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Antimalarial Activities of Various 4-Quinolinemethanols with Special Attention to WR-142,490 (Mefloquine)†

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Pilot appraisals of the activities of a selected group of 4-quinolinemethanols against acute *Plasmodium falciparum* infections in owl monkeys indicated that compounds of this class are equally active against infections with chloroquine-resistant and chloroquine-susceptible strains and that this efficacy is not compromised by concomitant resistance to pyrimethamine, and in addition, identified three derivatives with outstanding activity (WR-226,253; WR-142,490; and WR-184,806). WR-142,490, the second 4-quinolinemethanol evaluated in the above model, was five times as active as chloroquine against infections with the chloroquine-susceptible, pyrimethamine-resistant strain and had a much larger therapeutic index. Expanded evaluations designed to support projected studies in human volunteers provided full confirmation of the pilot appraisals and in addition showed: (i) that the activity of WR-142,490 was a function of the total dose delivered, single doses being as effective as three or seven fractional doses administered over as many days; (ii) that intravenous administration of this agent was feasible and effective; and (iii) that the compound was at least as active against infections with *P. vivax* as against infections with *P. falciparum*. Companion studies in rhesus monkeys infected with *P. cynomolgi* showed that WR-142,490 lacked prophylactic or radical curative activity, but that it was as effective as chloroquine as a companion to primaquine in a combination curative drug regimen. The results of human volunteer and field trials agree well with comparable segments of these experimental evaluations.

Between 1963 and 1976, approximately 300 4-quinolinemethanol derivatives were submitted to the Walter Reed Army Institute of Research for examination in that segment of the Malaria Research Program (U. S. Army Medical Research and Development Command) concerned with development of new agents effective against infections with strains of *Plasmodium falciparum* resistant to chloroquine and other currently available drugs. Essentially all of these compounds were evaluated in the Rane Laboratory, University of Miami, Florida, for curative and/or life-prolonging activities in mice infected with *P. berghei* (23; T. R. Sweeney, personal communication). From 1970 on, the derivatives that were most active in this rodent malaria model were examined in our laboratory on a pilot scale for capacity to control established infections with various drug-resistant strains of *P. falciparum* in owl monkeys. WR-142,490 (see Table 1 for structure), the second 4-quinolinemethanol to be appraised in the human plasmodium-owl monkey model, exhibited properties of unusual interest. Specifically, this agent, subsequently named mefloquine, displayed essentially equal activity against infections with the two test strains of *P. falciparum*, one highly resistant to chloroquine and the other to pyrimethamine, and effected cure of infections with either strain at well-tolerated doses. Dose for dose, WR-142,490 was at least five times as active as chloroquine against infections with the chloroquine-susceptible, pyrimethamine-resistant test strain and had a much larger therapeutic index.

The above observations led those at Walter Reed Army Institute of Research responsible for clinical testing of new agents to conclude that WR-142,490 was a worthy candidate for evaluation in human volunteers infected with chloroquine-resistant strains of *P. falciparum*. To facilitate design of such investigations, additional examinations of the properties of this compound in owl monkeys infected with various drug-resistant strains of this plasmodium were undertaken. These included: (i) expansion of the original pilot-type studies; (ii) comparison of the efficacies of treatment schedules of different durations; and (iii) explorations of the feasibility of

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delivering this agent via the intravenous route and its effectiveness when so administered. In addition, evaluations of the activities of WR-142,490 against infections with two strains of *P. vivax,* one susceptible to both chloroquine and pyrimethamine, the other chloroquine-susceptible and pyrimethamine-resistant, were pursued to insure that this 4-quinolinemethanol could control infections with both major human plasmodia, an essential requirement of any generally useful blood schizonticidal drug. The capacity of WR-142,490 to affect development and persistence of early and late tissue schizonts was also examined in an effort to determine whether this compound had either prophylactic or radical curative properties. Because infections with sporozoites of *P. vivax* in owl monkeys do not have the requisite reproducibility for such investigations, it was necessary to turn to rhesus monkeys challenged or infected with sporozoites of *P. cynomolgi* for appraisals of these activities. Finally, the capacity of WR-142,490 to serve as a companion drug to primaquine in a curative drug regimen was compared with that of chloroquine by using the *P. cynomolgi*-rhesus monkey model. The results of this group of developmental studies, as well as those of the pilot investigations that signaled the outstanding activity of WR-142,490, have been summarized in the current report.

MATERIALS AND METHODS

Infections with *P. falciparum* and *P. vivax* in owl monkeys. (i) Monkeys. A total of 375 subadult and adult owl monkeys (*Aotus trivirgatus griseimembra*), all of northern Colombian origin and imported directly from Barranquilla, was used in the experiments described in this report. The above total included approximately equal numbers of males and females, ranging from 850 to 1,100 g in weight at the time of assignment to experiments. The procedures employed in transporting, conditioning, housing, caging, and feeding these subjects and in maintaining and handling them during assessments of drug activities were identical with those described previously (29, 36). All monkeys were free of naturally acquired filarial and malarial infections as evidenced by negative searches of Giemsa-stained thick blood films prepared repeatedly during the latter phases of the conditioning period.

(ii) Strains of plasmodia. Five strains of *P. falciparum* (Uganda Palo Alto, Malayan Camp-CH/Q, Vietnam Monterey, Vietnam Oak Knoll, and Vietnam Smith) and two strains of *P. vivax* (New Guinea Chesson and Vietnam Palo Alto) were used in various experiments. The patient origins of these strains, their backgrounds before use in this laboratory, adaptation to growth in owl monkeys with intact spleens, and capacities to produce progressive disease have been detailed previously (L. H. Schmidt, Am. J. Trop. Med. Hyg., in press), as have the responses of standardized infections to treatment with chloroquine, pyrimethamine, and quinine (Schmidt, Am. J. Trop. Med. Hyg., in press). Apropos these responses, it should be noted that infections with the Vietnam Monterey and Vietnam Oak Knoll strains of *P. falciparum* are resistant to treatment with maximally tolerated doses of chloroquine and susceptible to treatment with tolerated doses of pyrimethamine. Infections with the Uganda Palo Alto and Malayan Camp-CH/Q strains are susceptible to treatment with chloroquine and refractory to treatment with maximally tolerated doses of pyrimethamine. Infections with the Smith strain are fully resistant to treatment with tolerated doses of either standard drug. Infections with the New Guinea Chesson strain of *P. vivax* are susceptible to treatment with both chloroquine and pyrimethamine. Infections with the Vietnam Palo Alto strain are susceptible to treatment with chloroquine and resistant to treatment with tolerated doses of pyrimethamine.

(iii) Inoculation and parasitological procedures. All infections were initiated by intravenous inoculation of 5×10^6 trophozoites obtained from a strain passage monkey during the ascending phase of the primary attack. Procedures used in obtaining blood from donor monkeys, diluting the samples to obtain an inoculum of appropriate size, inoculating recipients, and protecting these inoculees against fortuitous bacterial infections in the immediate post-inoculation period have been detailed previously (29, 36; Schmidt, Am. J. Trop. Med. Hyg., in press).

Giemsa-stained thick and thin blood films, prepared from the marginal ear vein, were used to determine the presence or absence of parasitemia, measure parasite densities, and assess the discrete effects of the test compounds on parasite morphology. Such examinations were initiated 18 h after inoculation and were repeated daily between 7:45 and 9:00 a.m. during pretreatment and treatment intervals and thereafter until thick blood films became negative and remained so for at least 5 consecutive days. Examination schedules followed thereafter, either to recrudescence or to cure of infection, have been detailed elsewhere (29, 36; Schmidt, Am. J. Trop. Med. Hyg., in press).

(iv) Procedures for assessing therapeutic activities. Pilot assessments of the activities of 12 selected 4-quinolinemethanols against infections with strains of *P. falciparum* resistant to chloroquine and pyrimethamine were carried out by procedures described and validated previously (Schmidt, Am. J. Trop. Med. Hyg., in press). Table 2 shows that every compound was not tested against the same strain or strains, a reflection of the fact that studies of this compound group covered a 6-year period and that concepts and operating conditions changed considerably in this interval. Specifically, the fully chloroquine-resistant, moderately pyrimethamine-susceptible Vietnam Monterey strain and the fully pyrimethamine-resistant, chloroquine-susceptible Uganda Palo Alto strain were used in pilot studies carried out before March, 1970. In mid-March of that year, the latter strain was replaced by the pyrimethamine-resistant Malayan Camp-CH/Q strain, then being used in human volunteer studies, in an attempt to establish closer relationships between evaluations in humans

and in the owl monkey test system. At the same time, the Vietnam Monterey strain was replaced by the equally chloroquine-resistant, but fully pyrimethamine-susceptible Vietnam Oak Knoll strain with the objective of obtaining a completely uncompromised delineation of the impacts of chloroquine resistance on the activities of test compounds. In mid-1972, the Vietnam Smith strain, fully resistant to chloroquine, pyrimethamine, and quinine, was added to the *P. falciparum* roster, with the dual objectives of appraising impacts of multidrug resistance on the activities of test agents and facilitating correlation of results acquired in the owl monkey model with those obtained in studies on human volunteers, which at that moment were focused on the responses of infections with the Smith strain and the almost equally multidrug-resistant Vietnam Marks strain (38).

Furthermore, Table 2 shows that in some pilot assessments, the activity of an agent was examined against infections with but a single strain. This occurred when the numbers of compounds submitted for such appraisals exceeded the capacity of our laboratory to mount studies on two strains, when the supply of the test agent sufficed for studies on but a single strain, or when, as from early 1975 on, access to owl monkeys was severely limited because of the export embargo imposed by the government of Colombia. In these situations, evaluations were pursued either with the Vietnam Oak Knoll or Vietnam Smith strain to be certain that the impact of chloroquine resistance on the activity of the compound under investigation was identified.

Procedures used in extended appraisals of the activity of WR-142,490 were essentially identical with those employed in pilot assessments. These additional evaluations were concerned with the effectiveness of this compound against infections with the Vietnam Palo Alto and New Guinea Chesson strains of *P. vivax*, as well as with complementing the pilot evaluations of its activity against infections with the various test strains of *P. falciparum*. Throughout these expanded studies, WR-142,490 was administered orally once daily for 7 consecutive days.

Investigations of the influence of the duration of treatment on the activity of WR-142,490, of the feasibility of administering this agent intravenously, and of its efficacy when so delivered, were undertaken to meet the needs of those considering trial of this quinolinemethanol in human volunteers. A preliminary examination of the first of the above issues in small groups of monkeys previously treated unsuccessfully with other types of test compounds suggested that established infections could be cured by single-dose and three-dose regimens. The results of these exploratory studies led to a major side-by-side evaluation of the efficacies of single-dose and three- and seven-consecutive-daily-dose oral treatment regimens against previously untreated infections with the Vietnam Oak Knoll and Malayan Camp-CH/Q strains of *P. falciparum*. Parallel experiments were carried out, each involving 39 monkeys inoculated with these strains. When the parasitemias of these subjects reached appropriate levels, they were assigned to one of three major treatment groups of 12 monkeys each, or to a control group of 3 monkeys (2 untreated controls and 1 treated either with chloroquine or with pyrimethamine). Each group of 12 was divided into four subgroups, the members of which received total course doses approximating 0.7, 2.75, 11.0, or 44.0 mg of WR-142,490 per kg of body weight delivered either as a single dose or in three or seven equal fractions on consecutive days. Treatment failures on any of the above doses were retreated whenever possible with the next higher dose in the original treatment schedule. As indicated elsewhere (Schmidt, Am. J. Trop. Med. Hyg., in press), this retreatment practice had a dual purpose: (i) to economize on the numbers of owl monkeys required to appraise activity; and (ii) to obtain signals of emergence of parasites resistant to the test compound.

The feasibility of administering WR-142,490 intravenously was examined in a group of 12 adult owl monkeys discarded as cured from previous therapeutic evaluations. This examination indicated that doses as large as 40.0 mg/kg of body weight could be infused into the midsaphenous vein over a 2-min period without evoking untoward reactions and that such doses could be repeated on 3 consecutive days without evidence of cumulative systemic toxicity or phlebitis. Push injection of 30.0-mg/kg doses of WR-142,490 or slower infusion of doses of 60.0 mg/kg evoked severe convulsive seizures which usually terminated fatally. With this information as background, the activity of this compound administered intravenously in single-dose or three-consecutive-daily-dose schedules was examined in groups of monkeys infected with the Vietnam Oak Knoll or Vietnam Smith strains of *P. falciparum* or the Vietnam Palo Alto strain of *P. vivax*. Except for the size of the monkey groups, which was smaller, and exclusion of the seven-daily-dose regimen, the pattern of this study was essentially a replica of that used in the above described evaluation of various oral dosage regimens.

Although the results obtained have not been tabulated in this report, one or more untreated control monkeys and one drug control monkey (treated with chloroquine in infections with chloroquine-resistant strains and pyrimethamine in infections with strains resistant to this pyrimidine) were included in both pilot and specially targeted studies. The results obtained with these controls certified that neither the virulence nor the drug susceptibility of the test strains was altered during routine passages.

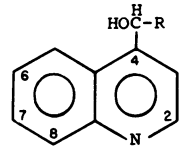
(v) Classification of therapeutic responses. Responses to drug treatment have been categorized as none (no effect on parasitemia), suppressed (reduction of parasitemia below levels encountered in concurrent or historical untreated controls), cleared (temporary clearance of parasitemia with subsequent recrudescence), and cured (no renewal of parasite activity for 90 days or more after delivery of the last dose of the test agent). The criteria for this categorization have been detailed elsewhere (Schmidt, Am. J. Trop. Med. Hyg., in press). It should be emphasized that these response categories are the counterparts of those employed in evaluating the efficacies of various test compounds against infections with *P. falciparum* in human volunteers (40).

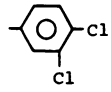
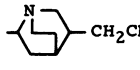
(vi) Test agents and their delivery. The structures of each of the 12 4-quinolinemethanols included

in this report, the identity of the laboratory that accomplished the original synthesis, and the origins of samples used in the current studies have been listed in Table 1. Eleven of the compounds were supplied as monohydrochloride salts, and the twelfth (WR-199,426) was supplied as the dihydrochloride. Doses delivered to both owl monkeys and rhesus monkeys were always calculated as base equivalents.

The procedures used for preparing solutions of the test compounds and administering them orally to in-

TABLE 1. *Chemical structures and sources of 4-quinolinemethanols evaluated for activities against infections with various strains of P. falciparum*



Compound WR- No.*	Substituents				
	On Position of Quinoline Nucleus				R on 4-methanol
	2	6	7	8	
7,930** (6)[a]		-Cl	-	-Cl	
30,090** (19)[a]		-Cl	-	-Cl	$-CH_2N(CH_2CH_2CH_2CH_3)_2$
142,490† (22)[a]	$-CF_3$	-	-	$-CF_3$	
177,602† (8)[a]	$-CF_3$	-	-	$-CF_3$	
226,253 (25)[a]	$-CF_3$	-Cl	-	-Cl	
183,544 (4)[b]	$-CF_3$	-	-	$-CF_3$	$-CH_2NHCH_2CH_2CH_3$
183,546 (4)[b]	$-CF_3$	-	-	$-CF_3$	$-CH_2N(CH_2CH_2CH_3)_2$
183,545 (4)[b]	$-CF_3$	-	-	$-CF_3$	$-CH_2NHC(CH_3)_3$
183,606 (4)[b]	$-CF_3$	-	-	$-CF_3$	$-(CH_2)_2NHCH_2CH_2CH_3$
184,806 (4)[a]	$-CF_3$	-	-	$-CF_3$	$-(CH_2)_2NHC(CH_3)_3$
177,504 (X)[a]	$-CF_3$	-	-	$-CF_3$	$-(CH_2)_2N(CH_2CH_2CH_2CH_3)_2$
199,426 (5)[c]	-	-	$-CF_3$	-	

*Items in parentheses = literature reference to synthesis. (X) = Synthesis by W. T. Colwell, Stanford Research Institute, Menlo Park, California. Letter superscript = source of sample evaluated: a - provided by WRAIR from "Prep Lab" run; b - original synthesis; c - W. Leimgruber, Hoffman LaRoche, Inc., Nutley, New Jersey.

**WR-7,930 and WR-30,090 designated SN-10,275 and SN-15,068 at time of synthesis.

†Diastereoisomers: WR-142,490 = erythro- form; WR-177,602 = threo- form.

fected owl monkeys were identical with those set forth in earlier reports (29, 36; Schmidt, Am. J. Trop. Med. Hyg., in press). All solutions were prepared fresh daily and delivered within 60 min of preparation. Intravenous administration of WR-142,490 was accomplished as follows. An amount of this compound, 5% in excess of that required for all monkeys to be treated, was placed in a sterile glass mortar and with the aid of light grinding with a Teflon pestle was dissolved in the volume of sterile saline needed to give a concentration of either 10.0- or 20.0-mg base per ml. These concentrations covered the requirements of the heaviest weight recipients of doses of 15.0 to 30.0 mg/kg; they were subdiluted in twofold steps in sterile saline for delivery of smaller doses. From 1.5 to 2.0 ml of the appropriate dilutions were injected slowly and steadily into the midsaphenous vein over a 2-min period.

Infections with *P. cynomolgi* in rhesus monkeys. (i) Monkeys. A total of 43 subadult rhesus monkeys (*Macaca mulatta*), imported directly from New Delhi, India, was used in the various experiments. The group included 16 females and 27 males ranging from 3.9 to 6.3 kg in weight at the time of inoculation. All were tuberculin negative on receipt and upon retest at 4-week intervals throughout residence in the colony. Conditioning, housing, feeding, and handling procedures were identical with those described previously (31).

(ii) Parasitological procedures. The *B* strain of *P. cynomolgi* was used in these studies, specifically, the subline maintained in our laboratories since May, 1959 (31), by serial monkey-to-mosquito-to-monkey passages at approximately 2-month intervals. Infections with sporozoites of this strain were employed for assessing the capacities of WR-142,490 to prevent infection or effect radical cure, and for determining whether this compound could serve as a companion to primaquine in a curative drug regimen. Monkeys committed to these evaluations were inoculated via the midsaphena with from 0.9×10^6 to 1.4×10^6 sporozoites derived from heavily infected *Anopheles freeborni* fed 12 to 14 days earlier on a passage monkey. Procedures for obtaining infected mosquitoes, preparing the sporozoite inoculum and measuring its size, inoculating monkeys, and following the course of infection in the latter subjects to patency, through treatment, relapse, and/or cure, were identical with those described previously (34, 35; Schmidt, Am. J. Trop. Med. Hyg., in press).

Infections with trophozoites were used for assessing the suppressive activity of WR-142,490. For this purpose, monkeys were inoculated via the midsaphena with 5×10^5 erythrocytic parasites derived from a monkey in the passage line. Procedures for acquiring the blood sample for the trophozoite inoculum, diluting it appropriately, inoculating recipients, and following parasitemias in these inoculees to and through treatment, recrudescence, or cure have been outlined elsewhere (32, 34, 35).

(iii) Assessments of diverse activities of WR-142,490. Five monkeys were used to determine whether WR-142,490 affected development of early tissue schizonts or, parenthetically, possessed prophylactic activity. Three of the group received 1.25-, 5.0-, or 20.0-mg/kg doses of this compound and one received 0.75-mg/kg doses of primaquine. In each case, the dose was administered the day before sporozoite challenge, 2 h before inoculation, and for 7 days thereafter. The fifth monkey served as an untreated control.

A total of 12 monkeys with established sporozoite-induced infections was used to determine whether WR-142,490 affected persistence of late tissue schizonts, i.e., whether it possessed radical curative activity. Eight subjects were inoculated specifically for this purpose. The remaining four, with already developed infections, were transferees from the prophylactic study described above. The primary attacks of nine of the group were treated with WR-142,490 in doses ranging from 1.25 to 40.0 mg/kg once daily for 7 consecutive days. Chloroquine was administered to the three remaining monkeys in daily doses of 5.0 mg/kg for the same time period. Relapses after primary treatment were retreated with the same agent. Chloroquine was administered at the original dose level in all cases; WR-142,490 was usually delivered at larger doses. Recurring parasitemias in monkeys treated with WR-142,490 were treated with chloroquine (5.0 mg/kg daily for 7 days) before any retreatment to insure that recrudescences were not being confused with relapses.

Four monkeys were used in the primary assessment of the dose of WR-142,490 required to cure trophozoite-induced infections. Three of these subjects were treated originally with WR-142,490 in doses of 2.5, 10.0, or 40.0 mg/kg daily for 7 days. The single treatment failure at the lowest of these doses was retreated with 10.0-mg/kg doses. The fourth monkey served as an untreated control.

A total of 37 monkeys was used to compare the capacities of WR-142,490 and chloroquine to serve as companions to primaquine in a curative drug regimen. A total of 21 subjects was infected with sporozoites specifically for this purpose; 12 others were derived from the radicul curative evaluation described above; and the remaining four subjects were transferees from a study of the prophylactic activity of a naphthoquinone derivative that had yielded entirely negative results. Of the 37 monkeys, 28 were originally treated with either 0.375 or 0.75 mg of primaquine per kg of body weight, plus 10.0 mg of WR-142,490 per kg of body weight once daily for 7 consecutive days. Five were treated similarly with either 0.375 or 0.75 mg of primaquine per kg, plus 2.5 mg of chloroquine per unit weight. Relapses on 0.375-mg/kg doses of primaquine in either group were retreated with 0.75-mg/kg doses plus the appropriate companion drug; relapses on 0.75 mg/kg were retreated with doses of 1.5 mg/kg. The primary attacks and first four relapses of the remaining four monkeys were treated either with doses of 10.0 mg of WR-142,490 per kg or doses of 2.5 mg of chloroquine per kg daily for 7 days to insure that neither of these agents effected cure of infections of the intensity used in this evaluation.

In all studies referred to above, the requisite quantities of freshly prepared solutions of WR-142,490, chloroquine, or primaquine, or combinations of either of the first two agents with primaquine were administered by stomach tube via well-established procedures (30). These agents were delivered between 8:00 and 8:30 a.m. daily, approximately 16 h after feeding on the preceding day.

RESULTS

Pilot studies (i) Structural characteristics of test compounds. As indicated in Table 1, structural variety among the compounds submitted for pilot evaluations was relatively limited. Of the 12 agents, 11 were substituted at positions 2 and 8 of the quinoline nucleus. Of the 11, 8 had trifluoromethyl substituents. The remaining three, WR-7,930, WR-30,090, and WR-226,253, were also 6-substituted; each of these had chloro substituents at positions 6 and 8. Four of the 11, of which 2 were diastereoisomers (WR-142,490 and WR-177,602), had 2-piperidyl groups attached to the 4-carbinol; the remaining 7 had alkylaminoalkyl side chains. The 12th agent, WR-199,426, had a trifluoromethyl substituent at position 7 of the quinoline nucleus and a 5-ethyl-2-quinuclidinyl group attached to the 4-methanol.

WR-7,930 and WR-30,090, the first two compounds listed in Table 1, were first synthesized during the World War II search for new antimalarial drugs and designated under code numbers SN-10,275 and SN-15,068 (39). Of the remaining 10 agents, 9 were synthesized specifically for the current Malaria Research Program. The 10th new agent was a product of an independent search for new antimalarial drugs pursued by F. Hoffman-LaRoche and Co., Ltd., Basel, Switzerland (5). WR-7,930 was included in the current pilot appraisals for reference purposes and because of high activity exhibited against *P. berghei* infections in mice. WR-30,090 was examined both because of its activity in the *P. berghei*-mouse model and because it was a candidate for evaluation in human volunteers.

(ii) Activities of test compounds. The results of the pilot assessments have been detailed in Table 2 and summarized and analyzed in Table 3. The latter table records the total dose (seven times the daily dose) of each compound required to cure 90% of infections with the respective test strains of *P. falciparum* (CD_{90}). This CD_{90} was calculated by the method of Litchfield and Wilcoxon (18). Table 3 also records the CD_{90}s of the various agents against infections with *P. berghei,* calculated by the same procedure from data acquired in the Rane Laboratory.

The analysis presented in Table 3 shows that WR-226,253, WR-177,602, WR-142,490, WR-184,806, and WR-7,930, in decreasing order, were the most active of the 12 compounds, significantly more active than the remaining 7. WR-226,253 exhibited striking activity against infections with the multidrug-resistant Vietnam Smith strain (the only strain against which it was tested); with a CD_{90} of 12.5 mg/kg, it was approximately twice as active as WR-177,602 and WR-142,490 (diastereoisomers) and seven times as active as WR-184,806. WR-142,490 was the most active of the agents tested against infections with the chloroquine-resistant Vietnam Oak Knoll and the pyrimethamine-resistant Malayan Camp-CH/Q strains. With CD_{90}s of 8.5 and 16.0 mg/kg against infections with these strains, this compound was three to five times more active than WR-184,806 and WR-7,930, its closest competitors.

Structure-activity correlations indicate that compounds with 2-piperidyl substituents on the 4-methanol side chain (WR-7,930, WR-142,490, WR-177,602, and WR-226,253) were uniformly more active than derivatives with alkylaminoalkyl substituents. Comparison of the data acquired on WR-226,253 and WR-7,930 suggests that trifluoromethyl substitution at position 2 of the quinoline nucleus may be productive of greater activity than phenyl substitution.

Except for WR-226,253, which was examined in the Rane Laboratory subsequent to study in our laboratory, all test compounds were selected for evaluation against *P. falciparum* infections in the owl monkey because of their outstanding curative or life-prolonging activities in mice infected with *P. berghei.* For this reason, the ranking of the agents in this rodent model is of some interest. As the data in Table 3, column 7, show, WR-142,490 was clearly the most active of the 12 compounds against infections with *P. berghei,* being 2 to 3 times more active than WR-177,602, WR-7,930, and WR-30,090, and 10 times more active than WR-184,806 and WR-226,253. The remaining six compounds were distinctly less active than any of the above. With two exceptions, this ranking agrees well with that in the human plasmodium-owl monkey model. The deviations involve WR-30,090, which was clearly more active against infections with *P. berghei,* and WR-226,253, which was distinctly more active against infections with *P. falciparum.* The poor performance of the latter compound in the rodent model is perplexing because, except for its substituent at position 2 of the quinoline nucleus, it is structurally identical with WR-7,930 (Table 1), which exhibited relatively high activity in both model systems.

As indicated earlier in this report, the remarkable activity of WR-142,490 against infections with the Vietnam Oak Knoll and Malayan Camp-CH/Q strains was noted in late July and early August, 1970. The CD_{90}s of this compound against infections with these strains, one chloroquine-resistant, the other pyrimethamine-resistant, were 8.5 and 16.0 mg/kg, respectively. This result was particularly impressive because studies on chloroquine (Schmidt, Am. J. Trop.

Med. Hyg., in press) had shown that this standard drug had a CD_{90} of approximately 90.0 mg/kg against infections with the chloroquine-susceptible, pyrimethamine-resistant Malayan Camp-CH/Q strain and that total doses of 280.0 mg/kg (2 × 20.0 mg/kg daily for 7 days), the maximum that could be tolerated, were essentially without effect on infections with the chloroquine-resistant, pyrimethamine-susceptible Vietnam Oak Knoll strain. Thus, WR-142,490 was not only equally active against infections with chloroquine-susceptible and -resistant strains, but was at least five times as active as chloroquine against infections with a strain susceptible to the latter drug. Furthermore, the initial pilot studies (Table 2) indicated that WR-142,490 had a much larger therapeutic index than chloroquine in infections where both agents were active. Although poorly designed in that WR-142,490 was delivered in doses far above those required for maximal therapeutic benefit, these studies showed that this compound was well tolerated in a total dose of 1,400.0 mg/kg, at least four times the maximum tolerated level of chloroquine delivered in the same dosage schedule. These observations on tolerability, coupled with those on activity, led those responsible for clinical evaluations of new agents to conclude that WR-142,490 merited examination in human volunteers. The results of studies aimed at supporting and facilitating these investigations are summarized in the following sections.

Expanded evaluations of the activities of WR-142,490 against infections with various strains of *P. falciparum* and *P. vivax*. (i) Activities of oral dosage regimens. All data acquired on the activity of WR-142,490 administered orally once daily for 7 days to monkeys infected with various strains of *P. falciparum* and *P. vivax* have been summarized in Table 4. As indicated in column 10 of this table, the CD_{90}s were 14.0 mg/kg for infections with the Vietnam Oak Knoll or Malayan Camp-CH/Q strains, 28.0 mg/kg for infections with the Vietnam Smith strain, and 8.0 and 14.0 mg/kg for infections with the Vietnam Palo Alto and New Guinea Chesson strains, respectively. These results show that there are differences in the activity of WR-142,490 against infections with different strains of *P. falciparum*, but that these differences are of modest magnitude and do not preclude cure of infections with the least responsive strain with well-tolerated doses. The results also indicate that the doses of WR-142,490 required to cure infections with various strains of *P. falciparum* will suffice for eliminating blood schizonts of *P. vivax* and controlling clinical manifestations of infections with this plasmodium.

Assessments of the influence of the dosage regimen on the activity of WR-142,490 administered orally were limited to infections with the Vietnam Oak Knoll and Malayan Camp-CH/Q strains of *P. falciparum*. The results of these appraisals (Table 4, column 10) in terms of the total dose required to achieve a common endpoint (CD_{90}) show that single doses and three fractional doses administered on consecutive days were equally effective and perhaps slightly more effective than seven fractional doses delivered once daily for 7 days. Rates of parasite clearance were essentially the same on all three dosage regimens (Table 4, column 8). These observations suggest that WR-142,490 could meet the need for a drug that can be employed in short-term treatment schedules.

(ii) Activity of intravenous dosage regimens. The capacity of WR-142,490 to cure infections with the Oak Knoll or Smith strains of *P. falciparum* or the Palo Alto strain of *P. vivax* was examined in two different intravenous dosage schedules. The results of this appraisal (Table 5, column 10) indicate that both single-dose and three-consecutive-daily-dose schedules were highly and equally effective in curing infections with the above strains. CD_{90}s attained with these intravenous regimens were essentially identical with those of comparable oral regimens (Tables 4 and 5, columns 10). Clearance of parasitemia may have been somewhat more rapid on the intravenous schedules. It is worth noting that WR-142,490 has a greatly reduced therapeutic index when administered via the intravenous route (cf. tolerated doses in feasibility studies and effective doses in pilot studies, above). Even so, the margin between effective and toxic doses is sufficiently great to permit delivery of this compound intravenously when oral administration is not possible.

(iii) Incidental observations. Examinations of thick and thin blood films prepared daily throughout the treatment period and for some days thereafter made it possible to assess the effects of WR-142,490 on both parasite numbers and morphology. Quantitative evaluations in infections with the chloroquine-resistant Vietnam Oak Knoll strain and the pyrimethamine-resistant Malayan Camp-CH/Q strain showed that decreases in parasite numbers from pretreatment levels of 40 to 100 per 10^4 erythrocytes to $<1/10^4$ levels occurred within 48 h of administration of uniformly curative doses in the single-dose regimen and within 96 h of delivery of the first dose of a similarly effective seven-daily-dose regimen. These early differences notwithstanding, the time required to clear all parasites and/or parasite debris from thick blood films of recipients of uniformly curative doses was inde-

TABLE 2. *Pilot assessments of the activities of various 4-quinolinemethanols against infections with chloroquine-resistant and pyrimethamine-resistant strains of P. falciparum*

Compound WR- no.	Strain[b]	Daily dose[c] (mg base/kg of body weight)	Responses to treatment (no.)[a]			
			Effect on parasitemia			Cured
			None	Suppressed	Clearance with recrudescence	
7,930	VnOK	1.25		1 (P)		1 (P)
		5.0		1 (R)		2 (P)
		20.0				2 (P)
	MC-CH/Q	1.25	2 (P)			
		5.0			1 (R)	3 (P_2, R)
		10.0				1 (R)
		20.0				2 (P)
30,090	VnOK	10.0	1 (P)	2 (P)		
		20.0			1 (R)	3 (P)
		40.0				5 (P_3, R_2)
	VnM	2.5		2 (P)		
		10.0			2 (P, R)	2 (P, R)
		40.0			1 (R)	2 (P)
	MC-CH/Q	10.0	2 (P)		1 (P)	
		20.0		3 (P_2, R)	2 (R)	1 (P)
		40.0		1 (R)		4 (P_3, R)
		80.0				1 (R)
	UPA	0.625	2 (P)			
		2.5		2 (P)		
		10.0			2 (P, R)	
		40.0			1 (R)	3 (R)
	VnS	5.0		3 (P)		
		10.0			2 (P, R)	3 (P_2, R)
		20.0			1 (R)	7 (P_3, R_4)
		40.0			1 (R)	3 (P)
		80.0				1 (R)
142,490	VnOK	0.39	3 (P)			5 (P_2, R_3)
		1.56				2 (P)
		3.125				2 (P)
		6.25				4 (P)
		12.5				2 (P)
		50.0				2 (P)
		200.0				
	MC-CH/Q	0.39	3 (P)		2 (P, R)	3 (P, R_2)
		1.56				2 (P)
		3.125				2 (P)
		6.25				4 (P)
		12.5				2 (P)
		50.0				2 (P)
		200.0		2 (P)		
	VnS	1.25			2 (P)	2 (R)
		2.5				4 (P_2, R_2)
		5.0				2 (P)
		10.0				
				1 (P)	2 (P)	
177,602	VnS	1.25			1 (P)	4 (P_2, R_2)
		2.5				5 (P_3, R_2)
		5.0				3 (P)
		10.0				
226,253	VnS	0.625	1 (P)	1 (P)		2 (P, R)
		1.25				2 (P, R)
		2.5				

TABLE 2 (*continued*)

Compound WR- no.	Strain[b]	Daily dose[c] (mg base/kg of body weight)	Responses to treatment (no.)[a]			
			Effect on parasitemia			Cured
			None	Suppressed	Clearance with recrudescence	
183,544	VnOK	1.25	2 (P)	1 (P)		
		5.0		1 (R)	3 (P_2, R)	1 (P)
		10.0		1 (R)		
		20.0				3 (P_2, R)
183,546	VnOK	1.25	2 (P)	1 (P)		
		2.5	2 (R)			
		5.0		1 (P)	3 (P_2, R)	
		20.0				2 (P)
183,545	VnOK	1.25	2 (P)	1 (R)		
		5.0	3 (P, R_2)	2 (P)		
		20.0		1 (R)	3 (R)	2 (P)
183,606	VnOK	1.25	3 (P)			
		5.0	3 (R)	3 (P)		
		20.0	1 (R)	1 (R)	2 (P, R)	4 (P_2, R_2)
184,806	VnOK	2.5		1 (P)	1 (P)	
		10.0				3 (P_2, R)
		40.0				2 (P)
	MC-CH/Q	2.5		1 (P)		1 (P)
		10.0				2 (P)
		40.0			2 (P)[d]	
	VnS	2.5		4 (P)		
		5.0			1 (R)	2 (R)
		10.0			1 (P)	3 (P_2, R)
		40.0				4 (P_3, R)
177,504	VnOK	2.5	2 (P)			
		5.0		1 (R)		
		10.0		1 (R)	2 (P)[d]	
		40.0				2 (P)
	MC-CH/Q	2.5	2 (P)			
		5.0		1 (R)		
		10.0			1 (P)[d]	1 (P)
		40.0			1 (P)[d]	1 (P)
	VnS	2.5	2 (P)	1 (P)		
		5.0	2 (R)			
		10.0		4 (P_2, R_2)	1 (R)	
		20.0		1 (R)	2 (R)	2 (R)
		40.0				6 (P_3, R_3)
199,426	VnS	1.25	2 (P)			
		2.5	2 (P)			
		5.0		2 (P)		
		10.0		2 (P)		
		20.0				2 (R)
		40.0			1 (R)	1 (R)
		80.0		1 (R)		1 (R)

[a] Letters in parentheses refer to treatment status of monkey. P, Initial treatment; R, retreatment. Subscripts indicate numbers of subjects in each category.

[b] VnOk and VnM, Chloroquine-resistant Vietnam Oak Knoll and Vietnam Monterey strains; MC-CH/Q and UPA, pyrimethamine-resistant Malyan Camp-CH/Q and Uganda Palo Alto strains; VnS, chloroquine-resistant, pyrimethamine-resistant Vietnam Smith strain.

[c] Dose administered once daily for 7 consecutive days.

[d] Subject died of intercurrent disease before end of the follow-up period required to ascertain cure.

TABLE 3. *Activities of various 4-quinolinemethanols against infections with strains of P. falciparum of diverse levels of susceptibility to chloroquine and pyrimethamine contrasted with the activities of these agents against infections with P. berghei*

Compound WR- no.	Approx CD_{90} (total dose, mg base/kg of body weight)[a]					
	Infections with strains of *P. falciparum*[b]					Infections with *P. berghei*[c]
	VnOK	VnM	MC-CH/Q	UPA	VnS	
7,930	70.0		50.0			60.0
30,090	195.0	>280.0	>280.0	>280.0	>280.0	80.0
142,490	8.5		16.0		28.0	24.0
177,602					21.0	45.0
226,253					12.5	250.0
183,544	100.0					>640.0
183,546	110.0					>640.0
183,545	>140.0					>640.0
183,606	>140.0					>640.0
184,806	55.0		45.0		90.0	250.0
177,504	210.0		ND[d]		210.0	640.0
199,426					140.0	500.0

[a] The respective agents were administered orally once daily for 7 consecutive days to monkeys infected with *P. falciparum* and subcutaneously in single doses to mice infected with *P. berghei*.

[b] See footnote *a*, Table 2, for susceptibility of respective strains to chloroquine and pyrimethamine and for abbreviations of strains.

[c] The data on which these calculations were based were acquired by the late Leo Rane, Dora Rane, and Arba Ager of the Rane Laboratory, University of Miami, and were made available to us through the courtesy of D. E. Davidson, Walter Reed Army Institute of Research.

[d] ND, Not determined.

pendent of the dosage schedule (Table 4). On the 7-day dosage regimen, the time required to reduce parasite numbers from pretreatment densities in excess of 40 parasites per 10^4 erythrocytes to a <1 level and to eliminate parasite residues from thick blood films was essentially the same for all three strains of *P. falciparum* and both strains of *P. vivax*.

Observations on the effects of WR-142,490 on parasite morphology were limited to the early ring stages of *P. falciparum* because, except when parasitemias are overwhelming, the larger asexual parasites are sequestered in the deep vascular circulation (Schmidt, Am. J. Trop. Med. Hyg., in press). Changes in the structures of early rings appeared within 24 h of administration of a curative dose, irrespective of regimen. The initial alterations included swelling of the blue-staining portion of the ring, with vacuolation, enlargement, and rarefaction of the chromatin mass. These changes were followed by collapse of the ring substance and coalescence of the chromatin into a ragged structure. These alterations were remarkably uniform throughout the parasite population. They were in no way accentuated in recipients of supracurative doses. In most respects, the changes evoked by WR-142,490 were identical with those produced by quinine.

Effects of WR-142,490 on asexual parasites of all stages could be identified in infections with both strains of *P. vivax*. The changes in morphology of early rings and merozoites within mature segmenters were essentially the same as those described above for *P. falciparum*. The larger ring stages and more mature trophozoites exhibited marked vacuolation of the blue-staining substances in the ring component, plus dissolution of the pigment, as well as swelling and rarefaction of the chromatin mass. Changes in relevant structures were exaggerated in schizonts. Complete loss of structure of all parasite stages followed. Serial examinations of thick films suggested that the degenerated larger and more mature parasitic forms were cleared more slowly from peripheral blood than were damaged early rings. Observations on the effects of WR-142,490 on the morphology of male and female gametocytes were too few to be meaningful.

As indicated previously, retreatment of treatment failures with progressively larger doses of the same test agent has been an important feature of all evaluation procedures. It not only economizes on the numbers of owl monkeys required for appraising the activity of a test compound, but more importantly, it can provide early signals of emergence of parasites resistant to that agent. As was shown many years ago in studies on the activities of proguanil and pyrimethamine in rhesus monkeys infected with *P. cynomolgi* (32, 33) and more recently in studies on the activities of *s*-triazines and 6-substituted

TABLE 4. *Activities of WR-142,490 (mefloquine), administered orally in various dosage schedules, against infections with the Vietnam Oak Knoll, Malayan Camp-CH/Q, and Vietnam Smith strains of P. falciparum and the Vietnam Palo Alto and New Guinea Chesson Strains of P. vivax*

Dosage Regimen			Responses to Treatment - No.**				Mean Day (Range) From		Approx. CD_{90} (Total) Mg/Kg
Individual Dose Mg/Kg	No. of Doses*	Total Dose Mg/Kg	Effect on Parasitemia: None	Effect on Parasitemia: Suppressed	Effect on Parasitemia: Clearance with Recrudescence	Cured	Initial Dose to Parasite Clearance†	Last Dose to Recrudescence	
Infections with Vietnam Oak Knoll Strain - P. falciparum									
2.74	1	2.74	3(P)	3(R)	-	-	-	-	8.5
10.94	1	10.94	-	-	-	3(P)	6	-	
43.75	1	43.75	-	-	-	3(P)	7.7(7-8)	-	
0.91	3	2.73	2(P)	1(P)	-	-	-	-	8.5
3.65	3	10.95	-	-	-	3(P)	7.7(7-8)	-	
14.58	3	43.74	-	-	-	3(P)	7	-	
0.39	7	2.73	3(P)	-	-	-	-	-	14.0
1.56	7	10.92	-	2(P,R)	-	$7(P_4,R_3)$	7.6(7-9)	-	
3.125	7	21.88	-	-	-	$5(P_2,R_3)$	7.8(7-9)	-	
6.25	7	43.75	-	-	-	5(P)	7.8(7-8)	-	
Infections with Malayan Camp-CH/Q Strain - P. falciparum									
2.74	1	2.74	2(P)	-	-	-	-	-	8.0
5.48	1	5.48	-	-	1(R)	2(R)	7.7(6-9)	13	
10.94	1	10.94	-	-	-	$6(P_3,R_3)$	6.8(4-9)	-	
43.75	1	43.75	-	-	-	3(P)	4.7(4-6)	-	
0.91	3	2.73	3(P)	1(P)	-	-	-	-	9.0
1.82	3	5.46	-	2(R)	-	1(R)	9	-	
3.65	3	10.95	-	-	-	$6(P_3,R_3)$	8.3(7-9)	-	
14.58	3	43.74	-	-	-	3(P)	5.7(5-6)	-	
0.39	7	2.73	3(P)	-	-	-	-	-	14.0
1.56	7	10.92	-	-	2(P)	$5(P_2,R_3)$	9.0(7-11)	16(15-17)	
2.5	7	17.5	-	-	-	8(R)	8.1(5-10)	-	
3.125	7	21.88	-	-	-	$5(P_2,R_3)$	8.0(7-9)	-	
6.25	7	43.75	-	-	-	5(P)	6.0(4-7)	-	
Infections with Vietnam Smith Strain - P. falciparum									
1.25	7	8.75	-	2(P)	-	-	-	-	28.0
2.5	7	17.5	-	2(P)	2(P)	2(R)	7.0(6-8)	20(19-21)	
5.0	7	35.0	-	-	-	$13(P_9,R_4)$	7.2(4-9)	-	
10.0	7	70.0	-	-	-	2(P)	7	-	
Infections with Vietnam Palo Alto Strain - P. vivax									
0.625	7	4.38	1(P)	1(P)	1(P)‡	-	8	-	8.0
1.25	7	8.75	-	-	-	4(R)	5.5(5-6)	-	
2.5	7	17.5	-	-	1(P)‡	$10(P_4,R_6)$	6.7(4-11)	-	
5.0	7	35.0	-	-	-	$9(P_5,R_4)$	5.9(4-9)	-	
Infections with New Guinea Chesson Strain - P. vivax									
0.625	7	4.38	1(P)	2(P)	-	-	-	-	14.0 or <
2.5	7	17.5	-	-	-	$6(P_3,R_3)$	6.5(3-9)	-	
10.0	7	70.0	-	-	-	3(P)	6.7(6-7)	-	

*Repetitive doses administered once daily on successive days.

**Letters in parentheses refer to treatment status of monkey. P = initial treatment; R = retreatment. Subscripts indicate numbers of subjects in each category.

†Days from first dose of drug to first of a series of five negative thick blood films on consecutive days. A single number without range implies identical clearance times for all subjects.

‡Death from cage trauma prior to completion of follow-up period; no recrudescence prior to death.

2,4-diaminoquinazolines in owl monkeys infected with *P. falciparum* and *P. vivax* (Schmidt, Am. J. Trop. Med. Hyg., in press), failure to control parasitemia on retreatment of a persisting infection with doses of an agent equal to or greater than those that are routinely curative on primary application is almost invariably a sensitive and reliable indicator of emer-

TABLE 5. *Activities of WR-142,490 (mefloquine), administered intravenously, against infections with the Vietnam Oak Knoll and Vietnam Smith strains of P. falciparum and the Vietnam Palo Alto strain of P. vivax*

Dosage Regimen			Responses to Treatment - No.**				Mean Day (Range) From		Approx. CD_{90} (Total) Mg/Kg
			Effect on Parasitemia						
Individual Dose Mg/Kg	No. of Doses*	Total Dose Mg/Kg	None	Suppressed	Clearance with Recrudescence	Cured	Initial Dose to Parasite Clearance†	Last Dose to Recrudescence	
Infections with Vietnam Oak Knoll Strain - P. falciparum									
3.75	1	3.75	-	3(P)	-	-	-	-	16.0
7.5	1	7.5	-	-	2(P, R)	4(P_2, R_2)	5.7(4-7)	15.5(15-16)	
15.0	1	15.0	-	-	1(R)	6(P_5, R)	5.6(5-7)	20	
30.0	1	30.0	-	-	-	3(P_2, R)	5.7(5-6)	-	
5.0	3	15.0	-	-	-	2(P)	7	-	15.0 or <
10.0	3	30.0	-	-	-	3(P_2, R)	6.0(5-7)	-	
Infections with Vietnam Smith Strain - P. falciparum									
3.75	1	3.75	3(P)	-	-	-	-	-	22.0
7.5	1	7.5	-	5(P_3, R_2)	1(R)	-	7	16	
15.0	1	15.0	-	-	3(P)	6(P_2, R_4)	6.6(5-8)	20.0(19-22)	
30.0	1	30.0	-	-	-	6(P_2, R_4)	5.7(5-7)	-	
5.0	3	15.0	-	-	1(P)	1(P)	7	20	22.0
10.0	3	30.0	-	-	-	3(P_2, R)	5.7(4-7)	-	
Infections with Vietnam Palo Alto Strain - P. vivax									
1.88	1	1.88	2(P)	-	-	-	-	-	7.0
3.75	1	3.75	-	1(P)	6(P, R_5)	-	6.5(5-8)	20.8(13-27)	
7.5	1	7.5	-	-	-	9(P_2, R_7)	4.9(3-7)	-	
15.0	1	15.0	-	-	-	4(P)	3.5(3-4)	-	
2.5	3	7.5	-	-	2(P)	2(R)	6.7(6-8)	17.0(15-19)	11.0
5.0	3	15.0	-	-	-	2(P)	5	-	
10.0	3	30.0	-	-	-	2(P)	4.5(4-5)	-	

*Repetitive doses administered once daily on successive days.

**Letters in parentheses refer to treatment status of monkey. P = initial treatment; R = retreatment. Subscripts indicate numbers of subjects in each category.

†Days from first dose of drug to first of a series of five negative thick blood films on consecutive days. A single number without range implies identical clearance times for all subjects.

gence of parasites resistant to the compound under investigation. The data in Tables 2, 4, and 5 show that in no case was the dose of WR-142,490 required to cure a previously treated infection larger than that required for cure in previously untreated cases. Insofar as the current studies have gone, they at least indicate that emergence of parasites resistant to this 4-quinolinemethanol does not occur rapidly in infections with *P. falciparum* and *P. vivax* and may signify that it is an event that is not likely to occur.

Activities of WR-142,490 against infections with *P. cynomolgi*. (i) Prophylactic and radical curative activities. Although appraisals of the prophylactic and radical curative activities of WR-142,490 were of limited dimensions, they sufficed to show that this compound was without effect on development of early tissue schizonts when administered throughout the entire incubation period in daily doses of 1.25 to 20.0 mg/kg (Table 6) and had little effect, if any, on persistence of developed tissue schizonts when delivered in doses up to 40.0 mg/kg daily for 7 days (Table 7). The relatively short extension of the relapse interval encountered in developed infections treated with the 20.0 and 40.0-mg/kg doses (Table 7, column 7) could well be ascribed to the continued presence of WR-142,490 in circulating blood in concentrations sufficient to destroy blood schizonts or inhibit their development.

(ii) WR-142,490 versus chloroquine as a companion drug to primaquine in a curative drug regimen. Determination of the dose of WR-142,490 required to eliminate blood schizonts was an essential preliminary to evaluating the capacity of this agent to serve as a companion drug to primaquine in a radical curative regimen. Data on the dose of WR-142,490 required to effect parasite clearance in the radical curative study (Table 7, columns 1 and 4), to-

gether with the results of the very limited appraisal of the capacity of this compound to cure trophozoite-induced infections (Table 8), indicated that 10.0 mg/kg administered daily for 7 days should suffice for the above purpose. This dosage of WR-142,490 was routinely employed in combination with various doses of primaquine in the companion drug evaluation. Chloroquine was administered in correspondingly effective doses of 2.5 mg/kg daily for the same time period.

As indicated in the upper section of Table 9,

TABLE 6. *Preliminary assessment of the prophylactic activity of WR-142,490 in rhesus monkeys challenged with sporozoites of the B strain of P. cynomolgi*

Daily dose (mg/kg of body weight)[a]		Monkey no.	Day of patency after challenge[b]	Days delay in onset of patency	Remarks
WR-142,490	Primaquine				
		7588	8		
1.25		7551	8	0	No protection
5.0		7583	8	0	No protection
20.0		7585	8	0	No protection
	0.75	7586	>68	>60	Completely protected[c]

[a] Doses administered once daily on the day before inoculation, 2 h preinoculation (zero time), and for 7 consecutive days thereafter.

[b] Inoculum = 1.3×10^6 sporozoites.

[c] Fully susceptible to rechallenge with 10^6 sporozoites 68 days after challenge for reported study.

TABLE 7. *Radical curative activity of WR-142,490 as exhibited in rhesus monkeys infected with sporozoites of the B strain of P. cynomolgi*

Daily dose (mg/kg of body weight)[a]		Responses to treatment (no.)[b]			Mean day (range) from:	
		Effect on parasitemia		Cured[c]	Initial dose to parasite clearance[d]	7th dose to relapse
WR-142,490	Chloroquine	Suppressed	Clearance with relapse			
1.25		1? (P)	0	0		
5.0		2 (P)	0	0		
10.0		0	7 (3P, $2R_1$, R_2, R_3)	0	5.1 (5–6)	10.1 (8–12)
20.0		0	3 (2P, R_1)	0	4.3 (3–5)	17.0 (15–20)
40.0		0	1 (P)	0	5.0	20.0
	5.0	0	6 (3P, $3R_1$)	0	4.3 (4–5)	12.3 (11–14)

[a] Doses administered once daily for 7 consecutive days.

[b] Letters in parentheses refer to status of infections at time of treatment: P, previously untreated primary attack; R_1, first relapse; R_2, second relapse; etc. Numbers preceding letters indicate number of infections in the relevant categories.

[c] All persisting infections or relapses on WR-142,490 were retreated with chloroquine (5.0 mg/kg of body weight) daily for 7 consecutive days. In all cases, infections relapsed 10 to 15 days after delivery of the seventh dose of chloroquine.

[d] Days from first dose to first of a series of five negative thick blood films on consecutive days.

TABLE 8. *Preliminary assessment of the blood schizonticidal activity of WR-142,490 as exhibited in rhesus monkeys infected with trophozoites of the B strain of P. cynomolgi*

Daily dose (mg/kg of body weight)[a]	Monkey no.[b]	Parasitemia (no. of parasites/10^4 erythrocytes)							Remarks
		Day pretreatment	Day of treatment				Day posttreatment		
			1	3	5	7	1	3	
0.0	7837P	20	156	1,560	122	30	60	254	
2.5	7732P	53	170	1,220	1,140	136	132	680	Retreated
10.0	7739P	45	110	8	<1	Neg.[c]	Neg.	Neg.	Cured
10.0	7732R	680	540	240	3	<1	Neg.	Neg.	Cured
40.0	7740P	73	86	1	Neg.	Neg.	Neg.	Neg.	Cured

[a] Dose administered orally once daily for 7 consecutive days.

[b] Each monkey inoculated intravenously with 5×10^5 trophozoites. P, Initial treatment; R, retreatment.

[c] Neg., Negative.

TABLE 9. *Capacity of WR-142,490 to serve as a companion drug to primaquine in radical cure of infections with sporozoites of the B strain of P. cynomolgi*

Determination	Daily dose (mg/kg of body weight)[a]			Responses to treatment		Mean day from last dose to relapse (range)
	WR-142,490	Primaquine	Chloroquine	No. of cures[b]	No. of relapses[b]	
This study	10.0	0.375		7 (2P, R_1, R_2, $4R_4$)	10 (4P, $2R_1$, $2R_2$, R_3, R_4)	25.2 (11–68)
	10.0	0.75		22 (3P, $10R_1$, $4R_2$, $3R_3$, $2R_4$)	4 (3P, R_2)	20.2 (11–30)
	10.0	1.5		4 ($3R_1$, R_3)	0	
		0.375	2.5	0	3 (3P)	12.7 (11–15)
		0.75	2.5	5 (2P, $3R_1$)	0	
1973–1975		0.375	2.5	7 (P, $4R_1$, $2R_2$)	18 (13P, $3R_1$, $2R_2$)	20.0 (7–60)
		0.5	2.5	29 (11P, $14R_1$, $4R_2$)	6 (4P, $2R_1$)	24.3 (11–71)
		0.75	2.5	46 (25P, $12R_1$, $9R_2$)	2 (P, R_1)	38.5 (31–46)

[a] Doses administered concomitantly once daily for 7 consecutive days.

[b] Letters in parentheses refer to status of infections at time of treatment; P, previously untreated primary attack; R_1, first relapse; R_2, second relapse; etc. Numbers preceding letters indicate number of infections in the relevant categories.

cure rates of 41, 85, and 100% were obtained when primaquine was administered in daily doses of 0.375, 0.75, or 1.5 mg/kg of body weight, respectively, in combination with 10.0-mg/kg doses of WR-142,490. Cure rates of 0 and 100% were attained when 0.375- and 0.75-mg/kg doses of primaquine were delivered in combination with 2.5-mg/kg doses of chloroquine. Because the numbers of infections treated with the latter combination were much smaller than those treated with primaquine and WR-142,490 and this difference in sample size could have prejudiced the comparison, attention has been directed to results acquired with the chloroquine and primaquine combination in more expansive evaluations pursued in an identical manner from 1973 to 1975 (30). The relevant data, summarized in the lower section of Table 9, show that delivery of 0.375- and 0.75-mg/kg doses of primaquine with chloroquine resulted in cure rates of 28 and 96%. Although these rates and those attained with the primaquine and 4-quinolinemethanol combination are not identical, they are close enough to suggest that at an appropriate blood schizonticidal dose, WR-142,490 could function as a companion drug to primaquine as effectively as chloroquine, or nearly so.

DISCUSSION

As was stated in the introduction to this report, the 4-quinolinemethanols have been investigated intensively in the current Malaria Research Program. Because of the magnitude and productivity of this effort and the promise that it offers in the direction of improved malaria therapy, both the background and evolution of these investigations merit detailed attention.

Current interests in the 4-quinolinemethanols rested upon studies pursued during the World War II Malaria Chemotherapy Program, investigations that stemmed from elucidation of the structural components of quinine (a naturally occurring 4-quinolinemethanol) essential for antimalarial activity (12), and development of procedures for synthesizing the essential moieties and modifying them (1, 17). Altogether, 177 derivatives, varying widely with respect to substituents on the 4-carbinol group and quinoline nucleus, were prepared during the World War II Program (3); 156 of these exhibited measurable activity against infections with *P. lophurae* in the duck and/or *P. gallinaceum* in the chicken (3, 11). Of the 156, 8 with greatest activity in these avian test systems were evaluated for tolerability and antimalarial properties in human volunteers (2). Four other derivatives, highly active against the avian malarias, were examined for tolerability only (2).

Each of the eight agents referred to above was compared with quinine for capacity to cure infections with trophozoites of *P. vivax*. Although these comparisons involved work with small numbers of volunteers, they sufficed to show that six of the compounds were distinctly less active than quinine against the above infections. One of the new agents had activity equal to that of this reference drug. The eighth derivative, SN-10,275 [2-phenyl-6,8-dichloro-α-(2-piperidyl)-4-quinolinemethanol], was at least three times as active as quinine. Unfortunately, it evoked phototoxicity in 8 of 19 volunteers, reactions of serious dimensions parallelling persistence of the agent in serum and lasting for 2 weeks to 10 months after delivery of the final

dose (2, 26). SN-13,710 [2-(*p*-chlorophenyl)-7-chloro-α-(di-*N*-butylaminomethyl)-4-quinolinemethanol], one of the four derivatives examined only for tolerability, was also phototoxic (2). Two of the eight compounds, SN-10,275, referred to above, and SN-2,157 [6-methoxy-α-(2-piperidyl)-4-quinolinemethanol], were appraised for capacity to prevent or cure infections induced with sporozoites of *P. vivax*; neither was active. Only one of the eight agents (SN-2,157) was examined for activity against infections with *P. falciparum*. Based on the dose required to achieve a curative result, this derivative was half as active against infections with this plasmodium as against infections with *P. vivax*.

Although synthesis of 4-quinolinemethanols and evaluation of the activities of the newly prepared derivatives against avian malarial infections continued throughout the World War II Program and for several years thereafter, examinations in human volunteers were concluded in mid-1944. This curtailment was due in part to disappointment with the activities of compounds examined to that date and concerns with the hazards of phototoxicity, but in larger part, to essentially full commitment of volunteer resources to studies on the 4-aminoquinolines as suppressive drugs and 8-aminoquinolines as radical curative agents.

There were several reasons for the renewed interests in the 4-quinolinemethanols in the current Malaria Research Program. First, with one possible exception, the known classes of blood schizonticidal drugs were not active against infections with strains of *P. falciparum* resistant to both chloroquine and pyrimethamine. The effectiveness of quinine against infections with some resistant strains suggested that as a class, the 4-quinolinecarbinols might have such activity. Second, although large numbers of compounds of this class had been synthesized before 1963, there were significant gaps in structure-activity explorations. Numerous possibilities, approachable with currently available chemical technology, existed for substituting both well-known and novel groupings into various positions on the quinoline nucleus and adding a variety of alkylaminoalkyl and other basic groupings to the 4-carbinol. Third, the clinical studies of the World War II Program referred to above suggested that phototoxicity was not a quality common to all quinolinemethanols that exhibited significant antimalarial activity. Development of two easily manipulated, inexpensive procedures for measuring phototoxicity in mice (15, 28) made it possible to determine whether a derivative that displayed promising antimalarial activity in an experimental animal model was phototoxic before examining this agent for tolerability and therapeutic activity in human volunteers.

Of the nearly 300 4-quinolinemethanols acquired in the current Malaria Research Program and examined for activity in the *P. berghei*-mouse model, approximately 100 were recovered from stores of antimalarial drugs prepared during the World War II Program. These derivatives were evaluated early in the current program for activity in mice infected with *P. berghei*. Significant numbers were also examined for phototoxicity in one of the mouse models (16). Two, WR-7,930 (the phototoxic compound previously designated SN-10,275) and WR-30,090 (formerly coded SN-15,068), exhibited outstanding and approximately equal activity against infections with *P. berghei* (see Table 1 for structures and Table 3 for activities), but strikingly different levels of phototoxicity (16, 28). The dose of WR-30,090 required to produce a minimal phototoxic reaction was from 10 to 50 times the amount of WR-7,930 required to produce a severe reaction. On the basis of these results (acquired before the development of the human plasmodium-owl monkey model and its use in evaluating activities of new agents), it was decided to prepare WR-30,090 for study in human volunteers. After completion of comprehensive examinations of the pharmacology and metabolic fate of WR-30,090 in lower animals (21; M. H. Heiffer, personal communication), the tolerability of this compound was explored cautiously in human volunteers (20). This exploration showed that doses of WR-30,090 up to and including 0.23 g could be administered every 8 h for 6 days without evoking phototoxicity or other untoward reactions.

Subsequent appraisals of the antimalarial activities of WR-30,090 in human volunteers showed: (i) that this agent was equally active against acute infections with trophozoites or sporozoites of chloroquine-susceptible and highly chloroquine-resistant strains of *P. falciparum* and was routinely curative of such infections when administered in a total dose of 4.14 g over a period of 6 days (20); (ii) that somewhat smaller doses sufficed to cure infections with trophozoites of the Chesson strain of *P. vivax*, but that full course doses of 4.14 g failed to cure infections with sporozoites of this strain (20); (iii) that eight weekly doses, each of 0.69 g, effected suppressive cure of 10 of 14 infections with sporozoites of the multidrug-resistant Smith strain of *P. falciparum* and 2 of 6 infections with sporozoites of the drug-susceptible Chesson strain of *P. vivax* (10); and (iv) that the activity of WR-30,090 against infections with *P.*

falciparum was not compromised by full resistance to pyrimethamine or partial resistance to quinine (10, 20).

The capacity of WR-30,090 to cure infections with chloroquine-resistant strains of *P. falciparum* acquired under field conditions was evaluated in two subsequent studies, one involving members of the Armed Services who had become infected while on duty in South Vietnam (7), the other an indigenous population in southeast Thailand (14). In the first of these investigations, 31 of 34 infections were cured by administration of 4.14 g of the compound over a 6-day period; in the second, 54 of 63 infections were cured by delivery of 4.5 g over the same period. Phototoxicity was not encountered in either of these studies; however, significant numbers of comparatively minor toxic reactions, attributed to WR-30,090, were recorded in the evaluation pursued in Thailand.

In two respects, the results of the clinical studies, summarized above, were critically important to continued interest in the 4-quinolinemethanols. First, they suggested that at least some members of this class of compounds could be expected to have essentially equal activity against infections with drug-susceptible and multidrug-resistant strains of *P. falciparum*. Second, they showed that antimalarial activity of a significant order could be obtained without phototoxicity and indicated that the risk of encountering such a toxic reaction could be appraised in simple, quick, and inexpensive tests in mice.

The clinical studies suggested that WR-30,090 would fall short of having the antimalarial properties required of a generally useful blood schizonticidal drug. In the first place, this compound had a small therapeutic index. This meant that essentially maximum tolerated doses had to be administered to insure that infections would be cured regularly. As would be expected, delivery of such doses to a population heterogeneous with respect to age and health status, as in the field study in southeast Thailand, had significant liabilities (14). Second, the total dose of WR-30,090 required for curative results was comparatively large, well above that which could be administered in a single dose or three equal fractions. Delivery of the requisite dose in three daily fractions for 6 consecutive days was not only laborious, but resulted in relatively slow control of fever and parasitemia. The size of the current dose, together with the limited water solubility of WR-30,090, would preclude administration of this agent via a parenteral route.

The foregoing limitations of WR-30,090 would have been predicted from the results of the pilot assessments of the activities of this compound in owl monkeys infected with various strains of *P. falciparum* (Tables 2 and 3). Unfortunately, these appraisals were not available when plans were formulated for evaluating the activity of WR-30,090 in human volunteers. It is worth noting that the selection of this derivative for study in volunteers rested largely on the activity that it displayed in mice infected with *P. berghei*, and that, contrary to most experiences with the quinolinemethanols, this agent was significantly more active against this rodent infection than against infections with *P. falciparum* in the owl monkey.

Three derivatives (WR-142,490, WR-184,806, and WR-226,253), each significantly more active than WR-30,090, emerged from the pilot studies described in this report. WR-226,253, probably the most active of the three, was submitted for examination in January 1976, shortly before this project terminated, and because of time restrictions could not be studied in depth. WR-142,490, only slightly less active than WR-226,253, was the first of the newly synthesized quinolinemethanols to be examined in the *P. falciparum*-owl monkey model, with results that were exceptionally promising. As shown in Table 2, this compound was equally active against infections with strains of the above plasmodium resistant to chloroquine, to pyrimethamine, or to both of these drugs, was 10 or more times as active as WR-30,090 against such infections and had a much larger therapeutic index. Although a side-by-side appraisal of the activities of WR-142,490 and chloroquine was not undertaken, the efficacies of these compounds could be compared indirectly by drawing upon the results of the current assessment of the activity of WR-142,490 against infections with the chloroquine-susceptible Malayan Camp-CH/Q strain (Tables 2 through 4) and those of an earlier evaluation of the activity of chloroquine against infections with the same strain (Schmidt, Am. J. Trop. Med. Hyg., in press). This comparison showed that, dose for dose, WR-142,490 was five times as active as chloroquine and because of its lesser toxicity had a significantly larger therapeutic index, 12 as contrasted with somewhat less than 4.

The expanded experimental studies of the antimalarial properties of WR-142,490 undertaken when it was decided to prepare this compound for evaluation in human volunteers provided full confirmation of the results of the pilot appraisals. In addition, they showed: (i) that the activity of WR-142,490 was a function of the total dose delivered, and as a corollary, that single doses were as effective as the same amount administered in three of seven equal fractions on as many days; (ii) that administration of this deriv-

ative intravenously was both feasible and effective; and (iii) that the compound was at least as effective against infections with the blood schizonts of *P. vivax* as against infections with the same forms of *P. falciparum*. Examination of the capacities of WR-142,490 to serve as a causal prophylactic or radical curative agent, by using infections with *P. cynomolgi* in the rhesus monkey as the experimental model, showed that this agent was devoid of activity against both early and late tissue schizonts. Studies in the same model indicated that as a companion drug to primaquine in a curative drug regimen WR-142,490 was essentially as effective as chloroquine. This latter demonstration could be highly important should it become desirable or necessary to embark upon wide-scale application of a combination suppressive-curative drug regimen in areas where strains of *P. falciparum* are resistant to the 4-aminoquinolines and the currently recommended chloroquine-primaquine regimen is of limited benefit.

Coincident with the above evaluations, preclinical studies of the pharmacology of WR-142,490 were being pursued elsewhere. These investigations showed that this derivative was devoid of phototoxicity when administered in maximum tolerated doses to mice (W. E. Rothe and M. Grenan, personal communications) and pigs (W. W. Bay, C. A. Gleiser, K. R. Pierce, and R. G. Feldman, personal communication), that it had acceptable levels of toxicity for various experimental animals (M. H. Heiffer, personal communication) and relatively reproducible patterns of absorption, distribution in blood and other tissues, excretion, and metabolism in rats (21).

Human tolerability studies (37) involving 42 volunteers in all showed that single oral doses of WR-142,490 up to and including 1,000.0 mg could be administered without untoward reactions. Single doses of 2,000.0 mg were equally well accepted by four of these volunteers; two other subjects had transient headaches and dizziness for 48 h after receiving such doses. No volunteer exhibited evidence of phototoxicity.

Highly controlled evaluations of the activities of WR-142,490 against infections with specific strains of *P. falciparum* and *P. vivax* in nonimmune subjects were limited in scope because of curtailment of the volunteer program. They sufficed to show: (i) that this compound was equally active against established infections with various drug-susceptible and multidrug-resistant strains of *P. falciparum* (37); (ii) that single oral doses of 1,000.0 mg were almost always curative and doses of 1,500.0 mg were uniformly curative of such infections (37); (iii) that single doses of 400.0 mg effected prompt clearance of fever and parasitemia, but were rarely curative (37); (iv) that a variety of dosage schedules, ranging from 250.0 mg weekly for eight doses to 1,000.0 mg every 4 weeks for three doses, effected suppressive cure of infections with sporozoites of the multidrug-resistant Vietnam Smith strain (9); and (v) that a single dose of 1,000.0 mg provided complete protection for 2 weeks and partial protection for 4 weeks against challenge with sporozoites of the multidrug-resistant Vietnam Marks strain (27). The results of preliminary studies of the activity of WR-142,490 against infections with the drug-susceptible Chesson and El Salvador strains of *P. vivax* suggested that trophozoite-induced infections could be cured by a single 400.0-mg dose (10) and showed that sporozoite-induced infections could not be cured by a single dose of 1,000.0 mg (37), but could be suppressed by repetitive weekly doses of 250.0 mg (10).

Preliminary reports of the results of two field-type studies of the activity of WR-142,490 provided general support for the findings in volunteers. Both investigations were pursued in Thailand in areas where infections with chloroquine-resistant strains of *P. falciparum* are highly prevalent. One dealt with the effectiveness of WR-142,490 in treating established infections (13). The second was concerned with the capacity of this compound to suppress infections with both *P. falciparum* and *P. vivax* during periods of intense malaria transmission (E. Pearlman, E. Doberstyn, S. Sudsok, W. Thiemanum, R. Kennedy, and C. Canfield, presentation at the 26th Annual Meeting, American Society of Tropical Medicine and Hygiene, November 1977, Denver, Colorado). In the first study, administration of a single dose of 1,500.0 mg of WR-142,490 as the hydrochloride salt effected cure of 29 of 29 naturally acquired *P. falciparum* infections, all presumably chloroquine-resistant. In the second study, each of three dosage regimens was remarkably effective in suppressing infections with both *P. falciparum* and *P. vivax* in individuals exposed repeatedly to bites of infected mosquitoes. There were but three infections with *P. falciparum* and four with *P. vivax* among 487 recipients of WR-142,490 in doses of either 180.0 mg once weekly, 360.0 mg once weekly, or 360.0 mg biweekly. In striking contrast, there were 19 infections with *P. falciparum* and 29 with *P. vivax* in the same time period among 36 recipients of placebos.

The accomplishments of WR-142,490 in both the human volunteer and field-type studies were in all important respects comparable to the attainments of this agent in counterpart experimental studies set forth in the body of this report, but in some respects, especially suppres-

sive usage, went farther. At this very early stage of its development, WR-142,490 (referred to as mefloquine, hereafter) must be viewed as a blood schizonticide of very high potency and breadth of action. If the potential that has been exhibited to date can be fully realized, this compound should be useful not only in areas where strains of *P. falciparum* resistant to both chloroquine and pyrimethamine are prevalent, but wherever the human malarias are transmitted. In short, mefloquine could assume the role of a generally useful blood schizonticidal drug.

Many carefully controlled studies, some of considerable dimensions, will have to be undertaken in widely separated geographic areas before it is known whether mefloquine can assume the position referred to above. Although a full listing of such investigations goes beyond the scope of this discussion, note will be taken of two interrrelated issues that deserve prompt attention. The first pertains to determining the total dose of mefloquine required for uniform cure of established infections with both drug-susceptible and multidrug-resistant strains of *P. falciparum* and the influence of the dosage regimen on this quantity. The limited evaluations pursued to date indicate that a dose of 1,500.0 mg of mefloquine hydrochloride (1,360.0-mg mefloquine base) delivered at a single sitting is invariably curative. A single-dose regimen is ideal from the viewpoint of supervising drug intake; however, as indicated below, it may have liabilities which limit its application. Therefore, it is important to determine to what extent the dosage schedule influences the total dose required for the same level of therapeutic efficacy, specifically schedules that involve administration of fractions of the total dose at intervals during 1 day or, at the most, on 2 or 3 successive days.

The second issue, so closely linked to the first that it can be explored simultaneously, pertains to determining the incidence and severity of untoward reactions associated with administration of single therapeutically effective doses of mefloquine and the influence of split-dosage regimens on such reactions. Single 1,500.0-mg doses were administered to a group of carefully selected human volunteers without evidence of toxicity (37); however, untoward reactions were reportedly exhibited when a more heterogenous group of patients in Thailand were treated with the same dose (13). Reactions encountered in "about half" of this patient group included "abdominal pain, dizziness, nausea, vomiting, and weakness". Although the severity of these symptoms was not described, it was indicated that they were transitory. If carefully controlled studies show that such reactions are clearly linked to administration of mefloquine, use of a single-dose regimen of 1,500.0 mg would be contraindicated. The fact that the observed toxic reactions were transitory suggests that they appeared when certain concentrations of mefloquine were reached in serum or other tissues and disappeared when concentrations dropped below these levels. It would be expected that these critical levels would not be attained on repeated administration of fractional doses and untoward reactions would thereby be avoided.

The possibility that parasites resistant to mefloquine might emerge quickly and thereby negate the therapeutic utility of this agent obviously merits attention. To date, there have been no signs of emergence of parasites resistant to this compound, either in the clinical studies or in experimental investigations which, as stated previously, were designed both to encourage this phenomenon and to identify it promptly. These negative observations are, perhaps, less reassuring than the fact that mefloquine, as a 4-quinolinemethanol, is closely related to quinine both in structure and mode of antimalarial action and that whereas differences in the susceptibility of various strains of *P. falciparum* and *P. vivax* to quinine have been recognized for years, development of quinine resistance is a relatively recent event, if it has occurred at all. All things considered, it appears unlikely that resistance to mefloquine is likely to appear early in the application of this compound, although it would be foolhardy to suggest that such a phenomenon will never occur. The optimism implicit in this prediction might appear to be challenged by a recent report (24) showing that two closely related strains of *P. berghei* acquired high levels of resistance to mefloquine after comparatively short exposure to this compound, in the case of one strain as rapidly as to pyrimethamine. The significance of this demonstration for any plasmodial infection other than that with *P. berghei* is clouded by the companion finding that resistance to mefloquine, unlike that to pyrimethamine, was an extremely labile characteristic, disappearing after the first passage of one of the strains through untreated mice.

In concluding this report, we submit that the systematic studies of the 4-quinolinemethanols pursued in the current Malaria Research Program can be considered to have been remarkably productive when accomplishments are compared with those of similar investigations. Two of the compounds included in the studies, WR-30,090 and mefloquine, exhibited sufficient activity in various experimental infections to warrant stepwise evaluation in human volunteers and in ity in various experimental infections to warrant stepwise evaluation in human volunteers and in

the field, where they exhibited high orders of efficacy against infections with multidrug-resistant stains of *P. falciparum,* thereby meeting one of the targets of the above Program. Mefloquine, by far the more active of the two compounds, developed entirely within the above Program, promises to be broadly useful, both in treating established infections and for routine suppressive purpose. If this promise is not realized, it will doubtless not be for lack of antimalarial activity, but rather because of toxicological attributes not identified in the small-scale studies pursued to date. Should unforeseen and insurmountable toxicity problems appear, there are two congeners of mefloquine that merit attention as possible substitutes. These derivatives, WR-226,253 and WR-184,806, exhibited slightly more and slightly less activity, respectively, than mefloquine in pilot appraisals in human plasmodium-owl monkey models and are sufficiently different from the latter compound and from each other in chemical structure to have different toxicological characteristics. Although it seems likely that mefloquine or one of these two standby 4-quinolinemethanols could meet the needs for a broadly active, generally useful blood schizonticidal drug, it would not seem wise to conclude synthesis and evaluation of new representatives of this chemical class until that accomplishment is a reality.

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