In a small number of patients tested by comparing maintenance-dosage requirements the effectiveness of cortisone (free alcohol) and cortisone acetate appeared to be about equal.

The relative incidence of endocrine complications from the various preparations could not be determined from the short-term studies involved. However, the greater antirheumatic activity of hydrocortisone (free alcohol) did not seem to be accompanied by a correspondingly greater tendency to produce adverse physiological effects. In several patients signs of hormonal excess present while on maintenance doses of cortisone acetate actually diminished or disappeared after transfers were made to smaller, but equally effective, doses of hydrocortisone (free alcohol).

The marked disparity in therapeutic effectiveness between hydrocortisone (free alcohol) and hydrocortisone acetate when given by mouth may be accounted for, at least in part, by differences in solubility of the compounds. The low solubility of hydrocortisone acetate may substantially lessen its alimentary absorption.

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According to a report from the Informacion Medica Española the Spanish Government has allotted money for the provision of homes for doctors; the municipality provides the ground and a large amount of the manpower for the building. The administration of these houses, which include facilities for primary health centres, is under the control of provincial councils. They are placed at the disposal of the medical officer of health of the district, who has two or three rooms for his medical work and five or six for his personal use; he pays a monthly rent not exceeding 2% of the cost of the house, and this is set aside for repairs and upkeep. Each is equipped with examination facilities and everything necessary for emergency operations; all medicaments are supplied by the municipality. So far 200 of these houses have been built, and by the end of this year there should be over 500.

PROGUANIL-RESISTANCE IN MALAYAN STRAINS OF PLASMODIUM VIVAX

BY

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Proguanil ("paludrine") has been widely used throughout the Federation of Malaya for the prevention of malaria since it first became generally available in 1947. Controlled experiments showed that proguanil in doses of 100–300 mg. once a week was an effective suppressive, and reduced parasite and spleen rates in the semi-immune populations on estates. Overt malaria was usually associated with irregular dosage; transmission, however, was light during the period of these experiments (Institute for Medical Research, 1950).

Proguanil was first used by the Army in Malaya in place of suppressive mepacrine early in 1949, with no apparent change in the malaria sickness rate. The present investigation started as an inquiry into an outbreak of malaria which occurred late in 1950 in a British Army unit engaged in operations against bandits in the Tampin district of the State of Negri Sembilan.

Malaria in the Tampin District

Parts of the Tampin district, and of the surrounding districts, have long been regarded as highly malarious. The Army unit concerned arrived in Malaya in the middle of 1947. The unit headquarters were established in Tampin from then until March, 1950, but detached parties were scattered over a wide area of perhaps 100 miles radius, working in the neighbouring States of Selangor, Pahang, Johore, and Malacca. The incidence of malaria during this period seems to have been low. In March, 1950, the unit was moved to Singapore for about six weeks, returning to Tampin in April, and remaining there until April, 1951, when it left for the Middle East.

The main operational differences between the early period and this later period of twelve months were that the detachments were now all working within a more restricted area, inside a radius of some 30 miles from Tampin, and that the malaria rate for several months was high.

The total strength of the unit was about 600 men, and at any one time perhaps 350 men might be engaged in jungle operations. These figures are merely totals; there was a continual interchange of individuals to and from the unit, and between its various sections. As was the standard Army practice in Malaya, the official suppressive dose was one 100-mg. tablet of proguanil daily.

Four malaria infections occurred between the return from Singapore in mid-April and the end of July, 1950; the sequence of events from then on is shown in Table I.

TABLE I.—Primary Attacks of Malaria (British Troops Only)

Parasite Species	1950					1951				Total
	Aug.	Sept.	Oct.	Nov.	Dec.	Jan.	Feb.	Mar.	Apr. 1–9	
<i>P. falciparum</i>	2	1	3	9	9	4	1	3	3	35
<i>P. vivax</i>	4	2	1	7	7	2	3	3	0	29
Total	6	3	4	16	16	6	4	6	3

FIG. 1.—Treatment chart of Case 1. *P. vivax*.

*Asexual parasites in thick blood films: + = Between 1-10 parasites per thick film field. ± = Less than 1 parasite per field, more than 1 in 10 fields. ±± = Less than 1 parasite per 10 fields, more than 1 in 100 fields.

The sudden increase in November and December, 1950, and most of the cases occurring thereafter, came from two detachments which had recently started nightly patrols along one particular section of the main railway line.

During the period of just over nine months from July 1, 1950, to April 9, 1951, the Tampin unit, from a strength of about 600 men, supplied 67 admissions for primary attacks of malaria to the Military Hospital at Kuala Lumpur, while other units totalling several thousands supplied only 34 fresh attacks during the same period. The maximum number from any one other unit was eight, and five of these had occurred in one month, October, 1950, from a party operating near the border of the Tampin district. The preponderance of attacks from the Tampin unit was most striking, and caused considerable debate. Either the suppressive discipline was poor or there was something unusual about the malaria parasites of the Tampin district.

The emergence in this area of strains of falciparum malaria resistant to treatment with proguanil had been reported by Edeson and Field (1950). Although the proportion of resistant falciparum infections had increased during the year 1950, haphazard suppression was still regarded as the most likely cause (Institute for Medical Research, 1951). Vivax infections resistant to proguanil treatment had not been encountered; and there had been no indication of any general failure of suppressive proguanil in the civilian population.

Naturally enough, however, suggestions were made that the high malaria rate of the Tampin Army unit might be due, not to irregular suppression, but to infection with parasites which were resistant to prophylactic proguanil. These suggestions were reinforced by the occurrence of 10 primary attacks (5 falciparum, 5 vivax) late in 1950 among men who had arrived in Malaya, after a thorough check of the unit's suppressive discipline had been carried out. None of these 10 men had been in the country for more than three months at the time of his attack; one had been here for only four

weeks, and two for only six weeks. So far as could be ascertained, they had taken suppressive proguanil regularly, and nine of them had proguanil present in their urine on the day when first seen by one of us (D. R. R.). Unfortunately this test merely confirmed that proguanil had been taken in the few days immediately preceding; the stories of continuous regular suppressive dosage remained "not proven."

Until January, 1951, there was no proof that any of these infections were proguanil-resistant. Proguanil in the Army was being used solely as a suppressive; acute malaria was treated with mepacrine and/or quinine. The Army medical authorities readily agreed to a proposal that one of us (D. S. M.)

should treat vivax infections with proguanil to obtain information about their response to treatment.

The next three patients with acute vivax malaria admitted from the Tampin unit were given a course of 300 mg. of proguanil daily for seven days, after which they immediately reverted to the suppressive dosage of 100 mg. daily, and returned to their unit. Clinical response to treatment was good, but all three were readmitted to hospital with febrile and parasitological relapses 11, 16, and 17 days respectively after resumption of the suppressive dosage. All affirmed that no doses had been missed; none of them had been out on operations since their discharge from hospital, and it seemed that the dose of 100 mg. of proguanil daily had failed to prevent these relapses.

A more strictly supervised investigation was clearly desirable, but unfortunately only three more vivax infections could be so treated before the unit left Malaya; their history is recorded below.

Procedure.—The original diagnosis was made in the Military Hospital laboratory. Once this had been established, duplicate thick blood films were taken daily and stained with Field's rapid stain; one set of these was examined by one of us (T. W.). It will be noted that Cases 1 and 3 were under observation in hospital for four days and seven days respectively before parasites were detected;

FIG. 2.—Treatment chart of Case 2. *P. vivax*.

FIG. 3.—Treatment chart of Case 3. *P. vivax*.

during this time no antimalarial drug was given. Proguanil dosage was 300 mg. daily for seven days, after which it was reduced to 100 mg. daily, and the patients remained in hospital under observation. Doses were given by the ward sister, and tests for proguanil in the urine were carried out frequently by the hospital laboratory.

Case Notes

Case 1 (Fig. 1).—Aged 21. In Malaya two and a half years. No previous history of malaria. Ill four days before admission, and blood film taken before being sent to hospital reported negative. Suppressive dosage said to be regular; proguanil present in urine when admitted to hospital.

Case 2 (Fig. 2).—Aged 28. In Malaya two and a half years. History of seven attacks of malaria in past five years, last attack being just over two years earlier. Ill four days before admission. Suppressive dosage said to be regular, but no urine test on day of admission was made.

Case 3 (Fig. 3).—Aged 19. In Malaya three months. No history of malaria. Ill six days before admission, and blood film taken before being sent to hospital reported to contain a few young trophozoites, probably *P. vivax*, but parasites not detected in hospital until seven days later. Suppressive dosage said to have been regular since day after arrival in Malaya; proguanil present in urine on day of admission.

Comment on Cases 1 to 3

All three patients showed a good clinical and parasitological response to the first treatment course of 300 mg. of proguanil daily for seven days. Despite this, parasites reappeared in each of them after 7, 12, and 13 days respectively on the daily dose of 100 mg. of proguanil, duly followed a day or two later by the recurrence of fever. Although Cases 2 and 3 were given 400 mg. of proguanil daily for the second treatment course, parasite clearance was somewhat slower.

We had hoped to treat a comparative series of vivax infections from other areas, but there were not enough cases; only two others have so far been treated. In both there was a good response to a dosage of 300 mg. daily for seven days. Both were kept in hospital for 20 days after resuming the suppressive dose

of 100 mg. daily, and so far 120 days have passed with no indication of a relapse.

The unit which took over the Tampin camp and operational areas in April, 1951, was warned of the necessity for rigorous suppressive discipline. No malaria infections occurred during April and May, but the figures since are those given in Table II.

By contrast with the previous year, however, 1951 has seen an increase of malaria among various other Army units in different parts of the country. Staff changes and other reasons unfortunately cut short our therapeutic experiments, and only one vivax malaria patient from the new unit in Tampin could be similarly observed in hospital.

TABLE II

Parasite Species	1951					
	June	July	Aug.	Sept.	Oct. 1-16	Total
<i>P. falciparum</i> ..	3	4	3	12	0	22
<i>P. vivax</i> ..	1	4	1	13	0	19
Total ..	4	8	4	25	0	41

Case 4 (Fig. 4).—Aged 24. In Malaya 10 months; in Tampin district two and a half months. No history of previous malaria. Ill four days before admission. Proguanil suppression said to have been regular, and proguanil present in urine when patient admitted to hospital.

Comment.—Treatment with 300 mg. of proguanil daily for 10 days gave rather slow parasite clearance in the primary attack. Parasites reappeared after only nine days on the suppressive dose of 100 mg. daily, followed three days later by onset of fever and symptoms; parasites this time persisted throughout a course of 400 mg. daily for 10 days. Reduction of dose to 100 mg. for just one day resulted in an immediate increase in parasites, followed next day by a fresh rise of temperature to 104° F. (40° C.); the attack was then terminated with quinine. This infection was more obviously resistant to proguanil therapy than any of the earlier ones, and apparently had been contracted in the same area.

FIG. 4.—Treatment chart of Case 4. *P. vivax*.

Discussion

The occurrence of malaria in persons taking suppressive drugs can be explained in various ways. Fairley *et al.* (1946b), after exhaustive investigation of a large-scale outbreak among troops taking suppressive mepacrine ("atebrin") in the Aitape-Wewak area of New Guinea, decided that both irregular dosage and relative resistance to mepacrine were involved. But resistance to a purely schizonticidal drug like mepacrine presents fewer problems than resistance to proguanil. Fairley *et al.* (1946a) concluded that mepacrine and other schizonticides had no action on the pre-erythrocytic stages of the human malaria parasites; their suppressive effect was due to their action on the asexual parasites reaching the blood at the end of the incubation period. If these blood forms become resistant, then ordinary suppressive doses will fail to prevent an attack.

The prophylactic action of proguanil, on the other hand, was fundamentally different. Proguanil had a direct effect on the pre-erythrocytic forms, and asexual parasites failed to reach the blood. Working with New Guinea strains, we found that in falciparum malaria the pre-erythrocytic forms were destroyed, that in vivax malaria their development was merely inhibited, and that overt malaria might occur after dosage was stopped. Proguanil was also an efficient schizonticide, producing radical cure of falciparum infections; and, although it did not destroy gametocytes, it sterilized them and prevented their development in the mosquito.

Covell *et al.* (1949) confirmed the lethal action of proguanil on the pre-erythrocytic forms of a Lagos strain of *P. falciparum*, and the sterilizing action on gametocytes; clinical cure of acute malaria was obtained, but the infections were not eradicated, and relapses occurred within a few weeks. Ciuca *et al.* (1948), however, found that proguanil did not invariably destroy the pre-erythrocytic forms of a Rumanian strain of *P. falciparum*.

Resistance to proguanil therefore may show itself in various ways. It may be a resistance of the asexual erythrocytic forms or of the pre-erythrocytic forms or of the gametocytes; and certain strains might prove to be resistant throughout the life cycle.

We can do little to resolve the conflict of opinion between those who hold that the excess of malaria in the two Tampin units was due mainly to irregular prophylaxis, and those who favour the idea of infection with strains resistant to prophylactic proguanil. One of us (D. R. R.) was regimental medical officer of the first unit for its last 18 months in Malaya. He considers that suppressive discipline was fair even before September, 1950, and was good from September onwards; the ten infections mentioned above as occurring in new arrivals after October, 1950, developed, he thinks, despite a regular prophylactic dosage from the time of reaching the country. To this opinion may be added a number of similar complaints from Africa (Davey and Smith, 1949; Bruce-Chwatt and Bruce-Chwatt, 1950; MacLeod, 1951), but proof of regular dosage was unobtainable in many of the examples given. We cannot be certain how many of the Tampin infections were due to irregular prophylactic dosage, but we suggest that some at least may have occurred in men who took their doses regularly.

Reverting to our therapeutic findings, it seems that probably in the first three patients, and certainly in the four observed in hospital, we were dealing with erythrocytic forms of *P. vivax* which were only temporarily suppressed by daily doses of 300 mg. of proguanil, and which could multiply sufficiently to produce clinical and parasitological relapses while 100 mg. daily was still being taken. Malayan strains of *P. vivax* had hitherto proved very sensitive to treatment with proguanil (Institute of Medical Research, 1950),* and the two vivax infections from other areas had

not relapsed over a much longer period. How might this degree of resistance have been produced, and what were the implications?

Experimentally, the erythrocytic forms of both *P. falciparum* and *P. vivax* have been rendered resistant to proguanil treatment by exposing them repeatedly to inadequate doses (Seaton and Adams, 1949; Seaton and Lourie, 1949; Cooper *et al.*, 1950a); but prolonged dosage during the pre-erythrocytic stage of *P. vivax* did not induce resistance in the erythrocytic forms which appeared after dosage was stopped (Cooper *et al.*, 1950b). We think it unlikely that each of our patients was originally infected with a sensitive strain which he then transmuted into resistant forms by widely spaced doses during sporadic bursts of parasitaemia, but this possibility cannot be dismissed entirely; three of the four patients had been in the country for ten months or more, though only one was known to have had malaria before. Such a method of producing resistant erythrocytic forms would seem to be ruled out for Case 3, who had been here for only three months. This man did not arrive in Malaya until December, 1950, by which time a great deal of attention had been paid to the suppressive discipline of his unit. He had no history of previous fever, and the parasite level at which he originally developed symptoms was low, indicating that this was probably a primary attack. We suggest that the balance of evidence is in favour of another hypothesis—namely, that these men had been infected by a strain of vivax malaria whose erythrocytic forms had already developed a partial resistance to proguanil.

Seaton and Adams (1949) and Seaton and Lourie (1949) have proved that when the erythrocytic forms of *P. falciparum* and *P. vivax* have become resistant to proguanil the erythrocytic parasites which appear in fresh victims, after mosquito passage of the infection, are also resistant. It is thus possible that under suitable local conditions mosquitoes may be transmitting strains of malaria whose erythrocytic forms are relatively resistant, as in these patients of ours. Confronted with this possibility, the medical officer in the Tropics wants to know, among other things, whether proguanil-resistance of the erythrocytic forms automatically implies a change in the response of the pre-erythrocytic forms to proguanil prophylaxis. If the erythrocytic forms are resistant, can the pre-erythrocytic forms of that particular strain complete their development despite a regular prophylactic dosage from the time of infection, and will proguanil thus be as powerless to prevent clinical attacks as it is to cure them when they occur?

Oddly enough, the experimental workers have not yet provided an answer to this most important question. The experiments on proguanil prophylaxis with human malaria parasites all seem to have been made on strains which responded well to proguanil treatment of acute attacks; this was so even with the Lagos strain of *P. falciparum* investigated by Covell *et al.* (1949). The only report of a prophylactic experiment with a resistant strain which we have seen is one by Hawking and Thurston (1951) on *P. cynomolgi* in monkeys. Proguanil given shortly before sporozoite inoculation, and daily for seven days afterwards, prolonged the incubation period by only one day in the treated monkey compared with an untreated control. There is unfortunately no indication of how the original proguanil-sensitive strain behaved when treated in the same way.

In Malaya to date, and probably elsewhere, strains of human malaria refractory to proguanil therapy occur only sporadically, yet their appearance has prompted the recommendation that proguanil should not be used by itself for the treatment of acute falciparum malaria. But the drug is being distributed as a suppressive on a very large scale, often without supervision, and there are indications that such resistant strains are becoming more common; the danger, therefore, is that they will become widespread. Before that occurs, the field worker needs to know whether proguanil can still be relied upon as a prophylactic against these strains, or whether he must seek elsewhere for protection. Clearly

*Dr. J. F. B. Edeson (personal communication) reports one resistant vivax infection in April, 1951, in Tampin Hospital, with asexual parasites still present on the seventh day of treatment with 300 mg. of proguanil daily.

we need a controlled experiment in proguanil prophylaxis, comparing proguanil-sensitive and proguanil-resistant strains of human malaria parasites, to decide whether there is in fact any significant difference in their response to regular prophylactic doses.

Summary

Fresh infections of falciparum and vivax malaria occurred late in the year 1950 among British troops in the Tampin district of Negri Sembilan, Federation of Malaya, shortly after they had started night patrols in one particular locality.

A similar incidence of malaria occurred in 1951 among troops from a different unit operating in the same areas.

The troops were on an official suppressive dosage of 100 mg. of proguanil daily, and suppressive discipline was thought to be good.

Treatment of some of the vivax infections revealed that their erythrocytic parasites were only temporarily suppressed by doses of 300 mg. of proguanil daily for 7 to 10 days. Parasitological and clinical relapses occurred 7 to 17 days after reverting to the normal suppressive dose of 100 mg. daily. One of these patients had been only three months in Malaya, and had been on regular suppressive proguanil from the day after arrival.

Possible explanations for these findings are discussed. Irregular dosage cannot be excluded as a possible cause of the incidence of malaria in the Tampin units, but it is thought that some infections may have developed in men who took their suppressive doses regularly. It is suggested that the proguanil-treated vivax patients may have been infected with a strain whose erythrocytic parasites were already partially resistant. If this may happen, as seems possible, then controlled experiments are needed to determine whether resistance of erythrocytic forms also implies that pre-erythrocytic forms may complete their development, and produce clinical attacks of malaria, despite regular prophylactic dosage from the time of infection.

Our thanks are due to Colonel P. F. Palmer, late R.A.M.C., A.D.M.S. Malaya, for permission to treat these patients; to Colonel D. W. Hughes, late R.A.M.C., Consultant Physician, FARELF, for criticism and advice, and to Brigadier R. Murphy, late R.A.M.C., D.M.S., FARELF, for permission to publish.

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The production of films covering the field of medicine and surgery is being encouraged in Spain by a newly created Association of Medical Cinematography. Exchange of similar films with foreign countries is planned. The general secretarial work is being undertaken by Dr. don Juan Fernán Pérez, calle de Fuencarral, No. 113, Madrid. He is director of *Vida Sana* and medical editor of the daily paper *Madrid*.

CHEMOTHERAPY AND CHEMOPROPHYLAXIS OF MALARIA

CLINICAL TRIALS IN 500 CASES AND
MASS PROPHYLAXIS IN A HYPERENDEMIC AREA

BY

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During the past three or four years a number of new drugs have been tested at the Calcutta School of Tropical Medicine for their therapeutic and suppressive values in malaria. The patients admitted to the attached hospital were utilized for the purpose, but the main work on the suppressive therapy was carried out in a rural area about 40 miles from Calcutta. A summary of the work is given in Tables II and III.

I. CHEMOTHERAPY

Only those patients who had fever with parasites in the blood and had no antimalarial drug outside were selected for the trials. The blood was examined twice daily (thick film method, using Field (1941) or J. S. B.* stain) until it became negative for asexual parasites, and thereafter once daily throughout the period of hospital observation. Of the 500 cases examined 51% had *P. vivax* and 42% *P. falciparum* infection; the rest had mixed (4.4%) or *P. malariae* (2.6%) infection. The following drugs were tried:

TABLE I.—Schedules of Treatment

No.	Compound Used	Route of Administration	No. of Cases
1	Proguanil (paludrine)	(A) Oral	209
		(B) Intravenous*	12
		(C) Intramuscular	12
2	Proguanil + pamaquin	Oral	30
3	Quino-pamaquin	"	13
4	M.5943	"	18
5	Chloroquine	"	75
6	Chloroquine + proguanil	"	13
7	Camoquin	"	80
8	Camoquin + proguanil	"	8
9-13	Neochin and other 4 indigenous drugs	"	30
			500

* One patient also had oral and intramuscular proguanil in addition to intravenous therapy.

1. Proguanil

Effect on Temperature and Parasite.—The usual route of administration was by mouth, and in only a small number of cases was the parenteral method used. Orally, various dosage schedules were tried either in a single dose of 0.1 to 0.8 g. or in divided doses of 0.3 to 0.8 g. given daily over 4 to 10 days. With any of these regimes an acute attack was terminated on the third day in most cases. A daily dose of 0.3 to 0.6 g., however, seemed to produce the best results, and we think that a course of 1.8 g. given over five

*Jaswant Singh and Bhattacharji (1944).