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GAMETOCYTOCIDAL AND SPORONTICIDAL EFFECTS OF PRIMAQUINE AND  
OF SULFADIAZINE/PYRIMETHAMINE IN A CHLOROQUINE-RESISTANT  
STRAIN OF PLASMODIUM FALCIPARUM<sup>1</sup>



by

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1. Introduction

With the realization that strains of Plasmodium falciparum in some parts of the world are resistant to chloroquine, increased attention has been given to newer drug regimens, including the combined administration of sulfonamide and pyrimethamine. It has been known that the asexual erythrocytic forms of some strains of chloroquine-resistant P. falciparum respond to certain sulfonamide-pyrimethamine combinations (DeGowin & Powell, 1964; Chin et al., 1966; Bartelloni et al., 1967; Harinasuta et al., 1967), but remarkably little information is

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available concerning the sporontocidal effects exerted by such combinations against chloroquine-resistant P. falciparum. In addition, relatively little information is available concerning sporontocidal or gametocytocidal effects of primaquine against chloroquine-resistant P. falciparum. The studies presented in this report were performed to assess the effects of a combination of sulfadiazine and pyrimethamine and the effects of primaquine against gametocytes of a strain of chloroquine-resistant P. falciparum from Malaya (Malaysia) that has been designated the Malayan (Camp.) strain.

## 2. Methods

Studies were carried out with healthy, adult, male volunteers at the University of Chicago - Army Medical Research Project at the Illinois State Penitentiary, Stateville Branch, Joliet, Illinois, United States of America. Conditions of study at this project have been described in detail previously (Alving et al. 1948; Powell et al., 1964); unintentional reinfection was precluded. Three Caucasian volunteers (Volunteers 1, 2 and 3) were infected with the Malayan (Camp.) strain of chloroquine-resistant P. falciparum. Volunteer 1 had a mosquito-induced infection and Volunteers 2 and 3 had infections induced by intravenous inoculation of small samples of blood containing approximately 500 000 asexual erythrocytic parasites. Asexual erythrocytic forms of the Malayan (Camp.) strain had proved resistant to all widely used synthetic antimalarial agents, including pyrimethamine administered alone in a dose of 50 mg daily for three days (DeGowin and Powell, 1965). A single study in which 50 mg of pyrimethamine had been administered daily for three days to a partially-immune volunteer infected with the Malayan (Camp.) strain had revealed that, in this volunteer, pyrimethamine administered alone exerted no appreciable sporontocidal effects against this strain; different groups of mosquitos (Anopheles stephensi) were allowed to bite this partially-immune volunteer before, during and after administration of pyrimethamine, and no alteration in development of oocysts or of sporozoites in mosquitos that bit this volunteer during or after administration of pyrimethamine was evident (Powell et al., unpublished observations). Studies presented in this report were intentionally carried out with partially-immune volunteers to minimize the likelihood that symptoms would necessitate concomitant administration of other agents, such as quinine, that might complicate the studies. Volunteers 1 and 3 had been treated previously with subcurative doses of quinine to relieve symptoms and to suppress asexual parasitaemia temporarily; Volunteer 2 had acquired partial immunity during a previous infection with this strain. Studies were initiated (1) when it appeared clinically that these volunteers had acquired a sufficient degree of immunity to make it unlikely that additional medication such as quinine would be necessary during the period of study and (2) when both continuing asexual parasitaemia and significant gametocytaemia were evident. Before initiation of these studies, parasites of the Malayan (Camp.) strain had been exposed to blood schizontocides such as chloroquine and quinine, but parasites of this strain that were employed to infect Volunteers 1, 2, and 3 had not been previously exposed to sulfonamides or sulfones or to primaquine.

On the 38th day after onset of the patent infection, Volunteer 1 received 500 mg of sulfadiazine every six hours for five days and 50 mg of pyrimethamine daily for three days. Treatment with these two agents was instituted concomitantly. Doses of sulfadiazine and of pyrimethamine administered were identical to those employed during previous studies carried out at this project to assess the blood schizontocidal effects of this combination of agents against the Malayan (Camp.) strain and against other strains of chloroquine-resistant *P. falciparum* (DeGowin and Powell, 1964; Powell et al., in preparation). Volunteers 2 and 3 each received a single dose of 45 mg of primaquine base. Drugs were administered orally and under very close supervision. Parasite counts, for both asexual forms and gametocytes, were performed daily with the method of Earle and Perez (1932).

Different groups of two- to three-day-old mosquitos (*A. stephensi*) were allowed to bite Volunteers 1, 2 and 3, beginning before administration of medication and at intervals thereafter. Each of these groups of mosquitos was allowed to bite one of these volunteers on only one occasion. Mosquitos were then kept under insectary conditions (temperature: 28-30°C; relative humidity: 80-90%). Randomly-selected mosquitos from each group were examined for oocysts and for sporozoites; at least 10 mosquitos from each group were examined for oocysts beginning on the sixth day after they had bitten a particular volunteer, and, with one exception (when only seven mosquitos were available for examination), at least 10 other mosquitos from each group were examined for sporozoites beginning on the 10th day after they had bitten a particular volunteer. Larger numbers of mosquitos were examined when available.

During studies with Volunteers 1 and 3, mosquitos from certain groups that had been allowed to bite one of these volunteers 12 to 14 days previously were allowed to bite other volunteers to determine conclusively whether or not mosquitos in these particular groups were infective. Seven additional healthy, Caucasian volunteers (Volunteers 4-10), all non-immune and all previously uninfected, participated in the latter phases of the investigations. Mosquitos that bit Volunteers 4-10 were examined immediately after they had obtained a blood meal. The number of sporozoites in the salivary glands of each of these mosquitos was graded from 1-plus to 4-plus (1-9 sporozoites: 1-plus; 10-99 sporozoites: 2-plus; 100-999 sporozoites: 3-plus; 1000 or more sporozoites: 4-plus); and the total number of pluses recorded for the mosquitos that bit a particular volunteer was referred to as "infectivity".

### 3. Results

#### Studies in Volunteer 1

Volunteer 1 was treated with a combination of sulfadiazine and pyrimethamine commencing on the 38th day after the onset of a patent infection with the Malayan (Camp.) strain (Figure 1). This volunteer had last received small doses of quinine

on the 29th day after the onset of patency; it is unlikely, therefore, that quinine influenced the results of these studies. Treatment with sulfadiazine and pyrimethamine was initiated about five to six days after the onset of a wave of gametocytaemia. Levels of asexual parasitaemia decreased after initiation of treatment with sulfadiazine and pyrimethamine, and radical cure of the infection resulted as evidenced by a lack of a recrudescence of asexual parasitaemia. No reduction in levels of gametocytaemia attributable to administration of sulfadiazine and pyrimethamine was evident (Figure 1).

Different groups of mosquitos were allowed to bite this volunteer on 13 occasions: 96 and 48 hours before, immediately before, 12 hours after, and 1, 2, 3, 4, 5, 6, 7, 11, and 14 days after institution of treatment. The sulfadiazine-pyrimethamine combination administered did not exert marked effects in preventing development and normal maturation of oocysts. Among different groups of mosquitos that were allowed to bite this volunteer before, during, or after treatment, the proportion of those examined that contained oocysts and the average number of oocysts (20.8) per infected mosquito remained relatively high (Figure 1). Oocysts detected appeared morphologically normal on examination with light microscopy. Among groups of mosquitos that had been allowed to bite Volunteer 1 during or after treatment with sulfadiazine and pyrimethamine, the proportion of those examined that contained sporozoites in the salivary glands was, in some instances, relatively low, but among mosquitos that had been allowed to bite Volunteer 1 on the 14th day after initiation of treatment, even though levels of gametocytaemia had at this point decreased to approximately 100 per mm<sup>3</sup>, approximately 30% of the mosquitos examined contained substantial numbers of sporozoites in the salivary glands (Figure 1). Sporozoites detected appeared normal morphologically.

Mosquitos from groups that had been allowed to bite Volunteer 1 immediately before, three days after, and 14 days after initiation of treatment were subsequently allowed to bite Volunteers 4, 5 and 6, respectively, 12 to 14 days after these particular groups of mosquitos had bitten Volunteer 1. Volunteer 4 was bitten by 17 mosquitos from the group of mosquitos that had bitten Volunteer 1 immediately before initiation of treatment. Volunteer 5 was bitten by 21 mosquitos from the group that had bitten Volunteer 1 on the third day after initiation of treatment. Volunteer 6 was bitten by 33 mosquitos that had bitten Volunteer 1 on the 14th day after initiation of treatment. During this phase of the studies, an effort was made to expose Volunteers 4, 5 and 6 to similar sporozoite inocula. Judging by the method of assessment of infectivity described previously, "infectivity" of mosquitos that bit Volunteers 4, 5 and 6 was 40 in each instance. Volunteers 4, 5 and 6 subsequently developed patent falciparum infections after prepatent periods of eight to 10 days, demonstrating conclusively that these particular groups of mosquitos were infective in each instance.

Studies with Volunteer 2

Volunteer 2 had been infected previously with the Malayan (Camp.) strain of chloroquine-resistant P. falciparum. Radical cure of the previous infection had been achieved by administration of quinine more than three months before initiation of these studies. This volunteer was then re-infected. Probably in large part because of previously acquired immunity, it was possible to initiate a study of sporontocidal and gametocytocidal effects of primaquine relatively soon after the onset of patency of the second infection. Volunteer 2 received a single dose of 45 mg of primaquine base on the 17th day of patency of the second infection, approximately five to six days after the onset of a wave of gametocytaemia (Figure 2). Asexual parasitaemia continued, without marked change, after administration of primaquine; in contrast, levels of gametocytaemia decreased markedly within two to three days after administration of primaquine (Figure 2). Subsequently, very low levels of gametocytaemia (10 to 20 per mm<sup>3</sup>) were detected intermittently and asexual parasitaemia remained evident (Figure 2). By the time of completion of this study, Volunteer 2 appeared clinically to have acquired a considerable degree of immunity; asexual parasitaemia continued, but at relatively low levels, and, although gametocytes were noted occasionally, no further waves of gametocytaemia developed.

Groups of mosquitos were allowed to bite this volunteer 24 hours before, immediately before, six and 12 hours after, and 1, 2, 3, 4, 8, 11 and 14 days after administration of primaquine (Figure 2); findings with mosquitos that bit this volunteer six hours after administration of primaquine are not noted in this figure but were similar to findings with mosquitos that bit this volunteer 12 hours after administration of primaquine. Examination of mosquitos from groups that bit this volunteer six and 12 hours after administration of primaquine revealed decreased formation of oocysts and sporozoites. Immediately before treatment the average number of oocysts per infected mosquito was 5.4; at both six and 12 hours after treatment an average of 2.0 oocysts were seen per infected mosquito; and none were found during subsequent examinations except for two oocysts in one infected mosquito 14 days after primaquine administration. Many of the oocysts and sporozoites detected in mosquitos that bit this volunteer six or 12 hours after administration of primaquine appeared abnormal (alterations detected were very similar to those noted during a corresponding phase of studies with Volunteer 3; the type of changes observed are described in detail subsequently). Oocysts or sporozoites were not detected in mosquitos that bit this volunteer 1, 2, 3, 4, 8 and 11 days after administration of primaquine. Among mosquitos that bit this volunteer 14 days after administration of primaquine, oocyst development was detected in one of 10 mosquitos examined, but no sporozoites were detected in salivary glands of 23 mosquitos examined (Figure 2).

Studies with Volunteer 3

Volunteer 3 received a single dose of 45 mg of primaquine base on the 34th day after the onset of patency of an infection with the Malayan (Camp.) strain. This volunteer had last received small doses of quinine on the 27th day of patency; it is not likely, therefore, that quinine influenced the results of the studies. Primaquine was administered five to six days after the onset of a wave of gametocytaemia (Figure 3). Asexual parasitaemia continued without appreciable change after administration of primaquine, but levels of gametocytaemia decreased strikingly within two days after primaquine was administered (Figure 3). Gametocytaemia began to increase again about eight days after administration of primaquine; during the next week gametocytaemia reached levels between 30 and 60 per mm<sup>3</sup>. Levels of gametocytaemia noted during the latter period, although relatively low, were higher than those detected in Volunteer 2 at a comparable time after administration of primaquine (Figures 2 and 3).

Different groups of mosquitos were allowed to bite Volunteer 3 on 11 occasions: 48 and 24 hours before, immediately before, 12 hours after, and 1, 2, 3, 4, 8, 11 and 15 days after administration of primaquine. Among mosquitos in the three groups that bit Volunteer 3 before administration of primaquine, a relatively high proportion of those examined for oocysts or sporozoites were positive (Figure 3); an average of 46.2 oocysts were seen per infected mosquito and oocysts and sporozoites detected appeared morphologically normal. Oocysts in mosquitos from these three groups that were examined on the sixth day after they had bitten Volunteer 3 had an average diameter of approximately 30 microns. Among mosquitos that bit this volunteer 12 hours after administration of primaquine, six of 10 mosquitos examined for oocysts were positive; however, an average of only 8.8 oocysts were detected per infected mosquito, and, in five of the six mosquitos that were positive for oocysts, the growth of oocysts was retarded (the average diameter of oocysts on the sixth day after these particular mosquitos had bitten Volunteer 3 was seven to 10 microns). Sporozoites were detected in the salivary glands of 11 of 85 mosquitos examined that had bitten this volunteer 12 hours after administration of primaquine, but in only two weakly-infected mosquitos did they appear morphologically normal; the sporozoites detected in salivary glands of the other nine mosquitos were distorted and thinner than normal with nuclei that were either swollen or not visible. Among mosquitos that bit this volunteer 24 or 48 hours after administration of primaquine, 20 out of 20 mosquitos examined for oocysts proved negative, but 11 of 170 mosquitos examined for sporozoites were positive (Figure 3); however, the sporozoites detected in salivary glands of 10 of these 11 mosquitos appeared abnormal. Mosquitos that bit this volunteer 3, 4, or 8 days after administration of primaquine proved consistently negative for oocysts and for sporozoites. Oocysts and sporozoites were detected in mosquitos that bit this volunteer 11 or 15 days after administration of primaquine (Figure 3); the average number of oocysts per infected mosquito was 1.7 and 4.3 respectively, and both the oocysts and the sporozoites appeared normal morphologically.

Mosquitos from groups that had bitten Volunteer 3 immediately before, 12 hours after, and one and two days after administration of primaquine were allowed to bite Volunteers 7, 8, 9 and 10, respectively, 12 to 14 days after these mosquitos had bitten Volunteer 3. During studies with Volunteers 7-10, it was not possible to obtain similar sporozoite inocula; instead, groups of 75 mosquitos were allowed to bite these volunteers. Volunteer 7 was bitten by 75 mosquitos from the group of mosquitos that had bitten Volunteer 3 immediately before administration of primaquine ("infectivity" was 124); Volunteer 7 developed a patent falciparum infection after a prepatent period of seven days. Volunteer 8 was bitten by 75 mosquitos from the group that had bitten Volunteer 3, 12 hours after administration of primaquine; Volunteer 9 was bitten by 75 mosquitos from the group that had bitten Volunteer 3 one day after administration of primaquine; and Volunteer 10 was bitten by 75 mosquitos that had bitten Volunteer 3 two days after administration of primaquine (the maximum "infectivity" recorded, including abnormal-appearing sporozoites, for any of the groups of mosquitos that bit Volunteers 8, 9 or 10 was 15). Volunteers 8, 9 and 10 did not develop patent falciparum infections during follow-up periods exceeding two months. The data indicate that, although the mosquitos that had bitten Volunteer 3 immediately before administration of primaquine were highly infective, the mosquitos that had bitten this volunteer 12 hours or one or two days after administration of primaquine were not infective.

#### 4. Discussion

The information obtained during these studies may be of considerable practical import. Of three partially-immune volunteers infected with the Malayan (Camp.) strain of chloroquine-resistant P. falciparum one received a combination of sulfadiazine and pyrimethamine and two single doses of primaquine approximately five to six days after the onset of waves of gametocytaemia. The studies performed were very similar, not only with respect to the levels of gametocytaemia present, but also with respect to the age of the gametocytes present at the time of administration of medication to these three volunteers. Although sulfadiazine and pyrimethamine exerted considerable blood schizontocidal effects with radical cure of the infection resulting in the volunteer studied (Volunteer 1) who received this combination of agents, the particular combination of sulfadiazine and pyrimethamine employed did not exert demonstrable gametocytocidal effects or marked sporontocidal effects in this volunteer. In the other two volunteers studied (Volunteers 2 and 3), who received primaquine, although primaquine was ineffective against blood schizonts of the Malayan (Camp.) strain, this drug, in striking contrast to sulfadiazine and pyrimethamine, exerted marked gametocytocidal and sporontocidal effects. Gametocytocidal effects of primaquine were evident within two to three days after administration of primaquine, and significant sporontocidal effects of primaquine were evident within 12 hours after administration of a single dose of this drug. These studies indicate that, in some instances in patients infected with strains of chloro-

quine-resistant P. falciparum such as the Malayan (Camp.) strain, (1) sulfonamide-pyrimethamine combinations may not be of value in preventing possible further transmission of infections except to the extent that blood schizontocidal effects limit or prevent subsequent formation of new falciparum gametocytes, and (2) primaquine, in contrast, may be of considerable potential value in preventing possible further transmission of infections.

The sporontocidal and gametocytocidal effects of primaquine against chloroquine-sensitive P. falciparum are well known (Jeffery et al., 1956; Young, 1959; Burgess & Bray, 1961; Gunders, 1961; Raffaele & Carrescia, 1962). Our findings with respect to the sporontocidal and gametocytocidal effects of primaquine against chloroquine-resistant P. falciparum are consistent with earlier observations reported by Jeffery and co-workers (1963). Primaquine is relatively rapidly metabolized in the body, and single doses of primaquine do not exert long-lasting antimalarial effects (Alving et al., 1962). Our studies, particularly those with Volunteer 3, make it very clear that although primaquine exerts pronounced sporontocidal and gametocytocidal effects against the Malayan (Camp.) strain, if asexual parasitaemia persists, new gametocytes may be formed and may be infective for mosquitos as early as 11 to 15 days after administration of primaquine. Clearly, if primaquine is administered for sporontocidal and gametocytocidal purposes in patients having patent infections with chloroquine-resistant P. falciparum, the value of this agent for these purposes may be relatively limited unless radical cure of infections is achieved by the use of other chemotherapeutic measures that result in complete elimination of asexual erythrocytic forms from the blood.

During our previous studies performed chiefly to assess blood schizontocidal effects of a combination of sulfadiazine and pyrimethamine against the Malayan (Camp.) strain of chloroquine-resistant P. falciparum, it has been apparent that although this type of combination of agents displays considerable potential value, particularly from the standpoint of achieving radical cure of infections, sulfadiazine and pyrimethamine administered concurrently have not been effective in eliminating gametocytes or in preventing the emergence of substantial numbers of gametocytes even when these two agents have been administered very early during initial acute attacks of malaria in non-immune volunteers (Powell et al., in preparation). Very similar findings with respect to gametocytes were noted during our previous studies performed mainly to assess blood schizontocidal effects of a combination of sulfoxone and proguanil against the Malayan (Camp.) strain (Powell et al., in press); treatment with sulfoxone alone or with a combination of sulfoxone and proguanil was instituted very early during initial acute attacks of malaria, before any gametocytaemia was evident, but these agents, although active against blood schizonts of this strain, did not prevent the subsequent emergence of substantial numbers of gametocytes, which then persisted in the bloodstream for several weeks. During one of the latter studies, an attempt was made to determine whether or not gametocytes of the Malayan (Camp.) strain emerging under these circumstances

were infective for mosquitos; studies performed were considerably less elaborate than those carried out during the present investigations, but the data obtained suggested that gametocytes emerging in the face of administration of a combination of sulfoxone and proguanil were not infective for mosquitos. During the studies with Volunteer 1 presented in this report, substantial numbers of gametocytes of the Malayan (Camp.) strain were present before initiation of administration of sulfadiazine and pyrimethamine to this volunteer. Proguanil and pyrimethamine, different sulfones or sulfonamides, or different combinations of these two types of agents may differ with respect to the sporontocidal effects exerted against the same strain of chloroquine-resistant P. falciparum. In addition, infectivity to mosquitos displayed by gametocytes of chloroquine-resistant P. falciparum that emerge after initiation of treatment with one of these agents or with a combination of these agents may differ from that displayed when mature gametocytes are present before initiation of such treatment.

Blood schizonts of the Malayan (Camp.) strain of P. falciparum are highly resistant both to proguanil and to pyrimethamine. Blood schizonts of other strains of chloroquine-resistant P. falciparum have, in some instances, appeared to be sensitive to one or to both of these drugs. Sporontocidal effects of proguanil, of pyrimethamine, of different sulfones and sulfonamides, and of different combinations of these agents against different strains of chloroquine-resistant P. falciparum may differ; the sporontocidal effects of pyrimethamine or of a combination of pyrimethamine and sulfadiazine against strains of chloroquine-resistant P. falciparum that are not resistant to the blood schizontocidal effects of pyrimethamine, for example, may differ considerably from effects exerted against the Malayan (Camp.) strain. Similarly, the sporontocidal and gametocytocidal effects exerted by primaquine against strains of chloroquine-resistant P. falciparum other than the Malayan (Camp.) strain may not be similar to the effects noted during the studies presented in this report.

Additional studies are warranted to obtain further information concerning the effects exerted or not exerted by these different agents or combinations of agents against gametocytes of different strains of chloroquine-resistant P. falciparum. Primaquine, particularly, appears to deserve considerable attention to determine the extent to which this agent will be of value in preventing transmission of infections with chloroquine-resistant P. falciparum. Our studies and the previous studies of Jeffery and co-workers (1963) suggest that primaquine may prove very useful in preventing further transmission of infections with chloroquine-resistant P. falciparum; this drug may afford one means of thwarting possible preferential transmission of infections with chloroquine-resistant P. falciparum under circumstances in which either prophylactic or therapeutic use of 4-aminoquinolines may tend to favour selection of falciparum parasites that are resistant to 4-aminoquinolines.

SUMMARY

Studies with volunteers were carried out to determine the effects exerted by a combination of sulfadiazine and pyrimethamine and the effects exerted by a single dose of primaquine upon gametocytes of the Malayan (Camp.) strain of chloroquine-resistant Plasmodium falciparum. Parasite counts, for both asexual forms and gametocytes, were performed daily. Infectivity of gametocytes was determined by allowing different groups of mosquitos (Anopheles stephensi) to bite the volunteers before and after commencement of treatment; these mosquitos were then examined for oocysts and for sporozoites beginning six and 10 days later, respectively. Some of these mosquitos were subsequently allowed to bite other untreated, and previously uninfected, volunteers to determine conclusively whether or not these particular groups of mosquitos were infective.

One volunteer received 500 mg of sulfadiazine every six hours for five days, and 50 mg of pyrimethamine daily for three days; administration of both drugs was commenced simultaneously. Although there was a marked effect upon blood schizonts, the particular combination of sulfadiazine and pyrimethamine employed failed to exert marked gametocytocidal or sporontocidal effects. Two volunteers each received a single dose of 45 mg of primaquine base. Primaquine, although not active against blood schizonts, exerted striking gametocytocidal and sporontocidal effects in both volunteers. Pronounced gametocytocidal effects were evident within two to three days after administration of primaquine, and sporontocidal effects of primaquine were evident within 24 hours after administration of this drug.

The effectiveness of primaquine against gametocytes of the Malayan (Camp.) strain of chloroquine-resistant P. falciparum emphasizes the need for further study of gametocytocidal and sporontocidal activity of primaquine and of related drugs against other strains of chloroquine-resistant P. falciparum. The results of these studies could point the way to the future role that drugs such as primaquine may play in preventing transmission of infections with chloroquine-resistant P. falciparum.

RESUME

On a étudié sur des volontaires les effets d'une association sulfadiazine-pyriméthamine et l'action d'une dose unique de primaquine sur les gamétocytes de la souche malaise (Camp.) chloroquino-résistante de Plasmodium falciparum. Chaque jour une numération parasitaire des formes asexuées et des gamétocytes a été effectuée. Le pouvoir infectant des gamétocytes a été déterminé en laissant différents groupes de moustiques (Anopheles stephensi) piquer les volontaires avant et après le début du traitement. La recherche des oocystes et des sporozoïtes sur ces moustiques a commencé respectivement 6 et 10 jours après la piqûre. Ensuite, on a laissé certains moustiques piquer d'autres volontaires non traités et jamais infectés auparavant, afin d'établir d'une manière définitive si ces moustiques étaient réellement capables d'infecter l'homme.

L'un des volontaires a absorbé 500 mg de sulfadiazine toutes les six heures pendant 5 jours et 50 mg de pyriméthamine quotidiennement pendant 3 jours, les deux médicaments étant, la première fois, administrés en même temps. Malgré une action marquée sur les schizontes du sang, cette association de sulfadiazine et de pyriméthamine n'a pas eu un effet gamétocytocide ou sporontocide très prononcé. Deux volontaires ont reçu chacun une dose unique de 45 mg de primaquine-base. Bien qu'elle n'ait aucune action sur les schizontes du sang, la primaquine a donné chez les deux volontaires des résultats remarquables : l'action gamétocytocide du produit s'est manifestée dans les 2 ou 3 jours qui ont suivi son administration, tandis que l'effet sporontocide s'est fait sentir dès les premières 24 heures.

L'efficacité de la primaquine contre les gamétocytes de la souche malaise (Camp.) chloroquino-résistante de P. falciparum fait clairement ressortir la nécessité de poursuivre les recherches sur l'action gamétocytocide et sporontocide de ce médicament et des produits analogues à l'égard d'autres souches de P. falciparum résistantes à la chloroquine. Les résultats de ces recherches indiqueraient sans doute comment des médicaments tels que la primaquine pourraient contribuer à l'avenir à empêcher la transmission des infections à P. falciparum chloroquino-résistant.

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Figure 1. Studies with Volunteer 1. Levels of parasitaemia in this and subsequent figures are plotted on a semi-logarithmic scale in the case of asexual parasites and on an arithmetical scale in the case of gametocytes. Ratios indicate numbers of mosquitoes that proved positive for oocysts or for sporozoites/number dissected. The insert (upper right) indicates the meaning of symbols used in this and subsequent figures.

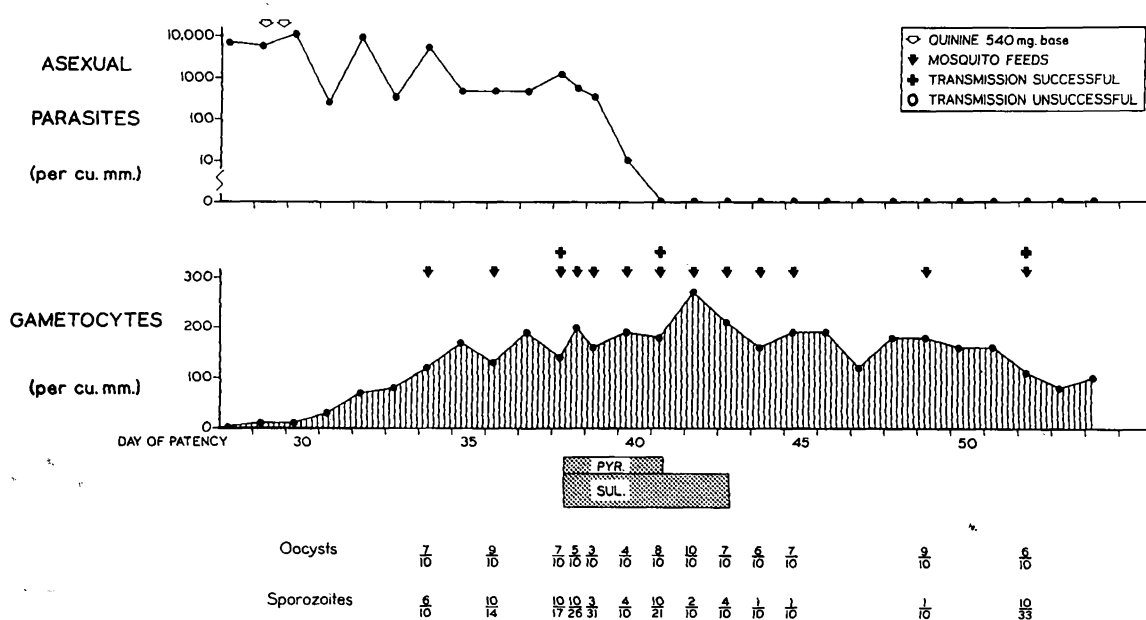


FIG. 2 STUDIES WITH VOLUNTEER 2 (see legend fig. 1)

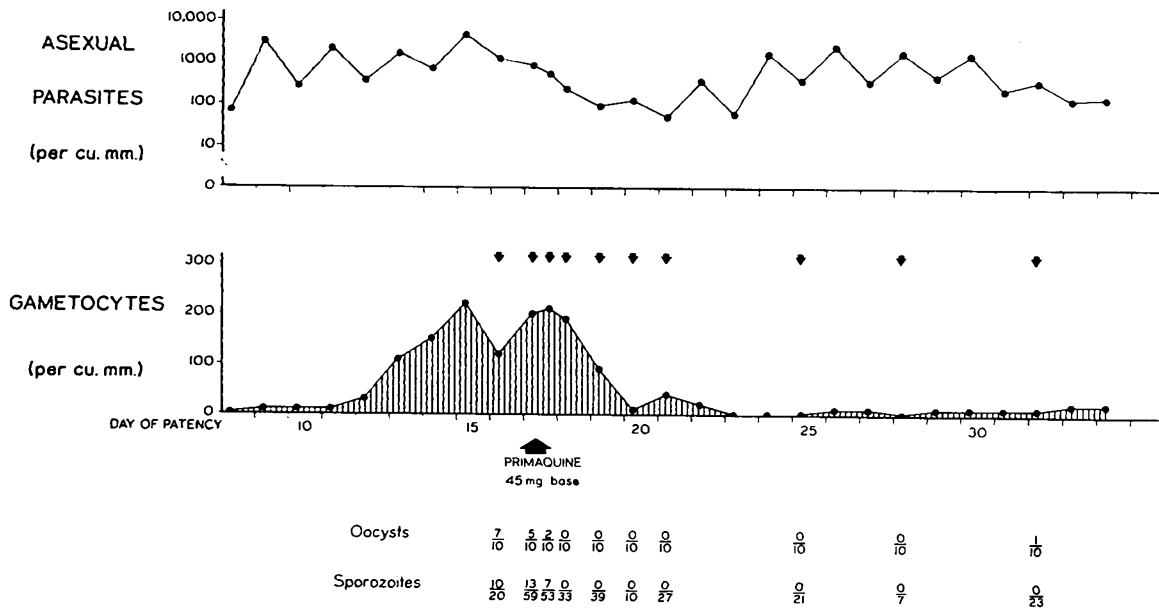
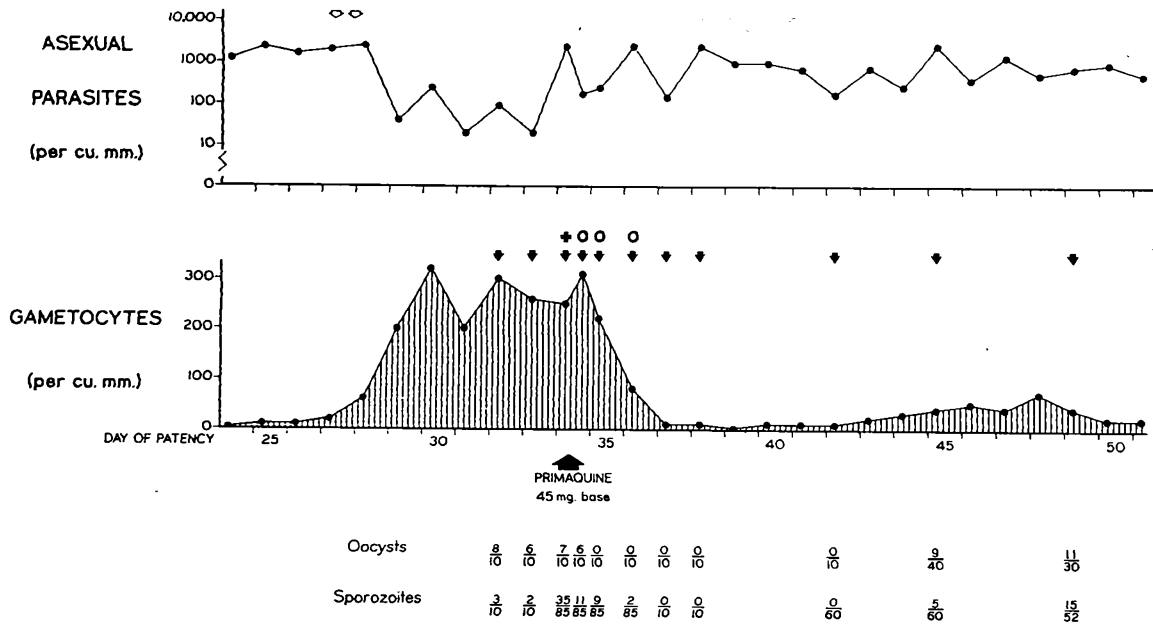


FIG. 3 STUDIES WITH VOLUNTEER 3 (see legend fig. 1)



The purpose of the WHO/Mal series of documents is three-fold:

- (a) to acquaint WHO staff, national institutes and individual research or public health workers with the changing trends of malaria research and the progress of malaria eradication by means of summaries of some relevant problems;
- (b) to distribute to the groups mentioned above those field reports and other communications which are of particular interest but which would not normally be printed in any WHO publications;
- (c) to make available to interested readers some papers which will eventually appear in print but which, on account of their immediate interest or importance, deserve to be known without undue delay.

It should be noted that the summaries of unpublished work often represent preliminary reports of investigations and therefore such findings are subject to possible revision at a later date.

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