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CHLOROQUINE-RESISTANT FALCIPARUM MALARIA IN
A SEMI-IMMUNE INDIGENOUS POPULATION IN NORTH MALAYA

by

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Introduction

The first verified cases of chloroquine-resistant falciparum malaria were reported from Colombia in South America (Moore & Lanier, 1961; Young & Moore, 1961). A similar situation was reported from Brazil by Rodrigues (1961) and Box et al. (1963).

In October 1962 three members of a team of seven that went on a field study from the Institute for Medical Research, Kuala Lumpur to the Pailin District of Western Cambodia contracted falciparum malaria. Once weekly chloroquine or Darachlor (a combination of chloroquine and pyrimethamine) were taken by the members of the team as prophylactic drugs. In two of these cases (Eyles et al., 1963) who were given normal therapeutic regimen of chloroquine a relapse was observed; the blood plasma in one case that relapsed twice showed concentrations of chloroquine generally considered to be therapeutic. Resistance to chloroquine was studied by transference of the strain to prison volunteers in the United States of America.

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Clinical case histories of several cases from various parts of Thailand which showed a relapse after chloroquine were reported by Harinasuta (1962). Young et al. (1963) who had studied a military person returning to the United States of America with falciparum malaria reported, by determining blood levels and by passage to prison volunteers, the existence of chloroquine-resistant strains of falciparum malaria in Thailand.

Towards the end of 1962 there were reports of a high incidence of falciparum malaria contracted by Commonwealth troops in North Malaya which relapsed in spite of returning to generally non-endemic areas at Taiping, Malacca or Kuala Lumpur and after full chloroquine treatment. Montgomery and Eyles (1963a & b) have confirmed the existence of chloroquine-resistant strains of falciparum malaria in North Malaya by treating these cases under observation in a base military hospital at Kinrara, Kuala Lumpur, and determining plasma levels for chloroquine. The relevant strains were transmitted to prison volunteers for further investigation.

A team from the Institute for Medical Research and the United States Public Health Service Research Unit went out during the first half of December 1962 to make a preliminary survey (Sandosham et al., 1963) of the malaria situation in North Perlis. It was found that in the adjoining areas (Kampongs: Padang Mawar, Sena and Kok Mak) where the Commonwealth units probably became infected with malaria, about half the indigenous people had malaria of which P. falciparum accounted for nearly 60%. The houses in the area had been sprayed with dieldrin for two years and A. balabacensis balabacensis caught near the tents occupied by the troops were found with oocysts and sporozoites. It was decided to return at a later date to Perlis to carry out a more detailed study.

At a meeting convened on 11 February 1963 by the Director of Medical Services, Federation of Malaya, it was decided to carry out a joint study with the United States Public Health Service and WHO to determine the effect of chloroquine on falciparum malaria among the semi-immune indigenous population in North Malaya. This field-work was carried out during the months of March and April 1963.

1. Description of the area of Perlis

Of the States of the Federation of Malaya (Fig. 1) Perlis (Fig. 2), situated at its north-western border with Thailand, is the smallest comprising only about 315 square miles. A chain of rugged limestone hills runs along the boundary separating Perlis from Thailand. The rest of the State is fairly flat with scattered limestone hills. The soil is generally considered poor and only about one-third of the land is cultivated, the main crop being rice. The south-west border of Perlis is open to the sea and the people along the coast, especially those at the mouth of the Perlis River, do some fishing.

Perlis has a population of a little over 100 000. About 80% of the people are of Malaysian stock, those living along the northern border having blood relations with the Thais. Though under different governments the people living on the boundary cross the borders with relative ease. The Chinese who form the rest of the population tend to concentrate in the towns, as elsewhere in Malaya, and are found mostly in Kangar, Padang Besar, Kaki Bukit, Arau and Kuala Perlis.

Climatically Perlis, together with North Kedah and Pulau Langkawi, approximates that of the monsoon countries to the north of Malaya. Here the rainfall is not distributed fairly evenly throughout the year as in the greater part of the rest of Malaya; it has seasonal extremes instead, the driest month in Perlis receiving less than one-sixth of the rainfall of the wettest month. This has resulted in this area being different from the rest of the country in its flora and fauna. The anophelines of the rice-fields and swamp forest which are abundant from May to November practically disappear during the rest of the year when malaria transmission practically ceases.

There has been an increase in the incidence of malaria in Perlis since 1957, the total number of admissions to the Government Hospital at Kangar being as follows: 1957 - 223; 1958 - 310; 1959 - 264; 1960 - 542; 1961 - 682; 1962 - 583. The results of a parasite survey carried out in the rural areas of Perlis from 11-14 December 1962 are shown in Table 1.

2. Method of investigation

Kangar, the capital, was used as the base of operations. After an initial blood survey it was decided to limit the investigations to four groups of kampongs (diffuse villages) which were to be visited daily. The places were:

- (1) Kampong Chantek (including Kampong Padang Mawar, Kampong Sena and Kampong Kok Mak);
- (2) Kampong Titi Tinggi;
- (3) Kampong Ulu Pauh;
- (4) Kaki Bukit and Padang Besar.

Kampong Wang Kelian and Kampong Kubang Tiga were left out because of their relative inaccessibility and lack of personnel to form additional teams. Kampong Ulu Pauh, which was similar to Kampong Chantek but had not been surveyed previously, was included to provide more cases for investigation.

The initial blood survey carried out in March 1963 showed a malaria incidence of 275 out of 1510 people examined (18.2%), of whom 119 had falciparum infection (43.3%). The impression obtained during this survey (no parasite counts were made at this stage) was that the intensity of infection has decreased in comparison with the results of December 1962. These findings were in keeping with the decrease in transmission of malaria following the onset of the dry season at the end of November 1962. All the subjects found positive were divided into two groups according to the single drug dosage given.

2.1 Chloroquine: 300 mg group (adult dose)

It was decided to give the people on the day of treatment designated D₀ 300 mg chloroquine base, those between six and 15 years of age receiving half this dose (150 mg). The dose of 300 mg was chosen in order to help sieve out early in the investigation those that were unlikely to prove resistant to chloroquine. We were aware that at Tampin in Negri Sembilan (see map) Wilson & Edeson (1954) had found that in all 40 cases of acute P. falciparum malaria with the average parasite count of 19 300/mm³ treated with 300 mg of chloroquine base the blood had remained positive

for only three days after commencement of treatment, most of them becoming negative on the third day after treatment (D_3). It was felt that with the milder infection (average parasitaemia being about $10^4/6/\text{mm}^3$) in a semi-immune population one could expect at least an equally good response if there was no resistant strain of falciparum malaria present among them. The weights were taken of all the 81 people receiving treatment. A thick blood film was taken and particulars as to date, age, sex, race, house number, history of fever, evidence of splenomegaly, etc., were entered in a stencilled form; 300 mg of chloroquine base (half dosage for those between six and 15 years of age) were given under the direct supervision of malariologist or parasitologist in charge of the team. The urine examined by the Mayer's test for qualitative evidence of the drug on the third day after administration of chloroquine proved positive in 67 out of 68 cases tested.

The blood films were examined by experienced microscopists generally, daily for five days including the day of treatment (D_0). Two hundred fields were examined and the trophozoites, schizonts and gametocytes were recorded separately. The number of parasites per 400 white blood cells was counted at the same time in order to be able to assess the number of parasites per mm^3 of blood (on a basis of a white count of 8000). If the parasites cleared and the blood remained negative for three days blood films were continued daily, if possible, for a further 14-day period. If the blood remained negative for a further period of 14 days after the initial five-day period the cases were dropped from further investigation.

If parasites cleared but recurred, patients were given 1200 mg chloroquine base (in doses of 600, 300 and 300 mg on three consecutive days). If patients failed to clear on the fourth day after the single dose treatment, full treatment was given as soon as possible and the day of commencement of full treatment was designated DF_0 . Subsequently, blood films were examined if possible daily for four weeks. If parasites did not clear on DF_7 blood was taken for chloroquine level, as soon after reappearance of parasites as possible.

2.2 Chloroquine: 600 mg group (adult dosage)

A small group of 11 (nine adults and two children) were given 600 mg of chloroquine base on D_0 and blood films examined daily from D_0 . The urine examined three days after treatment was positive for chloroquine in all eight cases examined. If the patients failed to clear blood has taken for plasma drug level on the seventh day. If the parasites cleared within five days and remained absent for three days, blood examinations were continued daily until recurrence or for four weeks after drug administration. Plasma was taken as soon as possible after recurrence. The patient was given 1200 mg chloroquine and was to be followed up subsequently if convenient.

3. Results

3.1 Chloroquine: 300 mg group (adult dosage)

Of the 81 falciparum cases treated with this dose of chloroquine (150 mg for six to 15 years old), 24 were found positive on D_5 and 29 more who had cleared had become positive before D_{19} giving 53 subjects or 65 per cent. of positives over this period (see Table II).

Fifty subjects were treated with 1200 mg in three days (or half this dose for six to 15 years old) and were examined for four weeks. Twelve of these (24%) showed a recurrence in six to 26 days after treatment. Their chloroquine level in plasma was determined. In five of these cases the plasma level, assessed on the same day or one or two days later varied from 10 to 57 $\mu\text{g}/\text{l}$ and in seven others it was less than 10 $\mu\text{g}/\text{l}$.

3.2 Chloroquine: 600 mg group (adult dosage)

Of the 13 cases belonging to the 600 mg group two dropped out early, leaving nine adults and two children. Of these, three adults were positive on D_5 , and four more recurred nine to 18 days after clearance, giving a total number of seven out of 11 (64%) (see Table III). The plasma was estimated for chloroquine as soon as possible after the breakthrough was evident or within at most two days and the results (see Table IV) showed blood levels varying from 15 to 81 $\mu\text{g}/\text{l}$. Two of these cases are shown in Fig. 7. The seven cases were given 1200 mg chloroquine (half for six to 15 years of age) and examined at the end of two weeks for evidence of

relapse. They were all negative and were sent away as the investigating team had to leave Perlis; however, the Medical Officer of Perlis (Dr Natarajan) re-examined them about 50 days after initial treatment. Three were positive; one for P. vivax and two for P. falciparum.

4. Entomological findings

In the course of the previous survey of the northern border of Perlis near Kampong Padang Mawar (Sandosham et al., 1963) mosquito catches were made with human bait in net-traps on five nights from 10-14 December 1962. The dry season had already commenced and the adult catches were relatively poor. During the present survey adult and larval catches were made over a more extended period and the dry spell with little surface collections of water had some bearing on the poor results.

The adult collection in December 1962 produced a total of 211 mosquitos of which the great majority (180) were A. philippinensis followed by 18 A. balabacensis, seven A. barbirostris, five A. peditaeniatus, four A. vagus and one or two A. campestris, A. nigerrimus and A. tesselatus.

The adult collection during the period 6-20 March produced 24 A. philippinensis, five each of A. campestris and A. barbirostris, lesser numbers of A. indiensis, A. peditaeniatus, A. kochi, and single specimens of A. sinensis, A. karwari, A. sundaicus and A. vagus.

The larvae collection during the period March to April 1963 was carried out in four localities (Chantek Complex, Kaki Bukit, Ulu Pauh, Titi Tinggi) and produced a total of 167 specimens of which the great majority proved to be of the A. barbirostris group (52 out of 147 larvae were found to be A. barbirostris). The remainder belonged to the A. hyrcanus group, A. aconitus, A. philippinensis and A. kochi. Out of 11 larvae of the A. hyrcanus group six that were bred out proved to be A. peditaeniatus, A. indiensis and A. sinensis.

In the Abi Reservoir and the surrounding catchment zone, which is not part of the area under investigation, larval catches included A. minimus and A. maculatus, both considered as malaria vectors of importance. The finding of a single specimen of another malaria vector, A. sondaicus, in Kampong Chantek about 10 miles away from the nearest brackish water zone deserves comment. This species is generally regarded as very rare or absent in the western coastal belt of Malaya north of the estuary of the Perak River. It was recently recorded from Pulau Langkawi. Among other known vectors were A. campestris, A. nigerrimus and A. balabacensis balabacensis, the latter having been found infected, two with oocysts and one with sporozoites out of 17 dissected, in our December 1962 survey.

Reid (1950) has made reference to the peculiar anopheline fauna of this part of Malaya which is somewhat similar to that of the monsoon regions to the north. A. minimus, A. ramsayi, A. jamesi and A. balabacensis balabacensis have not been recorded south of Kedah. The paucity of vectors in the areas under investigation would suggest the complete cessation of transmission during this dry period. It is very probable, therefore, that the recurrences of parasitaemia after treatment were not due to fresh infections.

5. Discussion

5.1 The comparison of response to 300 mg chloroquine base of the Perlis cases (22 in whom complete daily blood-film results are available for the first eight days) with that of the Tampin cases is shown in Fig. 3. Whereas in Tampin, in spite of heavier parasitaemia (19 300 per mm^3 as compared with 1046 per mm^3) 95% of the 40 cases had cleared on the third day and none were positive from the fourth to the sixth days, only 55% of these 22 Perlis cases had cleared on the third day and it was never higher than 64% even up to the seventh day.

In our cases, in order to avoid complications and to get maximum co-operation from the people, only those above the age of six were included and 150 mg of chloroquine base was given to all those between six and 15 years of age. In Tampin, however, a graded dosage was adopted for children, those between six and 12 receiving three-quarters of the adult dose and those over 12 being given full adult dose.

The question as to whether the lower dose given to the children in Perlis could have been responsible for lesser frequency of clearance of parasitaemia was investigated. The weights of children varied from 29 to 80 lbs, the mean being 54. Of those below 54 lbs in weight 57% (eight out of 14) had cleared before D₅ whereas of those above 54 lbs only 27% (three out of 11) had cleared. Dividing the body-weight into four groups the graph (Fig. 4) shows the percentage that cleared and the percentage that cleared but recurred subsequently. In both cases it was evident that the clearance rate after 300 mg was higher in the lower weight groups indicating that half dosage was on the low side for the heavier children although 64% (nine out of 14) below the mean weight had not cleared or had cleared but recurred.

Of the 50 cases that belonged to the 300 mg group and who were followed up after full treatment of 1200 mg chloroquine base, 12 showed the recurrence of parasitaemia within four weeks. Eleven out of these 12 were below 15 years of age and had received only the half dose of 600 mg chloroquine. However, there were also 21 children among 38 that did not break through. Taking the children who had received only 600 mg chloroquine base, 11 with an average weight of 54 lbs had a break-through whereas 21 with an average weight of 51 lbs did not break through. This would indicate that the dosage relative to the body-weight after full treatment probably did not play a big part in determining if there would be a break-through; it was more likely affected by the relative resistance of the strain of parasite to chloroquine.

Blood for determination of the chloroquine level was taken soon after the renewed presence of parasites was noted. The assessment of the chloroquine level in the plasma was carried out in the United States of America. As was to be expected, the chloroquine levels were relatively higher in those cases which broke through earliest after full treatment. The highest levels of chloroquine in this group were 23, 30 and 57 µg/l, but in view of the fact that the build-up of parasitaemia must have commenced some time before the break-through was evident and blood could be taken, the chloroquine level at the time of the initial break-through was probably higher. In some cases (Fig. 5) the parasite count was high in spite of a fairly high level of chloroquine in the plasma. Of the cases found to be

positive following 300 mg chloroquine base and given 1200 mg of chloroquine base, daily blood-film findings are available in 24 cases. All of these showed a complete clearance on D_4 , but in four cases there was recurrence of parasitaemia on D_5 , D_6 and D_7 .

5.2 The comparison of response to 600 mg chloroquine base of the Perlis cases (for seven cases of which daily blood-film results are available) with that of the Tampin cases is shown in Fig. 6. Whereas in Tampin, in spite of heavier parasitaemia ($28\ 250/\text{mm}^3$ as compared with $1083/\text{mm}^3$) not a single case out of 114 had parasites on day D_4 , there were in Perlis three out of seven with parasitaemia on that day, though negative on day D_2 or D_3 .

Summary and conclusions

The investigation indicates the existence of chloroquine-resistant strains of P. falciparum in Perlis, North Malaya, among the indigenous population.

When the semi-immune indigenous population of rural Perlis was given 300 mg (150 mg for those between six and 15 years of age) of chloroquine base, 24 out of 81 failed to clear by D_5 and a further 29 recurred before D_{19} after initially becoming free of parasites. When those whose blood became positive were given 1200 mg chloroquine base in three days (600 mg for those between six and 15 years of age) 12 out of 50 treated recurred within four weeks of treatment. Two of these had parasitaemia with chloroquine plasma levels of 18 and 23 $\mu\text{g}/\text{l}$ (Fig. 5).

Seven out of 11 given 600 mg chloroquine base cleared initially, but became positive between D_6 and D_{19} and in two of them the plasma level was 65 and 81 $\mu\text{g}/\text{l}$ one to two days after the positive blood slide was seen (Fig. 7).

It is probable that the chloroquine-resistant strains of P. falciparum found in Commonwealth troops by Montgomery & Eyles (1963a & b) were contracted in the area where the present survey was carried out.

Acknowledgement

It gives us great pleasure to acknowledge our indebtedness not only to our collaborators but particularly also to Dr S. Appadurai, the Chief Medical and Health Officer, Kedah and Perlis, and Dr I. Natarajan, the Medical Officer of Perlis, who were of such great assistance to us. The latter not only provided us with guides, health staff, laboratory accommodation and housing, but also saw to all our comforts at considerable personal sacrifice on his part.

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REFERENCES

- Box, E. D. et al. (1963) Chloroquine-resistant Plasmodium falciparum from Brazil, Amer. J. trop. Med. Hyg. 12, 300
- Eyles, D. E. et al. (1963) Plasmodium falciparum resistant to chloroquine in Cambodia (In press)
- Harinasuta, M. (1963) Chloroquine-resistant falciparum malaria in Thailand (In press)
- Montgomery, R. & Eyles, D. E. (1963a) Chloroquine-resistant falciparum malaria in Malaya, Trans. Roy. Soc. trop. Med. Hyg. 57, 409
- Montgomery, R. & Eyles, D. E. (1963b) A further study of chloroquine-resistant falciparum malaria in Malaya with observations on cross-resistance and response to other drugs (In press) WHO/Mal/418
- Moore, D. V. & Lanier, J. E. (1961) Observations on two Plasmodium falciparum infections with an abnormal response to chloroquine, Amer. J. trop. Med. Hyg. 10, 5
- Reid, J. A. (1950) Some new records of anopheline mosquitos from the Malay Peninsula with remarks on geographical distribution, Bull. Raff. Mus. 21, 48
- Rodrigues, D. C. (1961) Casos de malaria por Plasmodium falciparum resistentes al tratamiento pela chloroquina, Arch. Hig. (S. Paulo), 26, 231

- Sandosham, A. A. (1963) Chloroquine-resistant falciparum malaria in Malaya, Singapore Med. J. 4, 3
- Sandosham, A. A. et al. (1963) Malaria in Perlis, Med. J. Malaya, 18
- Wilson, T. & Edeson, J. F. B. (1954) Studies on the chemotherapy of malaria.
III. The treatment of acute malaria with chloroquine, Med. J. Malaya, 9, 115
- Young, M. D. & Moore, D. V. (1961) Chloroquine-resistance in Plasmodium falciparum, Amer. J. trop. Med. Hyg. 10, 317
- Young, M. D. et al. (1963) Drug resistance to Plasmodium falciparum from Thailand, Amer. J. trop. Med. Hyg. 12, 305

TABLE I. SURVEY RESULTS IN RURAL AREAS OF NORTH PERLIS, 11-14 DECEMBER 1962

Place	Total examined	Species					Malaria positive	Percentage
		<u>falciparum</u>	<u>vivax</u>	<u>malariae</u>	mixed	species unidentified		
Kampong Padang Mawar*	162	43	9	21	0	3	76	47
Kampong Chantek	108	24	16	6	0	5	51	47
Kampong Wang Kelian	118	6	12	16	1	2	37	31
Kampong Kubang Tiga	60	9	9	8	3	2	31	51
Kampong Titi Tinggi	166	19	22	8	1	3	53	32
Total	614	101	68	59	5	15	248	40.4

* Includes Kampong Sena and Kampong Kok Mak

TABLE II. RESULTS OF SINGLE TREATMENT WITH 300 mg BASE OF CHLOROQUINE FOLLOWED BY 1200 mg *

Kampong	Treated and followed up to D ₁₉	Positive on D ₅	Cleared but recurring between D ₆ and D ₁₉	Total	Percentage not radically cured by 300 mg	Given 1200 mg* and followed up for four weeks	Positive within four weeks after 1200 mg
Chantek Complex	19	6	11	17	90	15	2 (13%)
Titi Tinggi	17	3	5	8	47	8	1 (13%)
Ulu Pauh	30	9	8	17	57	16	6 (38%)
Kaki Bukit	15	6	5	11	63	11	3 (27%)
Total	81	24	29	53	65	50	12 (24%)

* Half this dose for subjects aged between six and 15 years.

TABLE III. RESULTS OF SINGLE TREATMENT WITH 600 mg BASE OF CHLOROQUINE FOLLOWED BY 1200 mg*

Kampong	Treated and followed up	Positive on D ₅	Cleared but recurring between D ₆ and D ₁₉	Total	Percentage not radically cured by 600 mg	Given * 1200 mg	Positive two weeks later
Chantek Complex	6	3	1	4	67	4	0
Titi Tinggi	3	0	2	2	67	2	0
Ulu Pauh	2	0	1	1	50	1	0
Total	11 (9 adults 2 children)	3	4	7	64	7	0

* Half this dose for children aged between six and 15 years

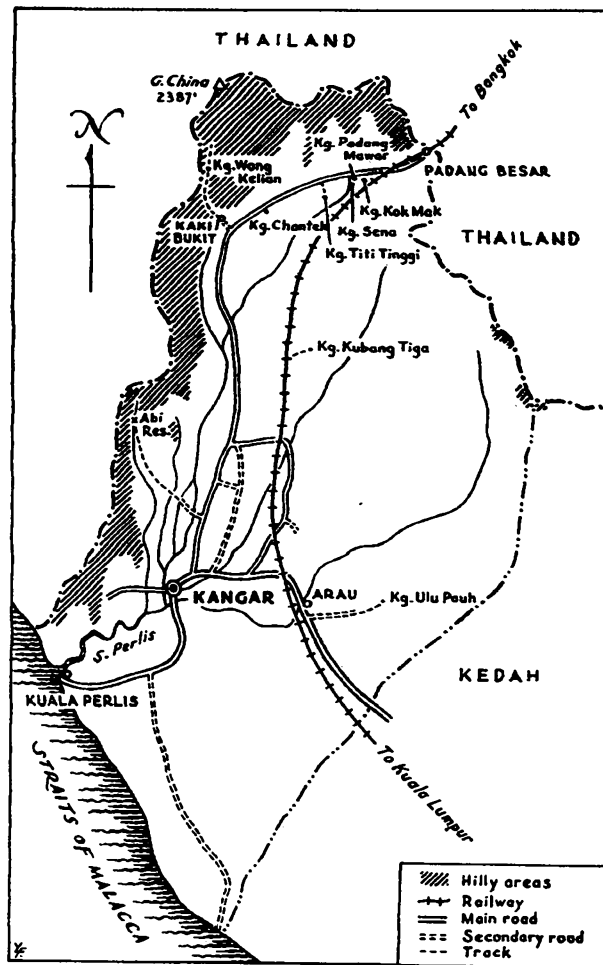
TABLE IV. THE BREAK-THROUGHS AFTER 600 mg OF CHLOROQUINE BASE

Number	Serial number	Name	Age	Weight	Sex	Day of break-through	Day blood taken	Chloroquine mg/litre
1	M S	Mahasa Bt. Hamid	18	102 lbs	F	D 5	D 5	65
2	C 57	Melor Bt. Arshad	23	100 lbs	F	D 5	D 6	81
3	M 25	Osman Bin Omar	18	120 lbs	M	D 5	D 7	41
4	T 107	Abu Bakar Bin Yam	17	105 lbs	M	D 9	D 11	42
5	U 41	Habsah Bt. Leh	12	62 lbs	F	D 11	D 13	15
6	C 98	Miah Bt. Abdullah	24	115 lbs	F	D 18	D 19	35
7	F 2	Baharom bin Abu Jeman	8	45 lbs	M	D 18	D 19	28



FIG. 1. MAP OF MALAYA WHO 31000

FIG. 2



SKETCH MAP OF PERLIS WHO 31001

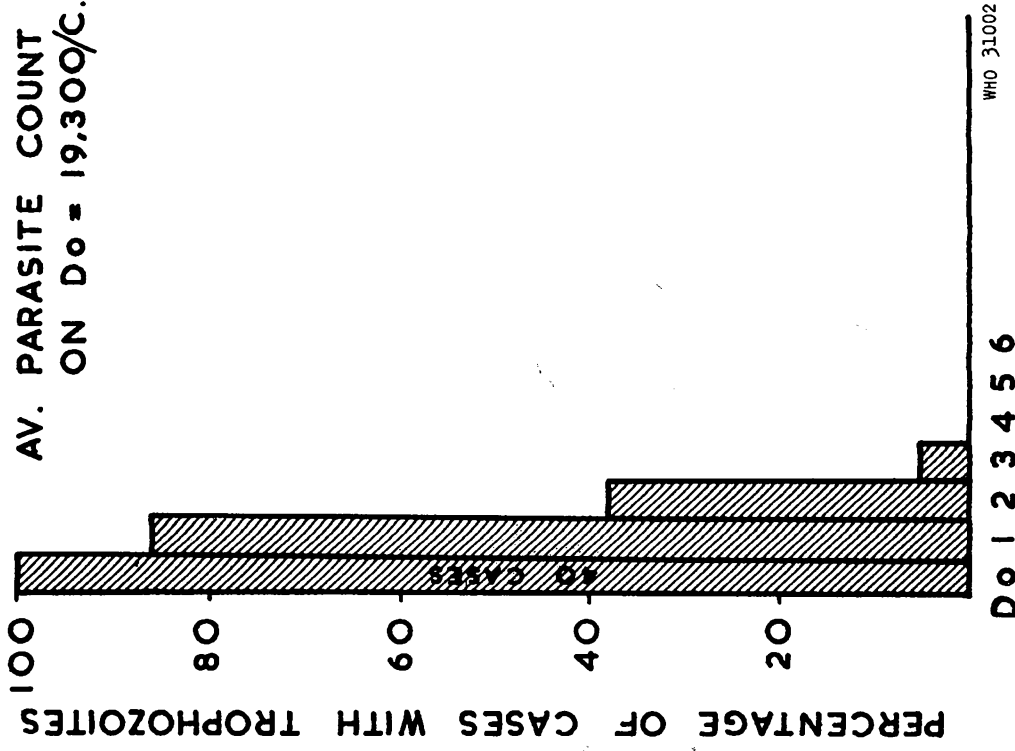
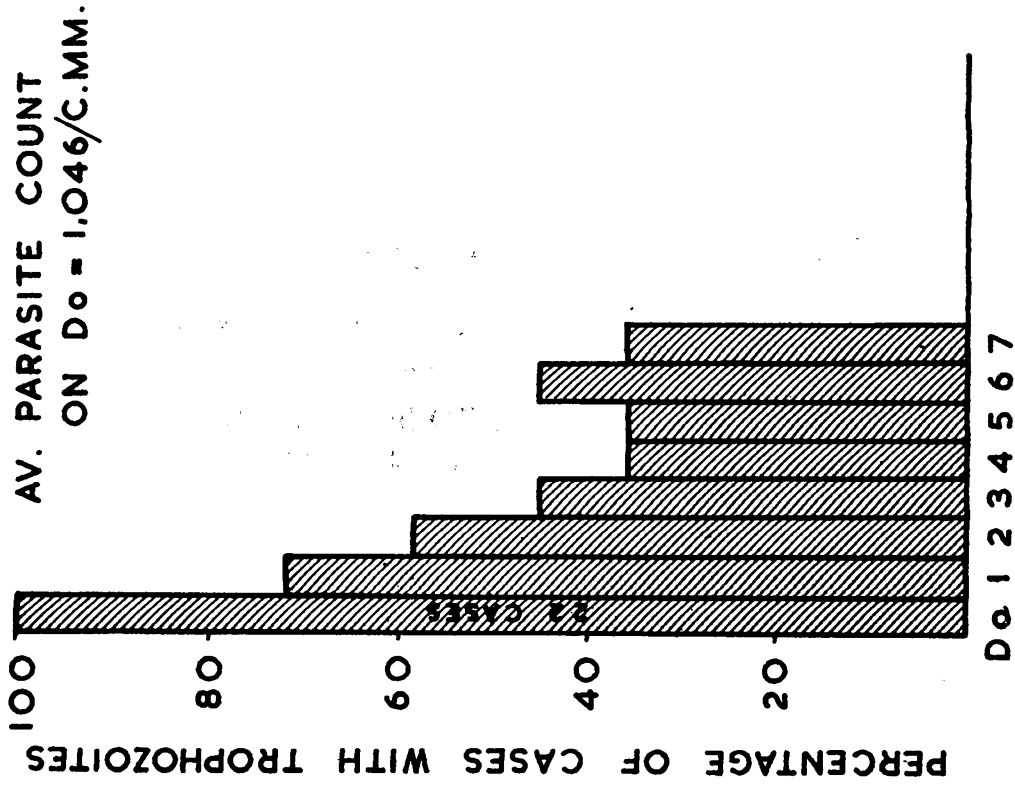


FIG. 3. 22 CASES IN THE 300 MG. GROUP FROM PERLIS COMPARED WITH 40 CASES FROM TAMPIN (WILSON & EDESON, 1954)

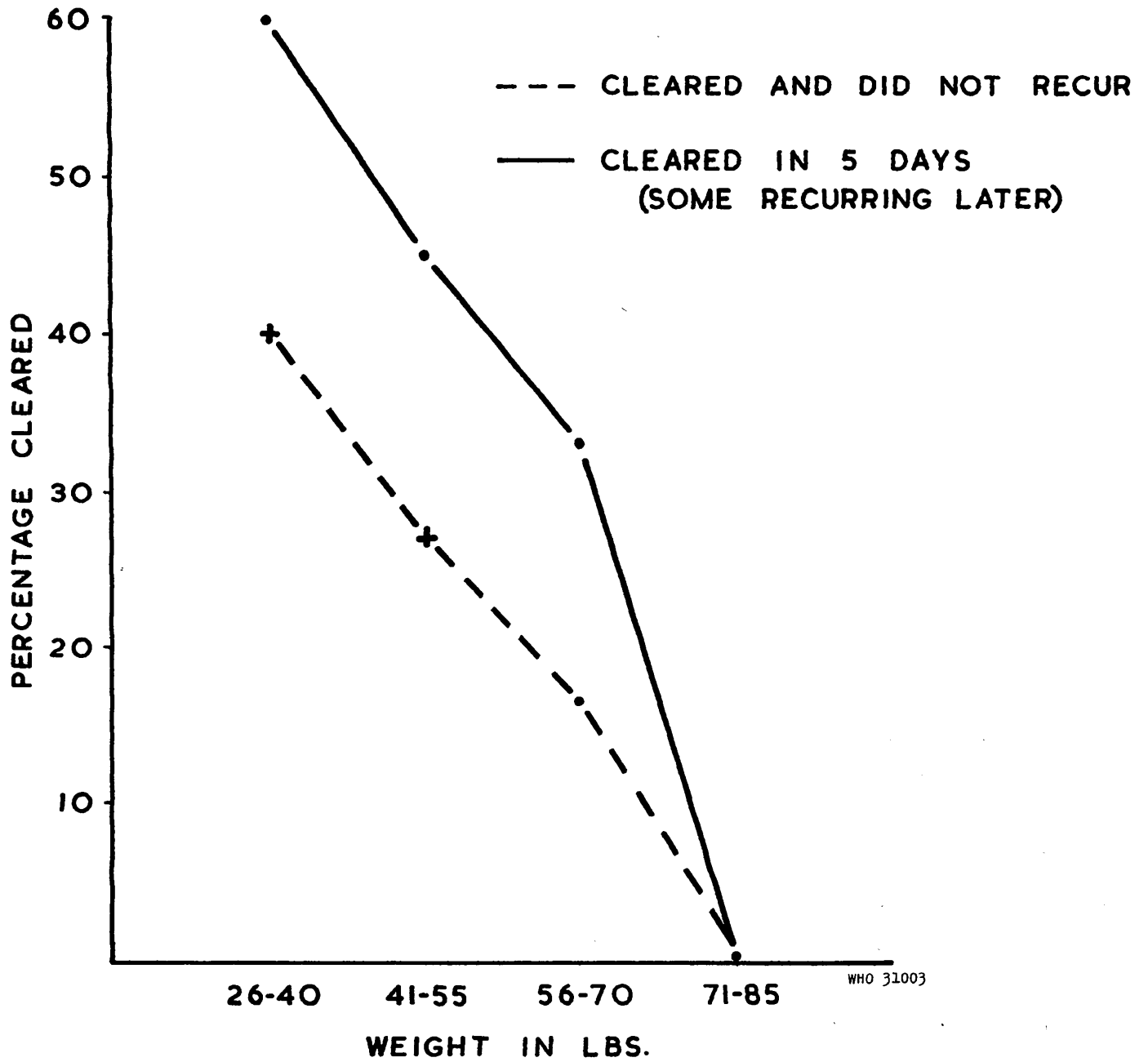


FIG. 4. RELATION BETWEEN WEIGHT AND CLEARANCE OF PARASITES. (DOSE OF CHLOROQUINE CORRESPONDING TO THE ADULT DOSE OF 300MG. BASE)

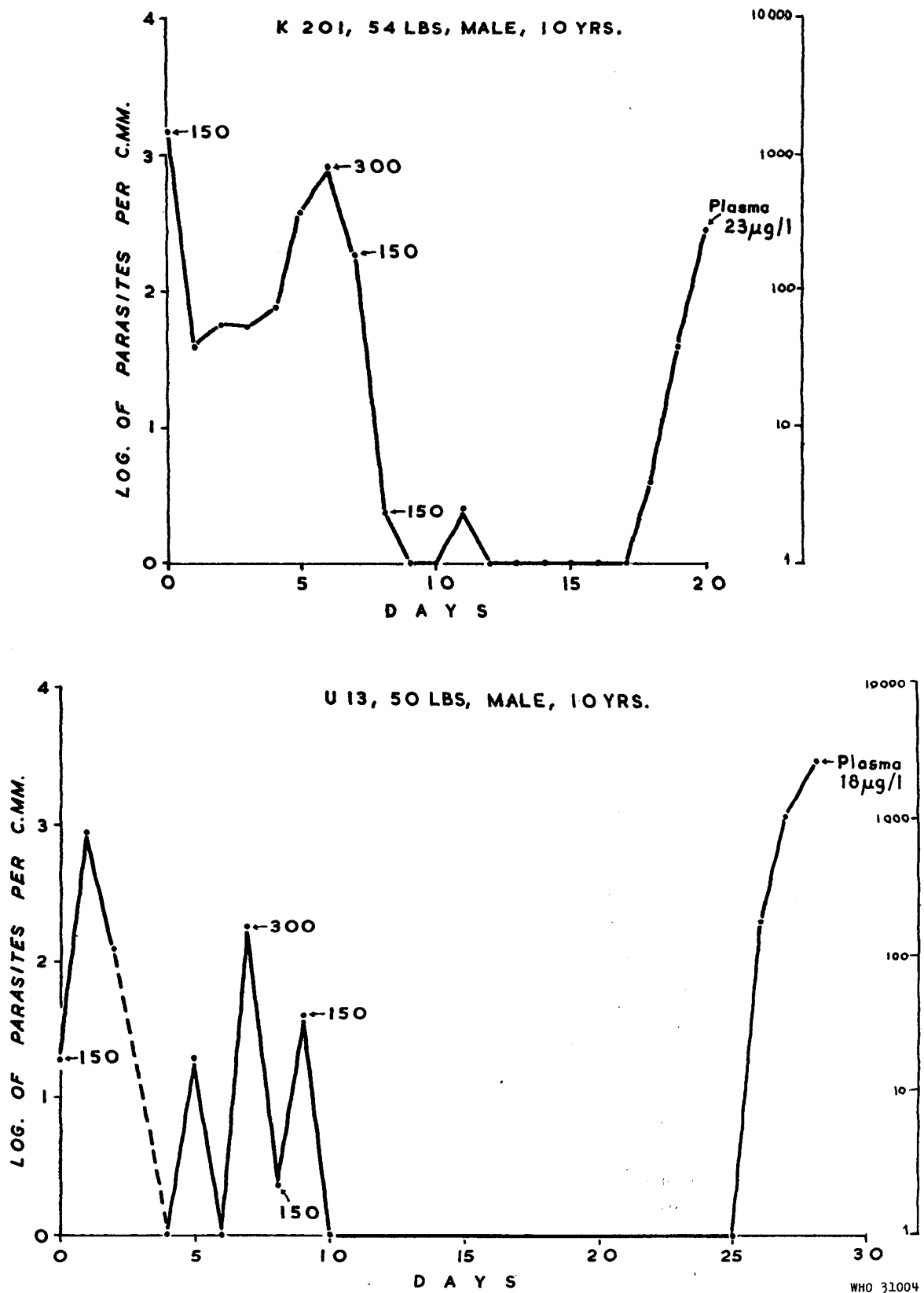


FIG. 5. GRAPHS OF TWO CASES BELONGING TO THE 300 MG. GROUP WHICH BROKE THROUGH AFTER FULL TREATMENT (1200 MG. FOR ADULTS). THESE TWO CASES BEING 10 YEARS OF AGE WERE GIVEN HALF DOSES. PLASMA LEVEL OF CHLOROQUINE SHOWN.

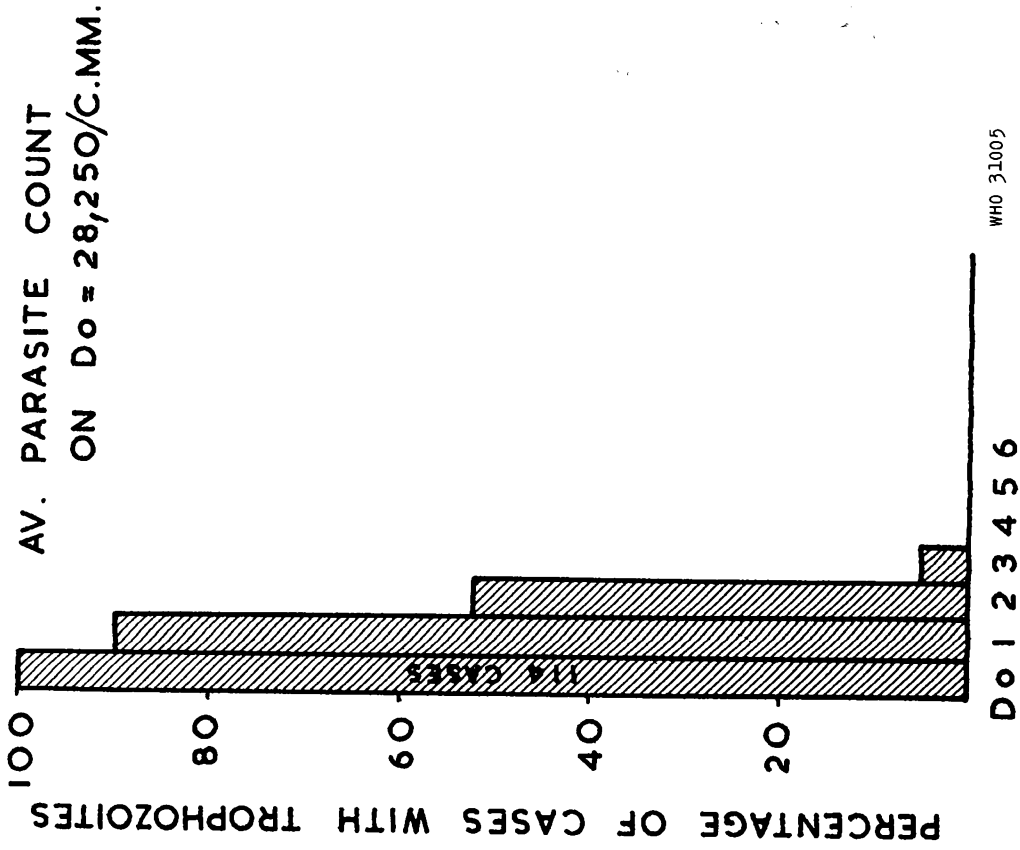
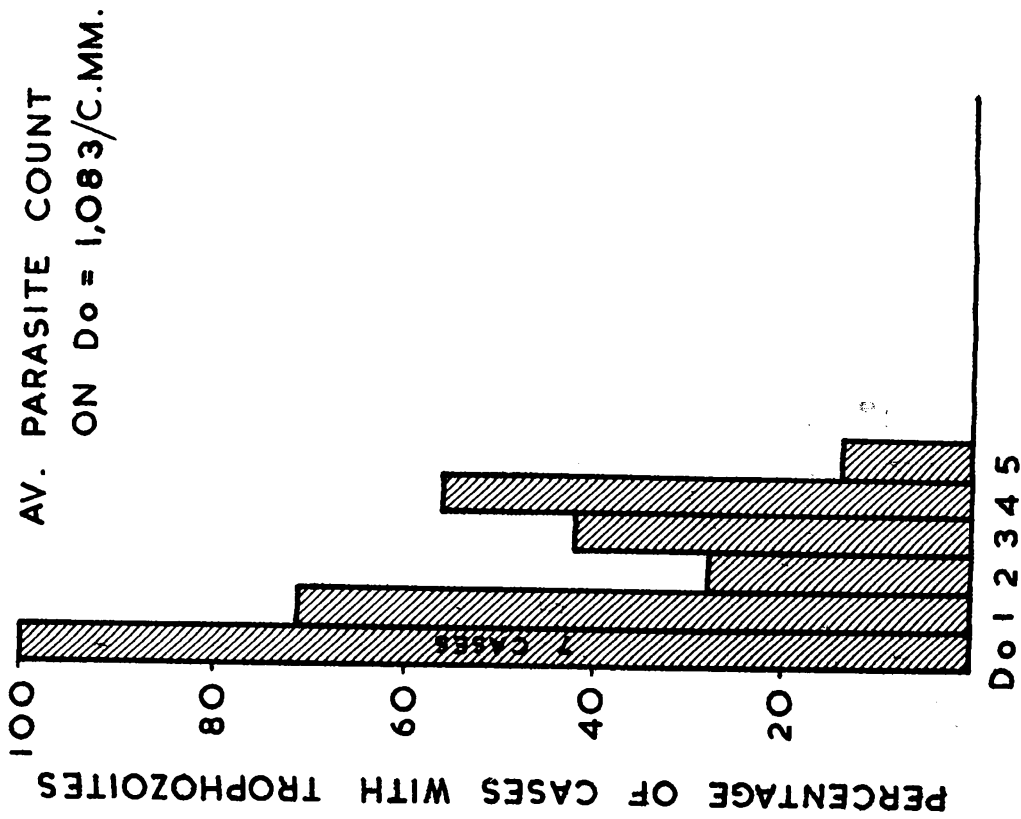


FIG. 6. 600 MG. GROUP. 7 CASES FROM PERLIS COMPARED WITH 114 CASES FROM TAMPIN (WILSON & EDESON, 1954)

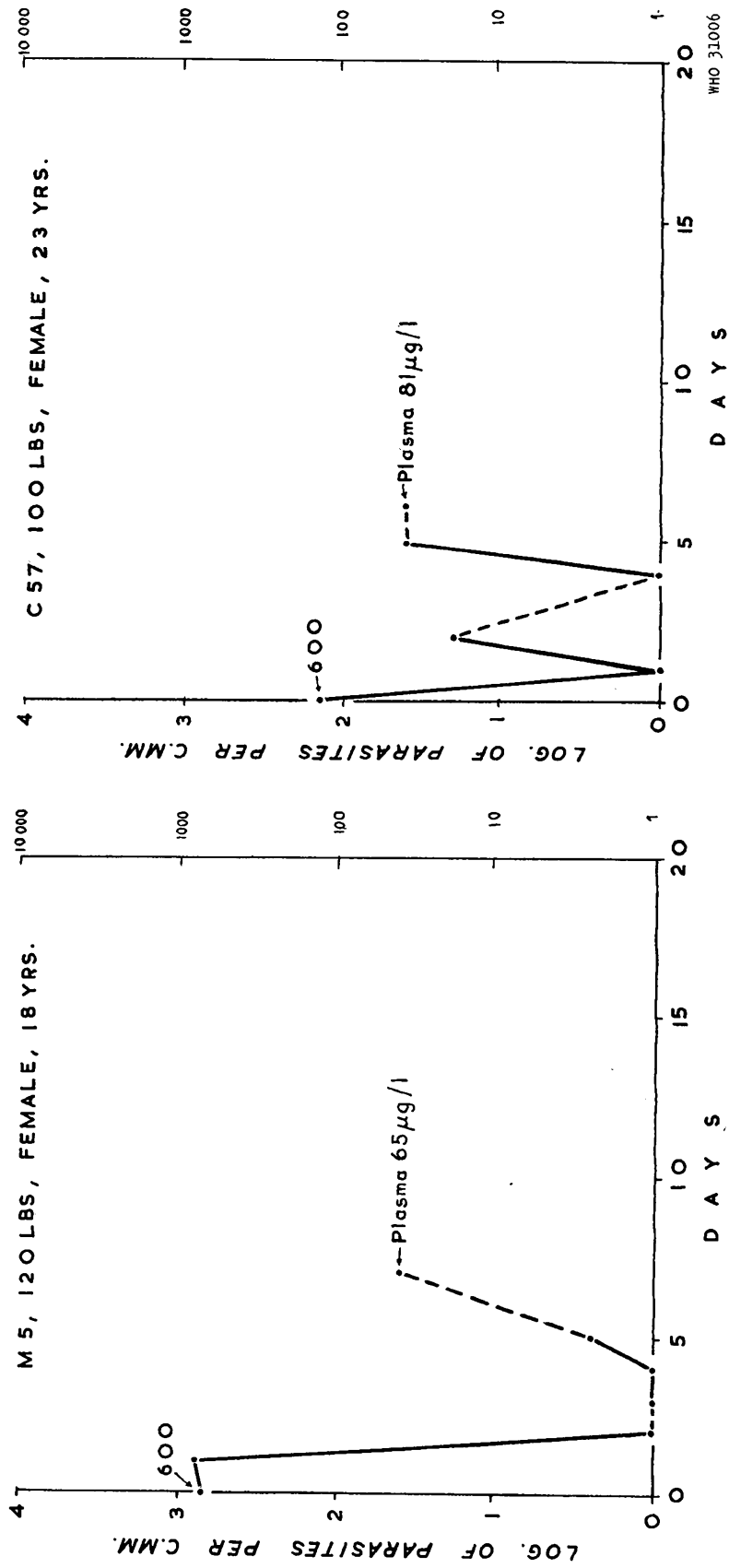


FIG. 7. GRAPHS OF TWO CASES GIVEN 600 MG. CHLOROQUINE BASE WHICH BECAME POSITIVE AFTER INITIAL CLEARING. PLASMA LEVEL OF CHLOROQUINE SHOWN.

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