. Amodiaquine is commercially available as syrup and tablets, but not for parenteral use.

Uses. Amodiaquine can be used as a substitute for chloroquine (Table 1). It is now also used in some areas with moderate chloroquine resistance. The magnitude of increased antimalarial efficacy is not great enough to warrant its use in non-immunes with suspected chloroquine resistant infections. The role of parenteral amodiaquine for treating moderately severe and severe falciparum malaria remains to be clarified, as does the appropriate total dosage for treating chloroquine resistant *P. falciparum* infections.

Diaminopyrimidines

Pyrimethamine is the only drug of this class in use for the treatment of malaria. Diaminopyrimidines are slowly acting blood schizonticides and because of the rapid and nearly complete development of resistance they should not be used alone to treat *P. falciparum* infections. Their antimalarial

activity is augmented by the addition of sulphonamides, leading to a synergistic, sequential block of folic acid synthesis.

Pyrimethamine

Antimalarial activity. Pyrimethamine is active against the erythrocytic stages of all four human malarias (blood schizonticide) and against the exoerythrocytic stages of *P. falciparum* and to a lesser extent *P. vivax* and perhaps *P. ovale* and *P. malariae*. It is not effective against hypnozoites of *P. vivax* and *P. ovale* and cannot be used for radical cure of these infections. It has no gametocytocidal activity, but has some sporonticidal activity.

Absorption and disposition. Pyrimethamine is absorbed relatively rapidly after oral administration. The peak plasma level is reached in two to six hours in healthy volunteers and then declines slowly with an elimination half-time of 80–95 hours (Jones and Ovenell, 1979; Ahmad and Rogers, 1980; World Health Organization, 1984). In malaria patients, plasma concentrations are 300–600 µg/l 24 hours after a standard therapeutic dose of pyrimethamine-sulfadoxine (Hoffman et al, 1985). Red cell and plasma concentrations are similar (Ahmad and Rogers, 1980). The drug is moderately bound to body tissues with a volume of distribution of approximately 3 l/kg (Ahmad and Rogers, 1980). Pyrimethamine has been reported to be 85–87% protein bound (Ahmad and Rogers, 1980).

Metabolism and elimination. Urinary excretion has been shown to continue for over 30 days and account for 16–32% of a single oral dose of 100 mg (Smith and Ihrig, 1959). After a single dose of 50 mg, a mean of 3.4% of the total dose was excreted daily for seven days (Sheehy et al, 1969).

Toxicity. No significant toxic symptoms have been reported for the doses of pyrimethamine used for treatment of malaria (Weniger, 1979b). It may be used for treatment of malaria in pregnancy. The question of teratogenic effects of long term chemoprophylaxis during pregnancy and the fatal complications associated with use with sulfadoxine are discussed in Chapter 7 and in the section on pyrimethamine-sulfadoxine below.

Measurement of levels. Spectrophotometric and chromatographic techniques have been used. An HPLC technique has recently been reported (Timm and Weidekamm, 1982). In vitro growth of drug sensitive *P. falciparum* is inhibited by 10 µg/l pyrimethamine (Nguyen-Dinh and Payne, 1980). Following a single 1.25 mg/kg dose this level is maintained for more than a week (Hoffman et al, 1985).

Mechanism of antimalarial action. Pyrimethamine is an inhibitor of dihydrofolate reductase, an enzyme that is essential for synthesis, by the parasite, of the active form of folate which is required for nucleic acid synthesis.

Resistance. Resistance of *P. falciparum* to pyrimethamine was first noted in

the 1950s shortly after pyrimethamine was introduced. Thus far the only mechanism of resistance to any antimalarial that has been clearly identified is the production of mutant dihydrofolate reductase in pyrimethamine resistant *P. berghei* (World Health Organization, 1984). It is assumed that resistance develops in the same way with *P. falciparum*.

Renal failure. No information is available on this point.

Formulations. Pyrimethamine is available as 25 mg tablets and as a syrup containing 6.25 mg pyrimethamine per 5 ml.

Uses. Pyrimethamine is no longer used by itself for the treatment of malaria (see sulfadoxine-pyrimethamine below).

Sulphonamides and sulphones

Sulfadoxine, sulfametopyrazine, and dapsone are the most commonly used antimalarials in this class. Only the two former compounds are used for treatment of acute malaria, while dapsone is used for chemoprophylaxis. Because of the toxicity of long acting sulphonamides, there is now renewed interest in the use of short acting drugs such as sulphamethoxazole, particularly for chemoprophylaxis.

Sulfadoxine and sulfametopyrazine

These are both long acting sulphonamides. Both are used in combination with pyrimethamine for the treatment or prophylaxis of malaria. Sulfadoxine has a longer half-life and is more commonly used.

Antimalarial activity. They are slow-acting blood schizonticides which are effective against sensitive strains of *P. falciparum*, but less so against the erythrocytic stages of the other species which infect man. They have no effect on exoerythrocytic stages, may lead to a brief increased production of gametocytes, and may have some sporonticidal activity.

Absorption and disposition. They are rapidly and well absorbed. They are highly bound to plasma proteins (Mandell and Sande, 1980).

Metabolism and elimination. Only a small proportion is metabolized, about 5% to the acetyl derivative and 2-3% to the glucuronide. Acetylation is genetically determined, some people being fast and some slow acetylators. Distinction between fast and slow acetylators is of little practical importance in treatment of malaria, since little of the drugs is metabolized. They are excreted slowly in the urine. The half-elimination time of sulfadoxine is estimated to be between 100 and 200 hours and that of sulphalene is about 65 hours (Mandell and Sande, 1980).

Toxicity. Sulphonamides are generally well tolerated, but they can cause

hepatitis, urticaria, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, agranulocytosis, serum sickness, haemolysis in individuals with glucose-6-phosphate dehydrogenase (G-6-PD) deficiency, methaemoglobinaemia in patients with hereditary nicotinamide adenine dinucleotide (NAD) methaemoglobin reductase deficiency, and kernicterus in premature infants (Mandell and Sande, 1980). Recently, severe cutaneous skin reactions have been associated with the use of pyrimethamine-sulfadoxine for chemoprophylaxis of malaria (see below) (Editorial, 1985a; Miller et al, 1986). Sulphonamides are contraindicated in the first month of life. There is no evidence that they are teratogenic; they are often used to treat pregnant women with acute malaria infections.

Mechanism of antimalarial action. Sulphonamides and sulphones inhibit plasmodial dihydropteroate synthetase an enzyme necessary for incorporation of *p*-aminobenzoic acid (PABA) into folic acid.

Resistance. Resistance to sulphonamides is widespread and they cannot be used alone for the treatment of malaria. The mechanism of resistance is unknown. Several reports indicate that rodent malaras can thrive in the absence of PABA and that sulphonamide resistance can be induced by passing parasites in PABA-deficient animals (World Health Organization, 1984).

Renal failure. No information is available on this in malaria.

Formulation. Oral and parenteral formulations of sulphonamides are available in different areas.

Uses. Sulphonamides are used only in combination with pyrimethamine. There is now interest in combining short acting sulphonamides such as sulphamethoxazole with trimethoprim or proguanil for daily chemoprophylaxis.

Pyrimethamine-sulfadoxine (pyrimethamine-sulfametopyrazine)

The combination of pyrimethamine (dihydrofolate reductase inhibitor) with a sulphonamide or sulphone (PABA inhibitor) has been shown to potentiate antimalarial activity and produce radical cure of malaria infections which are resistant to each of the individual components (World Health Organization, 1984). The most commonly used combination is pyrimethamine-sulfadoxine (SP, Fansidar) because the half-lives of the two components are long and similar (90–200 hours) allowing for single dose treatment and weekly chemoprophylaxis. Sulfametopyrazine (half-life 65 hours) has also been used with pyrimethamine for treatment and prophylaxis, and dapsone (half-life, 17–33 hours) with pyrimethamine (Maloprim) for prophylaxis.

Pyrimethamine-sulfadoxine (SP)

When first introduced, SP was considered an ideal drug for the treatment of

uncomplicated falciparum malaria; it was effective in a single dose and without significant side-effects. Resistance has developed in many parts of the world; in some parts of Thailand it is totally ineffective. In addition, its use has been associated with fatal skin reactions (see section on toxicity below).

Antimalarial activity. SP is effective for treating many *P. falciparum* infections resistant to 4-aminoquinolines and some which are resistant to pyrimethamine and sulfadoxine alone. It is effective for clinical cure of *P. vivax* infections, but the time until clearing of parasitaemia and clinical cure is significantly longer than with chloroquine. It has not been extensively tested against *P. malariae* or *P. ovale*. It has no effect on exoerythrocytic infections. It has no gametocytocidal activity and may have limited sporonticidal activity. Studies in Thailand have indicated that use of SP is associated with an increase in *P. falciparum* gametocytes during the subsequent month (Andre and Doberstyn, 1977) when compared to other antimalarials, and studies in Pakistan have shown the opposite (Strickland et al, 1986).

Absorption and disposition. Limited information suggests that the combination does not affect the pharmacokinetics of the constituents.

Metabolism and elimination. These are also the same for the combination as for the constituents.

Toxicity. Toxicity is as expected for the constituents. SP was first recommended for routine chemoprophylaxis of American travellers to chloroquine resistant malarious areas in 1982. From 1982 to July 1985 there were 24 cases of severe cutaneous reactions (erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis) documented in Americans taking SP; seven of the reactions were fatal. Six of the seven fatal reactions were in individuals who continued to take SP after the onset of the toxic symptoms. Twenty-three of the 24 reactions were associated with multiple (two to five) doses of SP. It is estimated that the incidence of fatal reactions in American travellers taking SP has been 1/11 000 to 1/25 000. It is thought, but not proven, that the reaction is to sulfadoxine and has no relationship to either pyrimethamine or chloroquine (see Chapter 7) (Editorial, 1985a; Miller et al, 1986).

SP is not recommended for infants less than one month of age. The safety of SP in pregnancy has not been established, but it has been used to treat malaria infections in pregnant women without complication (Main et al, 1983). Many think that it can be safely used for malaria chemoprophylaxis in pregnancy.

Measurement of levels. This is as for the constituents.

Mechanism of antimalarial action. The sequential blockade of folic acid synthesis potentiates the antimalarial activity of pyrimethamine and sulfadoxine.

Resistance. Resistance to SP has developed rapidly in some areas of the world. This is a major problem in Thailand and neighbouring countries, an important problem in Brazil and New Guinea, and an emerging problem in Indonesia, East Africa, and South America (Darlow et al, 1982; Pinichpongse et al, 1982; De Sousa, 1983; World Health Organization, 1984; Hoffman et al, 1985).

Renal failure. No information is available on this.

Formulations. Tablets and ampoules contain 500mg of sulfadoxine (or sulfametopyrazine, tablets only) and 25mg of pyrimethamine. SP is available as a syrup in some parts of the world.

Uses. The major use of SP is the treatment of uncomplicated, chloroquine resistant *P. falciparum* infections (Table 1). The parenteral preparation has been used with quinine for treating cerebral malaria (Naparstek et al, 1981). Oral SP is also used for chemoprophylaxis (see Chapter 7).

Tetracyclines

Tetracycline, doxycycline, and minocycline are weak and slowly acting blood schizonticides that can be used effectively to treat chloroquine and SP resistant *P. falciparum* infections in combination with other antimalarials. Because of their slow onset of action and inadequate efficacy when given alone, they should be used with a faster acting antimalarial such as quinine. The combination of quinine and tetracycline for seven days can be expected to cure 95% of multi-resistant *P. falciparum* infections (Pinichpongse et al, 1982).

Tetracycline

Antimalarial activity. Tetracycline is effective against the exoerythrocytic and erythrocytic stages of *P. falciparum*, but not gametocytes. Its activity against other species of malaria is unknown, but is thought to be inadequate.

Absorption and disposition, metabolism and elimination, measurement of levels and toxicity. See a standard textbook of pharmacology for details of this.

Mechanism of action. This is unknown but, by analogy with its mechanism of action in bacteria, it is thought to interfere with protein synthesis.

Resistance. Tetracyclines have not been extensively tested as single drug therapy in the field. When seven days of tetracycline were given with three days of quinine for treatment of *P. falciparum* in Eastern Thailand, an area with multi-resistant *P. falciparum*, seven of 71 patients had RI resistance, and none had RII or RIII responses (Boudreau et al, 1984). The combi-

nation of tetracycline and chloroquine was inadequate for treating chloroquine resistant *P. falciparum* infections in Thailand (Phillips et al. 1984).

Renal failure. See a standard textbook of pharmacology for details on this.

Children. Tetracyclines are not recommended for children less than eight years of age because of the possibility of causing tooth discoloration, hypoplasia of tooth enamel, and impaired bone growth.

Pregnancy. Tetracyclines are contraindicated in pregnancy for the same reasons as in young children.

Formulations. Oral and parenteral (see standard text).

Uses. Tetracycline is used in combination with a faster acting antimalarial, usually quinine, to achieve radical cure of multidrug resistant *P. falciparum* (Table 1). In populations where side-effects to quinine are common, the length of treatment with quinine can be reduced to three days if tetracycline is given with quinine. Tetracycline has also been used with amodiaquine (40–50 mg/kg) to achieve radical cure of *P. falciparum* from an area of Thailand known to have a high prevalence of chloroquine resistance (Noeypatimanond et al. 1983a).

Doxycycline

The actions of, and indications for, doxycycline are similar to those for tetracycline, but it only needs to be given twice daily.

Quinoline methanols

The only drug of this class in use is mefloquine.

Mefloquine

Mefloquine is the most important antimalarial drug developed by the US Army antimalarial drug development programme. When first developed it was thought to be the ideal antimalarial: effective against all species of human malaria, effective against multidrug resistant *P. falciparum*, administered in a single oral dose, rapidly acting, and without serious side-effects (Trenholme et al. 1975). However, isolated cases of resistance have been documented from many parts of the world (Editorial, 1983), and it appears that resistance is now developing in Thailand (Boudreau et al. 1982, 1984) and is present in Irian Jaya (Hoffman et al. 1985).

Antimalarial activity. Mefloquine has been shown to be an effective blood schizonticide against *P. falciparum*, *P. vivax* and *P. malariae* (Trenholme et al. 1975; Doberstyn et al. 1979a; Dixon et al. 1983, 1985; Editorial, 1983). It

has not been tested against *P. ovale*. Its other actions are unclear, but they are likely to be similar to that of quinine.

Absorption and disposition. Mefloquine is available in tablet form, but it is better absorbed as a liquid (Desjardins et al, 1979). Limited studies suggest that elimination half-life is prolonged in malaria patients compared to volunteers and in adults with malaria as compared to children (White, 1985). The pharmacokinetics are not the same as for quinine. There has been considerable individual variation in absorption and pharmacokinetics—observations which led early investigators to predict that there would always be a small percentage of *P. falciparum* infections not cured by mefloquine (Desjardins et al, 1979). In adult, non-infected volunteers given 17–22 mg/kg mefloquine in tablet form, the time required to reach peak whole blood concentrations was 12–28 hours, the peak whole blood concentration was 0.7–1.5 µg/ml, the apparent volume of distribution was 4.6–16.8 l/kg and the whole blood elimination half-life was 8.1–19.5 days (Desjardins et al, 1979). In another study in which plasma levels were measured, peak plasma levels of 1 µg/ml were reached in 2–12 hours, the apparent volume of distribution was 13.5–29.1 l/kg, and the terminal half-life was 15–33 days (Schwartz et al, 1982). In malaria patients given 15 mg/kg mefloquine in combination with SP, serum levels were 1.1–1.9 µg/ml after 24 hours (Hoffman et al, 1985).

The large volume of distribution indicates that the drug is extensively tissue bound. In plasma it is 99% bound to protein. Mefloquine is concentrated in erythrocytes by high affinity binding to the red cell membrane. In volunteers, the concentration in erythrocytes has been estimated to be double that in plasma (Schwartz et al, 1982), and in vitro as high as 60 times that in the extracellular fluid (San George et al, 1984). Pharmacokinetic data derived from plasma and whole blood measurements will differ. The volume of distribution, clearance, and terminal half-life have been shown to be decreased in children. When given to comatose patients by nasogastric tube, absorption was good, but less complete and rapid than in patients with uncomplicated malaria (Chanthavanich, 1985). It could not be detected in the cerebrospinal fluid or peritoneal dialysate of these patients.

Metabolism and elimination. The drug is primarily eliminated by biotransformation, and within four hours of oral intake the main metabolite, 2,8-trifluoromethyl-quinoline-4-carboxylic acid, can be detected in the plasma. Within a few days, the concentration of the metabolite exceeds the concentration of mefloquine; the metabolite has a much smaller volume of distribution. Only about 5% of a dose of mefloquine is excreted unchanged in the urine during four weeks. Clearance of mefloquine may be more rapid in children than in adults (World Health Organization, 1984).

Toxicity. No serious adverse reactions have been associated with the use of mefloquine. Side-effects were monitored in over 800 patients included in clinical trials throughout the world (World Health Organization, 1984). The overall incidence of reactions was: nausea 17.7%, vomiting 13.3%, diar-

rhoea 14.9%, dizziness 14.7%, abdominal pain 8.3%, self-limited sinus bradycardia 8.9%, and neuropsychiatric changes 0.9%. No adverse biochemical or haematological changes have been noted. No information is available on use in pregnancy.

Measurement of levels. A number of techniques have been used for measuring mefloquine levels. HPLC (Grindel et al, 1977) and gas-liquid chromatography with electron-capture detection (Heizman and Geschke, 1984) are recommended.

Mechanism of antimalarial action. This is unknown, but is thought to be similar to that of quinine.

Resistance. Most initial clinical trials showed cure rates of >95%. Resistant infections were attributed to inadequate absorption due to either vomiting or host factors. Cases of primary drug resistance were first described from Thailand (Boudreau et al, 1982) and East Africa (Bygbjerg et al, 1981). Among 62 patients treated with mefloquine in Thailand, five showed RI type resistance and two showed RII type resistance (Boudreau et al, 1984).

In vitro studies have been extensive. In vitro findings predictive of in vivo resistance have not been established by rigorous field testing. However, most investigators have considered growth of schizonts in the presence of 3.2 μmol mefloquine/l blood (1.2 μgml) as indicative of in vitro resistance (Smrkovski et al, 1983). Using this criterion, in vitro resistance has been documented in the Philippines (Smrkovski et al, 1983), Indonesia (Hoffman et al, 1985) and, with increasing frequency, in Thailand (G. Childs, personal communication). Recently the World Health Organization has indicated that it may be more appropriate to consider the growth of schizonts in the presence of 6.4 $\mu\text{mol/l}$ rather than 3.2 $\mu\text{mol/l}$ as indicative of resistance (D. Payne, personal communication).

The mechanism of drug resistance to mefloquine is unknown. It has not been established whether there is cross-resistance between mefloquine, quinine, and chloroquine. Limited observations in Thailand (K. Webster, personal communication) and Indonesia (Hoffman et al, 1986) suggest cross-resistance between quinine and mefloquine but not with chloroquine. Resistance to mefloquine develops more readily in *P. berghei* parasites that are already resistant to chloroquine than in those that are sensitive to chloroquine.

Renal failure. No information is available on this.

Formulations. Mefloquine is available as tablets of 250mg (Lariam).

Uses. Mefloquine (Lariam) is now commercially available only in Switzerland where its use is reserved for the treatment of multidrug resistant *P. falciparum* infections (Table 1). As resistance of *P. falciparum* to chloroquine and SP increases, the use of mefloquine, particularly in non-endemic areas, is likely to increase.

Mefloquine-pyrimethamine-sulfadoxine (MSP)

Mefloquine (M) has recently been released for clinical use in Thailand in combination with SP (MSP, Fansimef). The combination is being used in the hope that, as in experimental models, the emergence of resistance to the components by drug pressure and selection, especially to mefloquine, can be delayed. The animal studies suggest additive antimalarial activity (Merkli et al, 1980; Peters and Robinson, 1984). Multiple clinical trials indicate that the combination is well tolerated and curative in over 95% of *P. falciparum* infections (World Health Organization, 1984). There is, however, disagreement among malaria experts regarding the appropriateness of widespread use of the combination as opposed to the individual components. This disagreement is based on several facts and observations. In animal models there is no reduction in the rate of emergence of drug resistant *P. falciparum* by use of the combination if the isolate is already resistant to M or SP (Merkli et al, 1980; Peters and Robinson, 1984). In many areas where MSP is being used or will be used, resistance to SP is common. Fatal reactions to SP have been described (Editorial, 1985a; Miller et al, 1986). These reactions are rare and SP is still appropriately and extensively used. However, some people wonder about the wisdom of trying to preserve the efficacy of mefloquine by using a potentially dangerous drug. None of the human studies have demonstrated a clinical advantage of using the combination compared to the components. Limited observations from one clinical study (Hoffman et al, 1985) and one *in vitro* study (Milhous et al, 1983) have suggested that there may be antagonism between M and SP in some isolates.

Formulations. MSP (Fansimef) is available in tablets containing 250 mg of mefloquine, 25 mg of pyrimethamine and 500 mg of sulfadoxine.

Uses. MSP is recommended for the treatment of multidrug resistant *P. falciparum* (Table 1).

Sesquiterpene lactones

Qinghaosu and its derivatives are the only antimalarials of this class.

Qinghaosu and derivatives

Reports from China indicate that use of qinghaosu (QHS) and its derivatives, artemether and sodium artesunate, is associated with high clinical cure rates and more rapid defervescence and parasite clearance than with mefloquine, chloroquine, quinine, MSP or SP. Rates of recrudescence are high, indicating that improved dosage regimens or concomitant administration of another blood schizonticide is required (Qinghaosu Antimalaria Coordinating Research Group, 1979; China Cooperative Research Group of Qinghaosu and its Derivatives as Antimalarials, 1982; Guoqiao et al, 1982; Jiang et al, 1982a; Guoqiao, 1984; Li et al, 1984; Klayman, 1985).

Antimalarial activity. Available information indicates activity against the erythrocytic stages of *P. falciparum* and *P. vivax*, but not against exoerythrocytic stages of *P. vivax* or gametocytes of *P. falciparum* (L. Guoqiao and K. Arnold, personal communication).

Absorption and disposition. Plasma protein binding of artemether has been reported to be 77% (China Cooperative Research Group of Qinghaosu and its Derivatives as Antimalarials, 1982). No other human studies are available.

Metabolism and elimination. There are no available reports of human studies on this.

Toxicity. QHS and its derivatives are apparently well tolerated and have not been shown to produce haematological, renal, hepatic or electrocardiographic abnormalities. Little information is available regarding use in pregnancy. QHS was used in 16 pregnant women with cerebral malaria, 15 of whom survived (Guoqiao et al, 1984). QHS has been reported to be embryotoxic in rats and mice (China Cooperative Research Group of Qinghaosu and its Derivatives as Antimalarials, 1982; World Health Organization, 1984; Klayman, 1985).

Measurement of levels. Thin-layer chromatography (Xinyl et al, 1985) and HPLC (Klayman, 1985) have been used to measure levels in animals.

Mechanism of action. The mechanism of action of QHS is unknown but it is thought to act by interruption of protein synthesis. QHS and derivatives affect plasmodia in a number of ways, including inducing mitochondrial swelling (Jiang et al, 1985). Studies in China indicate that QHS works early in parasite development by destroying the tiny and small ring forms, as compared to other antimalarials which work later in the life cycle (Guoqiao et al, 1984; Li et al, 1984).

Resistance. Recrudescence rates for *P. falciparum* and *P. vivax* are high after treatment with QHS (Guoqiao et al, 1984). It is not yet clear whether this indicates resistance or inadequate dosages of the drug. Rates of *P. falciparum* recrudescence at one month were 10% for intramuscular artemether (oil preparation), 40-50% for QHS suppositories and intravenous artesunate, and 75% for oral QHS (Guoqiao et al, 1984; L. Guoqiao and K. Arnold, personal communication). Resistance of *P. berghei* to QHS has been easily induced in the laboratory.

Renal failure. Studies of the use of QHS in renal failure are incomplete, but it has apparently been well tolerated in patients with renal failure (Guoqiao et al, 1982; Guoqiao et al, 1984).

Formulations. QHS (tablet, rectal suppository, water and oil suspension for intramuscular use), artemether (oil suspension for intramuscular use) and

sodium artesunate (for intravenous use) have been studied in China. New formulations are apparently being developed.

Uses. The efficacy of QHS has only been evaluated in China. Available information suggests that the most important potential use for QHS is for rapid clearing of parasitaemia in patients with severe falciparum malaria. QHS reduces parasitaemia by 95%, 25% faster than quinine and clears parasitaemia twice as fast as quinine. However, historical comparisons do not indicate any difference in mortality between QHS- and quinine-treated patients with cerebral malaria. A controlled trial comparing QHS and quinine in severe malaria is required.

Phenanthrene methanols

This is another class of antimalarials developed by the US Army programme.

Halofantrine

The most promising drug in this class is halofantrine. It has been tested in volunteers with induced and naturally occurring malaria and found to be effective in multidrug resistant falciparum infections in Thailand. Initial trials in Thailand showed radical cures in only 65% of patients given a single 1500 mg dose. When the dosage regimen was modified to three 500 mg doses given at six-hour intervals, greater than 95% radical cures were achieved (World Health Organization, 1984). Further research is in progress to determine optimal formulations and dosing schedules.

8-Aminoquinolines

Primaquine is the only drug of this class in widespread clinical use.

Primaquine

Primaquine is the only drug used to prevent relapse (tissue schizonticide against late exoerythrocytic stages). It is also an excellent causal prophylactic (primary exoerythrocytic stages) and the only effective drug used to reduce transmission (gametocyticide and sporonticide). It is not used to treat acute blood stage infections.

Antimalarial activity. Primaquine is gametocytocidal and sporonticidal for all human species of malaria. It is highly effective against the exoerythrocytic (liver) stages of *P. falciparum* and *P. vivax* and probably *P. ovale* (activity against *P. malariae* unknown). It is an effective blood schizonticide, but only at dangerously high doses.

Absorption and disposition. Primaquine is rapidly absorbed after oral administration. Peak plasma levels are reached in one to three hours (Bruce-

Chwatt, 1981). Tissue distribution of the parent drug is unknown. Studies in animals with pamaquin, a related 8-aminoquinoline, indicated extensive tissue distribution, but there was no pamaquin in the tissues of a human who died of an overdose of pamaquin.

Metabolism and elimination. After oral administration, primaquine is rapidly converted in the liver to carboxyprimaquine. The elimination half-life of primaquine is three to seven hours. Twenty-four hours after a single dose, plasma concentrations of the metabolite are 50 times that of the parent compound. None of the metabolite has been detected in the urine, so it is likely that carboxyprimaquine is further metabolized before excretion. The antimalarial activity and toxicity of the metabolites are unknown, but antimalarial activity is likely to be significant since daily and even weekly dosage regimens have been successful (Greaves et al, 1980; Mihaly et al, 1984; Ward, 1985; White, 1985).

Toxicity. Gastrointestinal side-effects including nausea, vomiting, anorexia, dizziness, epigastric distress and abdominal pain or cramps can be expected in 5–10% of adults receiving 15–30 mg of primaquine base per day for 14 days. The incidence of gastrointestinal side-effects increases with increasing doses and is reduced by ingestion of the drug with meals (Weniger, 1979c).

Dose-dependent, reversible agranulocytosis and granulocytopenia have been described with extremely high doses of primaquine, but not with therapeutic doses. Dose-dependent, reversible methaemoglobinaemia is common with high doses of primaquine and has been described after usual therapeutic doses. It is less common in glucose-6-phosphate dehydrogenase (G-6-PD) deficient individuals than in normal individuals, since older erythrocytes are the major source of methaemoglobin and these are also the most susceptible to haemolysis. Methaemoglobinaemia may be severe in individuals with congenital deficiency of NAD methaemoglobin reductase.

Acute intravascular haemolytic anaemia is the most serious side-effect of primaquine. It is caused by oxidant stress in individuals with erythrocyte G-6-PD deficiency, an inherited X-linked trait occurring most frequently in Blacks and persons of Mediterranean and Asian extraction. In most Blacks who have 10–20% of normal G-6-PD activity, haemolysis is generally self-limited, even when drug administration is not stopped. Mediterraneans and Asians may have only 0–7% of normal activity and haemolysis is more severe and may continue even after the drug has been withdrawn. In adult Blacks weekly administration of 45 mg of primaquine base has been associated with less haemolysis than daily administration of 15 mg. If possible, testing for G-6-PD deficiency should be done before primaquine is given.

The safety of primaquine in pregnancy has never been established and its use is not recommended.

Measurement of levels. Recently HPLC and gas chromatography-mass spectrophotometry have been used to measure primaquine levels (Greaves et al, 1979; Baker et al, 1982; Ward et al, 1983).

Mechanism of antimalarial action. This is unknown, but is thought to involve an effect of a metabolite on the mitochondria of exoerythrocytic stage schizonts.

Resistance. Strains of *P. vivax* vary in the susceptibility of exoerythrocytic stages to primaquine. The Chesson type strain of *P. vivax* detected in New Guinea in 1944 and similar strains subsequently described in the Solomon Islands, Indonesia, and Thailand is relatively resistant to primaquine and requires doubling the dosage of primaquine (Bruce-Chwatt, 1981).

Renal failure. No information is available on this, but indications are limited.

Formulations. Primaquine is available in tablets containing 13.2 and 26.3 mg of primaquine phosphate, equivalent to 7.5 mg and 15 mg, respectively, of primaquine base.

Use. Primaquine is used for radical cure of *P. vivax* and *P. ovale* infections (tissue schizonticide) (Table 1) and for blocking malaria transmission (gametocyticide and sporonticide). It is sometimes used as a causal prophylactic for all four human malaria infections, but to be effective for causal prophylaxis it probably has to be given more frequently than once a week. More research is needed to establish the safety and efficacy of primaquine for chemoprophylaxis and for reducing transmission of malaria.

Biguanides

Proguanil, cycloguanil, and chlorproguanil are the three antimalarials of this class that have been used. Like pyrimethamine they are dihydrofolate reductase inhibitors. Because of their slow onset of action, in recent years they have only been used for causal prophylaxis of *P. falciparum* infections and suppressive chemoprophylaxis of all four human malarias. For reasons which are unclear, proguanil, the biguanide with the shortest half-life, is the only one of the three in common clinical use. Biguanides are highly inhibitory to the primary exoerythrocytic stages of *P. falciparum* (not *P. vivax*), to asexual erythrocytic stages of all four human malarias, and to the development of sporozoites in mosquitoes (probably all malaria). They are thus used as causal prophylactics (*P. falciparum*), suppressive prophylactics (all four human malarias), and transmission blocking agents (all four human malarias). Unfortunately, resistance of all stages of the parasites to biguanides may develop rapidly, either by biguanide drug pressure or by pyrimethamine drug pressure. Because of the rapid spread of chloroquine resistance and the lack of toxicity of biguanides, recently there has been renewed interest in the use of biguanides for chemoprophylaxis, either alone or in combination with other antimalarials such as short acting sulphonamides or sulphones. There is presently no indication for their use for treatment of acute malaria. Use of biguanides in chemoprophylaxis is discussed in Chapter 7.

Other antibiotics

Although many antibiotics, including chloramphenicol and rifampicin, have some antiplasmodial activity, only the tetracyclines and lincomycin derivatives and perhaps erythromycin have been shown to have significant antiplasmodial activity.

Clindamycin

Clindamycin is a slow-acting blood schizonticide which, both alone and with quinine, has been used for the treatment of falciparum malaria with moderately good to excellent results, but often with acute gastrointestinal side-effects. Based on the results of a number of studies (El Sadiq et al, 1985; Westerman, 1985), the manufacturer now recommends clindamycin 10mg/kg twice a day for five days for treatment of *P. falciparum* infections (Westerman, 1985). Further studies are required, but clindamycin may prove to be a useful adjunct to quinine or other rapid acting blood schizonticides for therapy of multiresistant *P. falciparum* in children who cannot be given tetracycline. Although clindamycin is often used in pregnancy, its safety during pregnancy has not been established.

Erythromycin

In vitro studies indicated that erythromycin and chloroquine were synergistic against chloroquine-resistant strains of *P. berghei* (Westerman, 1985). Unfortunately, field studies in Thailand (Phillips et al, 1984) and Africa (D. Brandling-Bennett, personal communication) showed that chloroquine and erythromycin were not effective for treating chloroquine resistant *P. falciparum* infections. Recently the combination of erythromycin and high dose amodiaquine was shown to be effective for clearing parasitaemia, but not for radical cure (52% recrudescence) in Thais with *P. falciparum* infections (Looareesuwan et al, 1985b). Clearing of parasitaemia may have been improved by addition of erythromycin, or may have been produced by high dose amodiaquine therapy alone.

Other blood schizonticides

Pyridinemethanols, triazines, acridines, pyronardine, piperazine, dabequine, and naphthoquinones have all been evaluated for treatment of malaria. None are ready for widespread clinical use (World Health Organization, 1984).

TREATMENT OF SPECIFIC INFECTIONS

P. falciparum: complicated

Any patient with a *P. falciparum* infection who has $\geq 3\%$ parasitaemia, an abnormal level of consciousness, renal, cardiac, hepatic or pulmonary dys-

function, shock, or severe diarrhoea or vomiting should be considered to have complicated malaria. Resistance to chloroquine has been reported from nearly all malarious areas of the world. The drug of choice for treating *all* patients with complicated malaria is quinine dihydrochloride by slow intravenous infusion (Table 1). This recommendation could be modified if one were practising in an area such as West Africa, the Caribbean, or Central America above Panama, where the parasites were known to be sensitive to chloroquine and patients with complicated malaria consistently responded to chloroquine, or in China where qinghaosu or its derivatives are available. If quinine dihydrochloride is not available, intravenous quinidine gluconate is an excellent substitute.

Quinine treatment

The dosage of quinine is dependent on the sensitivity of the organism to quinine. Parasites should be cleared from the circulation as rapidly as possible. In areas of the world, such as Thailand and Irian Jaya, where the minimal inhibitory concentration of quinine is high, a loading dose of 20 mg/kg quinine dihydrochloride (16.7 mg/kg base) administered in 3–6 ml/kg of intravenous fluid during two to four hours, followed by 10 mg/kg every eight hours for seven days, has been safely and successfully used to rapidly achieve and maintain plasma levels of 10–15 mg/l (White et al, 1983b; Hoffman et al, 1984a). Dosage regimens for complicated malaria in areas of the world where *P. falciparum* is more sensitive to quinine have not been established. Regardless of the dosages required, a loading dose should be used to rapidly achieve appropriate plasma levels of quinine, unless the patient has already received quinine. Patients, especially children and pregnant women, recovering from their infection may require increased doses of quinine on days five to seven to achieve radical cure of the infection with quinine alone (Chongsuphajasiddhi et al, 1981a; White, 1985). Quinine therapy is best monitored by measuring plasma levels of the drug by HPLC or benzene extraction fluorescence. Levels of 5–15 mg/l are required, depending on the sensitivity of the organism, and levels above 20 mg/l are considered dangerous. Toxicity is monitored by measuring blood pressure and by electrocardiogram. If plasma levels are unobtainable and the patient does not improve within 48–72 hours, individual doses should be reduced by 30%, but still given every eight hours. Since 80% of quinine is metabolized in the liver, renal failure is not an indication for a marked reduction in dosage and the same guidelines pertain. Quinine pharmacokinetics have not been studied in patients with severe parenchymal liver disease. If plasma levels cannot be followed, prudence would suggest reduction of doses by 50% in such patients. Levels of parasitaemia frequently increase in the six to 12 hours after initiation of therapy, but should be less than 25% of initial levels within 48 hours of the onset of therapy. Reports from New Guinea indicate that intramuscular quinine dihydrochloride is safe, well absorbed and effective in severe malaria (Stace et al, 1983). Others suggest that absorption of intramuscular quinine may be erratic in severe malaria (White, 1985) and abscesses and nerve damage at injection sites are

common (Guyer and Candy, 1979; Thuriax, 1982a,b). If it is possible to establish an intravenous infusion, delivery by this route is highly preferable. If an intravenous route cannot be established, quinine can be given by deep intramuscular injection (10–15 mg/kg) every 8–12 hours until the patient is able to tolerate oral medication. Slow intravenous injection over 15 minutes has been used, but is not recommended. Quinine therapy should be continued for at least seven days, but patients may be switched to oral quinine as soon as they are able to tolerate it. In South-East Asia, Irian Jaya and some other areas of the world, addition of tetracycline when the patient is able to tolerate oral medication is required for radical cure.

Quinidine treatment

If quinine is not available, quinidine gluconate can be used as an adequate replacement (Table 1). The same principles pertain to quinidine as to quinine therapy. In Thailand, a loading dose of 24 mg/kg salt (15 mg/kg base), followed by 12 mg/kg every eight hours has been safely and successfully used to achieve therapeutic levels of 5–10 mg/l. Renal excretion may comprise 20–35% of total excretion. In renal failure, plasma levels should be closely monitored. The adequacy of therapy and toxicity are otherwise monitored in the same way as for quinine.

Chloroquine treatment

In areas of the world where *P. falciparum* is still sensitive to chloroquine, it is used as the drug of choice for severe malaria (Table 1). Rapid intravenous administration of chloroquine has always been considered dangerous and intramuscular administration of the drug has been practised. There have been no published pharmacokinetic studies of the use of chloroquine in severe malaria and thus recommendations are widely variable. As with quinine, the elimination half-life is likely to be considerably longer in complicated malaria. Children may be more susceptible to toxicity than adults. If used in severe malaria, it is preferable to give chloroquine by slow intravenous infusion rather than by intramuscular injection. For adults, 6–10 mg/kg base should be infused intravenously over four hours. This dose is repeated every 12 hours for a total of three to four doses. Children should receive an initial dose of 5–8 mg/kg base, followed by two to three doses of 3.7–5 mg/kg every 12 hours. Further studies are required to determine optimal doses and whether administration of a loading dose would give more appropriate plasma levels without significant toxicity. Chloroquine should never be given by rapid intravenous injection because of considerable toxicity. If an intravenous infusion cannot be established, chloroquine may be given intramuscularly (5–10 mg/kg base, followed by two to three doses of 2.5 mg/kg base at 12-hour intervals).

Amodiaquine treatment

A parenteral formulation of amodiaquine is not commercially available. However, a recent study in Thailand showed that an intravenous infusion of

amodiaquine was well tolerated and effective in rapidly clearing parasitaemia in moderately ill patients with *P. falciparum* infections (Looareesuwan et al, 1985b). This regimen has not been studied in severe malaria and was associated with a high rate of recrudescence. Use of intravenous amodiaquine for severe malaria must still be considered experimental. It may prove to be useful as a substitute for parenteral chloroquine.

Qinghaosu treatment

Optimal dosage schedules for qinghaosu and its derivatives are still being determined. A number of formulations have been shown to be effective, but in China only three preparations, qinghaosu suppositories, artemether (oil preparation), and artesunate, are currently being evaluated (L. Guoqiao and K. Arnold, personal communication). All three are considered to be as effective as quinine for the initial treatment of cerebral malaria in adults. (Guoqiao, 1982; Guoqiao, 1984). They have a rapid onset of action and rapidly clear parasitaemia. However, they have to be used with another blood schizonticide because of a high rate of recrudescence. Artemether is given to adults as single intramuscular doses of 300mg on day 1 and 150–200mg on days 2 and 3. Sodium artesunate is given intravenously, 60mg twice on day 1 and once on days 2 and 3. Qinghaosu suppositories are given twice a day; 600mg doses on day 1 and 400mg doses on days 2 and 3.

Other antimalarials, including pyrimethamine-sulfadoxine (Naparstek et al, 1981), tetracyclines, and clindamycin, are sometimes used with quinine, but should never be substituted for quinine. Mefloquine is not available as a parenteral formulation, but a mefloquine suspension has been successfully administered to severe malaria patients by nasogastric tube (Chanthavanich et al, 1985). Preliminary findings indicate adequate bioavailability and clinical response.

P. falciparum: uncomplicated

The physician practising in a non-malarious area who sees only an occasional patient with *P. falciparum* infection should consider all *P. falciparum* infections acquired in Oceania, Asia, South America and East and Central Africa to be resistant to chloroquine. Infections acquired in West Africa, Caribbean, and Central America above Panama in 1986 are likely to be sensitive to chloroquine. Chloroquine may still be effective in treating falciparum malaria contracted in chloroquine-resistant areas, but in treating an individual patient only practitioners whose personal experience has shown this should continue to use chloroquine. In many cases, the combination of chloroquine and the immune response of an individual who has had numerous *P. falciparum* infections may be adequate to achieve clearance and radical cure of chloroquine-resistant organisms. Amodiaquine has been shown to be more effective than chloroquine in some areas of East Africa (Watkins et al, 1984; Brandling-Bennett et al, 1985) and Thailand (Hall et al, 1975b) with chloroquine resistance, but no more effective than chloro-

quine in the Philippines (Watt et al. 1985) and Pakistan (Khaliq et al. 1986). The same principles regarding use of chloroquine apply to the use of amodiaquine.

Chloroquine and amodiaquine treatment

Chloroquine is available as phosphate, and diphosphate salt (500 mg salt = 300 mg base). It is generally given as a total dosage of 25 mg/kg base during 48 hours (this may be given as 10 mg/kg, 10 mg/kg, and 5 mg/kg at 0, 24 and 48 hours or 10 mg/kg, 5 mg/kg, 5 mg/kg and 5 mg/kg at 0, 6, 24 and 48 hours). In treating chloroquine resistant organisms, increasing the total dosage to 40 or 50 mg/kg will increase the parasite clearance rates, delay the onset of recrudescences and may improve cure rates (Powell et al. 1964a,b; Hoffman et al. 1984b; Coosemans et al. 1985). Chloroquine, even at higher dosage levels, is not recommended for treating non-immunes infected with, presumably, chloroquine-resistant organisms. Amodiaquine is available as the dihydrochloride salt (500 mg salt = 300 mg base). The same dosage schedule as for chloroquine is commonly used. However, in two recent studies in Thailand 40–50 mg/kg amodiaquine base in combination with tetracycline (Noeypatimanondh et al. 1983b) or erythromycin (Looareesuwan et al. 1985b) was effective in clearing chloroquine resistant *P. falciparum* parasitaemia.

If the *P. falciparum* is presumed to be resistant to chloroquine, pyrimethamine-sulfadoxine, quinine, quinine plus tetracycline, mefloquine, and MSP (Fansimef) are the mainstays of therapy. In some areas, amodiaquine or amodiaquine plus tetracycline or erythromycin can be used, and in selected patients there may be a role for clindamycin alone or in combination with quinine or other antimalarials.

Pyrimethamine-sulfadoxine (SP) treatment

Ten years ago SP appeared to be an even more ideal antifalciparum agent than chloroquine, primarily because it could be given in a single dose. In recent years the prevalence of resistance of *P. falciparum* to SP has increased in most malarious areas of the world. In some areas of Thailand it is of little value. Prevalence of resistance is high in Brazil and Colombia, and Papua New Guinea, but much lower in Irian Jaya and Africa (Darlow et al. 1982; Pinichpongse et al. 1982; De Sousa, 1983; World Health Organization, 1984; Hoffman et al. 1985). SP can be used as a first line drug for the treatment of acute uncomplicated infection acquired in areas with low levels of resistance, but patients should be monitored closely. SP is given as a single dose of three tablets to an adult. Each tablet contains 500 mg of sulfadoxine and 25 mg of pyrimethamine. Children should receive 25 mg/kg sulphadoxine and 1.25 mg/kg pyrimethamine.

Quinine sulphate treatment

Quinine sulphate is given as 10 mg/kg every eight hours for 7–10 days.

Cinchonism will occur frequently within this regimen. In areas of the world where parasites are less sensitive to quinine, it should be combined with tetracycline 15–25 mg/kg/day in four equally divided doses, or doxycycline 3–5 mg/kg/day for seven days. Use of this quinine–tetracycline regimen is associated with 95% radical cure rates (Pinichpongse et al., 1982). It is likely that substitution of clindamycin (10 mg/kg twice a day for five days) for tetracycline would result in similar cure rates. Studies in Thailand have shown that the combination of three days of quinine with tetracycline is also associated with high radical cure rates (Boudreau et al., 1984). Quinine is used to reduce parasitaemia while waiting for the slow onset of tetracycline's schizonticidal activity.

Mefloquine and MSP treatment

Mefloquine has recently been introduced for clinical use in Switzerland and Thailand. In Switzerland, mefloquine (Lariam) is only available for treatment of multiresistant organisms and in Thailand it has been introduced combined with SP in a single tablet (Fansimef). Mefloquine can be given as a single dose, is effective against all species of *Plasmodium* that infect humans, has a rapid onset of action, is not associated with any serious side-effects and is effective against most strains of multiresistant *P. falciparum*. However, in vivo and in vitro resistance to mefloquine and MSP have now been documented (Bygbjerg et al., 1981; Boudreau et al., 1982, 1984; Smrkovski et al., 1983; Hoffman, 1985). While mefloquine and MSP are unquestionably the best commercially available single dose antimalarials, they will possibly be less effective in coming years as resistance develops. Mefloquine is given as a single dose of 15–25 mg/kg or as MSP in combination with SP (Fansimef) as three tablets for an adult, each containing 250 mg of mefloquine, 500 mg of sulfadoxine, and 25 mg of pyrimethamine. Children may require higher doses than adults.

P. vivax, P. malariae, and P. ovale: complicated

Any patient thought to have a pure infection with *P. vivax*, *P. malariae*, or *P. ovale* and the clinical manifestations of severe malaria, should be assumed to have a mixed infection and treated as a patient with complicated *P. falciparum* infection.

P. vivax and P. ovale: uncomplicated

Erythrocytic stage

Chloroquine is the drug of choice. *P. vivax* is much more sensitive to chloroquine than is *P. falciparum*. There have been no well documented cases of resistance of *P. vivax* or *P. ovale* to chloroquine. Chloroquine or amodiaquine is given in the same dosage as outlined above for uncomplicated *P. falciparum* infections. Quinine, mefloquine, and SP are also effective. Use of SP is often associated with a longer time until clinical cure

and clearing of parasitaemia (Doberstyn et al, 1979b). The tetracyclines and chloroguanides do not appear to have any effect on *P. vivax*.

Exoerythrocytic stage

To achieve radical cure, that is elimination of exoerythrocytic stages of the parasite, primaquine must be given. It is administered as 0.25 mg/kg base once daily for 14 days. If the patient has G-6-PD deficiency it is given as 0.75 mg/kg once a week for eight weeks. However, if the patient has severe G-6-PD deficiency (Mediterranean and Asian type), it may be preferable to treat relapses with chloroquine. In New Guinea and other areas of Asia, the Chesson and other strains of *P. vivax* have been shown to be less sensitive to primaquine and may require increased doses: 0.5 mg/kg/day for 7-14 days and 0.25 mg/kg for 28 days have been used.

***P. malariae*: uncomplicated**

Chloroquine is the drug of choice. Mefloquine is also effective.

RECOGNITION OF HIGH RISK PATIENTS

The major challenge to the clinician managing malaria patients is to recognize those patients at risk of developing complicated, severe malaria and to prevent death in those who have complicated disease (Chapter 3). Most malaria patients recover quickly and uneventfully after initiation of appropriate antimalarial therapy. However, some patients deteriorate rapidly. Recent studies in Thailand indicate that, even when modern intensive care facilities are available, mortality for patients with severe falciparum malaria is 15-25% (White et al, 1982; Warrell et al, 1983; Phillips et al, 1985).

High risk patients

Any malaria patient with $\geq 3\%$ parasitaemia (hyperparasitaemia), history or findings of abnormal level of consciousness (cerebral malaria), prolonged hyperthermia, pulmonary, cardiac, hepatic, or renal dysfunction, or high output diarrhoea or vomiting should be considered to have severe malaria and to be a high risk patient requiring immediate intravenous antimalarial therapy and intensive care. Input and output, right heart or pulmonary artery wedge pressures and arterial blood gases should be monitored and facilities should be available for mechanical ventilatory support, haemo- or peritoneal dialysis, exchange transfusion and continuous infusion of vaso-pressors. Although most such patients will be infected with *P. falciparum*, all malaria patients with parasitological or clinical findings indicating severe disease should be treated the same. Severe disease is sometimes associated with *P. vivax*, *P. ovale*, and *P. malariae* infections, but more commonly a mixed infection with a low level of *P. falciparum* parasitaemia is mistakenly called a pure infection with one of the other species.

Hyperparasitaemia

Any patient with 3% or more of erythrocytes parasitized, regardless of other clinical findings, should be considered to have hyperparasitaemia and to be at high risk of developing other complications. Patients with hyperparasitaemia, who otherwise appear to have uncomplicated disease, frequently have a seizure within 24 hours of initiation of therapy and then go into a deep, prolonged coma. The laboratory should provide the clinician with the species of *Plasmodium* and the level of parasitaemia.

The cut-off concentration for hyperparasitaemia of 3% is arbitrary. Not all patients with hyperparasitaemia develop severe disease but, as the parasite count increases, the risk of developing severe disease also increases. A review of 2316 cases of *P. falciparum* infections treated in Kuala Lumpur in the 1930s and 1940s indicated that only 5% of 2266 patients who survived had asexual parasite counts greater than 100000/ μ l blood (approximately 3% parasitaemia), while 78% of patients who died had counts exceeding this concentration. Only 0.3% of survivors had a count greater than 500000/ μ l blood, while 45% of fatalities did (Field, 1949). Among 28 US servicemen in Viet Nam who developed acute renal failure secondary to malaria, 20 (71%) had >10% parasitaemia (Stone et al, 1972). Seven of 12 patients in Bangkok with acute pulmonary insufficiency secondary to malaria had >30% parasitaemia; six of the seven died (Punyagupta et al, 1974). Among 89 patients with cerebral malaria in Irian Jaya, mortality was 45% in those with >5% parasitaemia and 12% in those patients with <5% parasitaemia (Hoffman et al, 1984a).

Cerebral malaria

This is a condition in which patients with *P. falciparum* infections are delirious, obtunded, stuporous, or comatose, and the abnormal state of consciousness cannot be attributed to a post-ictal state, a CNS depressant, hypoglycaemia or another infection. A lumbar puncture should be performed to exclude meningitis and encephalitis. Mortality may be as high as 20–60% for comatose patients and 10% for those with stupor, and probably less than 5% for those with delirium or obtundation. However, delirious patients have a higher mortality than patients with uncomplicated malaria and may on occasion deteriorate rapidly. All malaria patients with a history or finding of abnormal level of consciousness, regardless of other clinical findings, should be treated as having severe malaria. There is presently no proven adjunct to antimalarial therapy and basic, intense supportive care for patients with cerebral malaria. The testing of other forms of therapy, such as exchange transfusion and the comparison of outcomes from different parts of the world require attention to defining the patient's level of consciousness, level of parasitaemia, history of malaria exposure, and ethnic and genetic background. Otherwise it will be difficult to extrapolate findings from one setting to another.

The clinical findings of the other conditions associated with severe malaria are described in Chapters 3 and 5, and the treatment of these complications is described below.

GENERAL ANCILLARY THERAPIES

Antipyretics

Oral temperature should be kept below 38.5°C. Temperatures above this are associated with an increased incidence of seizures. Prolonged hyperthermia (temperature >40°C) is associated with a poor outcome. Quinine is an antipyretic, but is usually inadequate by itself for reducing temperature. Acetaminophen and aspirin may be given orally or by rectal suppository to patients with uncomplicated disease. In the severely ill patient, cooling blankets, fanning, and sponging are frequently necessary and, in the tropics, clinicians often accept the risk of agranulocytosis and use parenteral antipyretics such as dipyrone.

Fluid and electrolyte therapy

Parenteral therapy is only required in patients with severe disease. Fluid therapy must be monitored so as to maintain adequate renal perfusion and to prevent fluid overload leading to pulmonary oedema. This can be accomplished with intravenous fluids, bladder catheterization, and frequent careful clinical examinations and monitoring of input and output. It is optimally carried out in an intensive care unit with right heart or pulmonary artery catheterization and frequent monitoring of blood electrolytes, blood urea nitrogen, creatinine, glucose and arterial blood gases. Mild hyponatraemia (Na^+ , 120–134 mEq/l) is common, but generally of little clinical importance. It has been suggested, but not proven, that it is due to inappropriate antidiuretic hormone production. In some cases it is undoubtedly due to overhydration. When the serum Na^+ falls below 120 mEq/l, fluid restriction is advisable if there is no dehydration.

Nursing care

Careful attention must be paid to maintenance of the airway and to prevention of pulmonary aspiration and other complications found in critically ill patients. Patients with severe disease should be nursed on their sides and turned frequently.

Corticosteroids

From 1967 to 1982, corticosteroids were the most commonly recommended and used adjunct to antimalarials in the treatment of cerebral malarial (Daroff et al, 1967; Oriscello, 1968; Woodruff and Dickin, 1968; Blount, 1969; Smitskamp and Wolthuis, 1971). In 1982, Warrell and colleagues reported the results of a double blind study of moderate doses of dexamethasone given for 48 hours to comatose patients with cerebral malaria in Thailand (Warrell et al, 1983). The study showed that the use of dexamethasone was not associated with a reduction in mortality, was not associated with a significant increase in all complications or any single compli-

cation, but was associated with a 33% prolongation time from initiation of therapy until full recovery of consciousness. A similar study in Irian Jaya, Indonesia, has just been completed. In this study, a dosage of dexamethasone eight times higher than that used by Warrell and colleagues (initial dose 3 mg/kg, total dosage during 48 hours 11.4 mg/kg) was evaluated and found to be of no value in reducing mortality in cerebral malaria (Hoffman, unpublished). Cerebral malaria is not an indication for the use of dexamethasone in any dose. Corticosteroids are sometimes recommended for treating the pulmonary aspiration and pulmonary oedema of severe malaria, but their value has never been confirmed.

Exchange blood transfusion

Regardless of the patient's clinical status, if >20% of erythrocytes are parasitized with *P. falciparum*, the chance of complete recovery is less than 50% when standard antimalarial therapy and supportive measures are used. There have been a number of case reports of patients with hyperparasitaemia who were successfully treated with 5–10l whole blood exchange transfusion and antimalarials (Nielson et al, 1977; Kurathong et al, 1979; Yarrish et al, 1982; Kramer et al, 1983; Files et al, 1984) and one report of plasma exchange (Bambauer and Jutzler, 1984). It has been proposed that the beneficial effect of exchange transfusion is related to removal of parasitized erythrocytes, erythrocyte and parasite debris and mediators and the provision of unparasitized erythrocytes, platelets, and clotting factors. There have been no controlled studies which have evaluated the efficacy of exchange transfusion. However, because of the poor prognosis associated with hyperparasitaemia, most experts would recommend exchange transfusion for all patients with greater than 15% parasitaemia and any patient with >5% parasitaemia who has evidence of cerebral involvement or other organ dysfunction. The value of large (5–10l) and small (2–4l) exchange transfusions compared to standard therapy needs to be critically evaluated.

Other measures

Heparin (Munir et al, 1980), adrenaline (epinephrine) (Patrick, 1982) and low molecular weight dextran (Smitskamp, 1971) have all been advocated for treatment of severe malaria. None have been critically evaluated in controlled trials. Many clinicians with experience in treating severe malaria doubt their efficacy and none of these are recommended.

TREATMENT OF THE COMPLICATIONS OF MALARIA

Anaemia

Most malaria patients develop anaemia primarily caused by haemolysis and bone marrow dysfunction (see Chapter 3). Specific treatment of anaemia is

not necessary in most patients, who only require antimalarial therapy. However, if the haematocrit is less than 21% or is falling rapidly in a patient who is critically ill, blood transfusion is required. The anaemia of malaria can be worsened by oxidant-induced haemolysis in individuals with G-6-PD deficiency. If possible, individuals from population groups with a high prevalence of G-6-PD deficiency should be screened before being treated with primaquine.

Seizures

Seizures are common in malaria patients. It is often impossible to distinguish between febrile seizures and seizures caused by hypoglycaemia or associated with cerebral malaria. Seizures are frequently recurrent and prolonged in patients with cerebral malaria and a seizure in a patient with hyperparasitaemia is often the first sign of rapid clinical deterioration. Diazepam is used for status epilepticus (0.1–0.4 mg/kg intravenously during two to five minutes and repeated every 20 minutes if no response to a maximum of 1–2 mg/kg per 24 hours; children may require higher doses at slower rates than adults) and Dilantin, carbamazepine, phenobarbitone (phenobarbital) or other anticonvulsants for prevention of recurrence. Reduction of temperature is important in preventing seizures. Hypoglycaemia and electrolyte imbalance should be corrected, but they are uncommon causes of seizures in malaria patients. There have been no studies of the value of short term prophylactic anticonvulsants in malaria patients with cerebral involvement, hyperparasitaemia, hyperthermia, or a single seizure. Some clinicians recommend their use.

Hypoglycaemia

Plasma glucose of less than 40 mg% has been shown to occur in 8% and 15% of cerebral malaria patients in Thailand and Indonesia, respectively (White et al, 1983d; Hoffman et al, 1984a). It is more common in pregnant patients and those who are critically ill or have hyperparasitaemia. It most commonly occurs after institution of quinine therapy, but can occur before and can be recurrent. Clinical diagnosis is difficult in critically ill patients. Glucose levels should be monitored every six hours and whenever there is clinical deterioration. This can be done at the bedside using commercially available dipsticks (Dextrostix, Ames) which are analysed by using a colour chart or hand-held reflectance colorimeter (Dextrometer, Ames). Treatment is with 50% dextrose (1–2 mg/kg) followed by a four-hour infusion of 10% dextrose; glucagon has also been used. If the glucose level is > 60 mg% after a four-hour infusion, 10% dextrose is discontinued, 5% dextrose infusion begun, and glucose levels are monitored every six hours.

Renal failure

Renal failure in falciparum malaria may be associated with hyperparasit-

aemia, hypovolaemia, or intravascular haemolysis which lead to decreased renal capillary blood flow, decreased renal blood flow, and haemoglobinuria (blackwater fever), respectively. All may end in a clinical syndrome suggesting acute tubular necrosis. When faced with a patient with presumed renal failure, the clinician must exclude hypovolaemia as the cause of azotaemia and oliguria. If possible, pulmonary artery catheterization should be undertaken, a bladder catheter passed, haematocrit, glucose, electrolytes, blood urea nitrogen and creatinine and arterial blood gases measured, and a urinalysis and electrocardiogram performed. If there is no evidence of fluid overload, the central venous or pulmonary arterial wedge pressure is low and the urine specific gravity is high, a fluid challenge with normal saline should be undertaken. This can be accomplished by estimating percentage dehydration and administering maintenance and replacement fluids accordingly. If there is <20 ml/hour urine output after right heart pressures have increased to adequate levels and after what is considered adequate volume replacement, increasing intravenous doses of a diuretic such as frusemide (furosemide) should be tried (initial dose 0.5 mg/kg with doubling the dose every 30 minutes if there is no response). If this is unsuccessful, a vasopressor which increases renal blood flow, such as dopamine, may be tried. If all these manoeuvres are unsuccessful, the patient is in the oliguric stage of acute tubular necrosis and management is that of any such patient with strict attention to fluid and electrolyte balance, and institution of dialysis when indicated. Haemodialysis is preferable to peritoneal dialysis, but is generally unavailable in areas of the world where most cases of severe malaria are found. Peritoneal dialysis is generally adequate, but less preferable because of the risk of bleeding and infection and, theoretically, because splanchnic blood flow may be reduced in severe malaria and solute clearance across the peritoneum may also be relatively reduced (Canfield et al, 1968; Donadio et al, 1969).

Clearance of quinine is not substantially altered by renal failure, since only 20% of total clearance is through the kidneys (White et al, 1982). Recommendations for use of quinine in patients with severe malaria and oliguric renal failure are as for any patient with severe malaria (see above). If possible, dosage should be adjusted according to plasma levels. If these are not available and the patient is not improving after 2-3 days of therapy, individual doses should be reduced by 30% and the electrocardiogram and blood pressure carefully monitored for evidence of toxicity. Haemodialysis is thought to remove quinine and a standard dosage is used (Donadio et al, 1969). The same principles apply to the use of quinidine. However, it should be recognized that there is a greater chance of developing toxicity because up to 35% of quinidine may be cleared through the kidneys.

There is little information available on the use of chloroquine in renal failure, either with or without dialysis. If chloroquine must be used it should be used at a standard dosage.

Fresh whole blood should be used for transfusion, careful attention paid to general care and nutrition, the dosages of all other drugs adjusted appropriate to the level of renal failure and the polyuric phase of recovery expected and treated appropriately.

Pulmonary oedema

Pulmonary oedema is an uncommon, but frequently fatal, complication of severe *P. falciparum* infection that is most often associated with hyperparasitaemia (Punyagupta et al, 1974). It resembles adult respiratory distress syndrome (ARDS) and it is likely, but unproven, that the primary abnormality is increased permeability of pulmonary capillaries (Chapter 3). Although pulmonary artery wedge pressures may be normal in these patients, the use of excessive fluids is dangerous. Prevention requires careful fluid management with maintenance of adequate cardiac output and peripheral perfusion, but low right heart pressures. Treatment is that of pulmonary oedema and ARDS in a critically ill patient. Intermittent positive pressure ventilation (IPPV) with positive end expiratory pressure (PEEP) is the mainstay of treatment. It is unlikely that high frequency jet ventilation or intermittent mandatory ventilation will prove to reduce mortality when compared to IPPV with PEEP. Corticosteroids are frequently used in ARDS, but have never been shown to reduce mortality.

Pneumonia

Aspiration pneumonia is common in cerebral malaria patients who are unconscious and have frequent seizures and vomiting. Nursing on the side, anticonvulsants, and antiemetics may be helpful for prevention. Treatment is that of aspiration pneumonia.

Gram-negative sepsis

Gram-negative organisms are often cultured from the blood of patients with severe falciparum malaria. These unconscious patients have multiple intravenous lines and urinary catheters and sometimes have diarrhoea. The sources of infection may be similar to those of nosocomial infections in other severely ill patients. However, passage of organisms from the gut, through an intestinal wall subjected to the stress of microcirculatory obstruction by parasitized erythrocytes, is also possible. Any patient who is not responding to antimalarial therapy as expected should be investigated for bacteraemia and empirical institution of antibiotic therapy considered.

Hypotension, shock and myocarditis

Most malaria patients have low but normal arterial blood pressures and postural hypotension is common. Postmortems on humans and studies in non-human primates indicate that myocardial microcirculatory obstruction with parasitized erythrocytes is frequent (Miller, 1969; Jervis et al, 1972; Uys et al, 1984). However, even in patients with cerebral malaria, clinical or electrocardiographic evidence of myocarditis or myocardial ischaemia is rare, as is marked hypotension with evidence of decreased organ perfusion. If severe hypotension is present, gram-negative sepsis, pulmonary oedema, metabolic acidosis, gastrointestinal haemorrhage, hypovolaemia and

splenic rupture should be suspected. Treatment with fluids, blood, or vasopressors may be required.

Splenic rupture

This is an infrequent complication which is essentially the only fatal complication of *P. vivax* infection, but can occur with all malarias. Diagnosis is dependent on suspicion and demonstration of blood in the peritoneum. Treatment is surgical.

Disseminated intravascular coagulation (DIC)

While chemical DIC is common, clinically important DIC with bleeding is rare in malaria patients (Chapter 5). If encountered, it is usually found in patients with multi-organ failure and hyperparasitaemia. Clinically significant DIC should be treated with fresh whole blood. The use of heparin is controversial, but it is generally no longer recommended.

TREATMENT OF MALARIA IN SPECIAL GROUPS

Malaria in semi-immunes

Individuals with a history of repeated malaria infections may require lower doses of antimalarials and often can be treated with an antimalarial which would not be effective in treating *P. falciparum* infections in non-immunes. They rarely develop severe malaria. In the past, semi-immunes were often treated with lower doses of chloroquine than non-immunes (10 mg/kg compared to 25 mg/kg base). This is no longer recommended by some malariologists because of the potential for selecting resistant organisms. There have been case reports and immunological studies indicating that a semi-immune becomes fully susceptible to malaria infection and the development of severe malaria within 12 months of leaving a highly malarious area; whatever immunity is acquired over many years is rapidly lost (Editorial, 1985b).

Malaria in pregnancy

Pregnant women are apparently at higher risk of developing severe and fatal malaria than non-pregnant women. They should be treated promptly with appropriate doses of antimalarials and closely monitored for complications. Hypoglycaemia which may be quinine related is more common in pregnant women than in other groups with severe malaria. Quinine has long been thought to induce uterine contractions and abortion. Ten women between 30 and 40 weeks of gestation with severe falciparum malaria, all of whom received standard doses of 10 mg/kg quinine, were evaluated in Thailand. No deleterious effects of quinine infusion on uterine or fetal function were detected (Looareesuwan et al, 1985a). Severe falciparum malaria requires treatment with doses of quinine adequate for parasite inhibition and malaria

is associated with spontaneous abortion. Uterine and fetal activity must be monitored in pregnant women with severe malaria receiving quinine, but quinine should be administered in doses expected to be effective against the parasite so as to prevent death of the patient. In complicated malaria, concern about quinine inducing labour is of secondary importance to providing adequate doses of quinine so as to save the patient's life. Uncomplicated acute infections can be safely treated with chloroquine, quinine, and SP. Mefloquine has not been adequately evaluated in pregnancy, and tetracyclines and primaquine are not recommended in pregnancy because of potential toxicity to the fetus. Pregnant women who develop *P. vivax* infections should be treated with chloroquine and then placed on weekly chloroquine chemoprophylaxis (Chapter 7). Radical cure with primaquine can begin after delivery.

Malaria in children

Treatment of malaria in children is essentially the same as treatment in adults. Children with severe malaria are apparently more susceptible to life threatening side-effects associated with parenteral use of chloroquine and are usually treated with lower parenteral doses (see above). They may also require up to a 50% increase in doses of quinine during the last days of therapy to achieve radical cure of falciparum infections (see above) (Chongsuphajaisiddhi et al, 1981a).

TREATMENT OF MALARIA IN AREAS WITH LIMITED FACILITIES

A health care worker supplied with chloroquine, SP, quinine, tetracycline, and an antipyretic can adequately treat all acute, uncomplicated malaria infections. Treatment of patients with severe malaria is best accomplished in a facility equipped to provide modern intensive care, including exchange blood transfusion. Unfortunately, most patients with severe malaria are not treated in such facilities. Most patients with severe malaria can be adequately evaluated and treated in outlying hospitals where the following are available: quinine dihydrochloride; intravenous fluids; a parenteral antipyretic; dipsticks to check glucose; 50% dextrose; blood for transfusion; diazepam; an antibiotic such as chloramphenicol; an antiemetic; urinary catheters; a nursing staff trained to measure vital signs and input and output and to suction, turn, and cool severely ill patients; and a laboratory that can stain and read malaria films, measure the haemoglobin concentrations or haematocrit, and count cells in the cerebrospinal fluid. An algorithm for fluid therapy, initially based on maintenance requirements, temperature (insensible losses) and estimated state of hydration, and subsequently on input and output, is helpful. The most important component of therapy is the provision of adequate doses of antimalarial as soon as possible. Any patient with suspected severe malaria should be started on parenteral antimalarial therapy within 10 minutes of first being seen. There is no reason to await the results of a malaria blood film before initiating therapy. Patients who do not respond as

expected or deteriorate should have repeated blood films examined quantitatively and be frequently checked for hypoglycaemia and suspected of having, and treated for, gram-negative sepsis.

TREATMENT OF SYNDROMES ASSOCIATED WITH CHRONIC MALARIA

Tropical splenomegaly syndrome

Patients with the tropical splenomegaly syndrome may be debilitated, severely anaemic and unable to function normally because of splenic pain or mass (Chapter 4). Long term malaria chemoprophylaxis with chloroquine or proguanil has been effective in dramatically improving clinical condition, anaemia, and activity and in reducing spleen size (Sagoe, 1970; Lowenthal et al, 1971; Crane et al, 1973). This is presumably secondary to the reduction in malaria antigen load that leads to the immunological abnormalities thought to be responsible for pathogenesis of the condition. There is usually improvement in the general condition within six months, but significant reduction in spleen size may take several years or may not occur in about 20% of patients (Crane et al, 1973; Hoffman unpublished). In some areas, moderate residual splenomegaly is common even after long term chemoprophylaxis, deteriorate while on therapy, or are unable to take such therapy. Although there is concern about the long term infectious risks to patients in the tropics who have had splenectomy, there is evidence that splenectomy is appropriate and beneficial to highly selected patients who have failed on chemoprophylaxis (Hamilton et al, 1971; Crane et al, 1972). If possible, patients should receive pneumococcal vaccine before splenectomy and be maintained on malaria chemoprophylaxis after splenectomy. There has never been a trial comparing medical versus surgical treatment of patients with tropical splenomegaly syndrome.

Nephrotic syndrome

The nephrotic syndrome is thought to be associated with *P. malariae* infection and caused by glomerular immune complex deposition (Chapter 4) (Hendrickse et al, 1972; Houba et al, 1975; Greenwood and Whittle, 1981). It should be treated with antimalarials and standard measures used for treatment of nephrotic syndrome.

REDUCTION OF TRANSMISSION

The only effective gametocytocidal and sporonticidal drug in general use is primaquine. A single 45 mg dose of primaquine base is usually effective in preventing infection of mosquitoes. The effectiveness of properly administered primaquine in reducing transmission has never been rigorously studied (Tigertt, 1985).

REFERENCES

- Adelusi SA, Dawodu AH & Salako LA (1982) Kinetics of the uptake and elimination of chloroquine in children with malaria. *British Journal of Clinical Pharmacology* **14**: 483-487.
- Ahmad RA & Rogers HJ (1980) Pharmacokinetics and protein binding interactions of dapsone and pyrimethamine. *British Journal of Clinical Pharmacology* **10**: 519-524.
- Ahmad RA & Rogers HJ (1981) Salivary elimination of pyrimethamine. *British Journal of Clinical Pharmacology* **11**: 101-102.
- Andre RG & Doberstyn EB (1977) A preliminary report on the evaluation of the sporonticidal effect of pyrimethamine-sulfadoxine, quinine, and quinine-pyrimethamine against *Plasmodium falciparum*. In Tan DSK (ed.) *Current Concepts in the Diagnosis and Treatment of Parasitic and Other Tropical Diseases in South East Asia*. Proceedings of the 18th SEAMEO-Tropical Medicine Seminar, Kuala Lumpur, Malaysia, 2-5 August, 1977.
- Avraham H, Golenser J, Gazitt Y, Spira DT & Sulitzeanu D (1982) A highly sensitive solid-phase radioimmunoassay for the assay of *Plasmodium falciparum* antigens and antibodies. *Journal of Immunological Methods* **53**: 61-68.
- Baker JK, McChesney JD, Hufford CD & Clark AM (1982) High performance liquid chromatographic analysis of the metabolism of primaquine and the identification of a new mammalian metabolite. *Journal of Chromatography* **230**: 69-77.
- Bambauer R & Jutzler GA (1984) Malignant falciparum malaria successfully treated with plasma exchange. *Plasma Therapeutic Transfusion Technology* **5**: 343-347.
- Barker RH Jr, Suehseng L, Rooney W et al (1986) Specific DNA probe for the diagnosis of *Plasmodium falciparum* malaria. *Science* **231**: 1434-1436.
- Bass CC & Johns FM (1915) A method of concentrating malaria plasmodia for diagnostic and other purposes. *American Journal of Tropical Disease* **III**: 298-303.
- Beale GH et al (1978) Genetics. In Killick-Kendrick R & Peters W (eds) *Rodent Malaria*, p 213-245. London: Academic Press.
- Bergquist Y & Domeij-Nyberg B (1983) Distribution of chloroquine and its metabolite desethyl-chloroquine in human blood cells and its implication for the quantitative determination of these compounds in serum and plasma. *Journal of Chromatography* **272**: 137-148.
- Bergquist Y & Frisk-Holmberg M (1980) Sensitive method for the determination of chloroquine and its metabolite desethyl-chloroquine in human plasma and urine by high-performance liquid chromatography. *Journal of Chromatography* **221**: 119-127.
- Blount RE Jr (1969) Acute falciparum malaria: field experience with quinine/pyrimethamine combined therapy. *Annals of Internal Medicine* **70**: 142-147.
- Boudreau EF, Webster HK, Pavanand K & Thosingha L (1982) Type II mefloquine resistance in Thailand. *Lancet* **ii**: 1335.
- Boudreau EF, Pang LW, Dixon KE et al (1984) Comparable efficacy of mefloquine and the combination of quinine and tetracycline therapy for falciparum malaria in eastern Thailand. Presented at the Joint Meeting of the Royal and American Societies of Tropical Medicine and Hygiene, 33rd Annual Meeting of the American Society of Tropical Medicine and Hygiene, Baltimore, December 2-6, 1984. Abstract 167.
- Brandling-Bennett AD, Watkins WW, Oloo AJ, Koech DK & Spencer HC (1985) Sensitivity of *Plasmodium falciparum* to 4-aminoquinolines in coastal and western Kenya. Presented at the Joint Meeting of the American Society of Tropical Medicine and Hygiene and the American Society of Tropical Veterinary Medicine, 34th Annual Meeting of the American Society of Tropical Medicine and Hygiene, November 3-7, 1985. Abstract 57.
- Brooks MH & Barry KG (1969) Fatal transfusion of malaria. *Blood* **34**: 806-810.
- Bruce-Chwatt LJ (ed.) (1981) *Chemotherapy of Malaria*, 2nd edn. Geneva: World Health Organization.
- Byghjerg IC, Schapira A, Flachs H & Gomme G (1981) Mefloquine resistance of falciparum malaria from Tanzania enhanced by treatment. *Lancet* **i**: 21-26.
- Canfield CJ, Miller LH, Bartelloni PJ, Eichler P & Barry KG (1968) Acute renal failure in *Plasmodium falciparum* malaria. *Archives of Internal Medicine* **122**: 199-203.
- Chanthavanich P, Looareesuwan S, White NJ et al (1985) Intragastric mefloquine is absorbed rapidly in patients with cerebral malaria. *American Journal of Tropical Medicine and Hygiene* **34**: 1028-1036.

- China Cooperative Research Group of Qinghaosu and its Derivatives as Antimalarials (1982) Metabolism and pharmacokinetics of Qinghaosu and its derivatives. *Journal of Traditional Chinese Medicine* 2: 25-30.
- Chongsuphaisiddhi T, Sabcharoen A & Attanath P (1981a) In vivo and in vitro sensitivity of falciparum malaria to quinine in Thai children. *Annals of Tropical Paediatrics* 1: 21-26.
- Chongsuphaisiddhi T, Sabcharoen A, Chanthavanich P & Attanath P (1981b) Treatment of falciparum malaria in Thai children in 1981. Abstracts, the Faculty of Tropical Medicine, Mahidol University, Bangkok, p 2.
- Clyde DF (1983) Theoretical constraint to cross-resistance between chloroquine and mefloquine. World Health Organization meeting of principal investigators of the regional collaborative studies on drug resistant malaria—Jakarta, Indonesia, 2-6 May, 1983. SE/MAL/DRUG/83/24.
- Coosemans MH, Hendrix L, Barutwanayo M, Butoyi G & Onori E (1985) Pharmacoresistance de *Plasmodium falciparum* au Burundi. *Bulletin of the World Health Organization* 63: 331-338.
- Cramer G & Isaksson B (1963) Quantitative determination of quinidine in plasma. *Scandinavian Journal of Clinical and Laboratory Investigation* 15: 553-556.
- Crane GG, Pryor DS & Wells JV (1972) Tropical splenomegaly syndrome in New Guinea. II. Long term results of splenectomy. *Transactions of the Royal Society of Tropical Medicine and Hygiene* 66: 733-742.
- Crane GG, Hudson P & Hudson BET (1973) The effect of suppressive antimalarial therapy in tropical splenomegaly syndrome in New Guineans. *Papua New Guinea Medical Journal* 16: 46-50.
- Darlow B, Vrbova H, Gibney S et al (1982) Sulfadoxine-pyrimethamine for the treatment of acute malaria in children in Papua New Guinea I. *Plasmodium falciparum*. *American Journal of Tropical Medicine and Hygiene* 31: 1-9.
- Daroff RB, Deller JJ Jr, Kastl AJ Jr & Blocker WW Jr (1967) Cerebral malaria. *Journal of the American Medical Association* 202: 679-682.
- Desjardins RE, Pamplin III CL, von Bredow J, Barry KG & Canfield CJ (1979) *Clinical Pharmacology and Therapeutics* 26: 372-379.
- De Sousa J (1983) A phase II clinical trial of mefloquine in Brazilian male subjects. *Bulletin of the World Health Organization* 61: 815-820.
- Dixon KE, Pitaktong U, Bamnetpandh S, Teopipithaporn S & Na-Nakorn A (1983) Treatment of acute case of *Plasmodium malariae* malaria with mefloquine. *American Journal of Tropical Medicine and Hygiene* 32: 631-632.
- Dixon KE, Pitaktong U & Phintuyothin P (1985) A clinical trial of mefloquine in the treatment of *Plasmodium vivax* malaria. *American Journal of Tropical Medicine and Hygiene* 34: 435-437.
- Doberstyn EB, Phintuyothin P, Noeypatimanondh S & Teerakiartkamjorn C (1979a) Single-dose therapy of falciparum malaria with mefloquine or pyrimethamine-sulfadoxine. *Bulletin of the World Health Organization* 57: 275-279.
- Doberstyn EB, Teerakiartkamjorn C, Andre RG, Phintuyothin P & Noeypatimanondh S (1979b) Treatment of vivax malaria with sulfadoxine-pyrimethamine and with pyrimethamine alone. *Transactions of the Royal Society of Tropical Medicine and Hygiene* 73: 15-17.
- Donadio JV, Whelton A & Kazyak L (1969) Quinine therapy and peritoneal dialysis in acute renal failure complicating malarial haemoglobinuria. *Lancet* i: 375-379.
- Editorial (1983) Development of mefloquine as an antimalarial drug. *Bulletin of the World Health Organization* 61: 169-178.
- Editorial (1985a) Revised recommendations for preventing malaria in travellers to areas with chloroquine-resistant *Plasmodium falciparum*. *Morbidity and Mortality Weekly Report* 34: 185-195.
- Editorial (1985b) *Plasmodium falciparum*: a major health hazard to Africans and Asians returning home. *Lancet* ii: 871-872.
- Edstein M, Stace J & Shann F (1983) Quantification of quinine in human serum by high-performance liquid chromatography. *Journal of Chromatography* 278: 445-451.
- El Sadiq El Wakeel, Homeida MMA, Ali HM, Geary TG & Jensen JB (1985) Clindamycin for the treatment of falciparum malaria in Sudan. *American Journal of Tropical Medicine and Hygiene* 34: 1065-1068.

- Field JW (1949) Blood examination and prognosis in acute falciparum malaria. *Transactions of the Royal Society of Tropical Medicine and Hygiene* **43**: 33-46.
- Files JC, Case CJ & Morrison FS (1984) Automated erythrocyte exchange in fulminant falciparum malaria. *Annals of Internal Medicine* **100**: 396-397.
- Fitch CD (1983) Mode of action of antimalarial drugs. *Ciba Foundation Symposium* **94**: 222-232.
- Franzen L, Shabo R, Perlmann H et al (1984) Analysis of clinical specimens by hybridisation with probe containing repetitive DNA from *Plasmodium falciparum*. A novel approach to malaria diagnosis. *Lancet* **i**: 525-527.
- Frisk-Holmberg M, Bergquist Y, Termond E & Nyberg-Demeij B (1984) The single dose kinetics of chloroquine and its major metabolite desethylchloroquine in health subjects. *European Journal of Clinical Pharmacology* **26**: 521-530.
- Garnham JC, Raymond K, Shotton E & Turner P (1971) The bioavailability of quinine. *Journal of Tropical Medicine and Hygiene* **70**: 264-269.
- Greaves J, Evans DAP, Gilles HM & Baty JD (1979) A selected ion monitoring assay for primaquine in plasma and urine. *Biomedical Mass Spectrometry* **6**: 109-112.
- Greaves J, Evans DAP, Billes HM et al (1980) Plasma kinetics and urinary excretion of primaquine in man. *British Journal of Clinical Pharmacology* **10**: 399-405.
- Greenwood BM & Whittle HC (1981) *Immunology of Medicine in the Tropics*. London: Edward Arnold.
- Grindel JM, Tilton PF & Shaffer RD (1977) Quantitation of the antimalarial agent mefloquine, in blood, plasma and urine using HPLC. *Journal of Pharmaceutical Sciences* **66**: 834-837.
- Guo X, Jian H, Fan T & Huang W (1984) Comparative evaluation of parasite counts in capillary blood, bone marrow and intradermal smears in patients with cerebral malaria. *XI International Congress for Tropical Medicine and Malaria*, September 16-22, 1984, Calgary, Canada.
- Guoqiao L, Xingbo G, Rui J et al (1982) Clinical studies on treatment of cerebral malaria with qinghaosu and its derivatives. *Journal of Traditional Chinese Medicine* **2**: 125-130.
- Guoqiao L, Guo X, Hwa-Xiang J & Rui J (1984) Clinical studies on qinghaosu and its derivatives in the treatment of falciparum malaria and cerebral malaria: a review. *Journal of Traditional Chinese Medicine* **5**: 26-28.
- Gustafsson LL, Walker O, Alvan G et al (1983a) Disposition of chloroquine in man after single intravenous and oral doses. *British Journal of Clinical Pharmacology* **15**: 471-479.
- Gustafsson LL, Rombo L, Alvan G et al (1983b) On the question of dose-dependent chloroquine elimination of a single oral dose. *Clinical Pharmacology and Therapeutics* **34**: 383-385.
- Guyer B & Candy D (1979) Injectable antimalarial therapy in tropical Africa: iatrogenic disease and wasted medical resources. *Transactions of the Royal Society of Tropical Medicine and Hygiene* **73**: 230-232.
- Haggis AW (1941) Fundamental errors in the early history of cinchona. *Bulletin of the History of Medicine* **10**: 568-592.
- Hall AP (1972) Quinine infusion for recrudescences of falciparum malaria in Vietnam: a controlled study. *American Journal of Tropical Medicine and Hygiene* **21**: 851-856.
- Hall AP, Czerwinski AW, Madonia EC & Evensen KL (1973) Human plasma and urine quinine levels following tablets and intravenous infusion. *Clinical Pharmacology and Therapeutics* **14**: 580-585.
- Hall AP, Hanchalay S, Doberstyn E & Burnetphune S (1975a) Quinine dosage and serum levels in falciparum malaria. *Annual Report of SEATO Medical Research Laboratories* 241-250.
- Hall AP, Segal HE, Pearlman EJ, Phintuyothin P & Kosakal S (1975b) Amodiaquine resistant falciparum malaria in Thailand. *American Journal of Tropical Medicine and Hygiene* **24**: 575-580.
- Hamilton PJS, Stuiver PC & Zeigler JL (1971) Splenectomy in tropical splenomegaly syndrome—a five year follow-up. *Journal of Tropical Medicine and Hygiene* **74**: 230-232.
- Harinasuta T et al (1962) Chloroquine resistance in *Plasmodium falciparum* in Thailand. *First Regional Symposium on Scientific Knowledge of Tropical Parasites*, University of Singapore, 5-9 November 1962, pp 148-153. University of Singapore.
- Heizmann P & Ceschke R (1984) Determination of the antimalarial mefloquine in human

- plasma by gas chromatography with electron-capture detection. *Journal of Chromatography* **311**: 411-417.
- Hendrickse RG, Adeniyi A & Edington GM (1972) Quartan malarial nephrotic syndrome. Collaborative clinicopathological study in Nigerian children. *Lancet* **i**: 1143-1148.
- Hill LM & Malkasian GD (1979) The use of quinidine sulfate throughout pregnancy. *Obstetrics and Gynecology* **54**: 366-368.
- Hoffman SL, Harun S, Dimpudus AJ & Marwoto HA (1986) In vitro studies of the sensitivity of *Plasmodium falciparum* to mefloquine in Indonesia. *Proceedings of the Third National Parasitology Seminar*, Bandung, August 1983 (in press).
- Hoffman SL, Dimpudus AJ, Campbell JR et al (1985) RII and RIII type resistance of *Plasmodium falciparum* to combination of mefloquine and sulfadoxine/pyrimethamine in Indonesia. *Lancet* **ii**: 1039-1040.
- Hoffman SL, Rustama D, Punjabi NH et al (1984a) Cerebral malaria in Jayapura, Irian Jaya: clinical observations in 45 patients. Presented at the *XI International Congress for Tropical Medicine and Malaria*, Calgary, Alberta, 16-22 September, 1984.
- Hoffman SL, Masbar S, Hussein PR et al (1984b) Absence of malaria mortality in villagers with chloroquine-resistant *Plasmodium falciparum* treated with chloroquine. *Transactions of the Royal Society of Tropical Medicine and Hygiene* **78**: 175-178.
- Houba V (1975) Immunopathology of nephropathies associated with malaria. *Bulletin of the World Health Organization* **54**: 416.
- Jervis HR, Sprinz H, Johnson AJ & Wellde BT (1972) Experimental infection with *Plasmodium falciparum* in *Aotus* monkeys. II. Observations on host pathology. *American Journal of Tropical Medicine and Hygiene* **21**: 272-281.
- Jiang J, Guo X, Li G, Kong YC & Arnold K (1982a) Antimalarial activity of mefloquine and qinghaosu. *Lancet* **ii**: 285-288.
- Jiang JB, Huang JC, Liang DS et al (1982b) Long incubation of *Plasmodium vivax* multi-nucleatum as demonstrated in three experimental human cases. *Transactions of the Royal Society of Tropical Medicine and Hygiene* **76**: 845-847.
- Jiang J, Jacobs G, Liang D & Aikawa M (1985) Qinghaosu-induced changes in the morphology of *Plasmodium inui*. *American Journal of Tropical Medicine and Hygiene* **32**: 424-428.
- Jones CR & Ovenell SM (1979) Determination of plasma concentrations of dapsone, mono-acetyl dapsone and pyrimethamine in human subjects dosed with Maloprim. *Journal of Chromatography* **163**: 179-185.
- Khalik AA, Fox E, Sarwar M & Strickland GT (1986) Amodiaquine fails to cure chloroquine resistant *Plasmodium falciparum* in the Punjab. *Transactions of the Royal Society of Tropical Medicine and Hygiene* (in press).
- Kitchen SF (1949) Symptomatology: general considerations. In Boyd MF (ed.) *Malariaology*, vol. 2. Philadelphia: WB Saunders, 966 pp.
- Klayman DL (1985) Qinghaosu (artemisinin): an antimalarial drug from China. *Science* **228**: 1049-1055.
- Kramer S, Campbell CC & Moncrieff RE (1983) Fulminant *Plasmodium falciparum* infection treated with exchange blood transfusion. *Journal of the American Medical Association* **249**: 244-245.
- Kurathong S, Srichaikul T, Isarangkura P & Phanichphant S (1979) Exchange transfusion in cerebral malaria complicated by disseminated intravascular coagulation. *Southeast Asian Journal of Tropical Medicine and Public Health* **10**: 389-391.
- Le Bras J & Payet M (1978) Concentration of parasitized erythrocytes in malaria diagnosis. *Transactions of the Royal Society of Tropical Medicine and Hygiene* **72**: 552.
- Lepes T, Molineaux L & Wernsdorfer WH (1980) Monitoring of drug sensitivity in *Plasmodium falciparum*. Geneva: WHO MAP, 1980:80.2.
- Li G, Guo X, Arnold K, Jian H & Fu L (1984) Randomised comparative study of mefloquine, qinghaosu, and pyrimethamine-sulfadoxine in patients with falciparum malaria. *Lancet* **ii**: 1360-1361.
- Looareesuwan S, White NJ, Karbwang J et al (1985a) Quinine and severe falciparum malaria in late pregnancy. *Lancet* **ii**: 4-8.
- Looareesuwan S, White NJ, Benjasurat Y et al (1985b) Intravenous amodiaquine and oral amodiaquine/erythromycin in the treatment of chloroquine-resistant falciparum malaria. *Lancet* **ii**: 805-808.
- Lowenthal MN, O'Riordan EC & Hutt MSR (1971) Tropical splenomegaly syndrome in

- Zambia: further observations and effects of cycloguanil and proguanil. *British Medical Journal* **i**: 429-432.
- Mackey L, McGregor IA & Lambert PH (1980) Diagnosis of *Plasmodium falciparum* infection using a solid-phase radioimmunoassay for the detection of malaria antigens. *Bulletin of the World Health Organization* **58**: 439-444.
- Mackey LJ, McGregor IA, Paounova N & Lambert PH (1982) Diagnosis of *Plasmodium falciparum* infection in man: detection of parasite antigens by ELISA. *Bulletin of the World Health Organization* **60**: 69-75.
- Main EK, Main DM & Krogstad DJ (1983) Treatment of chloroquine-resistant malaria during pregnancy. *Journal of the American Medical Association* **249**: 3207-3209.
- Mandell GL & Sande MA (1980) Antimicrobial agents. Sulfonamides, trimethoprim-sulfamethoxazole, and urinary tract antiseptics. In Goodman LS & Gilman A (eds) *Pharmacological Basis of Therapeutics*, 6th edn, pp 1106-1125. New York: Macmillan.
- Merkli B, Richle R & Peters W (1980) The inhibitory effect of a drug combination on the development of mefloquine resistance in *Plasmodium berghei*. *Annals of Tropical Medicine and Parasitology* **74**: 1-9.
- Mihaly GW, Ward SA, Edwards G, L'e Orme M & Breckenridge AM (1984) Pharmacokinetics of primaquine in man: identification of the carboxylic acid derivative as a major plasma metabolite. *British Journal of Clinical Pharmacology* **17**: 441-446.
- Milhouz WK, Weatherly NF, Bowdre JH and Desjardins RE (1983) Interaction of mefloquine and a fixed combination of sulfadoxine and pyrimethamine (Fansidar) against *Plasmodium falciparum* in vitro. Presented at Joint Meeting of American Society of Tropical Medicine and Hygiene and American Society of Parasitologists, San Antonio, Texas, December 4-8, 1983.
- Miller LH (1969) Distribution of mature trophozoites and schizonts of *Plasmodium falciparum* in the organs of *Aotus trivirgatus*, the night monkey. *American Journal of Tropical Medicine and Hygiene* **18**: 860-865.
- Miller L (1975) Transfusion malaria. In Greenwalt TJ and Jamieson GA (eds) *Transmissible Disease and Blood Transfusion*, pp 241-266. Orlando: Grune and Stratton.
- Miller KD, Lobel HO, Satriale RF et al (1986) Severe cutaneous reactions among American travellers using pyrimethamine-sulfadoxine (Fansidar®) for malaria prophylaxis. Submitted for publication.
- Mucenski CM, Guerry P, Buesing M et al (1986) Evaluation of a synthetic oligonucleotide probe for diagnosis of *Plasmodium falciparum* infections. Submitted for publication.
- Munir M, Tjandra H, Rampengan TH, Mustadjab I & Wulur FH (1980) Heparin in the treatment of cerebral malaria. *Paediatrica Indonesiana* **20**: 47-50.
- Mutabingwa TK, Hills E & Kilama WL (1982) Response of *Plasmodium falciparum* to chloroquine and to quinine, in hospital patients in Muheza, Tanzania. *World Health Organization* 1982, WHO MAL 84.1012.
- Naparstek Y, Weiler-Ravell D, Shemer J et al (1981) *American Journal of Tropical Medicine and Hygiene* **30**: 1342-1343.
- Neiva A (1910) Über die Bildung einer chininresistenten Rasse des Malariaparasiten. *Memorias do Instituto Oswaldo Cruz* **2**: 131-140.
- Nguyen-Dinh P & Payne D (1980) Pyrimethamine sensitivity in *Plasmodium falciparum*: determination in vitro by a modified 48-hour test. *Bulletin of the World Health Organization* **58**: 909-912.
- Nielson R, Kohler RB, Chin W, McCarthy LJ & Luft FC (1977) Case report. The use of exchange transfusions: a potentially useful adjunct in the treatment of fulminant falciparum malaria. *American Journal of Medical Science* **277**: 325-329.
- Nocht B & Werner H (1910) Beobachtungen über relative Chininresistenz bei Malaria aus Brasilien. *Deutsche Medizinische Wochenschrift* **36**: 1557-1560.
- Noeypatimanond S, Malikul S, Benjapong W, Duriyanonda D & Ungkasvithongkul M (1983) Treatment of *Plasmodium falciparum* malaria with a combination of amodiaquine and tetracycline in central Thailand. *Transactions of the Royal Society of Tropical Medicine and Hygiene* **77**: 338-340.
- Ochs HR, Greenblatt DJ & Woo E (1980) Clinical pharmacokinetics of quinidine. *Clinical Pharmacokinetics* **5**: 150-168.
- Oriscello RG (1968) Cerebral malaria. *British Medical Journal* **iii**: 617-618.
- Patrick I (1982) Managing cerebral malaria. *British Medical Journal* **284**: 1954.

- Peters W (1970) *Chemotherapy and Drug Resistance in Malaria*. London: Academic Press.
- Peters W & Robinson BL (1984) The chemotherapy of rodent malaria. XXXV: Further studies on the retardation of drug resistance by the use of a triple combination of mefloquine, pyrimethamine and sulfadoxine in mice infected with *P. berghei* and '*P. berghei* NS.' *Annals of Tropical Medicine and Parasitology* **78**: 459-466.
- Phillips RE, Karbwang J, White NJ et al (1984) Failure of chloroquine-erythromycin and chloroquine-tetracycline combinations in treatment of chloroquine-resistant falciparum malaria in eastern Thailand. *Lancet* **i**: 300-302.
- Phillips RE, Warrell DA, White NJ, Looareesuwan S & Karbwang J (1985) Intravenous quinidine for the treatment of severe falciparum malaria. Clinical and pharmacokinetic studies. *New England Journal of Medicine* **312**: 1273-1278.
- Pinichpongse S, Doberstyn EB, Cullen JR et al (1982) An evaluation of five regimens for the outpatient therapy of falciparum malaria in Thailand 1980-81. *Bulletin of the World Health Organization* **60**: 907-912.
- Pollack Y, Metzger S, Shemer R et al (1985) Detection of *Plasmodium falciparum* in blood using DNA hybridization. *American Journal of Tropical Medicine and Hygiene* **34**: 663-667.
- Powell RD & McNamara JV (1972) Quinine: side effects and plasma levels. *Helminthological Society of Washington. Proceedings* **39**: 331-338.
- Powell RD, Brewer GJ, Alving AS & Millar JW (1964a) Studies on a strain of chloroquine-resistant *Plasmodium falciparum* from Thailand. *Bulletin of the World Health Organization* **30**: 29-44.
- Powell RD, Brewer GJ, Degowin RL & Alving AS (1964b) Studies on a strain of chloroquine-resistant *Plasmodium falciparum* from Vietnam. *Bulletin of the World Health Organization* **31**: 379-392.
- Punyagupta S, Srichaikul T, Nitiyanant P & Petchclai B (1974) Acute pulmonary insufficiency in falciparum malaria: summary of 12 cases with evidence of disseminated intravascular coagulation. *American Journal of Tropical Medicine and Hygiene* **23**: 551-559.
- Pussard E, Verdier F, Clavier F et al (1985) A new approach to pharmacokinetics of amodiaquine and its contribution of prophylaxis and treatment of *Plasmodium falciparum* malaria. Joint Meeting of the American Society of Tropical Medicine and Hygiene and the American Society of Tropical Veterinary Medicine. *34th Annual Meeting of the American Society of Tropical Medicine and Hygiene*, November 3-7, 1985, Miami, Florida.
- Qinghaosu Antimalaria Coordinating Research Group (1979) Antimalaria studies on Qinghaosu. *Chinese Medical Journal* **92**: 811-816.
- Sabchareon A, Chongsuphajaisiddhi T & Attanath P (1983) Serum quinine concentrations following the initial dose in children with falciparum malaria. *Southeast Asian Journal of Tropical Medicine and Public Health* **13**: 556-562.
- Sagoe A-S (1970) Tropical splenomegaly syndrome: long-term proguanil therapy correlated with spleen size, serum IgM, and lymphocyte transformation. *British Medical Journal* **iii**: 378-382.
- Salako LA, Walker O & Iyem AO (1984) Pharmacokinetics of chloroquine in renal insufficiency. *African Journal of Medicine and Medical Science* **13**: 177-182.
- Sanders JP & Dawson WT (1932) Efficacy of quinine in malaria. *Journal of the American Medical Association* **99**: 1773-1777.
- Sanders JP (1935) Treatment of malaria with a short course of quinidine. *American Journal of Tropical Medicine* **15**: 651-660.
- San George RC, Nagel RL & Fabry ME (1984) On the mechanism for the red-cell accumulation of mefloquine, an antimalarial drug. *Biochimica et Biophysica Acta* **803**: 174-181.
- Schwartz DE, Eckert G, Hartmann D et al (1982) Single dose kinetics of mefloquine in man. Plasma levels of the unchanged drug and of one of its metabolites. *Chemotherapy* **28**: 70-84.
- Sheehy TW, Reba RC & Parks GR (1969) Combined pyrimethamine-quinine therapy for chloroquine-resistant *P. falciparum* infections. *Southern Medical Journal* **62**: 152-156.
- Shmidskamp H & Wolthuis FH (1971) *British Medical Journal* **i**: 714-716.
- Silamut K, White NJ, Looareesuwan S & Warrell DA (1985) Binding of quinine to plasma proteins in falciparum malaria. *American Journal of Tropical Medicine and Hygiene* **34**: 681-686.

- Smith CC & Ihrig J (1959) Persistent excretion of pyrimethamine following oral administration. *American Journal of Tropical Medicine and Hygiene* 8: 60-62.
- Smitskamp H & Wolthuis FH (1971) New concepts in treatment of malignant tertian malaria with cerebral involvement. *British Medical Journal* i: 714-716.
- Smrkovski LL, Buck RL, Alcantara AK, Rodriguez CS & Uylangco CV (1983) In vitro mefloquine-resistant *Plasmodium falciparum* from the Philippines. *Lancet* ii: 322.
- Stace J, Shann FA, Walters S et al (1983) Serum levels of quinine following intramuscular administration to children. *Papua New Guinea Medical Journal* 26: 21-24.
- Stone WJ, Hanchett JE & Knepshield JH (1972) Acute renal insufficiency due to falciparum malaria. *Archives of Internal Medicine* 129: 620-628.
- Strickland GT, Fox E, Sarwar M, Khaliq AA & MacDonald M (1986) Effects of chloroquine, amodiaquine and Fansidar on *Plasmodium falciparum* gametocytemias. *American Journal of Tropical Medicine and Hygiene* (in press).
- Taggart JV, Gate DP, Berliner RW et al (1948) Studies on the chemotherapy of the human malaras. III. The physiological disposition and antimalarial activity of the cinchona alkaloids. *Journal of Clinical Investigation* 27: 80-86.
- Thuriaux MC (1982a) Quinine by intravenous infusion for falciparum malaria. *British Medical Journal* 285: 1429.
- Thuriaux MC (1982b) A prevalence survey of lower limb motor disorders in schoolage children in Niger and an estimation of poliomyelitis incidence. *Tropical and Geographical Medicine* 34: 163-168.
- Tigertt WD (1985) A role for 8-aminoquinolines in falciparum malaria? Editor's page. *American Journal of Tropical Medicine and Hygiene* 34: 651-652.
- Timm U & Weidekamm E (1982) Determination of pyrimethamine in human plasma after administration of Fansidar or Fansidar-mefloquine by means of high-performance liquid chromatography with fluorescence detection. *Journal of Chromatography* 230: 107-114.
- Trenholme GM, Williams RL, Desjardins RE et al (1975) *Science* 190: 792-794.
- Trenholme GM, Williams RL, Rieckmann KH, Frischer H & Carson PE (1976) Quinine disposition during malaria and during induced fever. *Clinical Pharmacology and Therapeutics* 19: 459-467.
- Uys CJ, Burns DG, Tiltman AJ & Philcox DV (1984) Clinicopathological conference. Fever, diarrhoea and confusion. *South African Medical Journal* 65: 519-523.
- Verdrager J (1964) Observations on the longevity of *Plasmodium falciparum*: with special reference to findings in Mauritius. *Bulletin of the World Health Organization* 31: 747-751.
- Walker O, Birkett DJ, Alvan G, Gustafsson LL & Sjoquist F (1983) Characterization of chloroquine plasma protein binding in man. *British Journal of Clinical Pharmacology* 15: 375-377.
- Walliker D (1982) Genetic variation in malaria parasites. *British Medical Bulletin* 38: 123-128.
- Ward SA, Edwards G, L'Orme M & Breckenridge AM (1983) Determination of primaquine in biological fluids by reversed phase high-performance liquid chromatography. *Journal of Chromatography* 305: 239-243.
- Ward SA, Mihaly GW, Edwards G et al (1985) Pharmacokinetics of primaquine in man. II. Comparison of acute vs chronic dosage in Thai subjects. *British Journal of Clinical Pharmacology* 19: 751-755.
- Warhurst DC (1981) The quinine-haemin interaction and its relationship to antimalarial activity. *Biochemical Pharmacology* 30: 3323-3327.
- Warhurst DC, Robinson BL & Peters W (1976) The chemotherapy of rodent malaria. XXIV. The blood schizontocidal action of erythromycin upon *Plasmodium berghei*. *Annals of Tropical Medicine and Parasitology* 70: 253-258.
- Warrell DA, Looareesuwan S, Warrell MJ et al (1983) Dexamethasone proves deleterious in cerebral malaria. *New England Journal of Medicine* 306: 313-319.
- Watkins WM, Spencer HC, Kariuki DM et al (1984) Effectiveness of amodiaquine as treatment for chloroquine-resistant *Plasmodium falciparum* infections in Kenya. *Lancet* i: 357-359.
- Watt G, Long GW, Padre N et al (1985) High-grade amodiaquine resistance in the Philippines. Presented at the Joint Meeting of the American Society of Tropical Medicine and Hygiene and the American Society of Tropical Veterinary Medicine. 34th Annual Meeting of the American Society of Tropical Medicine and Hygiene, November 3-7, 1985. Abstract 279.
- Weniger H (1979a) Review of the side effects and toxicity of chloroquine. World Health Organization, 1979, WHO MAL/79.906.

- Weniger H (1979b) Review of the side effects and toxicity of pyrimethamine. World Health Organization, 1979. WHO/MAL/79.907.
- Weniger H (1979c) Toxicity and side effects of primaquine and other 8-aminoquinolines. World Health Organization, 1979. WHO/MAL/79.905.
- Wesselhoeft C (1914) The discovery of the cinchona bark. *New Orleans Medical and Surgical Journal* 68: 702-727.
- Westerman RL (1985) Clindamycin as an antimalarial. Presented at the Joint Meeting of the American Society of Tropical Medicine and Hygiene and the American Society of Tropical Veterinary Medicine. 34th Annual Meeting of the American Society of Tropical Medicine and Hygiene, November 3-7, 1985. Abstract 289.
- White NJ (1985) Clinical pharmacokinetics of the antimalarial drugs. *Clinical Pharmacokinetics* 10: 187-215.
- White NJ, Warrell DA, Bunnag D et al (1981) Quinine in falciparum malaria. *Lancet* ii: 1069-1071.
- White NJ, Looareesuwan S, Warrell DA et al (1982) Quinine pharmacokinetics and toxicity in cerebral and uncomplicated falciparum malaria. *American Journal of Medicine* 73: 564-572.
- White NJ, Looareesuwan S & Warrell DA (1983a) Quinine and quinidine: a comparison of EKG effects during the treatment of malaria. *Journal of Cardiovascular Pharmacology* 5: 173-175.
- White NJ, Looareesuwan S, Warrell DA et al (1983b) Quinine loading dose in cerebral malaria. *American Journal of Tropical Medicine and Hygiene* 32: 1-5.
- White NJ, Looareesuwan S & Silamut K (1983c) Red cell quinine concentrations in falciparum malaria. *American Journal of Tropical Medicine and Hygiene* 32: 456-460.
- White NJ, Warrell DA, Chanthavanich P et al (1983d) Severe hypoglycemia and hyperinsulinemia in falciparum malaria. *New England Journal of Medicine* 309: 61-66.
- Woodruff AW & Dickinson CT (1968) Use of dexamethasone in cerebral malaria. *British Medical Journal* iii: 31-32.
- World Health Organization (1973) Chemotherapy of malaria and resistance to anti-malarials: Report of a WHO Scientific Group. *World Health Organization Technical Report Series* 529: 30-35.
- World Health Organization Scientific Group on the Chemotherapy of Malaria (1984) *Advances in Malaria Chemotherapy*. Geneva: World Health Organization.
- Xinyi N, Liyi H, Zhihong R & Zhenyu S (1985) Metabolic fate of Qinghaosu in rats: a new TLC densitometric method for its determination in biological material. *European Journal of Drug Metabolism and Pharmacokinetics* 10: 55-59.
- Yarrish RL, Janas JS, Nosanchuk JS, Steighigel RT & Nusbacher J (1982) Transfusion malaria. Treatment with exchange transfusion after delayed diagnosis. *Archives of Internal Medicine* 142: 187-188.