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DRUG RESISTANCE IN PLASMODIUM FALCIPARUM  
FROM THAILAND

by

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The failure of certain 4-aminoquinoline drugs to cure infections of a strain of Plasmodium falciparum originating in Colombia, South America, was reported recently (Moore & Lanier, 1961; Young & Moore, 1961; Young, 1961; Young, 1962). A strain of P. falciparum apparently originating in Thailand, which also shows a poor response to synthetic drugs, is the subject of this paper.

The patient (JHK) had no history of malaria before entering Thailand on 11 November 1962. After leaving Thailand on 20 November 1962, the patient received primaquine 15 mg base daily for 10 days (Table 1). Following the onset of symptoms of fever, chills, and sweating on 24 November, the patient was admitted to a hospital on 4 December, at which time P. falciparum parasites were found. He was treated with 2.1 g chloroquine and 0.09 g primaquine and released on 19 December. He was readmitted on 26 December with symptoms and parasites. Between 28 December and 17 January, a period of 21 days, he received a total of 4.2 g chloroquine which eliminated the symptoms without clearing the parasites from the blood. A total of 6.3 g chloroquine given within a 44-day period had not eliminated the infection; the patient returned to the United States of America for further investigation and was put under detailed study just as the third clinical episode occurred.

The present report presents the information obtained during the subsequent 9-1/2 month observation period and from further studies in 6 inmate volunteers in whom the infection was induced.

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### Materials and Methods

The drugs were given under supervision. Blood was drawn, often daily from JHK and less frequently from the others, to determine the chloroquine levels in the plasma by the method described by Brodie et al. (1947). Urine was collected frequently to detect the presence of chloroquine by the Haskins (1958) test. Thick blood films were made daily until the infections appeared to be eliminated and less frequently thereafter. The final dates of examination are shown in Table 2. Parasites were counted in the Giemsa-stained thick blood smears against 500 white blood cells for the first patient, JHK, and against 100 white blood cells for the six prisoner volunteers; these figures were converted to the number per cm based on the white blood cell count for that day. The dosages used in this report are in terms of base for all drugs except for quinine sulfate, mepacrine dihydrochloride dihydrate, and proguanil monohydrochloride, which are expressed in grams of the salt. A relatively new drug, BW 377054, also was used. It belongs to a series of hydroxynaphthalenes with the formula 2,5 bis(cyclohexylaminoethyl) naphthalene-1:6 diol dihydrochloride. The dosages shown for this drug are in terms of the salt which is equivalent to 83.9 per cent. of the base. Occasionally, to reduce the parasitaemia, 2.0 g or less of quinine sulfate were given, divided in doses ranging from 0.375 g to 0.65 g. When given in larger amounts, the quinine was administered in approximate 0.65 g (10 grains) doses 3 times daily.

### Observations

#### JHK

The major events in the history of JHK are shown in Table 1 and Figure 1. Our observations began on the first day of the third clinical episode, 28 January 1962. He was given 1.5 g chloroquine in 3 days. On the fourth day the chloroquine level was 346 micrograms per litre of plasma ( $\mu\text{g}/\text{litre}$ ). Parasites were absent only on days 7 and 9, after which they increased, and symptoms returned on day 11, at which time the chloroquine level was 149  $\mu\text{g}/\text{litre}$ . The patient became acutely ill on 11 February and received 2 intramuscular injections of 0.6 and 0.3 g chloroquine respectively. The next day the plasma level reached 749  $\mu\text{g}/\text{litre}$  (Figure 1). A total of 2.1 g was given in this regimen, with the elimination of the parasites for 6 days, their temporary appearance for 1 day, then their absence for another 9 days. They reappeared on observation day 35 when the

plasma chloroquine level was 56  $\mu\text{g/litre}$ . During the 35 day period, 31 daily determinations of chloroquine plasma levels were done. The range was from 749 to 34  $\mu\text{g/litre}$ , with an average of 197  $\mu\text{g/litre}$ ; median of 149  $\mu\text{g/litre}$ . The Haskins test for chloroquine in the urine was positive throughout this period. A total of 9.9 g of chloroquine base had been used against the first 4 malaria episodes without eliminating the infection.

On day 37, the fifth clinical episode occurred. Quinine, 0.65 g, was given on days 38 and 39 each. The parasites disappeared for 4 days. Five days after their reappearance, fever returned. Quinine, 0.375 g, given on observation days 49 and 50 each, eliminated the parasites for 10 days. The parasites returned on day 62 and the fevers on day 66. Pyrimethamine, 0.1 g, given on day 70 eliminated the fever but not the parasites.

A second 0.1 g dose was given on day 83 after which both the asexual and sexual parasites increased gradually during the next 10 days. On observation day 95, or 160 days after the first onset of the infection, parasites were still present. Quinine, 2.0 g daily, was given for 7 days. The parasites disappeared and as they had not reappeared by the end of the observation on 17 October, 168 days later, apparently a cure had been effected.

#### Blood-induced infections in volunteers

Infected blood was drawn from JHK, deep frozen, and shipped to the Atlanta Federal Penitentiary, where it was injected into volunteer patient 233 on 27 February 1962. The infection became patent on 14 March (day 1 in Figure 2). Blood sub-inoculations were made to volunteer patients 224 and 226 on 20 March, and the infections became patent on 24 March in both patients.

After the infection developed in patient 233, quinine was given on two occasions, viz. 3.0 g in 5 doses and 1.3 g in 3 doses respectively, to reduce the severity of the infection (Figure 2, Table 2). The parasites and fever symptoms were eliminated temporarily each time. On the 49th day of the infection, when the parasite count was 9828 per cm, the hydroxynaphthalene derivative, BW 377054, was at the rate of 0.3 g every 12 hours, for a total of 1.2 g. Forty-four hours later the parasites had increased and the symptoms had become more severe, indicating the drug was not effective. Proguanil was given 0.1 g t.i.d. for 5 days, for a

total of 1.5 g. The parasites disappeared 3 days after starting the drug, but returned after an absence of 14 days. This episode was treated with quinine, 2 g daily for 3 days, resulting in the disappearance of the parasite for 13 days. Upon the return of fever, when the parasite count was 41 705 per cm, the combined treatment of 0.6 g chloroquine and 0.05 g pyrimethamine was given in a single dose. The parasites were reduced in number but not eliminated. On the 110th day of the infection, quinine, 2.0 g daily for 5 days, eliminated the parasites within 48 hours. The patient left the prison 29 days later apparently cured, as he had not reported a return of the illness 81 days later.

The infection in patient 224 was challenged on the fourth day of patency with the 1.5 g regimen of chloroquine (Figure 2, Table 2) when the parasite count was 415 per cm and the temperature 102.0°F. The parasites were reduced only temporarily with an absence of fevers for 6 days. The fevers returned on a daily basis on day 13, when the parasite count was 1407 per cm. Both the parasites and fevers increased until day 19 when the former count was 15 138 per cm and the temperature 102.4°F. On day 19, amopyroquine, 0.15 g, was given intramuscularly. The fevers continued and 3 days later the parasite count had risen to 23 712 per cm. On day 24, Anopheles/freeborni mosquitoes were allowed to bite this patient in preparation for future transmission experiments. Then mepacrine was given at the standard regimen of 2.8 g in 7 days. The fever disappeared 2 days and the parasites 4 days after the initiation of therapy. After an absence of 20 days, the parasites reappeared. Quinine, 2.0 g daily for 4 days, eliminated the infection.

The infection in patient 226 was challenged on the fourth day of patency with a single 0.6 g dose of chloroquine which did not prevent the parasites from increasing thereafter (Figure 2, Table 2). A total of 2.0 g quinine given on days 9 and 10 produced temporary absence of parasites for 4 days. On day 22, the parasite count was 9528 per cm. Amopyroquine, 0.15 g, was given intramuscularly on day 22 and again on day 24. By day 28, the parasites had increased to 37 650 per cm. Fevers occurred each day. On day 28, the hydroxynaphthalene derivative (BW 377C54) was started, 0.3 g every 12 hours for 4 doses. The parasite density was decreased temporarily.

On day 33, 0.1 g pyrimethamine was given, after which the parasites increased. On day 40, the 2.8 g regimen of mepacrine was started. The parasites disappeared on the fifth day after initiation of this treatment. They were still absent on day 63 but, as the patient was leaving the project, a precautionary treatment of 2.0 g quinine daily for 5 days was given.

#### Effect of suppressive regimens of chloroquine

An experiment was performed to determine if 0.3 g chloroquine weekly could suppress or suppressively cure mosquito-transmitted infections of this strain of malaria. As indicated above A. freeborni mosquitos were infected by biting patient 224 on the 24th day of his patent infection and after he had been treated with 1.5 g of chloroquine and 0.15 g of amopyroquine.

Chloroquine was given to patients 271 and 272, 10 days and 3 days before and 3 days after the mosquitos bit. These patients, together with patient 276 who did not receive the weekly drug doses, were bitten randomly by the same group of mosquitos on 30 April 1962.

The parasites and symptoms developed at about the same time in patients receiving the drug and in the control, indicating that the chloroquine afforded no protection (Table 3, Figure 3). In fact, one patient (No. 271) receiving the drug had a parasitaemia 1 day before the control (No. 276) patient who received no drug. Tests on the blood and urine showed the presence of chloroquine. Following the appearance of parasites, the next (fourth) weekly dose of chloroquine was increased to 0.6 g in patients 271 and 272 on the third and second day of parasite patency respectively, without any apparent effect on the increasing number of parasites.

On the seventh day of the infection in patient 272, the parasite count was 14 592 per cm and the temperature was 103.0<sup>0</sup>F. The standard 1.5 g regimen of proguanil was begun. Although the parasites had been reduced to 4142 per cm 3 days later, the symptoms were still severe, so quinine (2.0 g daily for 5 days) was started also. The fevers responded quickly and the parasites apparently were eradicated.

The second treatment given to patient 271 was mepacrine in the standard 2.8 g regimen. The parasites were cleared rapidly but relapsed after 34 negative days. The combination of 0.6 g amodiaquine and 0.05 g pyrimethamine was given in a single dose. The parasites were reduced but not eliminated. Quinine, 10 g in 5 days, cured the infection.

Patient 276, who was the control on the suppressive experiment, received the 1.5 g regimen of chloroquine starting on the fourth day of parasite patency. The parasites were absent for only a few hours on the fifth day after the beginning of treatment. Pyrimethamine, in a single 0.1 g dose, was given on the 14th day of patency, at which time the parasite count was 2071 per cm and the chloroquine level was 143 µg/litre. The parasite count continued to increase for the next 6 days. Six grams of quinine, given in 3 days, apparently cured the infection.

The sporontocidal effect of pyrimethamine

The infection had been induced in patient 226 by the inoculation of infected blood from patient 233. During the first 23 days of patency he had been treated with chloroquine, quinine, amopyroquine, and the hydroxynaphthalene derivative drug during which time parasites were absent from the blood smears for only 3 days (Figure 2). To determine the sporontocidal effect of pyrimethamine, *A. freeborni* were fed daily for eight days, incubated at about 75° F., and dissected from 5 to 7 days later to determine the oocyst infection on the gut. After the second daily feeding of the mosquitos on the patient, 0.1 g pyrimethamine was given. The ratios of mosquitos infected, before and after the drug, were as follows.

Mosquitos	Days in relation to drug administration							
	-1	0	1	2	3	4	5	6
Infected	10	7	10	7	8	10	5	8
Dissected	10	10	10	10	9	11	10	9

Although the number of oocysts varied, each group of mosquitos fed after drug administration contained one or more specimens with over 100 oocysts per gut, which is considered a heavy infection. Additional specimens from each group, dissected after 10 to 14 days of incubation, showed older maturing oocysts and/or sporozoites in the salivary glands, indicating a normal development.

It is concluded that 0.1 g pyrimethamine had no sporontocidal effect. Against susceptible strains, one-fourth of this amount, i.e. 25 mg, exerts a rapid effect, often complete within 24 hours (Burgess & Young, 1959).

#### Discussion

Plasmodium falciparum strains susceptible to chloroquine are normally eliminated from the blood by plasma levels averaging 10-30 µg/litre (Berliner et al., 1948; Earle et al., 1948). In our studies, plasma levels in this range and often much higher either failed to prevent the initial appearance in the blood stream of the parasites, failed to prevent their increase in numbers, or at best gave only a temporary reduction in numbers or temporary elimination from the blood-stream. The plasma levels of the chloroquine were within the ranges expected for the various dosages used and indicate that the failure of the drugs to act was not due to a lack of the drug in the blood-stream. The urine gave a positive test for chloroquine as further evidence of the ingestion of the drug.

It appears evident from the data obtained on the Thailand strain of P. falciparum infections in seven patients, that these parasites are resistant to chloroquine in the usually curative doses of 0.6 g and 1.5 g (Jeffery et al., 1956; Covell et al., 1955). Neither did a larger total dose of 2.1 g eliminate the infection, as the infection relapsed after a 16-day interval in JHK. The infection in the original patient (JHK) was not eliminated by multiple regimens of chloroquine although he received a total of 9.9 g during a period of 11 weeks.

Chloroquine given in weekly suppressive doses, started before the transmission of malaria by mosquito bites, failed to suppress or to delay the appearance of the parasites in the blood-stream. Against susceptible strains of parasites such regimens result in suppression and, when extended, in a suppressive cure (Covell et al., 1955).

Table 2 summarizes the trials of the synthetic antimalarials in the 7 patients. A total of 19 trials with individual drugs and 2 trials with drug combinations was made without a successful cure.

Amopyroquine, a relatively new 4-aminoquinoline, a close chemical analogue of amodiaquine, has been reported by Hoekenga (1962) to be effective against certain P. falciparum strains from Panama. It was tried in a single injection of 150 mg in patient 224 and 2 injections of 150 mg each, 48 hours apart, in patient 226. The fevers continued and the parasitaemias increased during the following week. The results were inferior to those obtained by Hoekenga.

Pyrimethamine, when used therapeutically, gave poor results. Pyrimethamine also failed to exert a sporontocidal effect, although in susceptible strains this effect is exerted very rapidly (Burgess & Young, 1959). It is evident that both the sexual and asexual parasites of this strain were resistant to pyrimethamine.

Proguanil, 1.5 g, given over a period of 5 days, was administered twice. In patient 233, the parasites were cleared from the blood-stream but returned after 14 negative days. In patient 272, the parasites not only increased but symptoms became worse and fever was continuously present for 72 hours. The parasites appear to be resistant to this drug.

Mepacrine tended to remove the parasites from the blood-stream fairly rapidly in 3 patients, but in 2 cases that were followed sufficiently long relapses occurred. Previously, it was reported that 4 of 6 cases of the Colombia strain relapsed after mepacrine (Young, 1962). This gives a total of 8 cases of chloroquine-resistant P. falciparum treated with mepacrine of which 6 have relapsed. It has been stated that most strains of P. falciparum are radically cured by mepacrine (Covell et al., 1955).

BW 377C54, a hydroxynaphthalene derivative, has been reported to exert a schizontocidal effect, similar to or superior to chloroquine, against Indian strains (Ray et al., 1959) with a 0.6 g dose, and against <sup>some</sup> African strains of P. falciparum with a 0.3 g dose (Bruce-Chwatt & Charles, 1957). Total dosages of 1.2 g given in 36 hours, i.e. 300 mg every 12 hours, temporarily abated the symptoms but did not clear the parasitaemia in patient 226. In patient 233, who received a similar regimen, the parasites increased and, because the symptoms were getting worse, another drug (proguanil) was started 8 hours after the end of the naphthalene-derivative regimen. This drug did not eliminate the infection.

Pyrimethamine was combined one time with chloroquine and another time with amodiaquine. Each time there was a disappearance of symptoms and a temporary reduction in parasites. The results indicate that these combinations have no advantage over the individual drugs against this strain.

Courses of primaquine were given to JHK on 2 occasions following exposure to infection (Table 1). The apparent lack of effect of primaquine against the parasites does not appear to be significant in this case, as the accepted action of the drug is against the stage in the liver, which may have been passed before the drug was begun.

This strain of P. falciparum differs from the chloroquine-resistant strain from Colombia, South America, in that the latter appeared to be susceptible to proguanil and to pyrimethamine. As proguanil resistance in P. falciparum was reported some years ago in Malaya, Viet Nam and Assam (India),<sup>1</sup> countries fairly near Thailand, it would be reasonable to suppose that such resistance could have been present in the P. falciparum parasites from Thailand before the introduction of chloroquine. Certainly, the susceptibility to pyrimethamine and proguanil of the chloroquine-resistant Colombia, South America, strain does not indicate any cross-resistance between chloroquine and these two drugs (Young, 1962).

One of the outstanding characteristics of this strain is its susceptibility to quinine. All of the infections treated with 8 or more grams of quinine, given at the rate of 2 g daily, and 1 of 2 infections treated with 6 g total, appeared to be eradicated. Smaller doses of quinine exerted a rapid temporary effect.

In addition to the chloroquine-resistant strain of P. falciparum from Colombia, there appears to be another resistant strain in the area of Porto Velho, Brazil (Rodriguez, 1961; Box, Box & Young (in press)). The present report adds a third documented chloroquine resistant strain from Asia, an area widely removed from the first two.

The Thailand strain differs from the two Western hemisphere strains in that the former appears to be resistant to more groups of drugs; it shows a poor response to all of the 7 synthetic drugs tried against it.

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<sup>1</sup> World Health Organization (1961) Chemotherapy of Malaria, report of a Technical Meeting, Wld Hlth Org. techn. Rep. Ser. 226

### Summary

1. A strain of Plasmodium falciparum, apparently originating in Thailand, has been studied in 7 patients for its response to various drugs.
2. The parasites showed a poor or no response to the usual therapeutic doses of the following drugs: chloroquine, amopyroquine, pyrimethamine, proguanil, and a new hydroxynaphthalene derivative. The parasites responded rapidly to mepacrine but relapsed. Weekly suppressive doses of chloroquine failed to prevent the mosquito transmission to and the occurrence of the infections in the recipients. Pyrimethamine failed to exert sporontocidal effect. Pyrimethamine combined with either chloroquine or amodiaquine demonstrated no advantage over these drugs singly.
3. The infections were cured by regimens of 8 g or more of quinine and appeared to be very sensitive to even small amounts of this drug.

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TABLE 1. HISTORY SUMMARY OF JHK WITH PLASMODIUM FALCIPARUM  
(THAILAND STRAIN) INFECTION

Date	Malaria attack		Symptoms	Parasites cm	Notes	Treatment (g)	
	Day of:	No.				Chloroquine	Other
(1961)							
Nov. 10					Exposed to malaria in Thailand	0.3 wk x 2	
Nov. 11-20					Left Thailand		
Nov. 20		1	+				Pr. 0.015 d. x 10 d.
Nov. 24			+	+	Hospital	1.5 in 3 d.	
Dec. 4			+		Hospital	0.6 s.d.	
Dec. 7			-		Discharged		
Dec. 19			+	+	Hospital		
Dec. 26			-		Hospital		
Dec. 28		2	-		Hospital	1.5 in 3 d.	
Dec. 29			-		Hospital		
(1962)							
Jan. 2							
Jan. 8							
Jan. 17			-	+	Parasites continually present	0.9 in 3 d.	
Jan. 27			-	+		1.8 in 4 d.	
Jan. 28		3	+	15 400	Returned to USA*	1.5 in 3 d.	

TABLE 1 (continued)

Date	Malaria attack		Symptoms	Parasites cm	Notes	Treatment (g)	
	Day of:	No.				Chloroquine	Other
Feb. 3	72			0	Parasites disappeared		
Feb. 4	73			16			
Feb. 5	74			0			
Feb. 6	75			540			
Feb. 7	76	4	+	400	Parasites continuously present		
Feb. 10	79		+	15 000			
Feb. 11	80		+	6 600		2.1 in 5 d. (0.9 i. . .)	
Feb. 16	85		-	0	Parasites disappeared		
Feb. 22	88			20	Parasites present 1 d. only		
Mar. 3	100		-	131	Parasites reappeared		
Mar. 5	102	5	+	1 533			
Mar. 6	103		+	3 345			
Mar. 9	106		-	0	Parasites disappeared		Q 1.3 in 2 d.
Mar. 13	110		-	54	Parasites reappeared		
Mar. 17	114	6	+	2 800			Q 0.65 in 2 d.

TABLE 1 (continued)

Malaria attack		Symptoms	Parasites cm	Notes	Treatment (g)	
Date	Day of: No.				Chloroquine	Other
Mar. 20	117	-	0	Parasites disappeared		
Mar. 30	127	-	20	Parasites reappeared		
Apr. 3	131	{ +	908	Parasites continuously present		Py. 0.1 s.d. Py. 0.1 s.d. Q 14.0 in 7 days
Apr. 7	135		2 332			
Apr. 20	148		101			
May 2	160	-	70			
May 7	165	-	0	Parasites absent		
Oct. 17	328		0			
Totals	328		7		9.9	Py. = 0.2; Pr. = 0.24; Q = 15.95.

+ = present; Pr. = Primaquine; d = day; s.d. = single dose; i.m. = intramuscular; Q = quinine;  
Py. = pyrimethamine; \* = daily observations began (Figure 1); Symptoms = Fevers of 100°F. or above with  
or without chills, sweating and headaches.

TABLE 2. SUMMARY OF RESPONSE OF PLASMODIUM FALCIPARUM  
(THAILAND STRAIN) TO VARIOUS DRUGS

Patient	Drugs (g)																		
	Chloroquine		Py 0.1	C 0.06 Py 0.05	A.0.6 Py 0.05	M	Ampyproquine		N	P	Q	Q	Q	Q	Q				
	0.6	1.5					2.1	0.15								0.15x2			
JHK	2	15	N.C.			2.8	0.15	0.15x2	1.2	1.5	0.65	1.3	2.0	3.0	6.0	8.0	10.0	14.0	
JHK			inc.								10	4							163 a
224		N.C.			20		N.C.		N.C.			4				160 b			
226	inc.		inc.		**		inc.		inc.	14		4		12	13			29 c	
233				N.C.	35													97 b	
271	inc.																		
272	inc.									N.C.						142 b		150 b	
276			inc.																
Totals:																			
7	3	3	1	4		3	1	1	2	2	1	2	1	1	3	1	3	3	1

Legend: the numbers below the double line indicate the number of days that the blood was negative following the initiation of treatment.

inc. = parasites increased within 48 hours after drug.

N.C. = parasites not cleared from blood stream

\* = cured

\*\* = treated with quinine 10 g + primaquine 0.045 g after 17 negative days to leave experiment

a = as of Oct. 17; b = as of Oct. 22; c = as of Aug. 13

M = mepracine; P = proguanil (Paludrine <sup>(R)</sup>); A = amodiaquine (Camoquin <sup>(R)</sup>); Q = quinine; C = chloroquine;  
 PY = pyrimethamine; N = hydroxynaphthalene derivative (EW 377C54)



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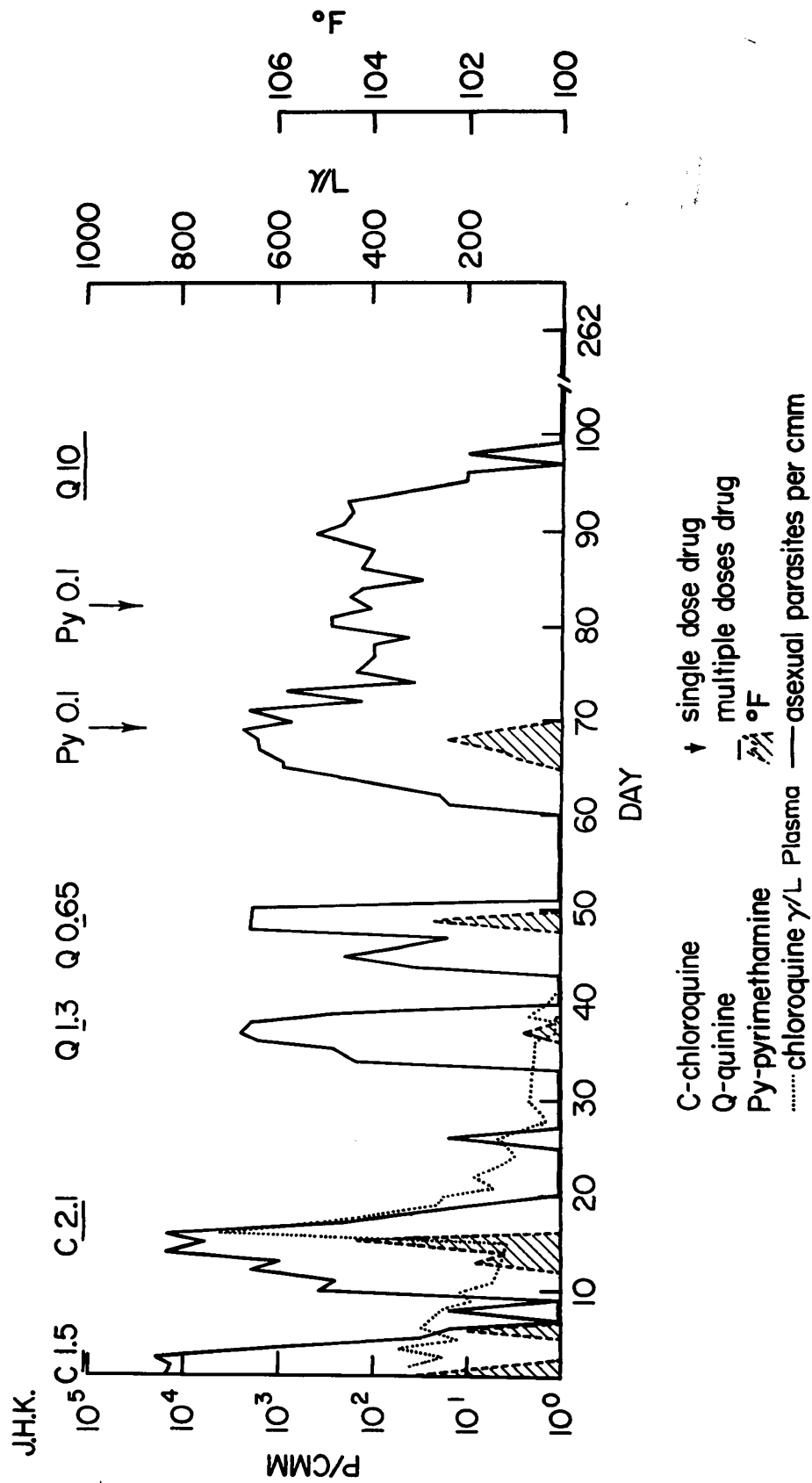


Figure 1. The response of Thailand Plasmodium falciparum to various regimens of drugs. Natural infection. JHK

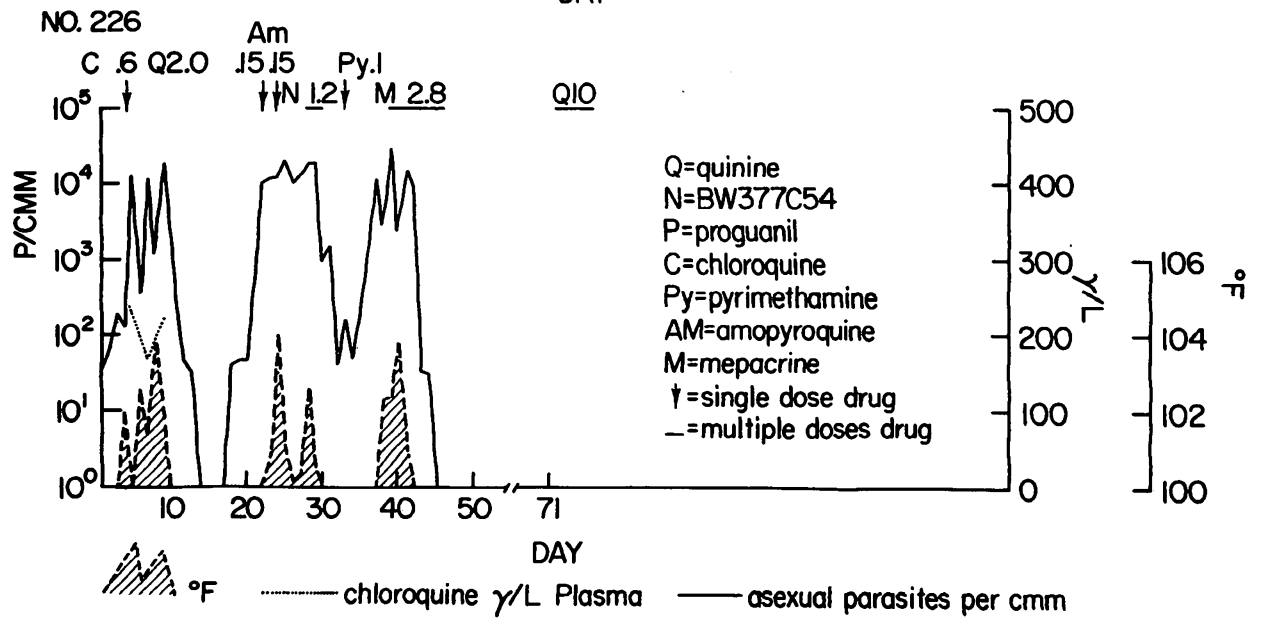
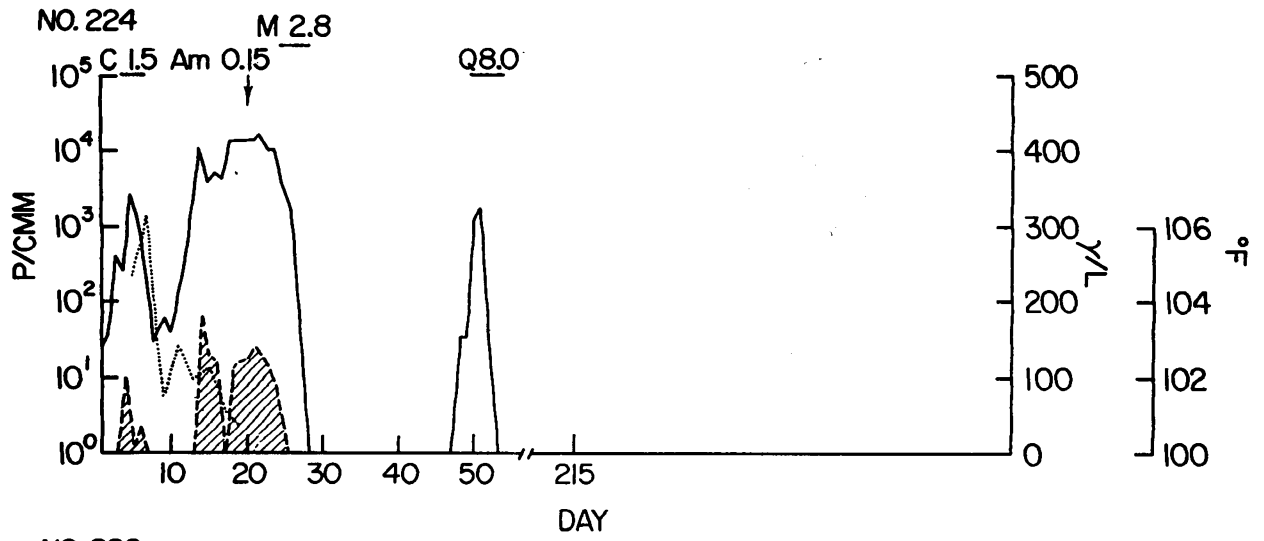
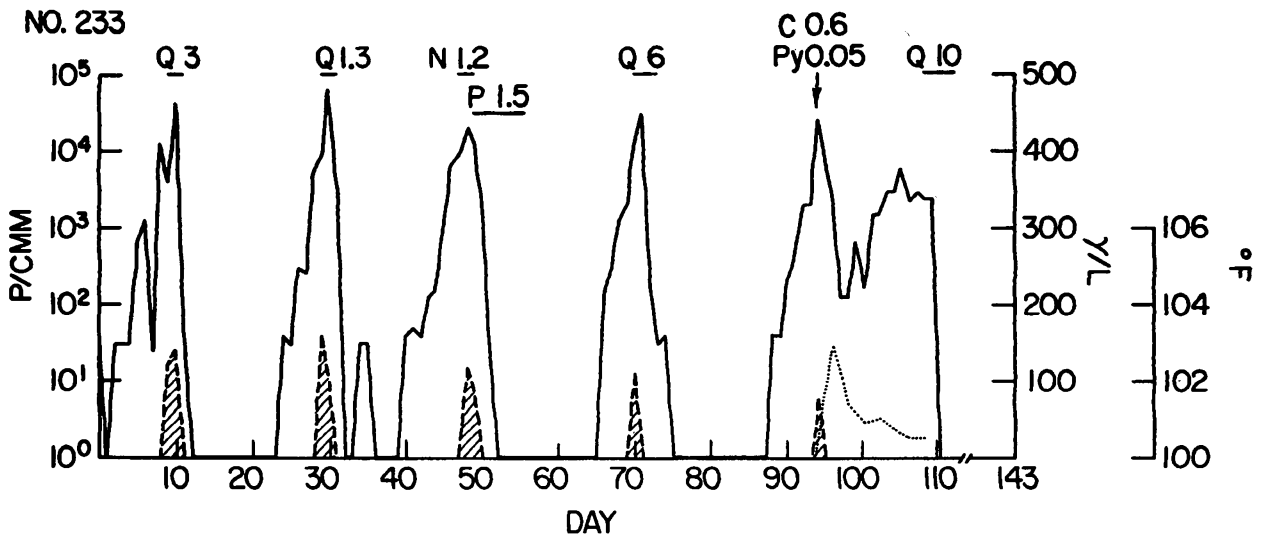


Figure 2. The effect of various drugs upon blood-induced infection of Thailand Plasmodium falciparum.

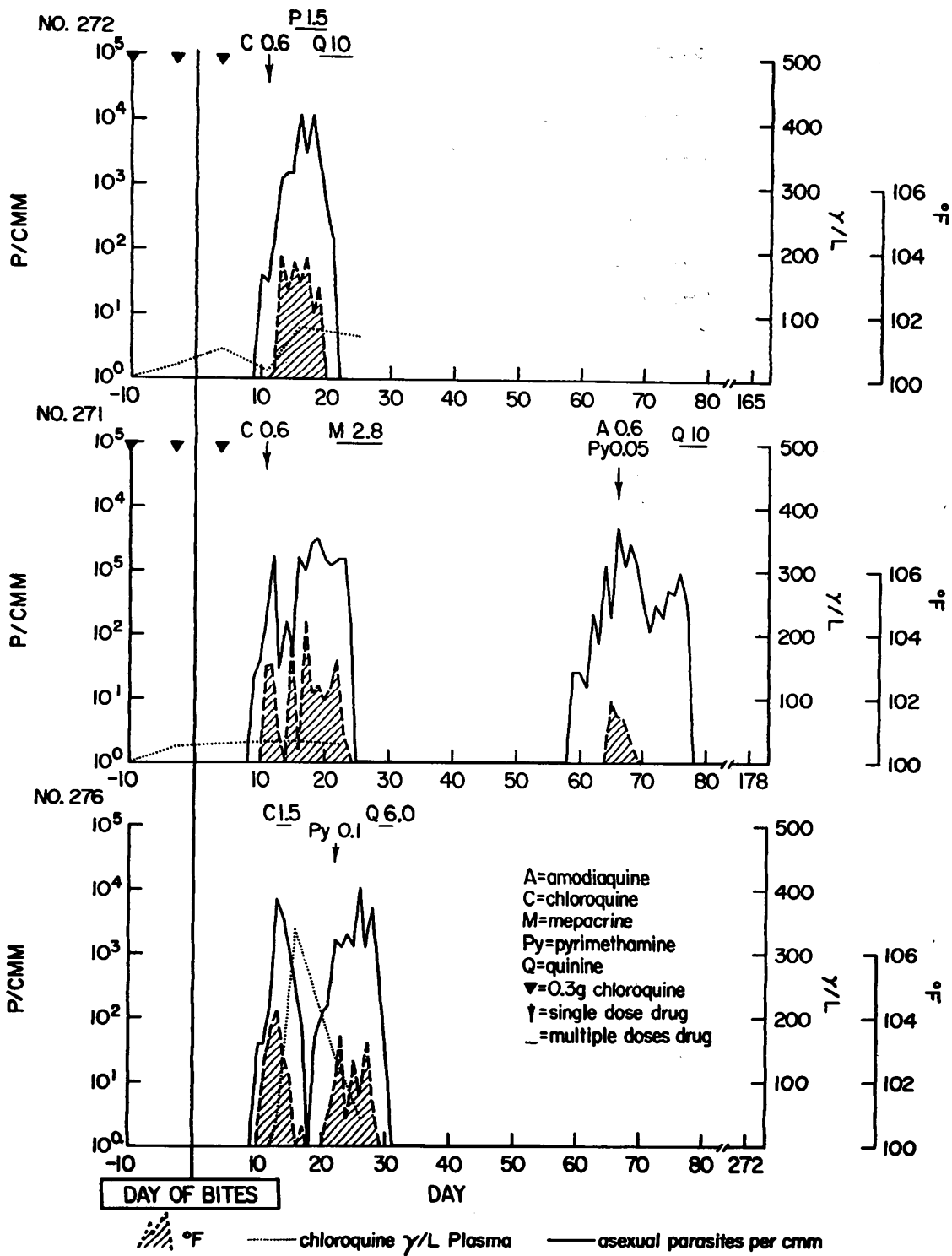


Figure 3. The response of sporozoite-induced Thailand *Plasmodium falciparum* infections to suppressive and to therapeutic regimens of drugs. Patients 272 and 271 received 0.3 gm chloroquine weekly twice before and once after mosquitoes bit. Patient 276 was the control and did not receive the weekly chloroquine.

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(a) to acquaint WHO staff, national institutes and individual research or public health workers with the changing trends of malaria research and the progress of malaria eradication by means of summaries of some relevant problems;

(b) to distribute to the groups mentioned above those field reports and other communications which are of particular interest but which would not normally be printed in any WHO publication;

(c) to make available to interested readers some papers which will eventually appear in print but which, on account of their immediate interest or importance, deserve to be known without undue delay.

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