

## Evaluation of Candidate Antimalarial Drugs in Monkeys

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**OBJECTIVE:** Potential antimalarial drugs are to be evaluated in macaque monkeys to determine both their toxicity and therapeutic effectiveness against experimentally induced infections of Plasmodium cynomolgi.

**DESCRIPTION:** To determine toxic levels, each drug tested is given to a group of four monkeys by the oral route unless special drug characteristics indicate otherwise. An initial dose of 1 mg/kg is given for 2 days and then successively increased by a factor of 3.16 at two day intervals until signs of toxicity occur. The dose will then be decreased by the same increment until the level at which the drug is tolerated for six days is reached. Twelve monkeys are used in the test for therapeutic effectiveness, two of which are infected but untreated controls. The remainder of the ten animals are paired and given selected doses of the test drug for seven consecutive days commencing on the fourth day following their infection with malaria. Initially, the drug doses administered in the test for therapeutic effectiveness are set at the highest dose of the drug that was determined to be not toxic in the toxicity test, and if therapeutically effective, this dose is reduced during subsequent tests successively to a non-effective endpoint. In the test for therapeutic effectiveness, the drug effect on the malaria infection is compared to that of untreated control monkeys for a thirty day period, at which time animals in which parasitemias have been eliminated are splenectomized to determine whether a cure has been achieved. At the conclusion of a test each monkey is autopsied and examined grossly for the presence of lesions.

**PROGRESS:** Testing so far has been limited to establishing consistent laboratory techniques and the reliability of the test systems. Seven drugs, including chloroquine, quinine, diformyl DDS, and four unknown drugs, have been tested for toxicity and their maximum tolerated doses determined. Three tests for therapeutic effectiveness have been initiated, one of which has been completed. Each of the seven drugs has been tested for therapeutic effectiveness at one dose level; all of them show strong evidence of antimalarial activity. The findings resulting from the testing of the three known drugs correspond with their activity as demonstrated clinically and in other test systems. These results indicate that testing of a large number of drugs whose antimalarial activity in primates has not been determined may begin soon.

**SUMMARY:** The program for using macaques in the evaluation of candidate antimalarial drugs is described. The three tests which have been initiated for therapeutic effects indicate that this will be a promising system.