ONE FALX MOVE AND YOU'RE DEAD: CURRENT CHEMOPROPHYLAXIS AND THERAPY OF MALARIA

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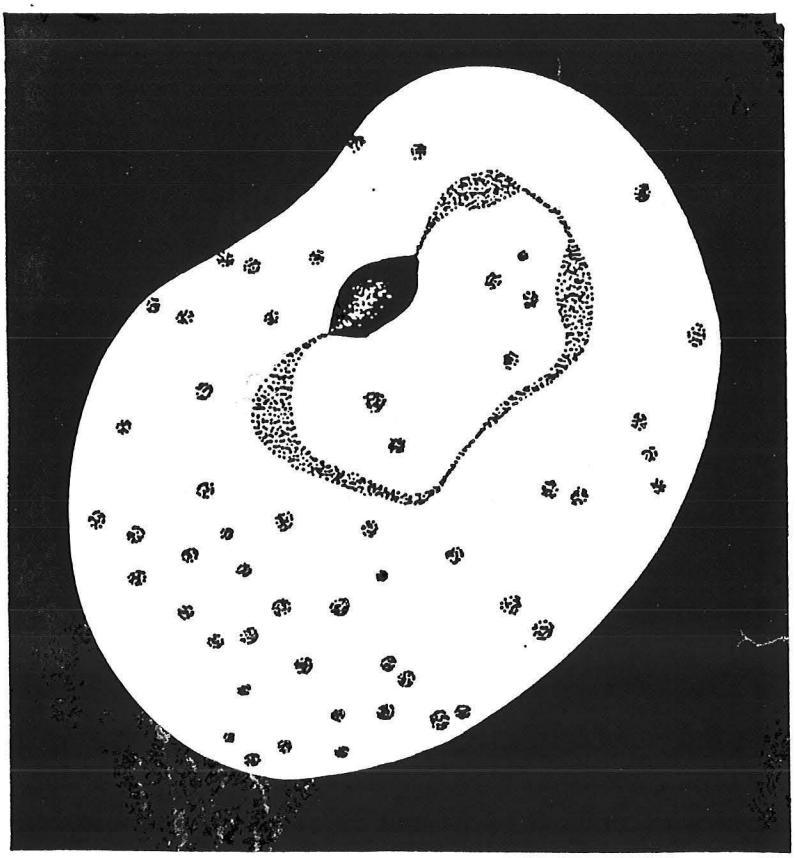


The Lord shall smite thee...with a fever....
Deuteronomy 28:22

Humanity has but three great enemies: fever, famine and war; of these by far the greatest, by far the most terrible, is fever.
Sir William Osler

The immediate future for antimalarial therapy appears grim....New drugs are needed desperately, but with limited commercial incentive for development of antimalarials, it is not clear where they will come from (1).
The Lancet, 1991

Introduction

Fever itself is Nature's instrument.
Thomas Sydenham

Several excellent reviews of malaria prevention (2), clinical management (3), chemotherapy (4,5), and chemoprophylaxis (6) have been published since 1990. This protocol summarizes material from these more extensive reviews and supplements them with additional information, emphasizing the most recent data.

Malaria in the World Today

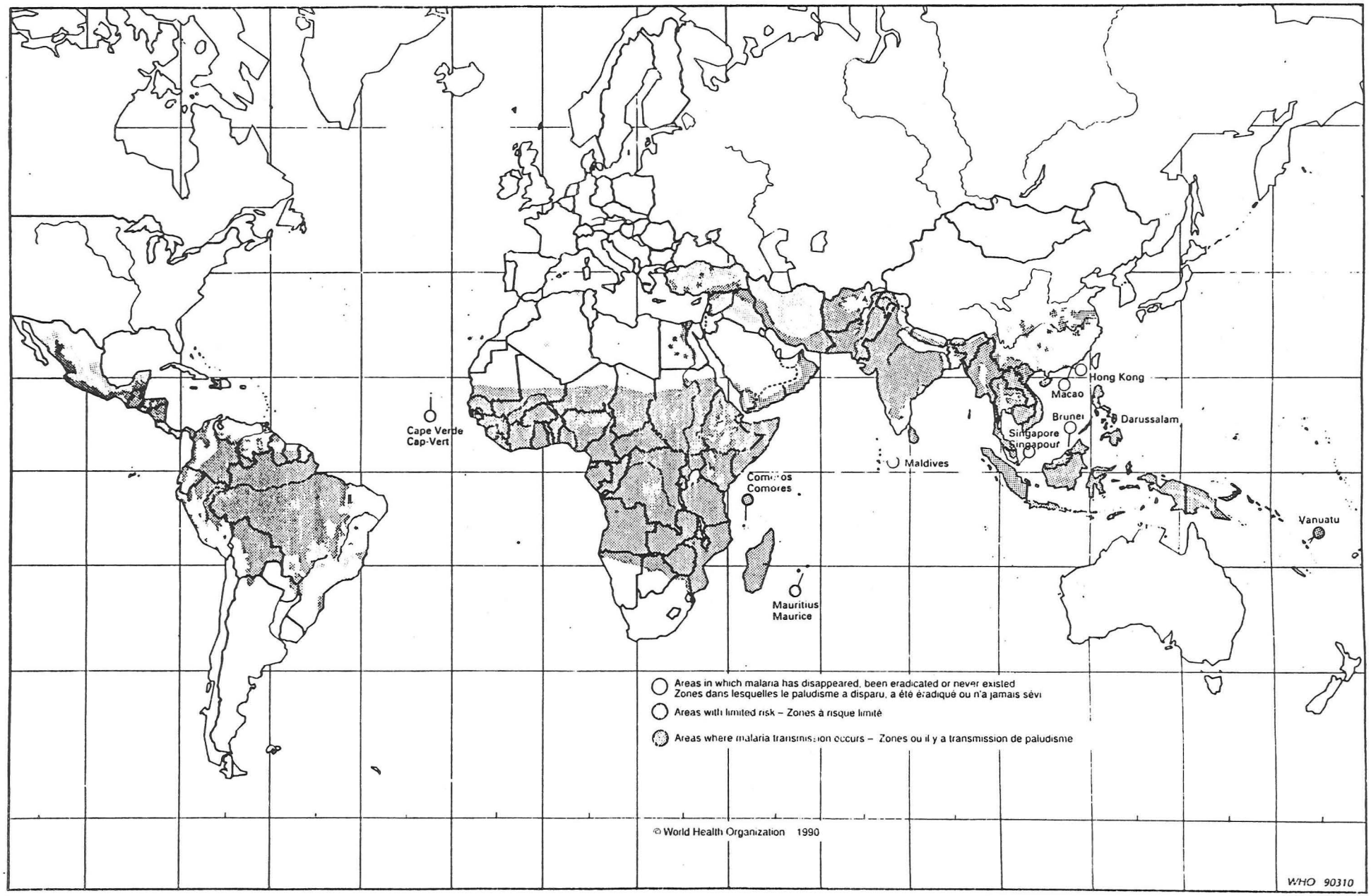
A horrid thing called the mal'aria, that comes to Rome every summer and kills one.
Horace Walpole, *Correspondence*

The World Health Organization (WHO) maintains global surveillance of malaria, although reports from Africa are notoriously irregular and incomplete. The latest summary data, from 1988, indicate that approximately 2.1 billion persons (41% of the global population) reside in malarious areas. The estimated annual incidence is 110 million clincal cases with a point prevalence of 270 million infected persons (Figure 1), with over 90% of the morbidity in sub-Saharan Africa (7).

Most (83%) cases reported in 1988 from outside Africa were concentrated in focal areas of Afghanistan, Brazil, China, India, Mexico, the Philippines, Sri Lanka, Thailand, and Vietnam (7).

Figure 1

Epidemiological assessment of the status of malaria, 1988
Evaluation épidémiologique de la situation du paludisme, 1988



During the 1980s the reported incidence of malaria increased in the Americas and Eastern Mediterranean region while declining in the Western Pacific and Europe and perhaps in Southeast Asia (Table 1) (7).

Table 1

Number of Malaria Cases Reported, by WHO Region (1000s), 1981-1988

WHO Region — Région OMS	1981	1982	1983	1984	1985	1986	1987	1988[c]
Africa[b, c] — Afrique[b, c]	6 754	6 042	2 726	4 420	3 373	3 046	3 309	3 285
Americas — Amériques	638	718	831	931	911	951	1 019	1 100
South-East Asia — Asie du Sud-Est	3 566	2 964	2 731	3 004	2 521	2 689	2 823	2 645
Europe	60	66	71	60	32	45	27	8
Eastern Mediterranean — Méditerranée orientale	207	308	305	335	391	610	564	602
Western Pacific — Pacifique occidental	3 464	2 487	1 839	1 361	1 066	786	758	704
Total (excluding Africa — à l'exclusion de l'Afrique)	7 935	6 543	5 777	5 691	4 921	5 081	5 191	5 059

[a] The information provided does not cover the total population at risk in some instances. population exposée.

[b] Mainly clinically diagnosed cases.

[c] Incomplete figures.

Although a mortality rate of 1,000,000 per year has been suggested, this figure may be too low (4).

In Southeast Asia and in Latin America malaria is typically seasonal or focal, and so the population does not acquire immunity to infection. Holoendemic stable and intense transmission with substantial immunity in the adult population characterize the disease in much of tropical Africa (4).

In holoendemic settings clinical cases and deaths are concentrated in children who have lost passive maternal immunity, but who have yet to acquire active immunity. In areas of focal or seasonal faciparum transmission all ages are at risk of disease and death, and fatalities may be concentrated among adults as a result of differential occupational exposure. Obviously, nonimmune visitors of all ages to either type of setting are at risk (4).

Merozoites of *P. vivax* infect new erythrocytes after binding to a Duffy blood group antigen (Fy^a or Fy^b). West African populations are characteristically Duffy antigen-negative (FyFy), and it is therefore not surprising that *P. falciparum* predominates in sub-Saharan Africa. Most cases in Brazil, the Dominican Republic, French Guiana, Guyana, Haiti, and Surinam are also from *P. falciparum* (7). In India

34% of cases reported in 1988 were attributable to *P. falciparum* infection (8).

The realities of traditional malaria control efforts in certain areas include reuse of unsterilized lancets, needles, and cotton balls and use of a single microscope slide to prepare thick smears directly from the fingers of several subjects. These practices create an obvious risk for transmission of HIV, HBV, and other bloodborne pathogens (9).

Malaria has been suggested to play a role in the etiology of Burkitt's lymphoma. For example, a recent report documents higher levels of Epstein-Barr virus (EBV)-containing mononuclear cells in the circulation of patients with acute malaria than in convalescent patients and healthy subjects from outside malarious areas (10).

Tropical splenomegaly or hyperreactive malarial splenomegaly is common in holoendemic areas. Most cases respond to antimalarial therapy. The demonstration of rearrangements of the immunoglobulin heavy chain gene in some patients with splenomegaly who demonstrate only transient and incomplete response to proguanil suggests that tropical splenomegaly may sometimes evolve into a clonal lymphoproliferative disorder indistinguishable from chronic lymphocytic leukemia (11).

Malaria may be introduced into an unreceptive area by infected mosquitoes transported aboard aircraft arriving from endemic zones. Five cases of falciparum malaria were diagnosed in the summer of 1989 in persons residing within 2 km of Geneva International Airport. The diagnosis was delayed in all cases (12).

Malaria in the United States

> I would rather ride on earth in an oxcart, with a free circulation, than go to heaven in the fancy car of an excursion train and breathe a *malaria* all the way.
>
> Henry David Thoreau, *Walden*

Certain epidemiologic terms are particularly relevant to the discussion of malaria outside endemic areas. Autochthonous infection may be either indigenous or introduced, the latter referring to transmission by mosquito bite from an imported case in an area normally free of the disease. Imported cases are those acquired outside a particular area, for example, the United States. Induced malaria is artificially transmitted, as by transfusion, sharing of needles, or deliberate malariotherapy. Relapses are defined as clinical symptoms or parasitemia occurring at

a longer interval after previous patent infection than that of the normal periodicity of clinical paroxysms. Cryptic cases are isolated ones in which epidemiologic investigation does not find associated secondary cases (13).

The Centers for Disease Control (CDC) maintain surveillance of malaria in the United States. Of 1102 cases with onset in 1989 reported to CDC, all but five were acquired abroad. There were four deaths. Nearly half (532, 48%) of the cases were diagnosed as infection with *P. vivax*, and the majority (448, 41%) of the rest were attributed to *P. falciparum*. In 68 cases (6%) the species was not reported (13).

Fifty-six per cent of reported cases were accounted for by the commonest combinations of country of origin and species of parasite. Most cases represented *P. vivax* infections from India, Mexico, and Central America or *P. falciparum* infections from sub-Saharan Africa (Table 2) (13).

Table 2

Malaria - The Origin of Species:
Ten Commonest Combinations
United States, 1989

Rank	Origin	Species	Cases	Proportion
1	India	*P. vivax*	135	12%
2	Mexico	*P. vivax*	126	11%
3	Nigeria	*P. falciparum*	121	11%
4	*Africa	*P. falciparum*	66	6%
5	Kenya	*P. falciparum*	37	3%
6	Nicaragua	*P. vivax*	33	3%
7	Liberia	*P. falciparum*	30	3%
8	Ghana	*P. falciparum*	28	3%
9	Guatemala	*P. vivax*	24	2%
10	India	*P. falciparum*	23	2%
Total (including other)			1102	100%

*Country unspecified. Includes "East," "West," "Central," and unspecified.

Most (591 cases, 54%) occurred in U.S. civilians, but cases in foreign civilians (476, 43%) were also common, while only 35 cases (3%) in the United States occurred in U.S. military personnel (13).

U.S. citizens usually became infected in Africa (59%) or Asia (21%). Infected foreign civilians were likely to

have come from Asia (31%) or Africa (31%), too, but also from Mexico (21%) or Central America (18%) (13).

Most (89%) falciparum infections had onset within the first month of arrival in the United States, whereas only 30% of vivax infections occurred so promptly (Table 3) (13).

Table 3

Imported malaria cases by interval between date of entry and onset of illness and by *Plasmodium* species, United States, 1989

Interval (in months)	*Vivax*	(%)	*Falciparum*	(%)	*Malariae*	(%)	*Ovale*	(%)	Total	(%)
< 1	81	(30.2)	208	(89.3)	6	(37.5)	1	(12.5)	296	(56.3)
1-2	67	(25.0)	18	(7.7)	5	(31.3)	4	(50.0)	94	(17.9)
3-5	57	(21.3)	3	(1.3)	2	(12.5)	0	(0.0)	62	(11.8)
6-11	58	(21.6)	4	(1.7)	3	(18.7)	3	(37.5)	68	(12.9)
12	5	(1.9)	0	(0.0)	0	(15.8)	1	(12.5)	6	(1.1)
TOTAL	268	(100.0)	233	(100.0)	16	(100.0)	9	(100.0)	526	(100.0)

The most numerous category of travelers who developed malaria were those who had friends or relatives in endemic areas (Table 4) (13).

Table 4

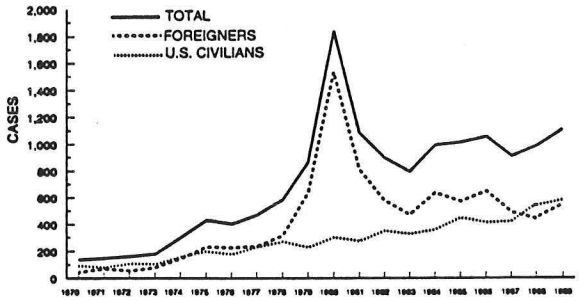
Imported malaria cases in U.S. civilians, by category, United States, 1989

Category	Cases	Percent
Tourist	84	14.3
Business representative	63	10.8
Government employee	4	0.7
Missionary	81	13.8
Peace Corps	10	1.7
Seamen/aircrew	2	0.3
Teacher/student	26	4.4
Visiting friends/relatives	175	29.9
Other	17	2.9
Unknown	124	21.2
TOTAL	586	100.0

Cases of malaria in U.S. civilians have shown a steadily upward trend over the past two decades, surpassing those in foreign civilians in 1988 (Figure 2) (13).

Figure 2

Cases of Malaria in U.S. Civilians and Foreigners, United States,* 1970-1989



* Includes Puerto Rico, the Virgin Islands, and Guam

Texas is second only to California in the number of cases of malaria reported annually (Figure 3) (13).

Figure 3

Malaria cases with onset in the United States, by state, 1989

The large number of cases seen in Texas is presumably due in part to infections acquired in Mexico. These are overwhelmingly caused by *P. vivax*. Over two-thirds of cases

imported from Mexico are in citizens of that country, with the remainder being in U.S. citizens returning home (Table 5) (13).

Table 5

Malaria: On the Border -
Cases Acquired in Mexico
United States, 1989

Characteristic	Number	Proportion
P. vivax	126	89%
P. falciparum	3	2%
Mexican civilian	97	68%
U.S. civilian	45	32%
Total	142	100%

In the Americas, vivax malaria predominates in Mexico and Central America. Falciparum malaria in Mexico is largely confined to the state of Oaxaca (7).

Recent cryptic cases of vivax malaria in California and Florida are suspected to have been transmitted by local vectors after feeding on parasitemic migrant workers. The potential for similar transmission occurs in other states, including Texas, in which populations of migrant workers are exposed to competent species of mosquito. Thus, malaria is a legitimate diagnostic consideration in cases of unexplained febrile illness even in local residents without a history of travel or transfusion (14).

Malaria at Parkland

The Medical Record Department at Parkland Memorial Hospital has identified 20 cases of malaria (ICD-9-CM codes 84.0-84.9, 771.2) seen at the hospital since 1983. Eleven of the patients had Hispanic surnames, eight had surnames suggesting an African origin, and one had an English surname. Cases peaked in 1984 (Table 6).

Table 6

Malaria Cases by Surname of Patient
Parkland Memorial Hospital, 1983-1991

Year	African	Hispanic	Other	Total
1983	1	2	0	3
1984	4	5	1	10
1985	1	4	0	5
1986	0	0	0	0
1987	1	0	0	1
1988	0	0	0	0
1989	1	0	0	1
1990	0	0	0	0
1991	0	0	0	0
Total	8	11	1	20

Prevention of Malaria

> It has long been familiar to physicians that there was produced by...marshes and swamps, a poisonous and aeriform substance, the cause, not only of ordinary fevers, but of intermittents;and to this unknown agent of disease the term marsh miasma has been applied.
>
> Macculloch, *Malaria*

Malaria stands as the paradigm of failure in attempts to eradicate infectious diseases of mankind. The collapse of the earlier worldwide malaria eradication campaign was a discouraging precedent that slowed efforts to mount the ultimately successful program by the World Health Organization to eliminate smallpox. The assault on smallpox benefitted from widely recognized characteristics of that disease: the inefficiency of interpersonal transmission of variola virus, the rarity of subclinical infection, the occurrence of a characteristic exanthem, the availability of a highly effective vaccine, the presence of durable immunity after vaccination or natural infection, the lack of a chronic carrier state, the absence of nonhuman reservoirs of infection, and the impermanence of live virus in the inanimate evvironment. Current initiatives to eliminate measles and dracunculiasis reflect recognition of important similarities in the epidemiology of these diseases and that of smallpox.

In contrast, malaria eradication and control measures have traditionally focused upon the anopheline vector. The ability of insecticide-resistant mosquitoes to disseminate intercontinentally has been documented by study of genetic polymorphisms in susceptible strains and in insects with

organophosphorus resistance mediated by amplification of nonspecific esterase (15).

Rapid emergence of insecticide-resistant mosquitoes and growing awareness of health hazards presented by pesticides have rechanneled efforts toward vaccine development. The various stages in the life cycle of *Plasmodium spp.* are antigenically diverse. Hence, the goals of candidate vaccines would differ in accordance with the source of the antigen employed. Merozoite vaccines could be employed to limit the severity of disease by inhibiting the successful propagation of successive generations of erythrocytic stages. Immunogens directed against gametocyte antigens might reduce transmission of disease by preventing transmission of the parasite to mosquitoes feeding on infected hosts, but such preparations, which have been dubbed "altruistic vaccines," would not be expected to protect the individual recipient. Most effort has gone into developing a vaccine directed against the dominant circumsporozoite (CS) protein, which might block the initial infection after a bite from an infected mosquito. The World Health Organization has published the proceedings of an April 1989 conference on development of a vaccine to pre-erythrocytic stages of the parasite (16). The current state of progress in this area has recently been reviewed (17). Problems have been encountered in developing satisfactorily immunogenic preparations of this protein, and new developments in adjuvant technology are under evaluation (18). Fundamental concerns about a vaccine directed against sporozoites include the possiblity of selecting for new, antigenically diverse strains and the requirement that the immune response eliminate sporozoites with extreme rapidity and thoroughness before the organism finds sanctuary in the liver. Even a tiny minority of surviving sporozoites could presumably consititute the nidus for a severe infection in a host with no immunity to successive stages of the parasite. A recent report documents complete protection of mice experimentally challenged with *P. yoelii* after immunization with a combination of homologous CS and a second antigen, sporozoite surface protein 2 (SSP2), in a model in which immunization with either CS or SSP2 alone afforded only partial protection (19).

Diagnosis of Malaria

> Faith is a fine invention
> For gentlemen who see;
> But microscopes are prudent
> In an emergency.
> Emily Dickinson, *Poems, Second Series*

Conventional microscopical diagnosis employing Giemsa-stained thin smears is insensitive in patients with low-

level parasitemia. Giemsa-stained thick smears provide greater sensitivity but demand considerable experience for proper interpretation. Much recent attention has been given to alternative diagnostic techniques. Some, such as those involving immunodiagnosis or nucleic acid hybridization, require technical sophistication and sacrifice direct morphologic confirmation of the infection. Enhanced microscopical techniques include fluorochrome staining. Kawamoto, at Nagoya University, has extended his efforts in the field of fluorochrome technology to develop a sensitive method for malaria diagnosis that employs a custom-designed interference filter to permit examination with a conventional light microscope in place of a more costly fluorescence apparatus. Employing acridine orange to stain DNA and RNA, Kawamoto confirmed that malaria parasite nuclei emitted green (535 nm) fluorescence, while parasite cytoplasm was bright red (650 nm) upon illumination with an interference filter exciting at 430 nm and 492-495 nm, respectively (20).

Improvements in polymerase chain reaction technique allow sensitive detection of plasmodium sequences in blood specimens with minimal interference from hemoglobin and other proteins in the original sample (21).

Clinical Characteristics of Severe Malaria

Show him death, and he'll be content with fever.
Persian proverb

The *Epidemics* of Hippocrates furnish a vivid early case report of algid (cold) malaria, one of the classic fatal forms:

Case I

Philiscus lived by the wall. He took to his bed with acute fever on the first day and sweating; night uncomfortable.

Second day. Generalized exacerbation,....A restful night.

Third day. Early and until mid-day he appeared to have lost the fever; but toward evening acute fever with sweating; thirst; dry tongue; black urine. An uncomfortable night, without sleep; completely out of his mind.

Fourth day. All symptoms exacerbated; black urine; a more comfortable night, and urine of a better colour.

Fifth day. About mid-day slight epistaxis of

> unmixed blood....A distressing night, snatches of sleep, irrational talk; extremities everywhere cold, and would not get warm again; black urine; snatches of sleep towards dawn; speechless; cold sweat; extremities livid. About mid-day on the sixth day the patient died. The breathing throughout, as though he were recollecting to do it, was rare and large. Spleen raised in a round swelling; cold sweats all the time. The exacerbations on even days (22).

On April 1, 1990, an 18-year-old woman from Sierra Leone presented in coma at Presbyterian Hospital of Dallas 6 d after she had arrived in the United States. A 2-3-week history of headaches followed by fever, nausea, and vomiting in the days prior to admission was obtained from the patient's mother. The patient's mental status had gradually deteriorated on the morning of admission. The past medical hsitory was remarkable for prior malaria as recently as 2 months earlier. A peripheral smear showed an estimated 20% *P. falciparum* parasitemia. Lumbar puncture revealed an opening pressure of 550 mm CSF. The patient was treated with intravenou quinidine with electrocardiographic monitoring, exchange transfusion, anticonvulsants, frequent blood glucose determinations, ventilatory support, and pressors. She never regained consciouness and was pronounced dead on the third hospital day.

Cerebral malaria was diagnosed in 61 (10%) of 586 children admitted to a district hospital in Kenya with a primary diagnosis of malaria. There were 12 deaths for a case-fatality rate of 20%. All deaths occurred in children with closed fontanelles. All fatal cases occurred in the 29 children who presented with or who subsequently developed signs of central or uncal herniation (case-fatality rate = 41%), with the other 32 children surviving ($X^2 = 16.5$, $p < 0.001$). In nine fatal cases signs of uncal herniation or rostrocaudal deterioration were observed after admission. Forty-seven children with cerebral malaria had lumbar punctures performed on admission; in 26 reliable measurement of the opening pressure was obtained. Cerebrospinal fluid pressure was high in all patients, with a mean of 22.6 cm. Mean cerebral perfusion pressure (52.6 mm Hg) was low. Reverse flow in the middle cerebral artery throughout diastole was recorded in the one fatal case among ten studied by transcranial doppler ultrasound. These findings may not be directly applicable to adults, however (23).

Survival in cerebral malaria can be at the price of catastrophic residual neurologic defit. A patient presenting to London's Royal Free hospital with 35% parasitemia with *P. falciparum* was left with decerebrate spasticity and coma vigile despite rapid reduction in parasitemia and avoidance of hypoglycemia, hypoxia, and seizures (24). Nonetheless, Wyler has cautioned against

premature acceptance of a bleak prognosis in patients with cerebral malaria (25).

Attention has been drawn to the possible contribution of host cytokines to the pathophysiology as well as the symptomatology of malaria (26). Among children with malaria who survive the first 20 h after initiation of therapy, persistent elevation of levels of tumor necrosis factor (TNF) and of interleukin-6 (IL-6) in plasma correlate with each other and with ultimately fatal outcome. No abnormalities in plasma concentrations of interleukin-1 (IL-1) and interferon gamma were found (27). The possible roles of other cytokines and of downstream mediators of inflammation, including platelet-activating factor and prostacyclins, remain to be elucidated, and the hypothetical therapeutic benefits of therapeutic intervention by measures to block the activity of these endogenous products remain to be demonstrated.

The suggestion has been made that local release of of cytokines including TNF, IL-1, IL-6, and lymphotoxin may occur in vascular beds upon schizogony in sequestered parasitized erythrocytes. Such a process might contribute to the pathogenesis of cerebral malaria even in the absence of concomitant or even prior high levels of these inflammatory mediators in the peripheral circulation (28).

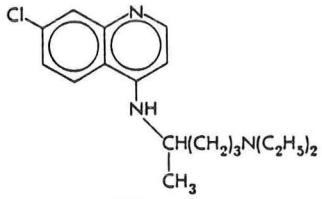
Currently Available Antimalarials

Antimalarial drugs are classified according to the stage of the parasite against which they exert their activity (5). Causal prophylactics prevent the symptomatic erythrocytic stage of the disease through their activity as tissue schizonticides against the initial hepatic forms of the parasite. Other tissue schizonticides act upon the latent hypnozoites of *P. vivax* and *P. ovale* to effect a radical cure of infection, preventing relapses. Most antimalarial drugs are used for their activity as blood schizonticides, acting upon asexual erythrocytic forms. Some drugs may also have gametocytocidal or sporontidical activity. The former would inhibit infection of mosquitoes, and the latter would inhibit the formation of oocysts and sporozoites in the infected vectors. Neither of these categories has intrinsic utility in the management of individual patients.

Chloroquine

Chloroquine (Figure 4) is derived from 4-aminoquinoline (29). Chloroquine cures infections with sensitive stains of *P. falciparum* and *P. malariae* and terminates an acute attack of *P. vivax* or *P. ovale* malaria, but does not eliminate hypnozoites of the latter two species in the liver (4).

Figure 4



Chloroquine

A total therapeutic dose of 25 mg base/kg is administered, either as a 10 mg/kg (typically 600 mg) loading dose followed by 5 mg/kg (300 mg) 6-8 h later and again daily on the next 2 d. A practical alternative is 10 mg/kg qd twice and 5 mg/kg on the third day. Higher doses of chloroquine offer no known advantage in settings of chloroquine-resistant strains (4).

Retinal damage is observed at a cumulative dose in the neighborhood of 1 g/kg. This dose corresponds to 40 therapeutic doses or to about 4½ years' prophylaxis at 300 mg per week. There is much interindividual variation in the dose required to elicit retinopathy (4).

Chloroquine is safely used in pregnancy (4).

Common side-effects include nausea, vomiting, headache, and impaired accommodation. Pruritus of the palms, soles, and scalp is not infrequent in Black Africans and some other ethnic groups. Photodermatitis, skin pigmentation, leukopenia, bleaching of hair, and rare marrow aplasias are also reported (4).

WHO terminology to grade the severity of chloroquine resistance has subsequently been extended to evaluations of other drugs (5). Resistance is said to be at the R I level if treatment of an infected patient with the drug renders parasitemia undetectable for 2 consecutive d, but relapse occurs within 28 d of completion of the treatment course. R II resistance denotes marked diminution of parasitemia for at least 2 d, but without achievement of a subpatent state and with eventual recrudescence. An R III response is no parasitologic response at all, with continuation of the disease as if no treatment had been given. Various degrees of chloroquine resistance in *P. falciparum* have now been reported from all the world's malarious regions with the exception of Mexico, Central America, the Caribbean, and the Eastern Mediterranean (Figure 5) (7).

Unitil recently Guinea-Bissau was one of the few remaining countries in Africa in which chloroquine-resistant *P. falciparum* had not been detected. However, an outbreak of

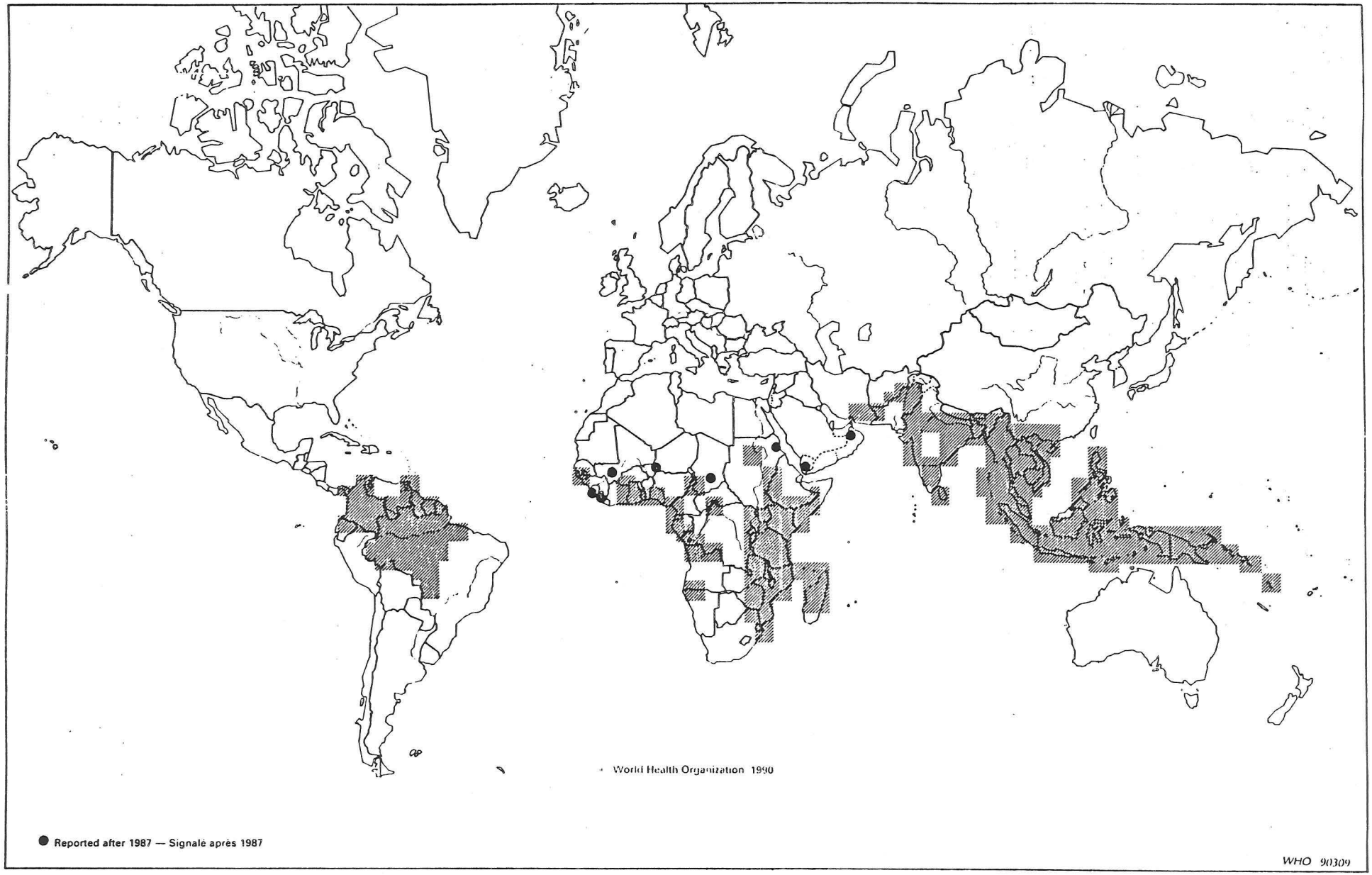
falciparum malaria in five Swedes living in the capital, Bissau, occurred in 1990 in the face of chloroquine prophylaxis documented by adequate blood concentrations of the drug. The cases responded to treatment with sulfadoxine and pyrimethamine (30).

With recognition of the association of chloroquine resistance with the presence of an active pump mechanism for removing the drug from the vacuoles of resistant parasites, much attention has been focused on drugs that can block this mechanism and reverse chloroquine resistance. Among the substances that block active efflux of chloroquine are chlorpromazine, daunorubicin, desipramine, nifedipine, verapamil, and vinblastine. Much work remains before any of these or other agents under study can be seriously considered for therapeutic use in combination with chloroquine in the ill patient. In addition to inherent drug toxicities, concerns about additive or synergistic cardiotoxicity with chloroquine and interference with normal distribution and disposal of chloroquine in the host must be addressed (4).

Chloroquine has inhibitory effects on thymidine uptake on GM-CSF-stimulated human marrow cells cultured *in vitro,* but this finding is of unclear clinical significance (31).

Figure 5

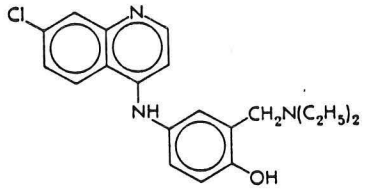
Areas where chloroquine-resistant *Plasmodium falciparum* has been reported



Amodiaquine

Amodiaquine (Figure 6), like chloroquine, is a 4-aminoquinoline derivative (29). Amodiaquine offers little therapeutic advantage over chloroquine in infections resistant to the standard drug. Reports of severe adverse reactions, principally toxic hepatitis and agranulocytosis, with an estimated attack rate of 0.05%, have reduced enthusiasm for the drug. Death is estimated to occur in 1 in 15,000 users (4).

Figure 6

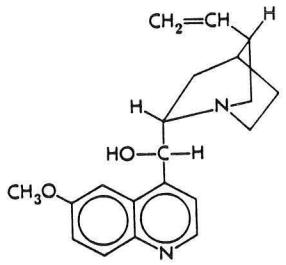


Amodiaquine

Quinine

Quinine (Figure 7) is a natural product that has been described as "a template for the development of synthetic antimalarials and from the 1930s onwards synthetic analogues" (29).

Figure 7



Quinine

The English word is derived from the Spanish *quina,* or cinchona bark, apparently a contraction of *quinaquina* or *quinquina* from the original Quechua word, perhaps in imitation of *Cinchona.* Who does not recall with fondness the story of Doña Francisca Henríquez de Ribera, Countess of Chinchón and Vicereine of Peru, who introduced the marvelous Jesuits' bark or Peruvian bark to Europe in the Seventeenth Century, thereby earning herself Linnean immortality?

Quinine is a rapidly-acting schizonticide administered as 10 mg salt/kg po or parenterally tid for up to 10 d. Cinchonism, with giddiness, transient hearing loss, tinnitus, and visual disturbances, is common at therapeutic blood levels (5-10 mg/l). Anorexia, nausea, vomiting,

abdominal pain, and diarrhea are also seen. Atrioventricular conduction disturbances may be observed. Rarer side-effects include urticaria, asthma, angioedema, thrombocytopenia, and hemolysis and require immediate discontinuation of the drug. A 10% attack rate of drug fever, generally beginning on day 8, was observed in U.S. forces in Vietnam (4).

Therapeutic doses of quinine may not be contraindicated in pregnancy (4).

Optimal therapy includes a 2-4 d course with coadministration of another schizonticide, either pyrimethamine/sulfadoxine or tetracycline (e.g., 250 mg po q6h for 7 d). Longer quinine courses may be substituted for multiple-drug therapy with contraindications to the supplemental drug or drugs, as with tetracycline in young children or pregnant women, or when resistance to the agents is suspected (4).

Hall, at London's Hospital for Tropical Diseases, cautions against quinine toxicity at plasma concentrations above 10 mg/l. He advocates an initial dose of quinine dihydrochloride of 10 mg/kg (up to 600 mg) in 250 ml NS over 4 h q12h, keeping fluid input <2000 ml per 24 h. (Patients who are ambulatory with 1% or less parasitemia and fever below 39°C may be treated with oral quinine). In patients with anuria or jaundice (most frequent with high levels of parasitemia) the dosing interval is extended to q24h. Exchange transfusion (approximately 6 units) is employed if parasitemia exceeds 30% and in many patients in coma with lesser parasitemia. Hall also advocates a controlled trial of exchange transfusion for parasitemia of 5-30%. He suggests that removal of parasitized cells would counterbalance loss of quinine by phlebotomy (32).

Quinine resistance has been documented in Thailand, where poor compliance with extended unsupervised regimens may have led to selection of tolerant strains. This development may also compromise the efficacy of mefloquine (4).

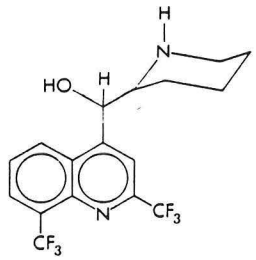
Quinidine

Quinidine is the dextrorotatory diastereoisomer of quinine. In 1989 malaria specialists at CDC reported on 14 patients seen in the United States with severe falciparum malaria who were entered into a protocol of therapy with intravenou quinidine by constant infusion after an initial intravenous loading dose. Nine of the patients also received exchange transfusions. Eleven of the 14 patients survived, and the regimen was regarded as safe and more practicable than one demanding distribution of parenteral quinine from central repositories (33).

Mefloquine

Mefloquine (Figure 8) is a quinolinemethanol related to quinine. A long-acting schizonticide, it has activity against falciparum strains resistant to 4-aminoquinolines, pyrimethamine/sulfadoxine, and quinine (4).

Figure 8



Mefloquine

Biweekly mefloquine prophylaxis (after a loading interval) was only 63% more effective than was chloroquine in preventing *P. falciparum* infections in Peace Corps volunteers in West Africa. Prophylaxis failures occurred in the second week of the two-week cycle and were not seen in volunteers at times in which blood concentrations of the drug were above 400 ˙g/l. Side effects were no more common than among those volunteers who had elected to use chloroquine instead (34).

In 1984 mefloquine was introduced in a fixed-ratio combination with sulfadoxine and pyrimethamine (MSP) to trat falciparum malaria in the Karen minority on the Thai-Burmese border. A study in 1986 showed greater than 98% efficacy with a single dose of mefloquine 15 mg/kg, sulfadoxine 30 mg/kg, and pyrimethamine 1.5 mg/kg. The results of a follow-up study conducted in the same population during the first half of 1990 have just been published this month. There was a 29% failure rate overall at 28 days, and in children under six years old only half of the cases were cured. Recrudescence occured in 27% of patients retreated with 25 mg/kg of mefloquine after early treatment failure on the initial regimen. Serum mefloquine concentrations were higher and elimination half-lives were longer in patients with treatment failure than in successfully treated control subjects (1).

No inhibitory effect of mefloquine myelopoiesis *in vitro* was seen at pharmacologic levels of the drug (31).

Treatment with two doses of mefloquine of a patient seven months after he had taken the drug prophylactically was followed by marked neutropenia (220/µl), which resolved

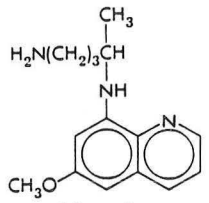
after 10 d. The sequence of events suggested immune-mediated destruction of leukocytes (35).

A single case of Stevens-Johnson syndrome was reported in a woman who developed mucosal and skin lesions within days of taking her first prophylactic dose on the eve of a trip to Southeast Asia (36).

Primaquine

Primaquine (Figure 9) is derived from 8-aminoquinoline (29). This drug is used for radical cure of relapsing vivax or ovale disease. It is not administered to pregnant women because of the risk of teratogenicity (4).

Figure 9



Primaquine

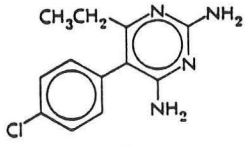
Tetracyclines

Tetracycline and doxycycline are effective blood schizonticides, but their slow onset of activity limits their usefulness in therapy to the latter part of a treatment course (4).

Antifols

The combination of pyrimethamine (Figure 10) and the long-acting sulfonamide sulfadoxime has been used for therapy of chloroquine-resistant falciparum malaria, particularly when presumptive treatment is required. An unacceptably high attack rate of severe skin reactions has led to discontinuation of the use of this combination as a prophylactic regimen. Resistance to the combination is particularly widespread in Thailand (4).

Figure 10



Pyrimethamine

Like pyrimethamine, trimethoprim is an inhibitor of dihydrofolate reductase. *P. falciparum* parasitemia was

abolished at 14 d in all of 44 children in Malawi available for follow-up after a 5-d course of trimethoprim 4 mg/kg and sulfamethoxazole 20 mg/kg bid. Although the required duration of therapy is a disadvantage, this combination is effective in areas in which malaria is not resistant to folate antagonists (37).

Trimethoprim/sulfamethoxazole treatment for an erroneous diagnosis of urinary tract infection temporarily suppressed the manifestations of falciparum malaria in a patient who contracted the disease near an airport in Switzerland (12).

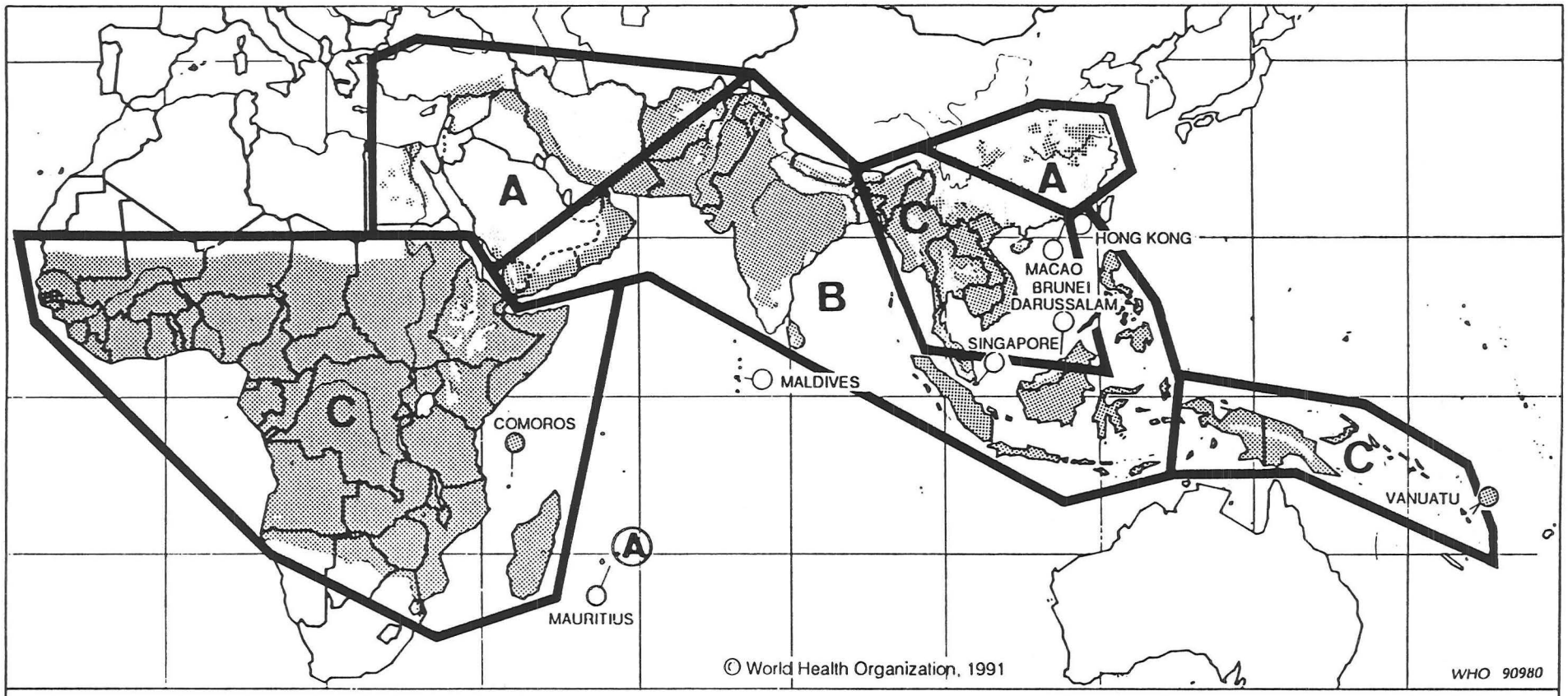
Prophylaxis

Prophylaxis for residents of holoendemic areas is generally restricted to certain groups at highest risk--particularly young children and pregnant women. Most adults develop some degree of active immunity as long as they reside in the area.

The need for malaria prophylaxis by a traveler depends upon the details of the itineray planned (Figures 11 and 12).

Figure 11

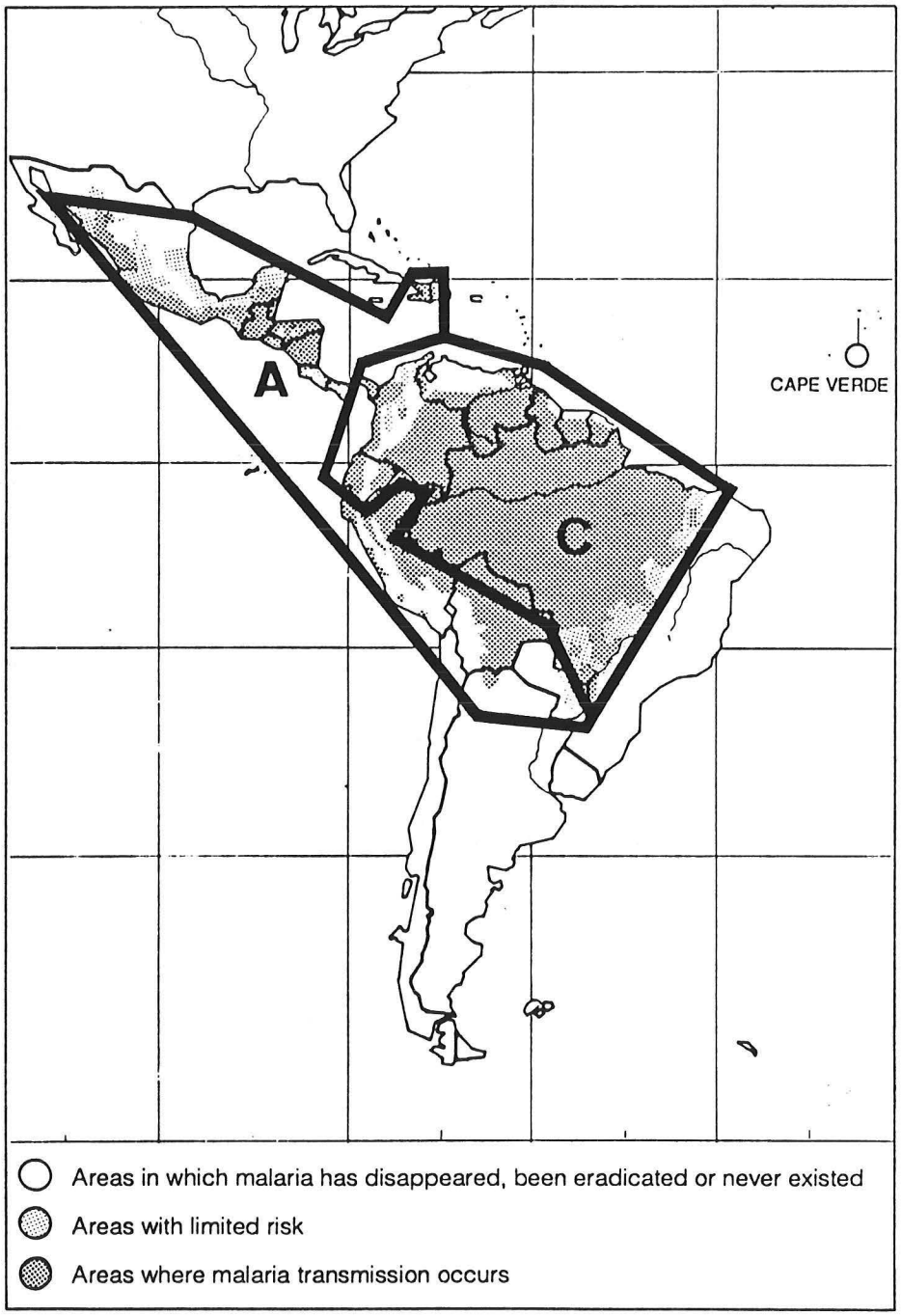
RECOMMENDATIONS FOR MALARIA DRUG PROPHYLAXIS BY AREA — 1991



Zone	Characteristics (for details by country, see yellow pages)	Recommendations concerning prophylaxis and/or stand-by treatment (see Table 3 for dosages/regimens; see Table 2 for adaptation of recommendations to individuals)
A	In zone A, risk generally low and seasonal; no risk in many areas (for example urban areas). *P. falciparum* absent or sensitive to chloroquine.	*either:* chloroquine prophylaxis without stand-by treatment *or* (in case of very low risk): no prophylaxis, with chloroquine stand-by treatment (to be used only when prompt medical attention is unavailable)
B	Low risk in most of the areas of zone B. Chloroquine, with or without proguanil, will protect against *P. vivax;* it may fail to prevent infection with *P. falciparum*, but may still alleviate the severity of disease.	**prophylaxis:** chloroquine + proguanil *or:* chloroquine alone (if proguanil is not available) *or:* (in case of very low risk): no prophylaxis **Carry one of the following for stand-by treatment** (to be used under medical guidance or when prompt medical attention is not available): quinine *or* sulfadoxine–pyrimethamine *or* sulfalene–pyrimethamine *or* mefloquine *or* halofantrine
C	In Africa, risk high in most areas of zone C, except in some high-altitude areas. Risk low in most areas of this zone in Asia and America, but high in parts of the Amazon basin (colonization and mining areas). Resistance to sulfadoxine–pyrimethamine common in zone C in Asia, variable in zone C in Africa and America.	**prophylaxis:** mefloquine *or:* doxycycline *or:* chloroquine + proguanil (if mefloquine and doxycycline are unavailable or contraindicated) *or:* (in case of very low risk): no prophylaxis **If no prophylaxis or prophylaxis with chloroquine + proguanil, carry one of the following for stand-by treatment** (to be used under medical guidance or when prompt medical attention is not available): quinine *or* mefloquine *or* halofantrine

Figure 12

Recommendations for Malaria Drug Prophylaxis by Area - 1991



A questionnaire survey of European and North American travelers departing Nairobi Airport in September 1987 revealed that although 97% of respondents used one or more

measures to prevent malaria, only 52% reported regular adherence to a chemoprophylactic regimen during their stay in Kenya and for four weeks thereafter. Compliance with chemoprophylaxis and adherence to antimosquito precautions varied with the origin of the traveler, with visitors from the United States most likely to report compliance (Table 7) (38).

Table 7

Compliance with Malaria Prophylaxis
and Antimosquito Precautions
in North American and European visitors
Departing Nairobi on Scheduled Flights, 1987

Country or region of residence	Proportion using prophylaxis regularly plus two or more antimosquito precautions
USA	58.6%
Canada	51.8%
Federal Republic of Germany	48.4%
United Kingdom	42.9%
Italy	36.7%
France	32.6%
Netherlands	32.1%
Scandinavia	29.2%
Overall	48.0%

Certain categories of visitors to Kenya, particularly these traveling on business, were unlikely to adhere to preventive measures (Table 8) (38).

Table 8

Groups of North American and European Visitors
Departing Nairobi on Scheduled Flights
Who Reported Little Compliance
with Malaria Prophylaxis
and Antimosquito Measures, 1987

Group	Proportion using prophylaxis regularly plus two or more antimosquito precautions
Business travelers	26%
Persons visiting friends and relatives	32%
Travelers staying >4 weeks	38%
Travelers under age 40	43%

Among 5216 respondents, 68 different chemoprophylactic regimens were reported. Compliance with chomoprophylaxis was low in visitors taking proquanil and in several other groups (Table 9) (38).

Table 9

Risk Factors for Poor
Compliance with Chemoprophylaxis
During and After Travel to Kenya
Among North American and European Visitors
Departing Nairobi on Scheduled Flights, 1987

Risk factor	Proportion reporting compliance
Proguanil users	31%
Persons visiting friends and relatives	37%
Travelers staying >4 weeks	39%
Travelers experiencing adverse reactions	40%
Young travelers from the United Kingdom	43%

A survey of Western European travelers returning from Kenya or West Africa to Switzerland on fights of Swissair or either of two charter companies was conducted in 1985-1988. Travelers had been well informed about the existence of a risk of malaria (99.0% of resondents), and 97.6% had used chemoprophylaxis, 94.1% regularly. Howver, only 55.4% had

been fully compliant with their regimens while in Africa and during their return. Furthermore, only 55.6% had employed measures to prevent mosquito bites (39).

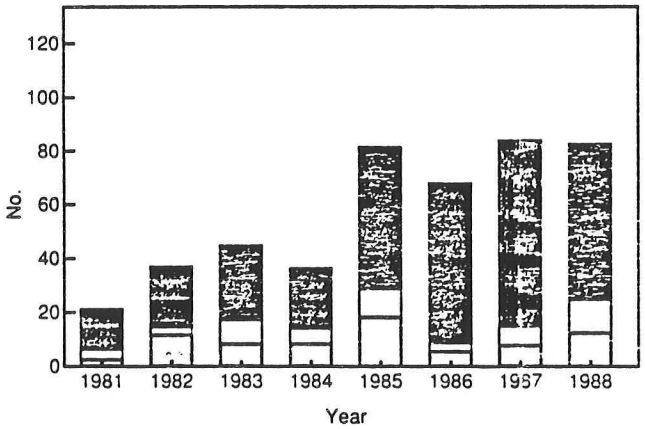
Four fatal cases of falciparum malaria were reported in this study, all in travelers taking chloroquine 300-450 mg weekly. In both East and West Africa this dose had no protective efficacy in comparison with no chemoprophylaxis whatsoever. Partial efficacy was seen with higher (600-750 mg) weekly doses. In contrast, mefloquine was highly effective and well tolerated as a prophylactic regimen at 250 mg weekly. However, 28% of travelers who took 750 mg for presumptive self-treatment after pyrimethamine/ sulfadoxine prophylaxis developed vertigo, nausea, and other side effects, often requiring one or more days of bed rest to recover (39).

Two travelers who had contracted falciparum malaria in Kenya died back in Switzerland on the same day in January 1990. One had delayed consulting a physician and the other was simply found dead at home. Neither of the deceased was thought to have used chemoprophylaxis (40).

National authorities reported five deaths in Canadian citizens in 1989 as a result of falciparum malaria contracted in East and Central Africa. Omitted or prematurely terminated chemoprophylaxis, delay in diagnosis, and delay in therapy were common themes. Canadian surveillance data indicate both a relative and an absolute increase in incidence of falciparum malaria seen in Canada in recent years (41).

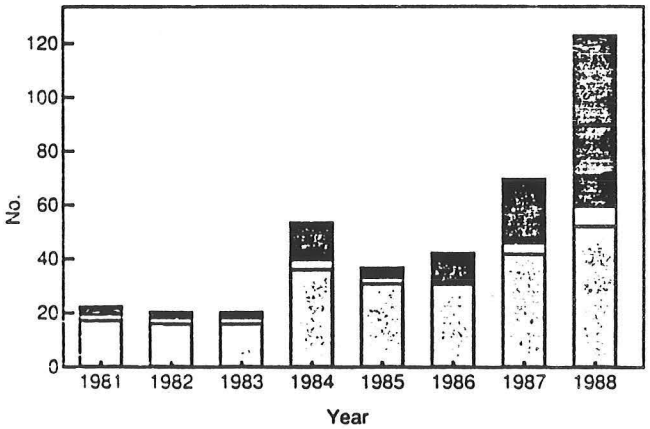
During the 1980s there was an increase in the number of cases of falciparum malaria in travelers from the United States to West Africa. Most cases among travelers to East Africa occurred despite chemoprophylaxis (Figure 13).

Figure 13



Plasmodium falciparum infections acquired by US travelers to East Africa from 1981 through 1988. Solid bars indicate chloroquine; open bars, other drug; and shaded bars, no chemoprophylaxis.

Figure 14



Plasmodium falciparum infections acquired by US travelers to West Africa from 1981 through 1988. Solid bars indicate chloroquine; open bars, other drug; and shaded bars, no chemoprophylaxis.

Many cases acquired in West Africa occurred in travelers who had not employed chemoprophylaxis (Figure 14) (42).

The difference in the proportion of cases occurring in patients not on prophylaxis was in part a function of the difference in the populations of travelers from this country to East and West Africa. Travelers from the United States to East Africa were predominantly adult tourists. Those going to West Africa were relatively young and often were visiting friends and relatives there (Table 10), two characteristics previously associated with omission of chemoprophylaxis (42).

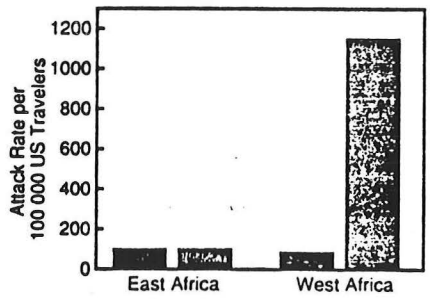
Table 10

Characteristics of US Travelers Who Acquired *Plasmodium falciparum* Infections in East and West Africa From 1986 Through 1988

Characteristics	Infections: East Africa, No. (%) (N = 238)	Infections: West Africa, No. (%) (N = 241)	χ^2 Test *P* Value
White	220 (92)	107 (44)	<.01
Age <10 y	10 (4)	45 (19)	<.01
Purpose of travel			
Tourism	131 (55)	22 (9)	<.01
Visit friends and relatives	5 (2)	81 (34)	...
Missionary	50 (21)	26 (11)	...
Business	27 (11)	19 (8)	...
Used chemoprophylaxis	216 (91)	102 (42)	<.01

In addition, the high prevalence of prior chemoprophylaxis in visitors to East Africa reflected the loss of efficacy of chloroquine in that area, whereas protection with that drug could still be demonstrated in the Western portion of the continent (Figure 15) (42).

Figure 15



Attack rates of *Plasmodium falciparum* per 100 000 US travelers to Africa in 1986 and 1987. Solid bars indicate chloroquine; shaded bars, no chemoprophylaxis.

In February CDC announced a change in the prophylactic mefloquine regimen for travelers to areas with chloroquine-resistant *P. falciparum*. Current recommendations call for 250 mg po to be taken one wk before arrival in the malarious area and then continued weekly throughout the period of stay and for 4 wk after departure. Contraindications to prophylactic mefloquine include known hypersensivitivy to the drug, weight less than 15 kg, pregnancy, use of β-adrenergic blockers, a history of epilepsy or psychiatric disease, and a need to carry out activities (such as piloting an aircraft) that require fine coordination and spacial discrimination (43).

Alternative regimens in the presence of a contraindication to mefloquine include daily doxycycline or chloroquine, but not both. Travelers electing the chloroquine regimen should also carry a treatment dose of pyrimethamine/sulfadoxine to be used if medical care is not promptly available (43).

When mefloquine is locally unavailable it may be purchased with a valid prescription from the United States at the Frankfurt and Paris (Charles de Gaulle and Orly) airports. The drug is also available, but only with a local prescription, at London's Heathrow and the Brussels airport pharmacy. Travelers transiting Amsterdam, Rome, or London's Garwick should not expect to obtain the drug there (43).

Therapy

Doubtful delay is worse than any fever.
Henry Constable, *Sonnets to Diana*

In malarious areas patients often present for medical care after having attempted self-medication, creating the potential for drug toxicity if loading doses of antimalarials are then prescribed. Since travelers who develop malaria after departing areas at risk may have had access to drugs for prophylaxis or treatment, a history of recent medication should carefully be sought before initiating therapy when the diagnosis is suspected, even in temperate areas (4).

Self-administration of antimalarial therapy in the 24-36 h prior to presentation poses the greatest risk of cumulative toxicity if loading doses are then administered. Parasitemia detected 3-7 d after medication raises the possibility of infection with a drug-resistant strain (4).

Last month CDC discontinued provision of parenteral quinine dihydrochloride for the treatment of severe falciparum malaria. Instead, a regimen of intravenous quinidine gluconate in an intensive care unit is

recommended. A loading dose of 10 mg (6.2 mg base)/kg over 1-2 h should be followed by a constant infusion of 0.02 mg/kg/min (44).

Parenteral quinidine therapy is indicated if the patient is vomiting and cannot retain oral drugs, if there is evidence of cerebral malaria, or if greater than 5% parasitemia is documented. Plasma quinidine levels above 6 mg/l, QT prolongation beyond 0.6 sec, or QRS widening of more than 25% from the baseline duration require slowing or suspending the infusion. Parenteral therapy should be continued until oral therapy is tolerated and until parasitemia is below 1%; this will generally occur within 2 d. Oral quinine is continued for a total of 3-7 d to be followed by a 7-d course of tetracycline (45).

Investigational Antimalarials

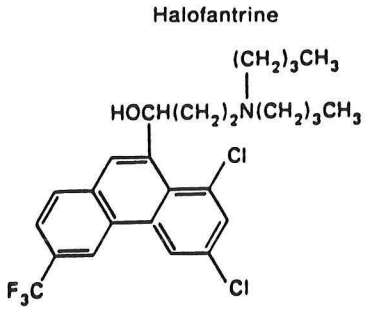
Fluoroquinolones

The quinolone antibacterial drugs were first synthesized in an effort to develop products with antimalarial activity, and the recognition of their greater activity against prokaryotes saved them from obvlivion. *In vitro* activity against *Plasmodium spp.* has been recognized, though, and in 1989 norfloxacin was reported to be efficacious against falciparum malaria in a small series reported from India (46). A more recent report on pefloxacin against falciparum malaria in Madagascar was less encouraging, however, despite the presumption that the pharmacokinetics of that fluoroquinolone should give it an advantage over norfloxacin (47).

Halofantrine

The phenanthrenemethanol halofantrine (Figure 16) is used in France and in Francophone Africa against chloroquine-resistant and antifol-resistant falciparum infection. Is future is clouded by concerns about cross-resistance with mefloquine-insensitive strains (4).

Figure 16



Artemisia derivatives

Artemisinin (Figure 17), or *chinghausuh* (Communist *qinghaosu*), is an endoperoxide sesquiterpene lactone isolated from the Chinese medicinal herb *Artemisia annua* L. (Chinese *chinghau*). Our own sagebrush belongs to the same genus. Artemether and sodium artensunate are synthetic modifications of the nautral product with more favorable pharmacokinetics (29).

Figure 17

Artemisinin is a nontoxic product with broad activity against the erythrocytic, but not the tissue stage of *Plasmodium spp.* References to the antimalarial activity of *A. annua* date back to Han Dynasty accounts. Artemisinin acts more rapidly than do chloroquine and quinine, with efficacy extending to cerebral malaria and to chloroquine-resistant *P. falciparum* infections). Studies in China revealed 100% cure rates in 1511 cases of infection with *P. vivax* and in 558 cases of infection with *P. falciparum.* One shortcoming was a relatively high attack rate of short-term relapse (Tables 11 and 12) (48).

Table 11

Artemisinin Therapy of Vivax Malaria

Formulation	Cases	Interval until fever subsided: range of averages (h)	Interval until clearance of asexual parasites: range of averages (h)	Recrudescence within one month	
				Cases	Proportion
Tablets	128	21.0-33.3	18.0-39.6	128	31.3%
Oil	318	20.0-30.0	22.0-32.1	213	18.8%
Oil suspension	132	21.9	28.3-48.0	114	13.2%
Water suspension	160	35.0	30.0-47.9	160	8.7%

Table 12

Artemisinin Therapy of Falciparum Malaria

Formulation	Cases	Interval until fever subsided: range of averages (h)	Interval until clearance of asexual parasites: range of averages (h)	Recrudescence within one month	
				Cases	Proportion
Tablets	83	34.3-45.8	37.0-41.3	60	85.0%
Oil	223	11.4-67.0	25.3-70.8	140	25.7%
Oil suspension	40	30.6-31.2	33.9-40.6	38	10.5%
Water suspension	181	34.7-44.5	46.4-55.1	83	13.3%

Future Directions

> Here lies a lady of beauty and high degree.
> Of chills and fever she died, of fever and chills,
> The delight of her husband, her aunts, an infant of three,
> And of medicos marveling sweetly on her ills.
> John Crowe Ransom, *Here Lies a Lady*

Numerous other drugs, including trioxanes, tetraoxanes, peroxides, Mannich bases, benflumethol, hydroxypiperaquine, hydroxynaphthoquinones, 8-aminoquinolines, pyridinemethanols, and acridinones are at various stages of evaluation or reassessment (4).

Medicinal plants used as traditional antimalarial remedies throughout the tropics have only begun to be assessed as sources of additional antiplasmodial compounds. Particular attention has been given to certain naturally-occurring alkaloids and terpenoids, but naphthoquinones, chalcones, and flavonoids have also been objects of interest (29).

Conclusions

> After life's fitful fever he sleeps well....
> William Shakespeare, *Macbeth, III, i*

Chloroquine is still an excellent prophylactic and therapeutic agent, but progress on combinations with agents to reverse chloroquine-resistance is eagerly awaited.

Oral quinine remains the drug of choice for most chloroquine-resistant falciparum infections, although quinine-resistant strains are a mounting concern. Intravenous quinidine should be used for severe cases. Antifols and tetracycline have a role in the latter stage or therapy.

Prophylaxis against chloroquine-resistant infection is a growing problem. Mefloquine is usually the drug of choice when it is available. Doxycycline is sometimes a necessary alternative. In some instances provision for presumptive self-treatment will be required. Some persons, particularly the elderly, young children, and pregnant women, should probably avoid travel to areas with drug-resistant falciparum disease. Measures to avoid mosquito bites remain very imporant.

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