

Evaluation of Experimental Antimalarial Drugs in Rhesus Monkeys
Infected with *Plasmodium cynomolgi*

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OBJECTIVE: To evaluate the effectiveness of selected experimental antimalarial drugs in suppressing *Plasmodium cynomolgi* parasitemias in rhesus monkeys. Experimental drugs were selected and furnished by the Division of Medicinal Chemistry, Walter Reed Army Institute of Research.

DESCRIPTION: Experimental antimalarial drugs being developed by the US Army Antimalarial Drug Program were evaluated in rhesus monkeys for suppressive activity against *Plasmodium cynomolgi* var. *bastianelli*. After a 6 week conditioning period in the laboratory, healthy, malaria-free Indian rhesus monkeys weighing 1.5–3.5 kg were infected by intravenous injection of 5×10^8 parasitized erythrocytes from a splenectomized donor monkey. On day 4, when parasitemia was at the peak (200–900,000/cmm) a 7-day course of daily drug administration was initiated. Blood parasites were counted daily for the first 15 days and every two days thereafter. At the end of thirty days, monkeys with negative blood smears were splenectomized. Only those monkeys which showed no recrudescence of parasitemia for 30 days after splenectomy were classified as cured. Clinical signs of drug toxicity or intercurrent disease which appeared during the course of study were recorded. Necropsy examinations were performed terminally.

Drugs were dissolved or suspended in a vehicle containing 0.3% methylcellulose in distilled water within one hour before administration. In most cases, drugs were administered by nasogastric intubation after an 18 hour fast, but parenteral routes have been elected in special situations. Each drug was tested over a range of doses to determine a minimum curative dose, a minimum effective dose and, sometimes, a maximum tolerated dose. Normally two monkeys were treated at each dose level, with doses spaced 0.5 log 10 apart (ie. 316, 100, 31.6, 10.0 3.16, 1.0 mg/kg, etc). Usually 6 to 10 monkeys were sufficient to permit evaluation of a single drug. Two vehicle-treated controls were included with each group of 10 drug-treated monkeys.

PROGRESS: Eighteen (18) experimental antimalarial drugs were evaluated during the year. These compounds and their minimum curative doses are listed in Table 1. Seven of these compounds are "standard" antimalarials. These baseline data will be used for comparative purposes when structurally related drugs are evaluated.

Two antimalarial drugs were tested in combination with sulfadiazine. WR 122455 (a phenanthrenemethanol) and sulfadiazine did not exhibit additive antimalarial activity when administered in combination. WR 93133 and sulfadiazine administered in combination had additive or synergistic antimalarial activity.

Table 1. Minimum Curative Doses of Antimalarial Drugs in *Plasmodium cynomolgi* Infected Rhesus Monkeys

Type of Drug	WRAIR Drug Number	Minimum Curative Dose (mg/kg/day)
2, 4-Diaminoquinazolines	WR 135403	0.1
	WR 151341	0.1
	WR 154907	0.1
	WR 162877	0.1
	WR 179214	0.316
Quinolines	WR 2977 (Amodiaquine)	10.0
	WR 4234 (Plasmochin)	31.6
	WR 7295 (Endochin)	NC ¹
	WR 187005	100.0
	WR 198557	10.0
Sulfones/sulfonamides	WR 448 (Dapsone)	10.0
	WR 7557 (Sulfadiazine)	100.0
Pyridinemethanols	WR 151312	10.0
Miscellaneous	WR 1543 (Atabrine)	31.6
	WR 2978 (Pyrimethamine)	1.0
	WR 3090	31.6
	WR 93133	31.6
	WR 194916	NC ¹

¹ Not curative. Compound ineffective at the highest dose tested (100 mg/kg).