The Medical Journal of Malaya
Vol. XVIII, No. 3, March 1964.

# DRUG-RESISTANCE IN FALCIPARUM MALARIA IN SOUTH-EAST ASIA

by

Prof. A. A. SANDOSHAM*

Senior Malaria and Filariasis Research Officer,
Institute for Medical Research, Federation of Malaya.

Dr. DON E. EYLES,

Scientist Director, U.S. Public Health Research Unit,
Institute for Medical Research, Federation of Malaya.

and

Col. R. MONTGOMERY,

Medical Specialist, British Military Hospital,
Kinrara, Kuala Lumpur.

Pampana (1963) defines resistance to an antimalarial as the capacity of a particular strain to survive when the drug has been administered to the vertebrate host at a dose that would normally destroy the parasites in the same stage of life cycle. Strains of **Plasmodium falciparum** in different parts of the world may differ in their degree of susceptibility to various drugs while the indigenous population of an area may be susceptible to infection to a varying extent. In order to determine if drug resistance in falciparum malaria existed in South-East Asia it would be desirable to establish what constituted the "dose that would normally destroy the parasites" among the indigenous population.

The most comprehensive work on the action of drugs on falciparum malaria in this part of the world has been carried out by the staff of the Institute for Medical Research, Federation of Malaya and published as a series chiefly in the Medical Journal of Malaya under the heading of "Studies on the chemotherapy of malaria, I to VII" during 1952-1959. Their work, however, does not include the recurrence rate of parasitæmia after the initial clearance following treatment in the absence of reinfection. This would have been difficult and expensive in an area where active transmission was going on. The information obtained in Malaya is outlined briefly and will provide some base line data for comparison with strains suspected of showing drug-resistance. It should be realized that information obtained in Malaya may not be equally applicable to other parts of S.-E. Asia.

In attempting to determine if a resistant strain existed in the country one could compare the results of treatment of the suspected strains with those obtained with the normal susceptible strains preferably in the same area and among the same ethnic group. One could compare (1) the rate of disappearance of parasitæmia in the blood, (2) the rapidity of disappearance of clinical malaria especially of fever, (3) the reappearance or otherwise of parasitological and clinical malaria in the absence of reinfection, and (4) the presence of parasitæmia in relation to the concentration of the drug in the blood plasma. If possible the suspected strain should be inoculated into a susceptible volunteer and tested for its reaction to the drug in question.

## 4-AMINOQUINOLINES

### Chloroquine

Wilson and Edeson (1954) using Resochin (a Bayer product of chloroquine diphosphate) gave 300 mg. chloroquine base to 7 cases of indigenous people in Tampin with falciparum infection (av. count 13,800 per c.mm.) and found that parasitæmia cleared in 2 days and fever in 0.6 days. Using Nivaquine (a May & Baker product of chloroquine phosphate) they gave 300 mg. chloroquine base to 40 cases of falciparum malaria (av. count 19,300 per c.mm.) and found that parasitæmia cleared in 2.3 days and fever in 1.1 days (Figs. I & II).

* A paper read by invitation at the Seventh International Congresses in Tropical Medicine and Malaria held at Rio de Janeiro, Brazil in September, 1963.

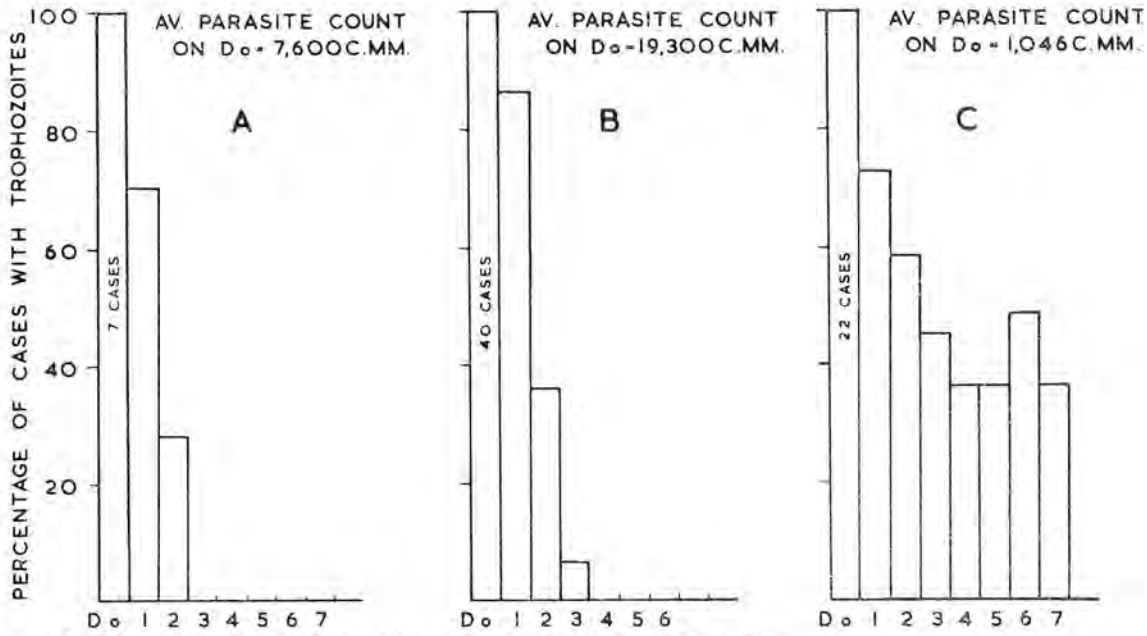



FIG. I. 300 MG. GROUP ORAL CHLOROQUINE TREATMENT
A. 7 CASES FROM TAMPIN WITH RESOCHIN (WILSON & EDESON, 1954)
B. 40 CASES FROM TAMPIN USING NIVAQUINE (WILSON & EDESON, 1954)
C. 22 CASES FROM PERLIS WITH "SPECIA" CHLOROQUINE DIPHOSPHATE (SANDOSHAM etal., 1963)

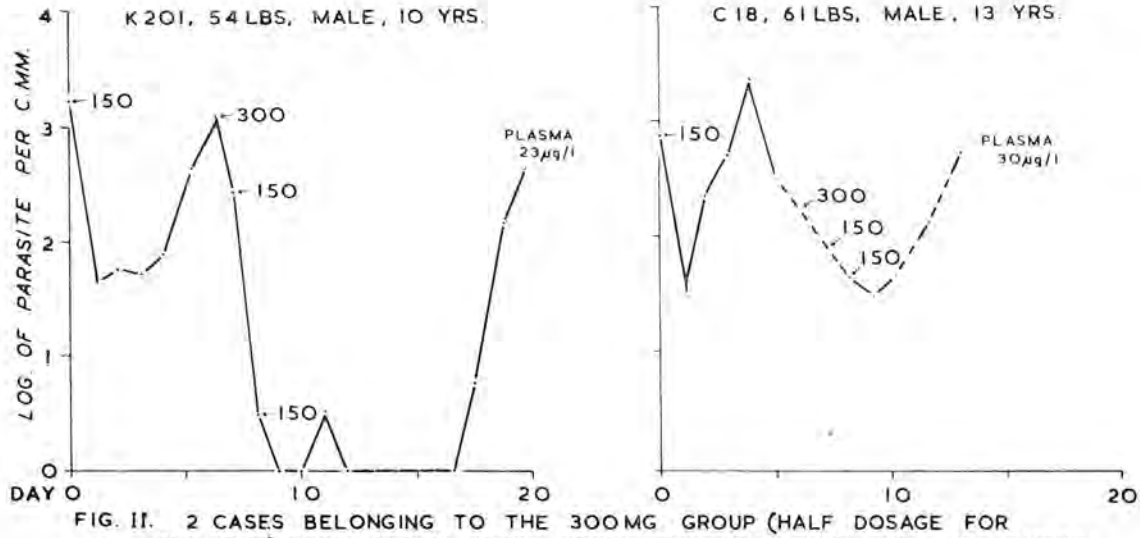



FIG. II. 2 CASES BELONGING TO THE 300 MG GROUP (HALF DOSAGE FOR CHILDREN) FROM PERLIS WHICH BROKE THROUGH AFTER FULL TREATMENT (1200 MG.). INTERRUPTED LINE MEANS NO BLOOD FILMS WERE EXAMINED DURING THAT PERIOD.

They gave single dose treatment of 600 mg. chloroquine base to 114 cases of falciparum malaria (av. count 28,250 per c.mm.) and found that parasitæmia cleared in 2.5 days and fever in 0.9 days. Several of their cases had trophozoite counts of over 100,000 per c.mm. and they concluded that 600 mg. was an effective single-dose treatment for the aver-

age Asian adult with acute falciparum malaria in Malaya. Laing (1955) working at Kuala Kangsar gave 600 mg. chloroquine base (Nivaquine) to 97 cases of falciparum malaria (av. count 8,356 per c.mm.). All but one (99 percent) had no parasitæmia within 48 hours and there was a 100 percent clearance within 72 hours after treatment (Figs. III & IV). However, for full treatment they used 1,500 mg. and this dosage should, according to Covell *et al.*, (1955) produce radical cure. This is substantiated by the work of Jeffery *et al.*, (1956) who found that only one of 46 cases relapsed after this dosage.

RESISTANCE TO CHLOROQUINE IN MALAYA — About 600 Australian soldiers belonging to the British Commonwealth Units stationed in Malaya were engaged in jungle operations near the Thai border in North Perlis during a period of about two months from August to October 1962. They were a non-immune population and were taking a daily prophylactic dose of 200 mg. of proquanil (Paludrine). About 10 percent of these men were admitted to medical units with malaria, **Plasmodium falciparum** predominating. The men were aware of the danger of contracting malaria and military discipline was such that there is no reason to believe that the prophylactic routine was not followed. A number of these cases were brought away from Perlis to their base camps near Malacca or Taiping. Although they had returned to places where there was little or no likelihood of reinfection, cases were said to have relapsed after full chloroquine therapy.

It was decided to find out if the Australian troops could have contracted their infection from the people of North Malaya near the Thai border. A brief survey in December 1962 (Sandosham *et al.*, 1963) showed that in the adjoining area to where the troops were camped about half the indigenous people had malaria of which **P. falciparum** accounted for nearly 60 percent. **Anopheles balabacensis balabacensis** caught near the tents occupied by the troops were found with oocysts and sporozoites.

A further study of this area was undertaken during March and April, 1963 by the Institute for Medical Research in collaboration with U.S.P.H. Service Research Unit and the World Health Organization to determine the effect of chloroquine on falciparum malaria among the semi-imune indigenous population there. The study (Sandosham *et al.*, in press) showed that when they were given 300 mg. chloroquine base 24 out of 81 failed to clear within 5 days after treatment and a further 29 recurred before the 19th day giving a total break-through of 65 percent. When those whose blood became positive were given 1,200 mg. chloroquine base 24 percent recurred within 4 weeks of treatment. Some of these had parasitæmia in spite of blood levels for chloroquine varying from 10 to 57 μg/litre. Seven out of 12 given 600 mg. chloroquine base either failed to clear or became positive between the 5th and 18th day and their blood levels for chloroquine soon after the break-through varied from 15 to 81 μg/litre. It was concluded that there was little doubt of the existence of chloroquine-resistant strains of **P. falciparum** occurring amongst the indigenous population of Perlis, N. Malaya and that the Commonwealth troops had contracted the infection while at manœuvres there.

Montgomery and Eyles (1963a) studied 27 Australian patients who returned from N. Malaya and were treated at the base British Military Hospital at Kinrara on the outskirts of Kuala Lumpur. Of these, ten cases were considered to show evidence of resistance to chloroquine, and two were described in detail. In none of these ten cases did chloroquine produce radical cure although 9 out of the 10 cases had received more than the generally recommended 1,500 mg. of the base. When the relapse attacks were treated again with chloroquine more than half of them were not cured as was evident from the persistence of low parasitæmia. Some of these cases relapsed a third time. The authors noted that the clearance of parasites and the disappearance of symptoms were slow. Though not cured by chloroquine, ordinary doses had an effect on the parasites and controlled the infection. The resistance, however, was not overcome even by increasing the amount of chloroquine to three times the recommended dosage. In two of these cases plasma levels of chloroquine were as high as 111 μg/litre and 66 μg/litre at the time when relapse occurred. One of the strains of **P. falciparum** from this group has been passed to prison

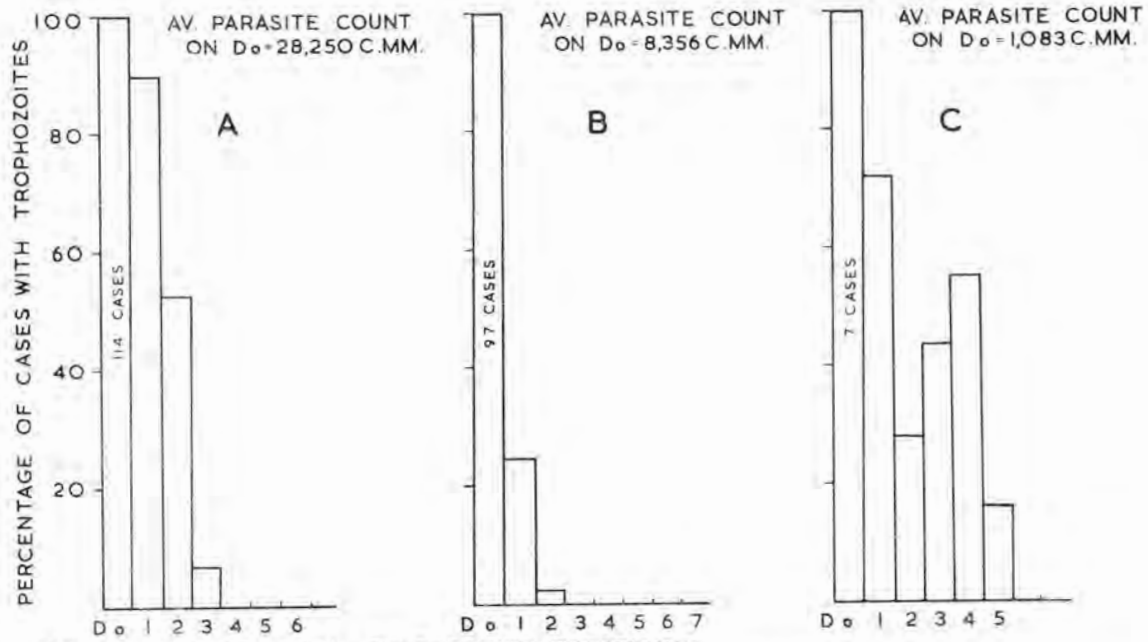



FIG. III 600 MG. ORAL CHLOROQUINE TREATMENT
A 114 CASES FROM TAMPIN WITH NIVAQUINE (WILSON & EDESON, 1954)
B 97 CASES FROM KUALA KANGSAR WITH NIVAQUINE (LAING, 1955)
C 7 CASES FROM PERLIS WITH "SPECIA" CHLOROQUINE DIPHOSPHATE (SANDOSHAM et al., 1963)

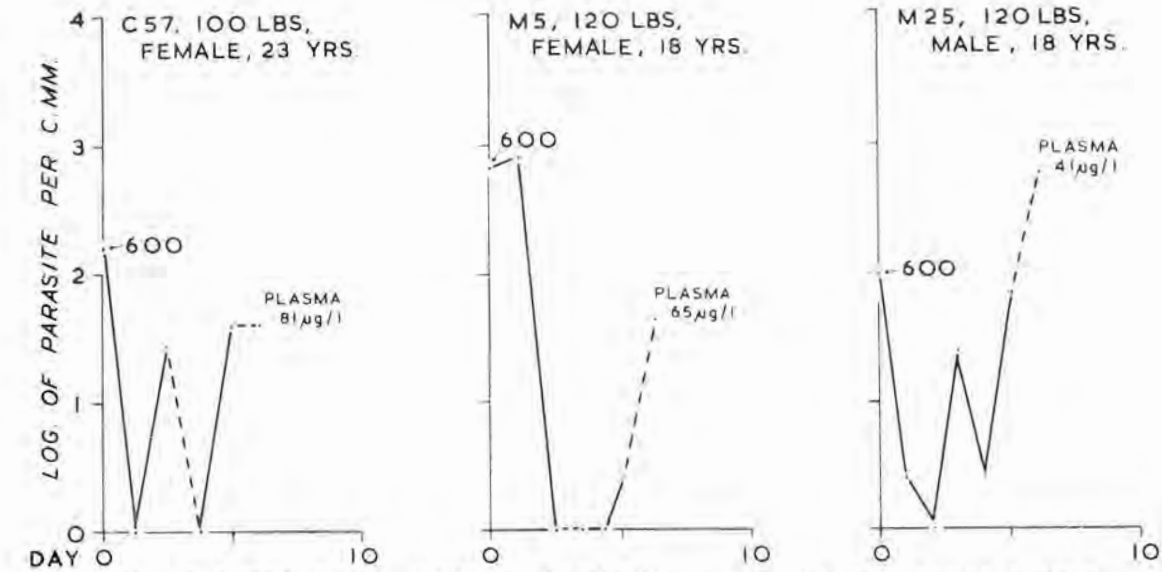



FIG. IV 3 CASES GIVEN 600 MG. CHLOROQUINE WHICH HAD PARASITAEMIA ON THE 5th DAY OR LATER AFTER INITIAL TREATMENT GIVING PLASMA LEVELS OF CHLOROQUINE

volunteers in the United States and Contacos *et al.*, (1963) have confirmed that it is resistant to chloroquine.

Montgomery and Eyles (1963b) had the opportunity to follow up the malaria histories of a similar group of Commonwealth troops (New Zealanders) who replaced the former group for a similar period. There were 137 cases of malaria notified of which 53 were diagnosed clinically. Of the 84 microscopically confirmed malaria cases 51 (61 percent) had **P. falciparum** infection. Since this unit had the benefit of experience of the previous group the prophylactic measures were more stringent. The troops took 200 mg. proguanil daily while in the area and in addition were given 300 mg. chloroquine base before going on leave during the operation. This leave was spent in places in Penang or Malacca where little or no transmission of malaria was taking place. One of the Companies was given 150–300 mg. of chloroquine base at approximately weekly intervals for 2 or 3 doses while it was operating in what was considered to be a highly infectious area.

In general, the first attacks of **P. falciparum** infection were treated with 2,400 to 2,700 mg. chloroquine base over a five to six day period. Of about 51 such cases 31 relapsed and laboratory confirmation of resistance was obtained in 28 of them. The chloroquine level in plasma was determined at relapse and before commencement of the treatment in 23 cases and the mean level was 27 μg/litre. In 14 cases the level was over 20 μg/litre. Six out of 12 cases under continuous hospital observation relapsed. Parasites recurred on the average of 14.2 days after the end of treatment and the mean chloroquine level was 43 μg/litre. Burliner *et al.*, (1948) consider 20 μg/litre as the minimum therapeutic level but it must be remembered that in many of the cases studied in Malaya blood was drawn some time after the appearance of the parasites during which there would have been some decay in the chloroquine level. Two strains from this group have been passed to prison volunteers in the United States and resistance to chloroquine has been confirmed (Contacos *et al.*, 1963).

Alving *et al.*, (1963) studied in prison volunteers a strain of **P. falciparum** contracted in Malaya which also originated from the Commonwealth troops and found it resistant to chloroquine.

Chloroquine-resistant strains appear to be confined to the North of Malaya bordering Thailand. Physicians in Malaya who have been alerted to the existence of this condition (Sandosham, 1963) have so far produced no evidence of its existence in the rest of Malaya. A brief survey carried out in Pulau Aur an Island about 50 miles to the East of Johore State by Warren *et al.*, (personal communication) showed no resistant strains there.

RESISTANCE TO CHLOROQUINE IN CAMBODIA — Seven members of the staff of the Institute for Medical Research, Federation of Malaya, Kuala Lumpur went on a field study to the Pailin District of the State of Battembang in Cambodia. The specific locality of exposure to infection was in and near the village of Pangrolim which lies within the World Health Organization medicated salt experimental project area. Chloroquine was used in the salt at the time of study although pyrimethamine had been used earlier. In spite of chloroquine prophylaxis three members came down with **P. falciparum** malaria on return to Kuala Lumpur (Eyles *et al.*, 1963). One of them (a Malay) relapsed twice after standard 1.5 gm. treatment and the chloroquine level in the plasma at time of relapse was 50 μg/litre and 80 μg/litre. Infection was ultimately eliminated with quinine. Blood was inoculated into prison volunteers in U.S.A. and the strain proved to be chloroquine-resistant. Another (a Malayan Chinese) also relapsed twice after chloroquine and pyrimethamine therapy. The third (an American) who had an attack of falciparum malaria responded to chloroquine treatment and did not relapse. Blood taken from him at the time of the first attack was inoculated into a prison volunteer in U.S.A. and the strain proved sensitive to chloroquine at the standard dose, but resistant at a 600 mg. dose (Contacos *et al.*, 1963).

CHLOROQUINE RESISTANCE IN THAILAND — Dr. (Mrs.) Harinasuta of the University of Medical Sciences, Bangkok at the Unesco Symposium on Scientific Knowledge of Tropical Parasites in Nov. 1962 gave clinical case histories of several cases from

various parts of Thailand which had not responded normally to chloroquine. There were one or two relapses after 1,500 mg. chloroquine base and in one case given 3,300 mg. it took 7 days for the parasitæmia to disappear.

Young *et al.*, (1963) studied a case of **P. falciparum** contracted by an American in Thailand which had shown poor response to chloroquine and confirmed that the strain was resistant to chloroquine by inoculating it into prison volunteers in the U.S.A. Alving *et al.*, (1963) confirmed the above findings by inoculating the same strain to volunteers. Montgomery and Eyles (personal Communication) found Cpl. L. a member of a Commonwealth Unit who had exposed himself to infection in Ubon, Thailand in mid year 1963 returned to Malaya with a chloroquine-resistant strain of falciparum malaria. He was given 2,800 mg. of chloroquine including 400 mg. given intramuscularly over a five day period. This is nearly double the standard dose. The parasite count the day after the start of the treatment period was 19,255 p.c.mm. The treatment did not clear the infection. The number of trophozoites dropped to 132 p.c.mm. and then immediately rose into the thousands. The patient was fever-free only for four days. Quinine was finally used to terminate the infection.

CHLOROQUINE – RESISTANCE IN VIETNAM — Powell *et al.*, (1963) have studied a strain of falciparum malaria contracted by an American in S. Vietnam near Nha Trang. He relapsed after each treatment with chloroquine and inoculation into prison volunteers in U.S.A. confirmed that the strain was resistant to chloroquine.

### Amodiaquine

Edeson *et al.*, (1955) had established that amodiaquine (Camoquin) was effective in curing all 187 patients with falciparum malaria in the Tampin area with a single dose of 300 to 600 mg. They obtained good results with a similar dose against vivax malaria also.

RESISTANCE TO AMODIAQUINE IN MALAYA — Cross resistance to amodiaquine is to be expected of strains of malaria parasites resistant to the closely related chloroquine. Montgomery and Eyles (1963b) selected four cases of New Zealand troops who had contracted the chloroquine-resistant strains of **P. falciparum** in Perlis and kept them under observation in the British Military Hospital at Kinrara. All four patients had previously relapsed after treatment with chloroquine and were having their first relapse except one whose relapse was the second. Two of these relapse cases had been treated with pyrimethamine without success and another of these had received 1,500 mg. proguanil without marked effect. Three of the four cases received 2,000 mg. of amodiaquine over a four-day period and one received 3,200 mg. One failed to clear, two relapsed in 10 to 15 days and the other one that had received the higher dose of amodiaquine and the proguanil treatment did not relapse.

Alving *et al.*, (1963) showed that the Malayan chloroquine-resistant strain transmitted to a prison volunteer in U.S.A. showed only a partial temporary response to amodiaquine (Camoquin) in 1,400 mg. dose.

## BIGUANIDES

### Proguanil (Paludrine)

RESISTANCE TO PROGUANIL IN MALAYA — Edeson and Field (1950) showed that whereas naturally acquired falciparum malaria in the Tampin area was effectively treated with a single proguanil dose of 100 mg. in 1947 and early 1948, it began to show resistance towards the end of 1948 and in the early months of 1949. In April, 1949 came the first failure after a standard proguanil course of 300 mg. daily for 7 to 10 days and there has been a steady increase in the number of cases that resisted proguanil. Wilson, Munro and Richard (1952) working in the same area reported fresh infections of falciparum malaria late in the year 1950 and in 1951 among British troops on an official suppressive dosage of 100 mg. of proguanil daily.

Walker and Reid (1953) showed that gametocytes of a proquanil-resistant strain of **P. falciparum** readily infected mosquitoes while daily doses of 100 mg. proguanil were still being taken; and also that daily doses of 100 mg. started 3 days before infective bites and continued for 10 days thereafter did not prevent the onset of falciparum malaria in the

recipient on the 11th-12th day. Laing (1956) produced evidence that naturally acquired proguanil-resistant infections of **P. falciparum** in the Tampin area of Malaya could readily infect mosquitoes and complete the sporogonic cycle while gametocytes were exposed to therapeutic doses of proguanil. He maintained that continued use of proguanil as a suppressive drug in preference to other antimalaria drugs in Malaya would appear to have an element of uncertainty. The British troops in Malaya have continued to rely on proguanil as the prophylactic drug.

Field *et al.*, (1954) pointed out that the Tampin District was not the only area with proguanil-resistant strains because when they started proguanil treatment in Kuala Lumpur in 1951 resistant falciparum infections were soon found there also and that the condition has since been found wherever it has been looked for in Malaya.

Presumably, proguanil was ineffective as a suppressant of both the chloroquine-resistant and susceptible strains of **P. falciparum** in Commonwealth troops exposed in North Perlis. In view of the fact that the troops were on proguanil prophylaxis at 200 mg. daily at the time of exposure it is justifiable to assume that there were strains of malaria parasites in N. Perlis which were resistant to proguanil. Montgomery and Eyles (1963b) gave one of the patients with chloroquine-resistant falciparum malaria 1,500 mg. (300 mg. per day for 5 days) proguanil. There was only a lowering of parasite count at the end of eight days after commencement of treatment. **Anopheles maculatus** fed on a patient after proguanil treatment developed sporozoites normally whereas Mackerras and Ercole (1947) had shown that in proguanil sensitive strains the maturation of sporozoites was prevented. Contacos *et al.*, (1963) found all three chloroquine-resistant Malayan strains transferred to prison volunteers in U.S.A. were also resistant to proguanil.

RESISTANCE TO PROGUANIL IN CAMBODIA — Contacos *et al.*, (1963) tested one of the chloroquine-resistant falciparum strains from Cambodia transmitted to prison volunteers in U.S.A. and found it resistant to proguanil as well.

RESISTANCE TO PROGUANIL IN THAILAND — Young *et al.*, (1963) found the chloroquine-resistant falciparum malaria transmitted to prison volunteers in U.S.A. also resistant to proguanil. Alving *et al.*, (1963) using the same strain as above and another from Thailand in volunteers in U.S.A. were able to obtain only temporary therapeutic effect with 2,610 mg. proguanil base.

RESISTANCE TO PROGUANIL IN VIETNAM — Powell *et al.*, (1963) found the chloroquine-resistant falciparum malaria transmitted to three volunteers in U.S.A. also resistant to proguanil in dosage of 2,610 mg. base.

RESISTANCE TO PROGUANIL IN OTHER PARTS OF S.E. ASIA — According to the W.H.O. report (1961) of a technical meeting on chemotherapy of malaria, resistance to proguanil in falciparum malaria has been reported in local strains in Indonesia, Assam, New Guinea and Vietnam.

## MEPACRINE

Field (1938) reported that in 560 cases of uncomplicated acute malaria treated in Kuala Lumpur either by oral atebrin or oral quinine atebrin had a slower action than quinine in falciparum malaria but had a more rapid action than quinine in vivax malaria. Wilson and Edeson (1958) found oral mepacrine to be less effective than oral chloroquine or amodiaquine. It was less rapid in its effect on heavy falciparum infections, and less reliable as a single dose treatment. No authenticated case of resistance to mepacrine has been reported in Malaya.

RESISTANCE TO MEPACRINE IN MALAYA — In a series of seven cases of chloroquine-resistant falciparum malaria treated with mepacrine Montgomery and Eyles (1963b) found that all relapsed after regimens ranging from 3,100 to 4,200 mg. over a period of 6 to 8 days. The mean time for clearance of parasites was 5.1 days after treatment and the mean time for recurrence was 12.9 days. The mean plasma level for 5 cases at time of relapse was 76 μg/litre ranging from 31 to 180 μg/litre. Contacos *et al.*, (1963) found that of the two strains (both from New Zealand) of chloroquine-resistant falciparum malaria transmitted to prison volunteers in U.S.A. one was susceptible and the other resistant to mepacrine.

RESISTANCE TO MEPACRINE IN CAMBODIA — Contacos *et al.*, (1963) tested one of the chloroquine-resistant falciparum strains from Cambodia transmitted to a prison volunteer in U.S.A. and found it resistant to mepacrine as well.

RESISTANCE TO MEPACRINE IN THAILAND — Young *et al.*, (1963) found that the chloroquine-resistant strains of falciparum malaria from Thailand transmitted to prison volunteers in U.S.A. relapsed after 2,800 mg. of mepacrine. Alving *et al.*, (1963) using the same strain as above and another from Thailand in volunteers in U.S.A. were able to obtain only temporary therapeutic effects after 2,198 mg. of atebrin.

RESISTANCE TO MEPACRINE IN VIETNAM — Powell *et al.*, (1963) found that the chloroquine-resistant strains of falciparum malaria from S. Vietnam transmitted to prison volunteers in U.S.A. showed only temporary therapeutic effect after a dosage of 2,198 mg.

**Pyrimethamine**

Wilson and Edeson (1953) treated 126 Asian patients from Tampin and Kuala Lumpur areas suffering from acute malaria with pyrimethamine and concluded that it was unsuitable for use against Malayan strains. This drug has therefore not been used much in Malaya. It was found that the response to pyrimethamine was not affected by **P. falciparum** strains having become resistant to proguanil.

RESISTANCE TO PYRIMETHAMINE IN MALAYA — Montgomery and Eyles (1963b) treated four cases of chloroquine-resistant falciparum malaria with 1,500 mg. of pyrimethamine over 3 days. In two cases the parasite count was not materially altered. In one case the count increased while the patient was under treatment and in the fourth only a slight lowering of the parasite count was produced. Confirmation of resistance to pyrimethamine was obtained by experiments which showed the development of mature sporozoites in **Anopheles maculatus** since Shute and Maryon (1954) had shown that such development did not occur with susceptible strains. Contacos *et al.*, (1963) found that of the three strains of chloroquine-resistant falciparum malaria transmitted to prison volunteers one was susceptible to pyrimethamine while the other two were resistant.

RESISTANCE TO PYRIMETHAMINE IN CAMBODIA — Contacos *et al.*, (1963) found that the chloroquine-resistant falciparum malaria strains from Cambodia tested in prison volunteers in U.S.A. was resistant to pyrimethamine as well.

RESISTANCE TO PYRIMETHAMINE IN THAILAND — Young *et al.*, (1963) found that the chloroquine-resistant falciparum malaria strain from Thailand in the American patient who had contracted it there and in the prison volunteers in U.S.A. was resistant to pyrimethamine as well in dosage of 100 mg. The parasites failed to clear at all or actually increased in numbers within 48 hours of administration of the drug. It failed to exert a sporonticidal effect and both the sexual and asexual parasites were resistant to pyrimethamine. Alving *et al.*, (1963) using the same strain as above and another from Thailand in volunteers in U.S.A. had no effects in one case and only temporary effects in 4 cases after 150 mg. daraprim.

RESISTANCE TO PYRIMETHAMINE IN VIETNAM — Powell *et al.*, (1963) found that the chloroquine-resistant falciparum malaria strain from S. Vietnam transferred to prison volunteers in U.S.A. was susceptible to pyrimethamine, all 8 cases treated with 150 mg. being radically cured.

RESISTANCE TO PYRIMETHAMINE IN NEW GUINEA — Meuwissen, J.H.E.T. (1961) showed that three months after the initiation of a test project wherein pyrimethaminised salt was distributed among the population of West Irian (New Guinea). **P. falciparum** appeared to have developed resistance to pyrimethamine. This strain was also cross resistant to proguanil.

**Quinine**

Quinine has been used extensively before World War I and Fletcher (1928) investigated a number of so-called quinine-resistant cases of malaria and showed that the resistance was apparent and not real. In most cases the quinine was not swallowed or was vomited.

RESPONSE TO QUININE IN MALAYA — Montgomery and Eyles (1963b) found quinine entirely satisfactory in 20 cases of chloroquine-resistant falciparum malaria, mostly given 20 gm. over 10 days. Contacos *et al.*, (1963) found all 3 chloroquine-resistant falciparum strains transferred to prison volunteers in U.S.A. sensitive to quinine. Alving *et al.*, (1963) found that the chloroquine-resistant falciparum malaria strain from Malaya transferred to a prison volunteer in U.S.A. was sensitive to quinine, a radical cure being obtained after 1620 mg. quinine base daily for 7 days.

RESPONSE TO QUININE IN CAMBODIA — Contacos *et al.*, (1963) found all three strains of chloroquine-resistant falciparum malaria transferred to prison volunteers in U.S.A. were sensitive to quinine.

RESPONSE TO QUININE IN THAILAND — Young *et al.*, (1963) found that the chloroquine-resistant falciparum malaria strain from Thailand transferred to prison volunteers in U.S.A. proved susceptible to quinine. All the infections treated with 8 or more gm. of quinine, given at the rate of 2 gm. daily, and 1 or 2 infections treated with 6 gm. total, appeared to be eradicated. Smaller doses of quinine exerted a rapid temporary effect. Alving *et al.*, (1963) using the same strain as above and another from Thailand had similar results with quinine.

RESISTANCE TO QUININE IN VIETNAM — Powell *et al.*, (1963) found that only in two out of four volunteers inoculated with the chloroquine-resistant falciparum malaria from Vietnam could radical cure be achieved after giving 1620 gm. quinine base daily for seven days.

**Discussion**

The existence of chloroquine-resistant falciparum malaria has been firmly established over an extensive area of South-East Asia including the countries of Vietnam, Cambodia, Thailand and Malaya. In the latter country, the resistant strains are known only from the area of the Thailand border. The exact extent of the distribution of the strains is not known in the other countries, except that in Thailand Harinasuta has studied patients whose infections failed to respond to chloroquine from areas East, North and Southwest from Bangkok.

Further work will be necessary to determine the actual extent of the problem, and this points to the necessity of stating clearly criteria adequate for the recognition of the resistance. Obviously, the chloroquine resistance, which has been shown to exist so clearly could not have been recognised had not the various investigators really had criteria in mind. On the other hand, most of these investigators had wide experience with malaria and were either engaged in research or had access to advice from laboratories conducting research. Criteria must be established that will enable the malariologist or physician who is not so fortunately located to recognise the resistance. They must be rigid, so that undue alarm will not be caused by incorrect evaluation. On the other hand, they must be sufficiently practical to allow recognition as the resistance does present a dangerous problem which must be detected where it exists so that remedial measures may be taken.

The detection of chloroquine resistance, and the establishing of criteria has been the subject of another paper on this programme and need not be discussed further at this time. It should be pointed out, however, that at the time the resistance of falciparum malaria to chloroquine was noted there were no laboratories in the S.E. Asian region performing the tests for the estimation of plasma chloroquine levels. It is to be hoped that facilities for doing the tests will be developed and made available for workers throughout the region. It should also be noted that Malaya was particularly fortunate in that clearance studies of chloroquine-sensitive strains had been made and were available for comparison. It would be desirable for more studies of this type to be done in S.E. Asia for possible future reference.

In light of the existence of chloroquine resistance, the failure of the strains to respond to amodiaquine is not surprising. A similar mode of action would be expected for the drugs as they are closely related. Likewise, it is probable that a similarity of mode of action is involved in the mepacrine resistance.

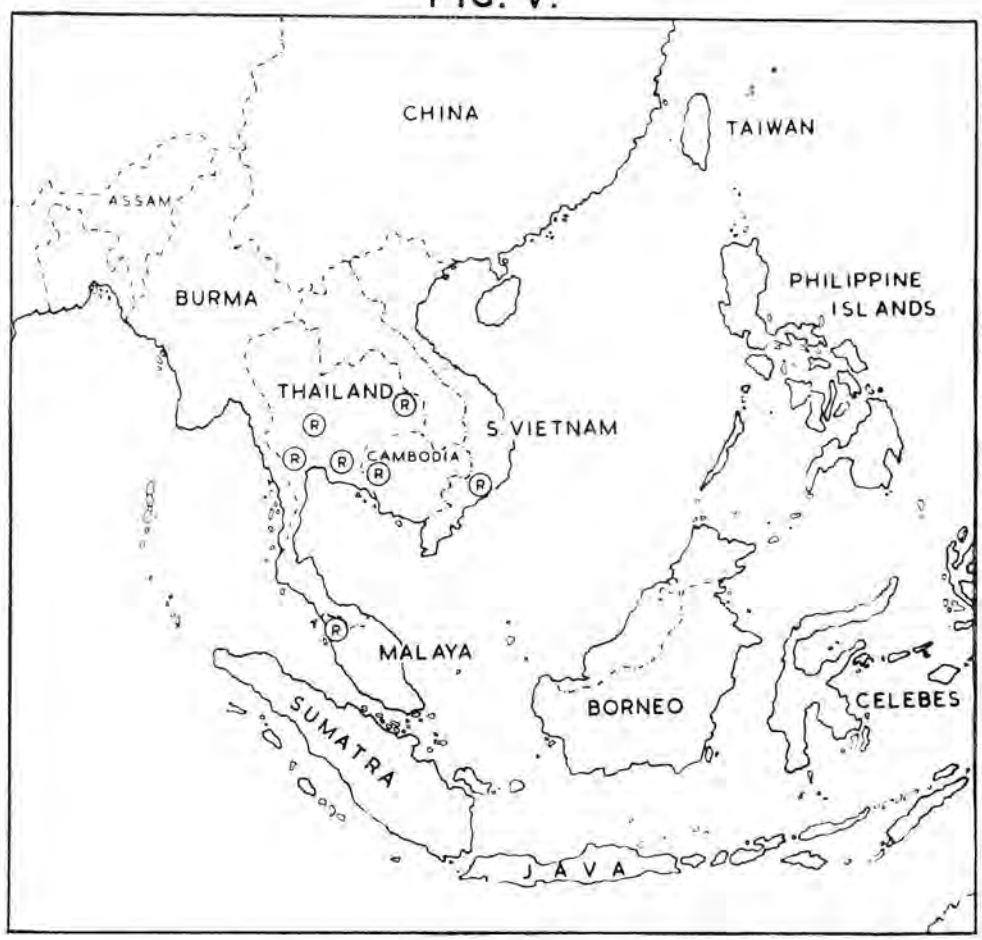
The resistance to proguanil is undoubtedly

unrelated and is presumably due to the widespread use of this drug in S.E. Asia. Possibly the pyrimethamine resistance represents a cross-resistance to proguanil, or in some areas perhaps to the use of pyrimethamine. This problem has been recognised for many years, so further discussion is unnecessary.

The implications of the widespread existence of drug-resistant falciparum malaria are great. In the first place, the cases of highest resistance pose a danger to life as in the case of Cpl. L. of a Commonwealth Unit, exposed to infection in Thailand, described earlier by Montgomery and Eyles. This patient was under close medical supervision. It is easy to visualise tragic results had not supervision been close. This is a clear instance of a dose nearly double the standard failing to clear parasites and alleviating symptoms only temporarily.

The resistance to chloroquine also poses a problem in the use of drugs in malaria eradication programmes in areas where the resistance exists. The cross resistance to related drugs and the coincident resistance to others makes the problem more serious and points toward the necessity of continuing the research for new and better antimalarial drugs. Certainly the mass treatment with 600 mg. of chloroquine frequently advocated would have little more than a temporary effect as the studies in a semi-immune population in Perlis showed that the majority of persons given this dosage soon had recurrence of parasitæmia if the parasites were cleared at all.

FIG. V.




(R) INDICATES AREAS IN S E ASIA WHERE CHLOROQUINE - RESISTANT STRAINS OF P FALCIPARUM HAVE BEEN SHOWN TO EXIST

The fact that chloroquine resistance was first seen in non-immune persons was probably not due to their immune status but to the fact that these persons returned to non-malarious areas where the recurrences and the failures to clear stood out in sharp relief, since reinfection was not possible.

The cause of the chloroquine resistance is not known. The use of chloroquine is so widespread that exposure to the drug might be the explanation, but in Malaya its emergence would not have been expected in rural Perlis where medical care is not nearly so readily available as near some of the larger centers.

A fascinating coincidence is that the principal mosquito vector in most if not all of the localities in S.E. Asia from which chloroquine resistance is known is **Anopheles balabacensis balabacensis.** Whether or not this is of significance is not known, and it must be acknowledged that a hypothesis to explain a connection is difficult to conceive.

**Summary**

The development of resistance of falciparum malaria to proguanil was recognised in Malaya about fifteen years ago. It has been reported to occur in several other parts of S.E. Asia.

Pyrimethamine-resistant strains of **P. falciparum** have been reported from many parts of the world and the drug has not been used much in S.E. Asia. The use of the drug in a medicated salt project in New Guinea and possibly also in Cambodia induced resistance to it; this New Guinea pyrimethamine-resistant strain showed cross resistance to proguanil.

Strains of falciparum malaria resistant to chloroquine (see Fig. V) have been shown to exist in N. Malaya, Cambodia, Thailand and S. Vietnam. If the existence of chloroquine-resistant falciparum malaria is not recognised the patient's life may be endangered. Chloroquine-resistance is associated with cross resistance to some of the other antimalarials and malaria eradication programmes may be adversely affected.

Chloroquine-resistant falciparum malaria could be expected to show cross resistance to the chemically allied amodiaquine. This was shown to be so in the Malayan strains. Chloroquine-resistant strains of falciparum malaria from Malaya, Cambodia, Thailand and S. Vietnam also proved to be resistant to proguanil, mepacrine and pyrimethamine. Generally, the chloroquine-resistant falciparum malaria strains have proved sensitive to quinine; the S. Vietnam strain however was refractory to quinine in two out of the four cases tested.

**ACKNOWLEDGEMENTS**

This paper reviews the efforts of a large number of people who studied the problem of drug resistance in S.E. Asia and who made their information freely available. The work involved the willing co-operation of a number of organizations including the World Health Organization, the Institute for Medical Research and the Division of Medical Services of the Federation of Malaya, the Royal Army Medical Corps Units in Malaya, the Laboratory of Parasite Chemotherapy of the U.S. Public Health Service (installations in Malaya and the United States) and others. The aid of the various persons serving these organizations is hereby recognised and acknowledged.

**REFERENCES**

ALVING, A.S., BREWER G.J. and POWELL, R.D. (1963) Summary of recent investigations on chloroquine-resistant P. falciparum from South-East Asia and Cl.-501 (personal communication).

BERLINER, R.W., EARLE, D.P. Jr., TAGGART, J.V., ZUBROD, C.G., WELCH, W.J., CONAN, N.J., BAUMAN, E., SCUDDER, S.T., and SHANNON, J.A., 1948. Studies on the chemotherapy of the human malarias. VI. The physiological disposition, anti-malarial activity, and toxicity of several derivatives of 4-aminoquinoline. **J. Clin.Invest., 27,** 98.

CONTACOS, P.G. *et al.*, (1963) Drug-resistant falciparum malaria from Cambodia and Malaya. **Trans.Roy.Soc.trop.Med.Hyg.** (in the press).

COVELL, G., COATNEY, G.R., FIELD, J.W. and SINGH, J. (1955). Chemotherapy of malaria. W.H.O. Monog. No. 27.

EDESON, J.F.B. and FIELD, J.W. (1950). Proguanil-resistant falciparum malaria in Malaya. **Bt.Med.J. 1,** 147.

———, WILSON, T., TURNER, L.H. and LAING, A.B.G. (1955). Studies on the chemotherapy of malaria. IV. The treatment of acute malaria with amodiaquine (camoquine). **Med.J.Malaya, 9,** 252.

EYLES, D.E., HOO, C.C., WARREN, M. and SANDOSHAM, A.A. (1963). **Plasmodium falciparum** resistant to chloroquine in Cambodia. **Amer.J.trop.Med.Hyg.** (in the press).

FIELD, J.W. (1963) The chemotherapy of malaria. **Bull.Inst.Med.Res.Fed.Malaya** No. 2 of 1938.

FIELD, J.W., STRAHAN, J.H., EDESON, J.F.B. and WILSON, T. (1954). Studies in the chemotherapy of malaria. II. The treatment of acute malaria with proguanil (paludrine). **Med.J.Malaya. 8,** 303.

FLETCHER, W. (1920). Notes on the treatment of malaria with the alkaloids of cinchona. **Stud. from Inst.Med.Res.** Kuala Lumpur, No. 18.

JEFFERY, G.M., YOUNG, M.D. and EYLES, D.E., (1956). The treatment of **Plasmodium falciparum** infection with chloroquine, with a note on infectivity to mosquitoes of primaquine — and pyrimethamine — treated cases. **Amer.J.Hyg., 64,** 1.

LAING, A.B.G. (1955). The single dose treatment of falciparum malaria with Nivaquine. A review of 164 cases treated at the District Hospital, Kuala Lumpur, **Med.J.Malaya. 9,** 216.

——— (1956). Proguanil resistance — extension to the gametocytes of **Plasmodium falciparum. Trans.R.Soc.trop.Med.Hyg., 50,** 496.

MACKERRAS, M.J. and ERCOLE, Q.N. (1947). Observations on the action of paludrine on malaria parasites. **Trans.R.Soc.trop.Med.Hyg., 41,** 365.

MEUWISSEN, J.H.E.T. (1961). Resistance of **P. falciparum** to pyrimethamine and proguanil in Netherlands New Guinea. **Amer.J.trop.Med. Hyg., 10,** 135.

MONTGOMERY, R. and EYLES, D.E. Chloroquine-resistant falciparum malaria in Malaya. **Trans. R.Soc.trop.Med.Hyg.,** (in the press).

———. A further study chloroquine resistant falciparum malaria in Malaya with observations on cross-resistance and response to other drugs. **Bull.Wld.Hlth.Org.,** (in the press).

PAMPANA, E. (1963). A textbook of malaria eradication **Oxford Univ. Press.** Lond.

POWELL, R.D., BREWER, G.J. and ALVING, A.S. (1963). Chloroquine-resistant **Plasmodium falciparum** from Vietnam (personal communication).

SANDOSHAM, A.A., 1963. Chloroquine-resistant falciparum malaria in Malaya. **Singapore Med. J. 4,** 3.

———, EYLES, D.E., PULL, J.H. and LING, D.S. Chloroquine-resistant falciparum malaria in a semi-immune indigenous population in North Malaya. (in press).

———, WHARTON, R.H., EYLES, D.E., WARREN, M. and CHEONG, W.H. (1963). Malaria in Perlis. **Med.J.Malaya. 18.**

SHUTE, P.E. and MARYON, M. (1954). The effect of pyrimethamine (Daraprim) on the gametocytes and oocysts of **Plasmodium falciparum** and **Plasmodium vivax. Trans.R.Soc.trop.Med.Hyg., 48,** 50.

WALKER, A.J. and REID, J.A. (1953). Resistance to proguanil in the gametocytes and pre-erythrocytic forms of **Plasmodium falciparum. Trans. R.Soc.trop.Med. Hyg., 47,** 580.

WILSON, T. and EDESON, J.F.B. (1953). Treatment of acute malaria with pyrimethamine. **Bt.Med.J. 1,** 1.

———, ——— (1954). Studies on the chemotherapy of malaria. III. The treatment of acute malaria with chloroquine. **Med.J.Malaya, 9,** 115.

WILSON, T. and EDESON, J.F.B. (1958). Studies on the chemotherapy of malaria. VII. The treatment of acute malaria in Malaya. **Med.J. Malaya, 12,** 471.

———, MUNRO, D.S. and RICHARD, D.R. (1952). Proguanil-resistance in Malayan strains of Plasmodium vivax. **Bt.Med.J., 1,** 564.

W.H.O. (1961). Chemotherapy of malaria. **W.H.O. tech.Rep.Ser.** No. 226.