

Antimalarial Activity of Tetracycline in Asymptomatic
and Acutely Ill Subjects with *Falciparum* Malaria

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OBJECTIVE: Previous investigations have suggested that chlortetracycline might inhibit the primary exo-erythrocytic development of *Plasmodium vivax* and *P. cynomolgi* in human volunteers and primates, respectively. It was also suggested that chlortetracycline might interfere with the multiplication and survival of early erythrocytic forms of *P. vivax* in human volunteers. The purpose of this investigation was to evaluate the antimalarial efficacy of tetracycline in subjects naturally infected with *P. falciparum*.

DESCRIPTION: The site selected for study was the provincial hospital of Trat city which is located in Southeast Thailand, approximately 400 km from Bangkok. A pilot study was performed in 16 adults who were asymptomatic and exhibited low density asexual parasitemias. Treatment consisted of 250 mg tetracycline orally administered 4 times daily for 10 days. Followup blood smear examinations were obtained for 30 days.

Upon completion of the pilot study, the efficacy of tetracycline was evaluated in acutely ill subjects with *P. falciparum* infections. Selected subjects were assigned to one of two treatment groups. One group received 640 mg of oral quinine sulfate thrice daily for 3 days, followed by 250 mg of tetracycline, 4 times a day for 10 days. The other group received a similar course of quinine followed by a conventional course of chloroquine (i.e., 1500 mg base over 48 hours). Followup blood smear examinations were performed on subjects in both groups for 33 days. The preliminary subcurative doses of quinine were administered to allay presenting symptoms and parasitemias.

PROGRESS: A presumptive radical cure was obtained in 12 of 16 subjects in the pilot study. In the remaining 4 subjects, tetracycline was discontinued within 72 hours because of the development of fever, headache and chills. The range of asexual parasitemias upon admission ranged from less than 20 to 4,460 per cmm. The mean parasite clearance time in the successfully treated patients was 4.6 days, with a range of 2 to 6 days.

Forty-one subjects were chosen for the quinine-tetracycline (QT) regimen. Treatment and followup examinations were successfully completed in 30 of whom there were 26 males and 4 females, ranging in age from 13 to 71 years (mean 23.8). The levels of asexual parasitemias upon initial presentation ranged

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from 870 to 120,500 per cmm with a geometric mean of 11,600 per cmm. Forty-seven subjects were chosen for the quinine-chloroquine (QC) regimen. Treatment and followup examinations were successfully completed in 36 of whom there were 33 males and 3 females, ranging in age from 14 to 71 years (mean 26.2). The level of asexual parasitemias ranged from 1,700 to 209,300 per cmm with a geometric mean of 13,900 per cmm.

Table I shows the presumptive radical cure rates among acutely ill subjects obtained with both treatments. The rate for the QT regimen (96.6%) was more than twice that for the QC regimen (41.6%). Four subjects who exhibited presumptive radical cures with the QT regimen had previously relapsed following a course with the QC regimen. If these 4 are excluded from the quinine-tetracycline group, the adjusted cure rate is 96.1%. Application of Fisher's exact probability test to either the adjusted or unadjusted rates demonstrated a very highly significant difference.

The single subject with a treatment failure in the QT group did not exhibit circulating asexual parasites until after the 19th day of observation. Of the 21 failures in the QC group, 4 subjects had incomplete clearing of parasitemias and 3 more had recrudescences within 12 days after initiating therapy. Recrudescences occurred on or before the 19th day of observation in 10 additional subjects in the QC group. The mean parasite clearance times for the QT and QC treatment group, as shown in Table 2, were similar.

Gametocytemia was observed in 7 of 12 subjects in the pilot study, who were treated with tetracycline alone, and in 12 of 30 treated with QT combination. The levels of asexual parasites and gametocytes during the observation period for a single subject from each of these regimens are shown in Figures 1 and 2. Although a presumptive radical cure was obtained in both patients, with clearance of asexual parasites at 4 and 5 days, respectively, the levels of circulating gametocytes were not apparently affected.

SUMMARY: The results indicate that tetracycline, alone or in combination with subcurative doses of quinine, can exert a blood schizontocidal effect resulting in radical cures of *P. falciparum* infections. Observations on circulating sexual parasites during the treatment and followup phases indicate that tetracycline has no apparent gametocytocidal effect.

REFERENCES:

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Table 1.
Radical Cure Rates in Acute Falciparum Malaria

Treatment*	No. Treated	No. Cured	% Cure
Quinine—tetracycline	30	29†	96.6
Quinine—chloroquine	36	15	41.6

* See text for dosage.

† Four subjects were quinine—chloroquine treatment failures.

Table 2.
Mean Parasite Clearance Times

Treatment	Response	No. of subjects	Mean Clearance (days)
Quinine—tetracycline	Cure	29	3.6
Quinine—chloroquine	Cure	15	3.2
Quinine—chloroquine	Failure*	17	3.6

* Excludes 4 subjects who exhibited incomplete clearing of asexual parasites.

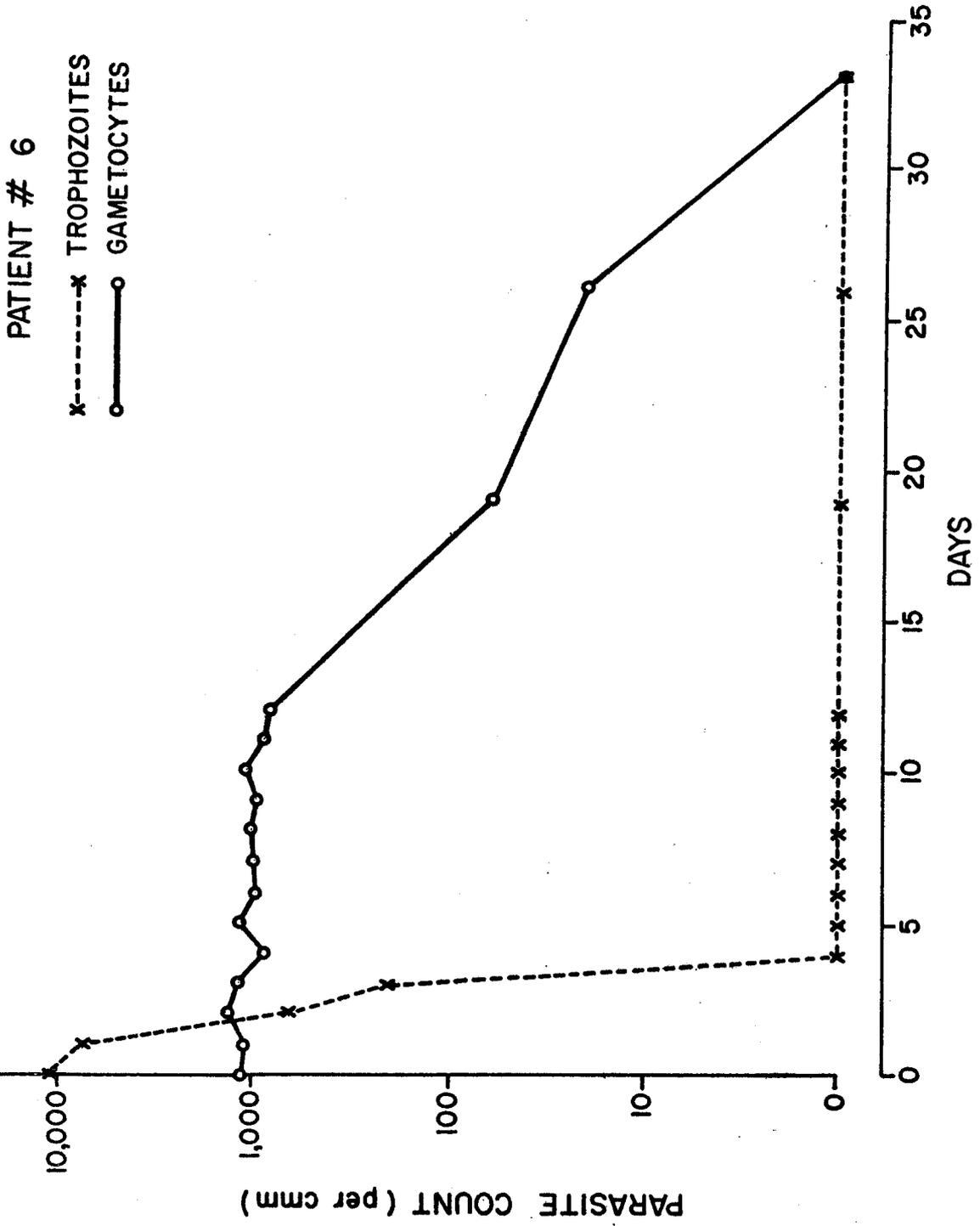


Figure 1. Effects of quinine-tetracycline therapy on circulating trophozoites and gametocytes.

PATIENT # 18

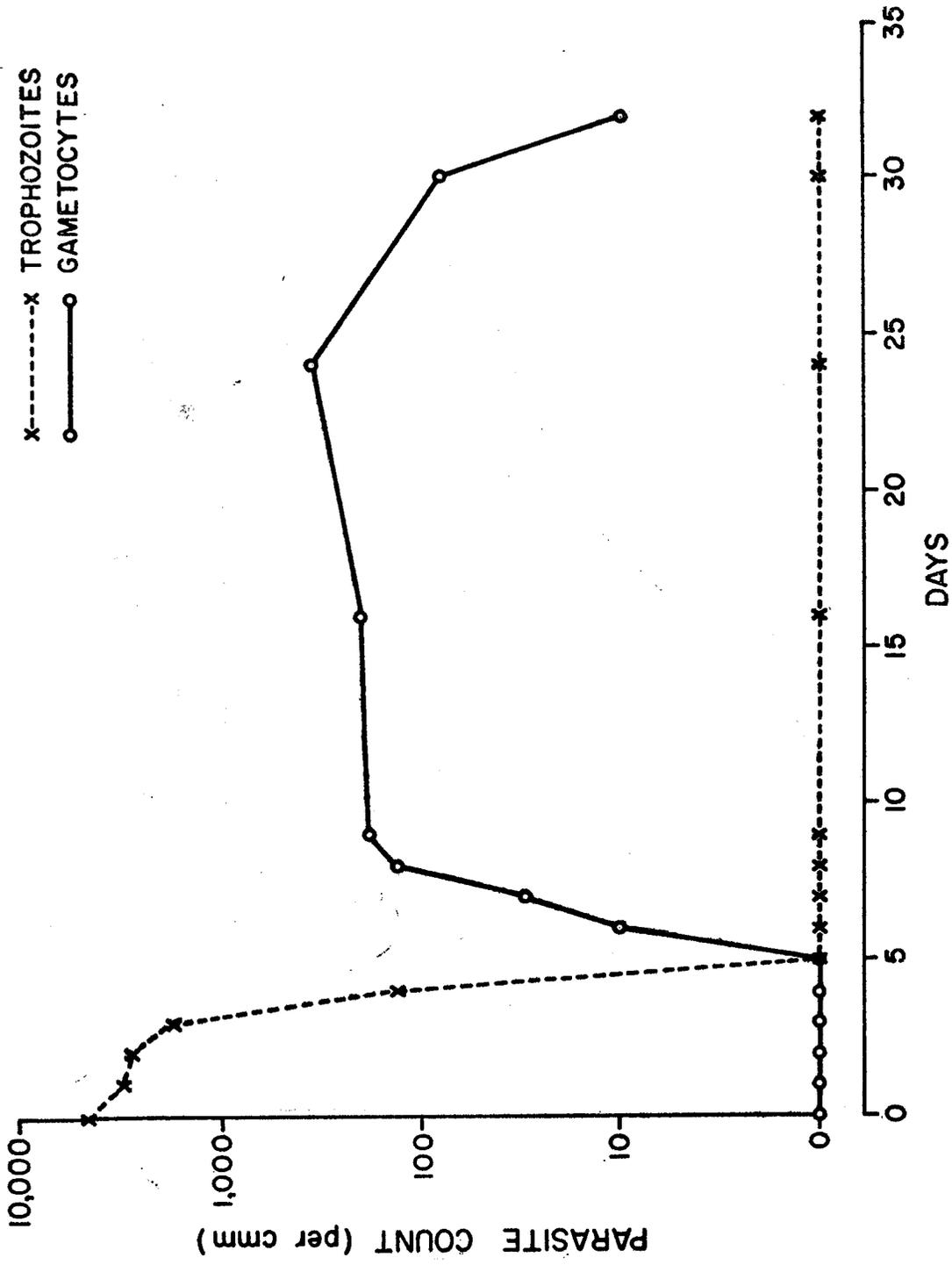


Figure 2. Effects of tetracycline therapy on circulating trophozoites and gametocytes