CHEMOTHERAPY OF MALARIA[1]

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Periodic fevers, undoubtedly of malaria, have been known and referred to for thousands of years. Although the incidence of the disease has varied in a given locality with time, periodic fevers had been reported from China and India through the Middle East well into the Mediterranean region for several millenia (1). Hippocrates, astutely recognizing the various types, classified intermittent fevers as being quotidian, tertian, or quartan. The association of the disease with swamps and marshlands was clearly seen even then, although it was widely believed that the noxious air in these areas caused the disease, hence the word "malaria" ("mala" = bad, "aria" = air).

That the disease has many times changed the course of history cannot be denied. Armies have been decimated (2); rulers of countries and leaders of major religions have been killed by malaria (3). A turning point in therapy of malaria in Europe was reached in 1632 with the successful treatment of Cardinal Juan di Luigi with cinchona bark brought from Peru. This efficacious remedy, in which quinine is the active ingredient, has enjoyed varying degrees of popularity for two centuries throughout much of the world ruled by European nations. By the mid nineteenth century, cinchona bark was accepted as the effective antimalarial that it is, for by then most of the religious objection to the "popish powder" was overcome. In addition, the influence of physicians who had been unsuccessful in treating malaria with cinchona was declining by that time.

In 1820 Pelletier and Caventou isolated quinine from cinchona bark (3). During the nineteenth century quinine finally became the drug of choice and remained so for the first decades of the twentieth century (3, 4). In fact, quinine had proven such a good suppressant for malaria that it is unlikely that a brisk synthetic antimalarial program would have started so early in this century had not all quinine sources been cut off from Germany during World War I. This spurred German chemists to initiate a continuing program that enabled them to synthesize pamaquine in 1926 (5), quinacrine in 1930 (6), and chloroquine in 1937 (7). Interestingly, the total synthesis of quinine was not reported until 1945 (8).

Meanwhile, other antimalarials were being developed during the 1940s and early 1950s: chlorguanide (9), pentaquine (10–12), primaquine (11, 13), and pyrimethamine (14). With this battery of agents, effective as suppressive and

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curative drugs, the malaria picture looked quite bright. However, it did not take very long for drug resistant strains to emerge (15). New programs were started to develop antimalarials effective against these resistant strains and old programs were revitalized. Some of these newer studies will be dealt with later in this review, but in order to understand more fully the differential effects of these compounds we shall briefly discuss the malarial parasite itself.

Life History of the Parasite

Four protozoan species cause naturally acquired human malaria: *Plasmodium falciparum*, *P. vivax*, *P. malariae*, and *P. ovale*. Figure 1 diagrams the life cycles of these species. Although not illustrated, the exoerythrocytic (liver) cycle is similar to the asexual erythrocytic one. Thus, merozoites from the liver invade the red blood cells initiating the erythrocytic cycle. All four species have a primary liver tissue phase, but *P. falciparum* does not have the secondary (persistent) liver tissue phase while the other three do. Thus *P. falciparum* does not cause the type of relapsing attacks found with the other three. Relapses, after a long time period free of erythrocytic forms, should not be confused with the short term attacks due to synchrony of the asexual erythrocytic schizogony cycle. If the cycle is synchronous, fever and other symptoms may display a tertian (48 hour) periodicity with *P. falciparum*, *P. vivax*, and *P. ovale* or a quartan (72 hour) periodicity with *P. malariae*.

Table 1 lists the stage of parasite development affected by drugs, as well as the usual clinical terminology associated with action on each stage. It can be seen that causal prophylaxis and clinical prophylaxis are not synonymous, nor are the terms radical curative and clinical curative synonymous.

TABLE 1. Developmental Forms of Plasmodia in the Human and Terms Used to Describe Drug Action on These Forms

Term	Form	Action
Suppressive	Asexual erythrocytic	Blood schizonticidal
Gametocytocide	Gametocyte	Gametocytocidal
Causal prophylactic[a]	Primary tissue schizont	Primary tissue schizonticidal
Radical curative[b]	Secondary (persistent) tissue schizont	Secondary tissue schizonticidal

[a] In addition, the term "clinical prophylactic" is used to indicate prevention of symptoms by a suppressive agent without necessarily preventing establishment of the exoerythrocytic forms.

[b] In addition, the term "clinical curative" is used to indicate relief of symptoms without necessarily causing complete destruction of malarial parasites in the body.

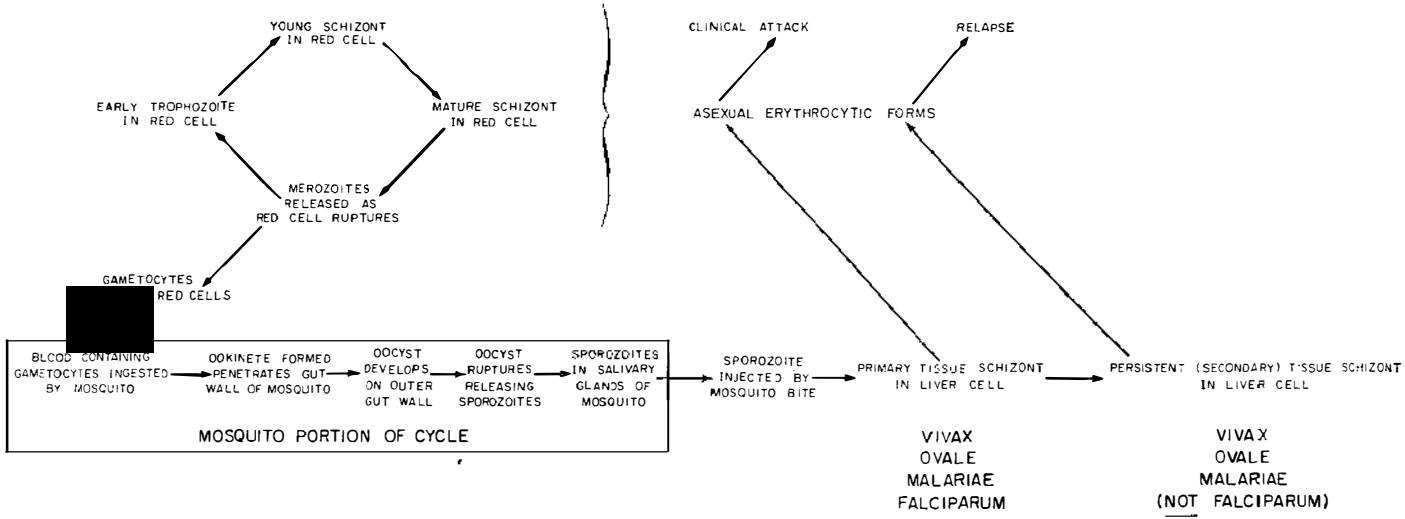

FIG. 1. Life cycle of human plasmodia. Photograph courtesy U.S. Army.

Permutations of actions exist. For example, since *P. falciparum* does not have persisting liver forms to provide a reservoir, complete suppression of asexual erythrocytic forms will eventually eliminate the infection completely from the body. Several drugs render gametocytes noninfective, but do not necessarily destroy them and are thus not classed as gametocytocides. However, since they prevent sporozoite development in the mosquito, they are called "sporontocides."

Obviously, a number of stages during the life cycle of the malaria parasite are available for chemotherapeutic attack. For a number of years potential antimalarials have been winnowed through various biological screens. It is worthwhile to consider some of these and their role in the development of newer antimalarial drugs.

Biological Screens for Antimalarials

A very comprehensive account of both early and more recent screening procedures has been presented by Peters (15). Several merit discussion here, however, either for historical perspective or because of their importance currently for antimalarial development. The first major in vivo screen was devised in Germany by Roehl in 1922 (16). He tested drugs administered orally by gavage in canaries infected with *P. relictum*. His screen led directly to the development of pamaquine by his collaborators in 1926 (17).

Although other avian species and avian malarial parasites have been used, the next burst of activity came during World War II. *P. gallinaceum* in the chick was developed as a test, and this combination was used extensively in the Allied countries (18, 19). This research helped lead to the discovery of chlorguanide and pentaquine (9–12) and the "rediscovery" of chloroquine (7).

Among the problems associated with avian test systems has been the poor correlation between drug effects obtained with avian plasmodia when compared to the eventual results in humans (20). It was therefore of great importance when standardized screens utilizing the newly described *P. berghei* in laboratory mice were fully reported in 1950 (21, 22). Again, the drug was given orally, which unfortunately may have led to discarding poorly absorbed compounds of potential merit.

The most massive antimalarial screening program in history, supported by the U.S. Army Research and Development Command, also has been utilizing *P. berghei* in laboratory mice. In this screen, developed by Rane (23), the candidate antimalarial is administered subcutaneously in peanut oil. Because this test uses severe rapidly lethal infection, one must be careful in analyzing border-line results. In addition, the oil-water partition coefficient of the compound may profoundly affect the results. In spite of possible drawbacks, however, over 180,000 compounds have been tested as of this writing.

Rodent malaria, however, is still not human malaria. Simian malarias have been investigated as models being more closely related to the human varieties. An excellent account of the primate malarias has been recently published (24). The species found to be of greatest utility is *P. cynomolgi* (25) which has been used by Schmidt (26, 27) as a model for *P. vivax* infection. In this screen, infected

rhesus monkeys were orally dosed with the drug. As with all animal screens, many modifications have been made regarding dosing regimen, infecting regimen, etc. (15).

A second simian species, also used in the rhesus monkey, is *P. knowlesi*. This virulent infection resembles *P. falciparum* in man, although therapeutic differences between the two species exist (28). *P. knowlesi* has not been used as extensively as *P. cynomolgi*, however (15).

Possibly the most important development in simian screens was the demonstration that the owl monkey, *Aotus trivirgatus*, could be infected with human malaria (29, 30). The *P. falciparum* infection has been standardized and is currently being used by Schmidt (31) as an important part of the U.S. Army antimalarial program.

The vertebrate in vivo screens are still the most important for antimalarial drug development. However, numerous in vitro and invertebrate in vivo techniques have been devised. These are well discussed by Peters (15).

Development of Plasmodial Resistance to Antimalarial Drugs

A number of reviews have been recently written on the problem of resistance development (15, 32–35) in naturally acquired human infections. This resistance is manifested as a decreased sensitivity of the pathogen to formerly therapeutic doses and regimens of a drug. This change may be so great as to render a drug completely ineffective against that particular new plasmodial strain. Cross-resistance to other drugs related either chemically or by mechanism of action also occurs often.

The activities of the major classes of drugs before resistance development are outlined in Table 2. Unfortunately it has not taken long for drug resistance to occur after widespread use of a given synthetic drug. Chlorguanide-resistant *P. falciparum* was reported by 1949 (36) and chlorguanide-resistant *P. vivax* by 1952 (37). Pyrimethamine resistance was reported by 1954 (38–40). Chloroquine resistance was documented by 1960 and 1961 (41–43). Primaquine resistance, although never a serious problem, was described in 1963 (44). Resistance to sulfones and sulfonamides has been described, with the added danger of cross resistance being discussed (45). Two interesting items on quinacrine resistance have appeared (46, 47), but the plasmodia involved apparently reverted to their original sensitivity and thus have not become a problem.

Quinine has been, and is still being, used with success, but great differences in strain sensitivity have been observed for over sixty years (48). Much more recently, however, a number of quite resistant strains have been isolated from Southeast Asia (49–51). These are usually associated with chloroquine cross-resistance.

Because of the development of resistant strains, as well as the possibility of mixed infections, many current prophylactic and treatment regimens involve combinations of drugs. The sulfones, administered alone and in drug combinations, will be discussed first.

TABLE 2. Original Therapeutic Activity of Widely Used Classes of Drugs Against *P. falciparum* and *P. vivax*[a]

Class (Example)	Form						
	Asexual Erythrocytic[b]		Mature Gametocyte[b]		Primary Tissue[b]		Secondary Tissue
	fal.	viv.	fal.	viv.	fal.	viv.	
Cinchona alkaloids (Quinine)	+	+	−		−		−
9-Aminoacridines (Quinacrine)	+	+		+			
4-Aminoquinolines (Chloroquine)	+	+	−	±[c]	−	−	−
8-Aminoquinolines (Primaquine)	±	±	+	+	+	+	+
Triazines and potential triazines (Chlorguanide)	+	+	+[d]	+[d]	+		
Diaminopyrimidines (Pyrimethamine)	+	+	+[d]	+[d]	+		?
Sulfones and sulfonamides (DDS)	+	±	−	−		−	−

[a] Activity before development of resistance.
[b] Abbreviations are: fal. = falciparum, viv. = vivax.
[c] Probably interferes with gametocyte formation, but doesn't destroy mature gametocytes.
[d] Interfere with mosquito sporogeny, but not gametocyte formation, and are thus termed sporontocides.

SULFONES

The antimalarial properties of sulfones have been known for a number of years (27, 52). It was found that sulfones act mainly on the asexual erythrocytic forms and that vivax infections did not respond as well as falciparum infections (27, 53–58). Activity of sulfones was also shown against *P. malariae* (54).

Diaminodiphenylsulfone.—Unfortunately the sulfones, as exemplified by DDS (4,4′-diaminodiphenylsulfone), do not have a broad range of activity even against *P. falciparum*. DDS has not been found to destroy mature gametocytes or to be sporontocidal (59). In addition, DDS acts slowly when administered during acute falciparum attacks (60, 61). Because of this and the relatively common recrudescences after DDS alone, a number of investigators have suggested using the drug in combination with other antimalarials (55, 62, 63).

One approach has been to use sulfones, which antagonize paraaminobenzoic acid incorporation into folic acid, with dihydrofolic acid reductase inhibitors. The rationale, attacking two points along a crucial metabolic chain, has been widely reviewed (64, 65). Weekly oral doses of DDS, 100 mg, and pyrimethamine, 12.5 mg, were very effective prophylactically in a 1-year study in Nigeria (66). In a separate therapeutic study, 15 Cambodian patients received a single 50 mg dose of pyrimethamine plus either 100 mg DDS daily for 1 or 5 days or 200 mg DDS daily for 1 or 5 days. Thirteen of these patients showed immediate responses but two recrudesced (45). DDS combined with cycloguanil has been shown to protect against falciparum strains resistant to pyrimethamine or chlorguanide but not against vivax strains resistant to either folic acid antagonist (57).

Chemotherapeutically, it was reasonable to try a DDS-pyrimethamine combination with other antimalarials. One of the frequently used oral regimens in Vietnam was concurrently administered quinine sulfate, 650 mg tid for 14 days, pyrimethamine, 25 mg tid for 3 days, and DDS, 25 mg for 28 days (67–70). "Cure rates" of 95% or greater were reported for falciparum malaria, but not all patients could be followed long enough to insure complete absence of later recrudescences. Ten days of quinine sulfate (650 mg tid) could be successfully substituted for the 14-day schedule (71) and the dose of pyrimethamine could safely be lowered to 25 mg bid for 3 days (72). Slightly decreased efficacy was seen when the quinine portion was reduced to 7 days (73).

DDS has been used in combination with drugs other than quinine and pyrimethamine. The history of its development as a chemoprophylactic, administered in conjunction with a chloroquine-primaquine combination, can be readily traced.

Several regimens have been used for malaria chemotherapy in American troops since World War II. Soldiers returning from the Korean conflict received 15 mg of primaquine base (26.5 mg as the diphosphate) daily for 14 days. Concurrently the standard weekly chloroquine dose (300 mg base, 500 mg as the diphosphate) was taken. This regimen was successful in helping to prevent the reintroduction of malaria into the United States (74). Concern over primaquine-induced

hemolysis prompted a series of studies indicating that weekly doses of 45 mg primaquine, even with weekly chloroquine, was a safe and relatively effective regimen against Chesson strain of *P. vivax* (75).

By 1961 the standard chemotherapeutic method was 600 mg chloroquine base plus 15 mg primaquine base the first day with 13 subsequent consecutive days of 15 mg primaquine each. However, a change to weekly administration of a single tablet (termed a C-P tablet) containing chloroquine phosphate (300 mg base) and primaquine phosphate (45 mg base) resulted in a safe, efficacious regimen (76).

Unfortunately, the large scale appearance of chloroquine-resistant *P. falciparum* forced a reevaluation of chemotherapeutic techniques for United States troops (77). It was shown that supplemental daily DDS therapy (25 mg) combined with weekly C-P prevented establishment of *P. falciparum* infection (62). By early 1966 field trials of the daily 25 mg DDS with the routine weekly C-P tablet were begun in Vietnam. Analysis of results indicated significant protection, with malaria attack rates down by 90% in a unit taking DDS compared to otherwise identically exposed units not taking DDS (78, 79).

In addition to prophylaxis, DDS has been used with a chloroquine-quinine combination for the treatment of chloroquine-resistant *P. falciparum*. One hundred fifty-five nonimmune patients with *P. falciparum* infection received quinine sulfate 650 mg tid for 7–14 days with 1.5 gm chloroquine over the first 3 days (600 mg initially, 300 mg each at 6 hr, 24 hr and 48 hr). Of these men 105 also received DDS, 25 mg, daily for 30 days following the chloroquine-quinine regimen. Only 3% of the sulfone-treated patients recrudesced during the follow-up period, whereas 41% of those not receiving DDS recrudesced within 3 weeks (80).

Unfortunately, a number of side effects may be associated with DDS therapy. The most widely known is the hemolytic effect (59). Hemolysis occurs more readily in people with glucose-6-phosphate dehydrogenase (G6PD) deficiency (81, 82), but high doses of DDS will cause hemolysis in humans with normal G6PD levels (83, 84). Methemoglobin production is also seen with DDS, especially at higher doses (81), and in combination with C-P (85, 86).

The most disturbing recent report of DDS toxicity concerns agranulocytosis in 16 United States soldiers on DDS prophylaxis, 8 of whom died of sepsis (87). The question of idiosyncratic reaction to DDS or its possible decomposition products is still unresolved. Certainly a very large number of people have taken the drug without showing this complication. However, scattered reports of agranulocytosis connected with DDS therapy have been published (88–91). Indeed, the use of DDS as a prophylactic for the Australian forces in Vietnam was discontinued in 1970 after two years use (91).

Other sulfones.—As previously mentioned, sulfones other than DDS have been tried against human malaria. Early observations were made on the antimalarial effects of the didextrose sulfonate derivative of DDS (27) and the dextrose diglucoside derivative of DDS (92). The DDS derivatives of greatest

interest today, however, are 4,4′-diformamidodiphenylsulfone (DFD) and 4,4′-diacetamidodiphenylsulfone (DADDS).

DFD, first synthesized in 1938, was shown to have antimalarial properties against avian (93) and rodent (94, 95) strains. The compound is of sufficient interest to have progressed recently to human tolerance and efficacy trials. DFD was shown to be well tolerated orally in single doses of 4800 mg and semi-weekly doses of 3200 mg each in 70 volunteers for up to 9 weeks, except for a marked decrease in hemoglobin in 2 men with G6PD deficiency (96). The same study included interaction of weekly C-P with DFD, 100 mg to 1600 mg, for up to 8 weeks in at least 14 volunteers. A dose-related methemoglobinemia was seen which was more pronounced with DFD plus C-P than with DFD alone.

In prophylactic tests against 5 chloroquine-resistant strains of *P. falciparum*, weekly DFD, 100–1600 mg, plus weekly C-P protected 93 of 99 volunteers. At 200 mg DFD plus C-P weekly, only 4 infections were seen in 118 separate lots of challenges to 38 volunteers (96). In general the results are similar to those obtained in earlier studies on daily DDS plus weekly C-P (61, 62).

An extension of the above studies demonstrated that 100–800 mg DFD plus C-P protected 41 of 45 men from the chloroquine-resistant Vietnam (Smith) strain (97). DFD, 800 mg, weekly with C-P protected all 9 volunteers challenged with the chloroquine-resistant Vietnam (Brai.) strain (97). A second laboratory compared the prophylactic efficacy of DFD and DDS against the chloroquine-resistant Vietnam (Marks) strain of *P. falciparum*. Approximately equal protection was seen among the various treatment groups. Weekly chloroquine, 300 mg, with daily DDS, 25 mg, protected 6 of 8 while the same chloroquine regimen with weekly DFD, 400 mg, protected 5 of 8 volunteers. Weekly C-P plus daily DDS, 25 mg, protected 7 of 8 while all 8 nonmedicated controls contracted malaria (86).

A limited investigation of the suppressive effect of DFD was carried out (96) against both chloroquine-sensitive (Uganda I) and chloroquine-resistant strains of *P. falciparum*. Single oral doses of 400–2000 mg cleared asexual parasitemia in 15 of 23 episodes, but 14 of those 15 recrudesced. However, single oral doses of 400–1600 mg of DFD when combined with oral trimethoprim (100–1500 mg total, divided over 24 hours) cleared all 20 episodes tested, with 9 radical cures (96).

While DFD is being studied as an oral antimalarial, DADDS development has been primarily as a parenteral repository drug. DADDS was reported to have antimalarial activity in animals in 1941 (27), but since this compound was considered toxic, further investigation was put off for some 2 decades. A report in 1965 emphasized that DADDS protected mice for several weeks against *P. berghei* challenge after subcutaneous injection. This protection was not as effective for the DDS-resistant line as the parent strain (98), however. Intramuscular dosing of rhesus monkeys protected them for 9–36 weeks against *P. cynomolgi* challenge. Attempted therapy of established *P. cynomolgi* infections with DADDS intramuscularly was disappointing, however (98), in that only slow suppression of parasitemia was seen.

More important was the repository protection of a 1:1 mixture of DADDS

and cycloguanil pamoate (98). When injected subcutaneously, the mixture (called CI-564) had broader repository action against DDS-resistant or triazine-resistant *P. berghei*. This led to a series of clinical studies on the combination. In Tanzania, the combination was given to school children for protection against *P. falciparum* (99). In all 24 infected children, intramuscular injection cleared all trophozoites within 2 days. Only 11 of 60 children observed for 5 months after injection developed parasitemia.

The following year, a study was published on 28 volunteers exposed to chlorguanide- and pyrimethamine-resistant *P. falciparum* strains (100). CI-564, 5–7.5 mg/kg body weight intramuscularly, protected 8 of 9 men, but this protection lasted less than 70 days. Infections in 15 volunteers cleared in from 3–7 days after injection, but 5 of the cases recrudesced.

Meanwhile, several studies were reported on the use of the combination against *P. vivax*. A single total dose of 450 mg was injected into 27 patrol officers to protect them in New Guinea. Within 8 months of their return to Australia, 10 of the men had suffered vivax malaria attacks (101). In another study (102) 2 volunteers were cured of a chlorguanide-sensitive vivax strain with CI-564 while the same dose of drug could not eliminate a chlorguanide-resistant strain in 2 other volunteers.

Six New Guinea villages were the site of the next reported test of CI-564 (103). Three comparable groups of about 200 people each were given deep intramuscular injection as follows: group 1, CI-564, from 188–450 mg, depending upon age; group 2, cycloguanil pamoate, 140–350 mg, depending upon age, plus a single oral dose of amodiaquine; group 3, DADDS, 90–225 mg, depending upon age. A few subjects reported mild localized reactions, but no systemic toxicity was seen. CI-564 protected against *P. falciparum* for a longer time than either component drug alone, with about 85% protection at 90 days postdose for CI-564 and about 30%–40% protection in the other 2 groups by 90 days. Protection against *P. vivax* was poor with DADDS, being undetectable within 30 days. The other 2 groups had complete protection for 60 to 90 days.

Nine hundred Brazilian children were divided into groups of 300 each (104). One group received ca 7.5–7.9 mg of CI-564 per kg of body weight on days zero, 120, and 240. A second group received the same dose of CI-564 plus a single dose of amodiaquine on days zero, 120, and 240. The third group served as controls. CI-564, either alone or combined with single dose amodiaquine, cleared all *P. falciparum* within 3 days and all *P. vivax* within 7 days. The prophylactic effects were also not different between the 2 treated groups. During the year-long study, 19 children in group one and 18 in group two developed patent infections. This contrasted with 113 control children developing infections during the study. Of the prophylactic failures, 22 were *P. falciparum*, 18 of which occurred 90–120 days after the previous injection. The remaining 39 failures were *P. vivax*, all of which occurred 90–120 days postdose.

The drugs were well tolerated systemically but temporary local reaction was frequently seen. These reactions appeared closely related to the skill of the person administering the injection, however (104). This problem has arisen

before. If the injection of these various repository preparations is not completely intramuscular, painful local tissue reaction with possible abscess and sinus formation may be seen. Thus the best results could usually be obtained by careful injection into the gluteus minimus (105).

Another field trial of CI-564 involved 186 Gambians (106). One group received CI-564, from 176 mg to 450 mg, depending upon age, every 4 months while the other group received the same dosage regimen plus a single oral dose of amodiaquine with each CI-564 dose. It is significant that just 153 volunteered for the second injection and only 106 for the third. Local tissue reaction consisted of tender swelling with 4 cases of suppuration. About 56% of the subjects in both groups had malaria, mainly falciparum, before treatment. These were all fully suppressed. Infection rates were approximately the same with both groups, averaging less than 1% by 60 days after any dose and 7%–13% by 120 days postdose.

Metabolism of sulfones.—A number of recent studies have attempted to link efficacy or toxicity of sulfones with their metabolism. Among the points investigated were methemoglobin production, acute toxicity, acetylation and dealkylation patterns.

The serum obtained from DDS users had been shown to produce methemoglobin in human erythrocytes in vitro (107). The suggestion that a hydroxylamine metabolite of DDS could be causing methemoglobin production was strengthened by observations that the dihydroxylamine derivative caused marked methemoglobin formation in dogs (108). In addition, the monohydroxylamine derivative (DDS-NOH) caused profound methemoglobin formation in erythrocytes in vitro (109). Microsomal systems have since been shown capable of producing DDS-NOH (110, 111). Finally the production of DDS-NOH from DDS has been demonstrated in vivo both in beagles (112) and in humans (113).

It has been established that isoniazide acetylation is under genetic control in humans (114–117) with differentiation into slow or rapid acetylators. Sulfa drugs have also been shown to acetylate under the same type of control (116–119). Recently, a number of studies have established the polymorphic character of acetylation of DDS in man (118, 120–124). No relationship between acetylation capacity and either plasma DDS concentration or half-life could be demonstrated, however (123, 124). Since these determinations often required separation and measurement of small amounts of closely related sulfones, methods to accomplish this have been developed and published (125–131).

Studying the toxicology of DDS from a biochemical approach, another group found that DDS inhibited the oxidation of pyruvate, apparently at steps requiring thiamine pyrophosphate, in rat and mouse tissue (132). This inhibitory effect was consistent with some of the toxic signs seen in these species and resembled those described for thiamine deficiency. The possible relationship was borne out by the twofold decrease of acute DDS toxicity in mice given thiamine hydrochloride.

A number of investigators suggested that derivatized DDS needs to undergo metabolism to unmask at least one primary aminophenyl group for antimalarial

activity to exist. Evidence does indicate that at least DFD and DADDS are metabolized in this manner. Several groups have shown the deformylation of DFD by mammalian liver homogenates (133, 134). Rates differed somewhat between laboratories, with the first reporting guinea pig > mouse > rat and the second reporting guinea pig ≧ human > mouse = rabbit = rat > dog. Studies on enzymatic deformylation of DFD by plasma (129) indicate mouse > rat > guinea pig > rabbit, with no measurable deformylation by either dog or human plasma.

DADDS has been shown by a number of investigators to undergo deacetylation in vivo (129, 130, 135–138). Deacetylation occurs in mouse and humans, where antimalarial activity of DADDS has been found.

The question of intrinsic antimalarial activity of DADDS and DFD has not really been answered. However, since DDS and its metabolites have been seen in vivo after administration of these two sulfones, it is a moot point except where a genetic or acquired inability to metabolize DFD or DADDS properly may occur.

SULFONAMIDES

A very large number of workers demonstrated antimalarial activity of the sulfonamides in animals and humans from 1937 on (139–144). Research continued actively during the decade of the 1940s (27, 145–153) but tended to abate as the newer and more rapidly acting agents became available.

Reports on treatment of human malaria with sulfonamides, either alone or in combination, increased again from 1959 to 1966 (55, 154–159). Since 1966 a large number of studies have been reported, especially on combination therapy. Most, although not all, of the combinations have been with inhibitors of dihydrofolic acid reductase. Thus, as with many sulfone combinations, 2 places along a broad path are blocked at the same time, hopefully synergizing or potentiating the antimalarial effect. The combination studies have been carried out because sulfonamides alone have relatively poor efficacy against *P. vivax*, and activity against *P. falciparum* has tended to be slow, with very variable cure rates. The majority of these reports have centered around two long-acting sulfonamides, sulfalene and sulfadoxine (sulphamethoxine).

Sulfalene (*2-sulfanilamido-3-methoxypyrazine*).—The first two published clinical trials on sulfalene were carried out on 27 and 55 Somali patients, respectively, with acute *P. falciparum* infections (159, 160). Adult doses were approximately 2.5 gm orally once a week, while 1.5–2 gm were the doses for children. All cases were cleared of asexual forms, but, as with other sulfa drugs, no effect was seen on gametocytes. No recrudescences were reported.

Other studies indicated that the response was not as predictable as first thought. In Senegal, ca 100 children received 125–500 mg twice monthly (161) without effect. The same dosage regimen plus 6.2–25 mg pyrimethamine virtually eliminated both *P. falciparum* and *P. malariae* in another 100 children. This unexpected refractoriness to sulfalene was pointed up in another study (162) where only 2 of 5 volunteers receiving 1 gm and 3 of 6 volunteers receiving 2.5 gm were cured of the normally "sensitive" Uganda strain of *P. falciparum*. In contrast, 1 gm of

sulfalene rapidly cured all 7 volunteers infected with the drug-resistant Malayan Camp strain (162). To elucidate this further, the laboratory compared efficacy against the original Uganda strain vs efficacy against the strain after induction of pyrimethamine resistance (163). They found enhanced sensitivity of *P. falciparum* connected with pyrimethamine resistance and postulated a shifting of parasite metabolism to account for it.

Other efficacy studies have been carried out on sulfalene-pyrimethamine combinations with varying results. Lighter infections of *P. falciparum* responded well (164–170) but very heavy infections responded slowly or poorly (166, 168, 169), resulting in death in several cases. In addition, slow or poor response was seen against *P. malariae* (165–167) and *P. ovale* (165).

Sulfalene has also been given clinically with trimethoprim (165, 167, 168, 171–176), another inhibitor of dihydrofolic acid reductase. The combination was usually given as a single oral dose, the ratio of the two compounds being quite variable within and between studies. The strain of *P. falciparum* studied seems more important in determining response than the absolute dose or ratio. For example, complete suppression of parasitemia in all 51 patients treated in West Cameroon was seen within 60 hours after a single oral dose (173). Single oral doses also cured 6 of 6 infected with the sensitive Uganda strain and 10 of 11 infected with the multiresistant Camp strain (171). However, 8 of 12 cases of the Malaya (Poo.) strain recrudesced (172) after a single oral dose. A 3 day dosage regimen cured 5 of 6 Malaya (Tay.) cases, but only 6 of 8 multiresistant Vietnam (Smith) strain patients (175). U.S. soldiers, 26 nonimmune receiving single doses and 10 semi-immune receiving multiple doses, showed recrudescence rates of 23% and 40% respectively (174).

The Smith strain is highly quinine, chloroquine, pyrimethamine, and chlorguanide-resistant (51). In addition, it had only a 75% clearance rate with sulfalene-trimethoprim (175). Interestingly then, 7 of 7 volunteers were cured of Smith strain with sulfalene, 250 mg qid for 1 day, combined with 1.66 gm quinine per day for 14 days (51).

The sulfalene-trimethoprim combination has also been tried against blood-induced *P. vivax* (176). Clinical cures were obtained in all 9 patients with sulfalene, 1 gm single dose, plus trimethoprim, 500 mg daily for 2 or 3 days. Single doses of sulfalene-trimethoprim were curative in only 5 of 12 subjects.

Sulfadoxine

sulfadoxine therapy, without other concomitant drugs, have been reported (57, 155, 157, 158, 177–182). The earliest report, in 1964, indicated that children in Tanzania were completely protected with weekly 500 mg doses (157). Oral sulfadoxine was studied in *P. falciparum* infection with typical results as follows: 22 of 25 semi-immunes responded to single oral doses of 250 mg to 1 gm (155); 1 gm cured 38 of 45 Tanzanians (177); 1–1.5 gm radically cured only 61% of Thai patients (178); in Tanzania doses as low as 25 mg reduced parasitemia by 90% (179); 8 of 9 patients in Malaya were cured by 100 mg, but response was slow (180). Single injections of sulfadoxine, 500 mg to 1 gm, cleared fever and asexual

parasites within 3 days in all 6 infants treated for *P. falciparum* in Upper Volta (181). Gametocytes persisted in spite of the treatment, however. Thus we see the same erratic response against *P. falciparum* as noted with sulfalene.

Single oral doses of 1 gm sulfadoxine failed in 5 of 13 *P. vivax* cases, and response was slow in the patients (180).

As with sulfalene, many studies were carried out in combination with a dihydrofolic acid reductase inhibitor, usually pyrimethamine (66, 157, 158, 177–180, 182–194). The earliest reported human study on the sulfadoxine-pyrimethamine combination was in 1964 (157). Weekly oral doses of 500 mg and 25 mg respectively (500 mg:25 mg) prevented all infection in Tanzanian children. Weekly pyrimethamine alone, 25 mg, could not prevent a 26% attack rate (157). A single oral dose of the combination (500 mg:12.5 mg) cured all 45 falciparum patients treated in another Tanzanian trial (177). One gm of the sulfa plus 50 mg pyrimethamine rapidly cured 17 of 19 Thai patients acutely ill with chloroquine-resistant *P. falciparum* (178). Fifteen U.S. servicemen with falciparum malaria, 10 of whom had recrudesced after chloroquine-quinine therapy, were cured by a single dose of 1 gm:50 mg (183). In the same study, the combination, 1 gm:50 mg, plus 14 days of quinine, 650 mg tid, cured 54 of 55 servicemen.

In Malaya, 49 falciparum infections were treated with varying ratios of the single dose combination (180). Five failures were seen, but even the successful cases responded much more slowly than comparably dosed patients in Tanzania. The same report (180) detailed 2 failures in 14 vivax infections. Slow response was seen, with gametocyte persistence. Thirty-seven semi-immune patients from Cambodia were given various ratios of the two combination constituents (185). All falciparum infections were rapidly cured, while 1 of the 4 vivax cases relapsed.

The combination, 125 mg:12.5 mg or 250 mg:12.5 mg weekly, gave virtually complete malaria suppression in Nigerian children in a 1-year study (66). Before treatment, parasitemia levels were very high, 75% having *P. falciparum* and 2% with *P. malariae.* Untreated controls remained high all year, and up to 25% of the children on pyrimethamine alone, 25 mg weekly, had parasitemia several times during the year.

The oral combination proved safe and effective against *P. falciparum* in another study on Nigerian children (190). The dose ranged from 125 mg:6.25 mg to 1 gm:50 mg, depending upon age. As with other studies in Africa, response of trophozoites was rapid in the 72 children while gametocyte response was slow.

Successful suppression of malaria was seen with very small doses of the combination biweekly in Gambian children (191). Doses as low as 20 mg:1 mg and 20 mg:2 mg cleared existing asexual parasitemia and prevented reappearance of parasites during the 6 month trial. Weekly pyrimethamine alone, 25 mg, did not clear all cases treated.

In Laos (193) the combination was effective, but slow, in suppressing both falciparum and vivax attacks. However, in acute attacks with fever over 38°, quinine, 600 mg tid, was administered concurrently for 7–10 days. The same report also details the complete prophylactic success in 130 adults on weekly doses of the combination, 500 mg:25 mg. Long-term therapy of this type must be monitored

periodically, however, for a follow-up report (194) indicated that leucopenia was seen in 10% of the subjects after 6 months.

Several reports caution against the indiscriminate use of sulfone-pyrimethamine or sulfonamide-pyrimethamine combinations because of possible induction of resistance and cross-resistance. None of 4 patients completely resistant to or recrudesced from prior DDS-pyrimethamine treatment responded to sulfadoxine-pyrimethamine (45). Only 1 of 5 patients who recrudesced from CI-564 therapy was cured by sulfadoxine-pyrimethamine treatment (192). Not only malaria parasites, but also bacteria may become resistant (2).

Sulfadiazine.—Sulfadiazine has been given in combination with pyrimethamine in a number of cases (154, 195–200). The earliest report on the combination was on highly immune Gambian children (154). Single oral doses of either 250 mg:0.01 mg/kg or 500 mg:0.1 mg/kg cleared all trophozoites from 21 children within 72 hours. *P. falciparum*, *P. malariae* and *P. ovale* were all represented in the cases. Neither sulfadiazine nor pyrimethamine alone cleared the asexual forms.

Later studies used multiple doses of the combination. Volunteers were rapidly cured of chloroquine-resistant falciparum by the combination, 2 gm:50 mg a day for 4 days (196). The combination of sulfadiazine, 2 gm a day for 3 days plus pyrimethamine, 50 mg a day for 5 days, slowly cleared but did cure volunteers of multiresistant falciparum (198). The same regimen was successful against the Malayan Camp strain of falciparum (199). Since gametocytes apparently are not affected by this therapy, the authors suggested concomitant primaquine therapy to prevent spread of the strains.

A radical cure was obtained in 57 of 60 nonimmune U.S. soldiers in Vietnam (197). They were given sulfadiazine, 300 mg a day for 5 days, pyrimethamine, 7.5 mg a day for 3 days and quinine, 1950 mg a day for 14 days.

Sulfisoxazole.—Sulfisoxazole has been used in combination with pyrimethamine plus either chloroquine or quinine (70, 201–203). Seventy-six U.S. soldiers were cured of falciparum malaria by the combination plus chloroquine (201). Chloroquine was given, 1 gm immediately, 500 mg at 6 hours, and 500 mg bid for 2 days, a total of 3.5 gm. Pyrimethamine was given, 500 mg immediately, with 25 mg q 8 hr for 10 doses, a total of 300 mg. Sulfisoxazole was given 1 gm qid for 6 days, a total of 24 gm.

In another report 75 U.S. marines received the drugs as follows: Chloroquine phosphate, 1 gm initially and 500 mg q 12 hr for five days; pyrimethamine, 25 mg q 8 hr for 9 doses; sulfisoxazole, 500 mg q 6 hr for 6 days (202). All patients were cleared of blood parasites within 5 days. Importantly, concomitant therapy with either folic acid or folinic acid did not inhibit the antimalarial effect, but did reduce the incidence of anemia and leucopenia, and enhanced favorable reticulocyte and platelet response.

A third report compared chloroquine vs quinine as part of the combination (70). Both groups of falciparum patients received sulfisoxazole, 50 mg q 8 hr

for 6 days, plus pyrimethamine, 25 mg tid for 3 days. One group (117 men) received quinine, 600 mg tid for 14 days; the second group (137 men) received chloroquine, 1 gm immediately and 500 mg bid for 5 doses. Cure rates were 98.3% for the quinine and greater than 94% for the chloroquine groups.

INHIBITORS OF DIHYDROFOLATE REDUCTASE

As previously noted, inhibitors of the folic acid cycle play a very important role in the chemotherapy of malaria. Unfortunately, resistance to these major drugs developed quite rapidly; in some cases to the point where tolerated doses would no longer be efficacious. To circumvent this, these drugs have been used increasingly in combination with other types of compounds. Some of these compounds are discussed in other portions of this review.

The three most important drugs are chlorguanide, cycloguanil, and pyrimethamine.

Chlorguanide and cycloguanil.—Chlorguanide is a slow-acting blood schizontocide that should not be used alone for treating acute malaria attacks in nonimmune patients (32). It is converted in the body to an active triazine metabolite called cycloguanil (204–207). Cycloguanil has been successfully used in man (208) although it is rapidly excreted (207).

Today chlorguanide is used primarily as a prophylactic. It has been recommended as the drug of choice for children (209), 25 mg daily for infants under 1 year and 50 mg daily for children 1–6 years old. The British Army has been using 100 mg daily for prophylaxis (210). Australian troops in Vietnam had used a daily combination of chlorguanide, 200 mg, plus DDS, 25 mg (2) with success. As already noted (91), DDS use in these troops was discontinued, possibly because of reports of agranulocytosis.

In volunteer studies on two chloroquine-resistant strains of *P. falciparum*, daily chlorguanide, 200 mg, for 8 weeks, protected against the Malaya (Poo.) and Malaya (Tay.) strains (211).

A number of studies characterizing various *P. falciparum* strains have been carried out. The Thailand (JHK) strain (212) proved partially refractory to 2.61 gm chlorguanide given over 10 days, with either an RI (clearing with recrudescence) or RII (partial suppression) response. The Vietnam (Sn.) strain, when treated with the same regimen (213), showed an RII or RIII (no effect) response. The Malayan (Camp) strain also showed an RI or RII effect with the drug, 100 mg tid, for 10 or 12 days (214). The Vietnam (Smith) strain exhibited an RIII effect (51). On the other hand, 100 mg tid for 5 days cured the Philippines (Per.) strain (215).

Because the active metabolite, cycloguanil, was of great interest, a repository injectable form was developed. When the pamoate salt was given intramuscularly, protection against both *P. falciparum* and *P. vivax* was afforded for up to 6 months (216–218). Unfortunately, cycloguanil pamoate (CI-501) does not provide regular protection against chlorguanide-resistant or pyrimethamine-

resistant strains (213, 219, 220). In addition, the problem of local tissue reaction, including abscess formation, has been encountered (105, 221).

A number of studies on the repository mixture of cycloguanil pamoate and DADDS have already been discussed. Some other combinations have been found effective for 1–2 months. CI-501 plus oral amodiaquine produced a more rapid disappearance of parasitemia than CI-501 alone in Senegal, but all antimalarial effects in both groups were gone within 3 months (222). CI-501, 350 mg intramuscularly, and chloroquine phosphate, 300 mg to 600 mg in a single oral dose, were given to semi-immune Nigerian children (223). Good suppression was seen for 6 weeks, but was not much better than from single doses of chloroquine alone.

Pyrimethamine.—Use of pyrimethamine in humans was first reported in 1951 (224). Single oral doses as low as 5 mg caused a slow disappearance of both falciparum and malariae infections in semi-immune children. In The Gambia (225) 0.25 mg/kg to 0.50 mg/kg cleared parasitemia, although not rapidly. Not truly gametocytocidal, pyrimethamine has been shown to be sporontocidal (226), thus interfering with mosquito transmission.

Unfortunately, plasmodial resistance to this very promising drug was reported by 1954 (38–40). This resistance persists following mass use and the resistant strain spreads to adjacent areas (227, 228). Also, a cross-resistance to chlorguanide has been amply demonstrated (15). Fortunately, this cross-resistance is not always complete (213).

In spite of potential for inducing resistance, pyrimethamine is still widely used for causal prophylaxis of *P. falciparum* and clinical prophylaxis of the other 3 species (229). The recommended adult dose is 25 mg once weekly.

Many of the more recent reports have involved combinations. One recent prophylactic trial in Panama involved biweekly dosing with pyrimethamine-primaquine for 2 years (230). *P. vivax* was completely eliminated during the major part of the second year. *P. falciparum*, however, was never completely eliminated, continuing in about 1% of the population.

The combination of quinine with pyrimethamine has recently been reported as effective against chloroquine-resistant *P. falciparum* (231–235). The first study reported an overall success of 95% in 220 men receiving extremely variable doses of the two drugs (231). Interestingly, the rate was 91% for pyrimethamine alone in 21 patients.

Quinine sulfate, 650 mg tid for 14 days, plus pyrimethamine, 25 mg tid for 3 days, cleared all 326 men treated (232), with recrudescences in 7.4% of the cases. An extension of these studies reported on a total of 2003 acute falciparum cases in U.S. soldiers in Vietnam (233). They received quinine, 650 mg q 8 hr for 14 days, and pyrimethamine, either 25 mg bid for 3 days or 25 mg tid for 3 days. All cases responded, but no recrudescence rates were given.

Other dihydrofolic acid reductase inhibitors.—The antibacterial agent trimethoprim [2,4-diamino-5(3′,4′,5′-trimethoxybenzyl) pyrimidine] in combination with

sulfalene has been discussed. A study on trimethoprim alone (236) against 2 strains of *P. falciparum* was very promising. Rapid parasite clearance in 10 volunteers occurred with 5 daily doses of either 0.5 gm/day or 0.75 gm/day against the Uganda I strain, with 9 cures. The drug was also effective against the pyrimethamine-resistant Camp strain. Three of 8 men were cured by 1.5 gm/day for 7 days. The 5 recrudescences were treated with a second course and 4 were cured.

Methotrexate has been used orally in 3 cases of *P. vivax* (237). All 3 showed clinical improvement within 48 hours, and the 2 who received primaquine for 14 days starting on day 7 were cured. The third man, not receiving primaquine, relapsed 21 days after cessation of methotrexate.

WR-38,839 [4,6-diamino-1,2-dihydro-2,2-dimethyl-1-(3,4-dichlorobenzyloxy)-1,3,5-triazine] in combination with sulfadiazine, has been shown to be a causal prophylactic against the Vietnam (Marks) strain of *P. falciparum* (238). Neither drug alone had any effect on the pre-erythrocytic stages. Biliary excretion studies in rhesus monkeys indicated that WR-38,839 may undergo enterohepatic circulation for several days (239). Although the compound is reported to have a very short blood half-life in man (238), the possibility exists that man also has an enterohepatic circulation which maintains a low but steady level.

AMINOQUINOLINES

An enormous body of literature exists on therapy with this group of compounds. The utility of 8-aminoquinolines as gametocytocides, causal prophylactics, and radical curatives has already been discussed. The importance of 4-aminoquinolines as suppressives in sensitive strains cannot be overemphasized; they remain the drugs of choice for treating these strains. Widespread treatment in malarious areas simply cannot be carried out under close medical supervision. One temporary solution has been to put the drug into salt and distribute this to the population (240–242). Unfortunately, widespread use of chloroquine, amodiaquine, etc., in suboptimal doses is an excellent technique for inducing and spreading resistance. In some reports the authors state that no resistance was seen and attribute failures to other factors. Other investigators conclude that resistance may have occurred.

QUININE

This drug still remains an important suppressant. Oral dosing, especially in combination, has already been discussed. It is important that acute attacks of chloroquine-resistant strains of falciparum still respond to quinine (212–214, 243, 244).

Intravenous quinine therapy is receiving renewed interest (233, 245–247). Successful treatment with continuous intravenous drip was reported in the 1940s (248). Suggested treatment for cerebral malaria has been quinine, 650 mg/500 ml 5% glucose q 8 hr by slow intravenous drip (245). This may be combined

with dexamethasone intramuscularly. Another study compared oral vs intravenous quinine in U.S. soldiers (246) for treatment of patients who had previously recrudesced. Both groups received pyrimethamine, sulfisoxazole and DDS in addition. The oral quinine group had a 67% recrudescence rate while the intravenous group had only a 14% rate.

Other Compounds

Tetracyclines.—Several recent reports have been published on the efficacy of tetracyclines against *P. falciparum* (249–251). Oral doses of 250 mg qid for 7 days cured all 10 men of the Camp strain, all 6 of the Uganda I strain and 3 of 4 volunteers of the Marks strain (249). Parasite clearance was slow, however. To decrease response time, a study in Thailand treated all acute cases first with quinine sulfate, 640 mg tid for 3 days (250). This was followed by either minocycline, 100 mg bid for 7 days, or tetracycline, 250 mg qid for 10 days. All 29 quinine-tetracycline patients were cured; 27 of 28 quinine-minocycline patients were cured.

Phenanthrenemethanols.—Oral studies on WR-33,063 [α-(diheptylaminomethyl)-6-bromo-9-phenanthrenemethanol] are being pursued in humans (252–254). Volunteers tolerated 1.15 gm qid for 10 days without adverse effect (252). Therapeutically, WR-33,063 gave excellent results in nonimmune volunteers infected with *P. falciparum.* Doses of 0.4 gm qid for 6 days cured 14 of 18 of the Vietnam (Smith) strain, all 6 of the Vietnam (Marks) strain, 2 of 3 of the Vietnam (Brai.) strain, all 5 of the Malayan (Camp) strain, and all 6 of the Uganda I strain (252).

The second major report details 2 separate studies (253). All 11 semi-immune patients with recrudescent falciparum malaria acquired in Vietnam were cured by WR-33,063, 400 mg q 6 hr for 6 days. Two additional men in the same series were cured with a variable schedule of WR-33,063 plus a sulfonamide. WR-33,063 cured 23 of 25 patients acutely ill with falciparum malaria from Vietnam. Of the uncured men, 1 showed an RI response and the other an RIII response. Of great importance was the almost complete absence of side effects, including the nausea and vomiting often observed with the quinine, pyrimethamine, dapsone combination (253). In addition, the average length of time observed for fever to fall to 99° was 70 hours with the combination and only 48 hours with WR-33,063.

A third study (254) indicated that weekly 800 mg doses of WR-33,063 did not interfere with the early development of mosquito-induced *P. falciparum* infections. Therapeutic doses of WR-33,063 were used to cure one of the volunteers, indicating that resistance had not developed.

WR-33,063 has been used against *P. vivax* infections (252), with clinical cures seen in 4 of 5 cases of the Chesson strain.

WR-33,063 appears to be poorly absorbed in several animal species (255, 256) but does seem to have extensive biliary secretion (239). An investigation into the

fate of oral radiolabeled WR-33,063 in humans indicated that blood levels peaked 4–6 hours after dosing (257). Urinary excretion for 2 weeks accounted for up to 13% of the dose, with at least 4 metabolites present.

A second compound of this series is also undergoing clinical trials at this time. So far, no human data have been published on WR-122,455 [α-(2-piperidyl)-3,6-bis(trifluoromethyl)-9-phenanthrenemethanol]. The compound shows good activity against *P. berghei* in mice (258). It is also active in the other in vivo antimalarial screens used in the U.S. Army program. Several preliminary metabolism studies in animals have been reported (239, 255, 259, 260). WR-122,455 was well absorbed orally but was excreted mainly via the feces. Extensive enterohepatic circulation was seen, and probably helped account for the slow excretion.

Quinolinemethanols.—WR-30,090 [α-(di-*n*-butylaminomethyl)-6,8-dichloro-2-(3′,4′-dichlorophenyl)-4-quinolinemethanol] was shown to be active in antimalarial screens during World War II (11). Oral studies in humans are currently being pursued. The compound was well tolerated by humans at 230 mg q 8 hr for 6 days (261). This dosage regimen, as well as lower doses, was used against several *P. falciparum* strains. WR-30,090 cured all 6 of the Uganda I strain, all 6 of the Malayan Camp strain, all 6 of the Malaya (Tay.) strain, all 5 of the Vietnam (Marks) strain, 2 of 3 of the Vietnam (Crocker) strain, and 29 of 32 of the Vietnam (Smith) strain (261).

In a second report (253), WR-30,090, 230 mg q 8 hr for 6 days, cured all 8 recrudescent cases of falciparum malaria acquired in Vietnam. Of 26 additional patients treated in Vietnam, 23 were cured and 3 had an RI response. The average time interval for fever to fall to 99° was 80 hours. As with WR-33,063, this compound caused virtually no side effects (253).

When given weekly at either 460 mg or 690 mg, WR-30,090 provided suppressive cures of mosquito-induced *P. falciparum* in 20 of 26 volunteers (254). Twenty-two of the 26 men were challenged with the chloroquine-resistant Vietnam (Smith) strain.

WR-30,090 has been used against *P. vivax* infections (254, 261). Clinical cures were seen in all 8 blood-induced Chesson strain cases, but two cases needed 2 courses of WR-30,090 treatment to produce this effect (261). In the same study, all 3 men with mosquito-induced infection relapsed within 31 days.

WR-30 090, weekly for 8 weeks, provided clinical prophylaxis against mosquito-induced *F. vivax* in 11 of 15 men (254). At least 6 of the 11 experienced malaria following completion of the prophylactic course.

WR-30,090 in animals did not cause the release, with subsequent depletion, of catacholamines seen with some other quinoline-methanols (262). Studies on the metabolic disposition of radiolabeled WR-30,090 indicated that the compound was poorly absorbed orally in both rhesus monkeys and rats (263). Blood levels peaked at 3 hours in rats and 8 hours in monkeys. WR-30,090 has been found to have a relatively low phototoxic potential in animals (264), and this appears to hold for humans also.

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