**Medicine.** — *Prophylactic use of plasmoquine in a dosage warranting reasonable safety for routine treatment.* [1]) By N. H. SWELLENGREBEL and A. DE BUCK. (Zoological Laboratory, Department of Tropical Hygiene, Royal Colonial Institute, Amsterdam.) (Communicated by Prof. W. A. SCHÜFFNER.)

(Communicated at the meeting of October 31, 1931.)

It would be of great practical importance in malariaprophylaxis to possess a drug which destroys the sporozoites on entering the human host. Quinine, undoubtedly, leaves the subject to be protected at a great disadvantage by failing to act until parasites have multiplied to fairly strong numbers.

Plasmoquine seems to open new vistas here by its specific action on sporozoites (JAMES, 1931), just as it has done by its specific action on gametocytes. JAMES, NICOL and SHUTE (1931) have demonstrated the possibility of preventing an outbreak of fever and the appearance of parasites in persons, subjected to numerous bites of heavily infected mosquitoes but protected by a daily dosage of 6 cg. of plasmoquine pure, administred at the end of the day preceding the infection, on the day the mosquitoes are allowed to bite and 5 days after. No such results were noted with prophylactic doses of quinine administered in the same way.

In their conclusion JAMES, NICOL and SHUTE point out that it will be necessary to ascertain what may be the smallest daily dose which will prevent malarial infection. This is, indeed, a question of much consequence to the practical sanitarian who is called upon to apply the result of these investigations in the field. For he is faced with the difficulty that 6 cg. of plasmoquine given daily is a dangerously high dosage.

KLIGLER and REITLER (1929) actually tried it out in the field in the shape of 6 cg. of plasmoquine combined with 0.75 gm. of quinine, for the purpose of malaria prophylaxis among Bedouins. They (KLIGLER and MER, 1930) had to admit that the experiment miscarried because this dosage was too toxic and the population refused to take it. They then reverted to a daily adult dosage of 3 cg. plasmoquine + 0.9 gm. of quinine without encountering any more difficulties.

Even with the object to cure malaria, a widespread tendency is noticeable to reduce the dose of plasmoquine in the compound mixtures. In India SINTON (1930) holds that the maximum daily dosage of the drug

[1]) The investigations on which this paper is based have been carried out with the support and under the auspices of the International Health Division of the Rockefeller Foundation.

to robust adults should not exceed 4 cg. He thinks it probable that even this dosage is excessive for routine treatment in view of the low margin of safety. He therefore suggests that the daily dosage should be reduced to at most 3 cg. combined with 2 gm. of quinine during the acute stage of the disease.

In the West-Indies MAC PHAIL (1929, 1930) found that plasmoquine cannot be utilized as an aid in field work in the dosage of 9—12 cg. recommended by the manufacturers and sponsors of the drug. He had to reduce this dosage, first to 6 cg. and later still to 3 cg. daily for 6 days, combined with 2 gm. of quinine. Only after arriving at this stage he felt satisfied that plasmoquine can be safely added to the stock of medicines entrusted to field dispensers.

In the face of statements like these, which agree with numerous others, no health-officer will be found prepared to carry out prophylaxis with a daily dosage of 6 cg. of plasmoquine. Probably he will hardly give more than half that amount. He will feel justified in recommending such small doses of plasmoquine because SINTON (1930) has found them effective to cure and to prevent relapses. Also because OTTOLENGHI and BROTZU (1929) showed that a daily dosage of plasmoquine as low as 2 cg., alone or combined with 0.25 gm. of quinine, prevented a clinical and parasitological outbreak of malaria in subjects taking this dose 2 days previous to being bitten by infected Anopheles, on the day of infection and on 7 subsequent days.

Taking for granted that this is a correct picture of the attitude practical sanitarians will adopt, our object in the experiments to be described here, was to find out whether plasmoquine pure in a dosage practically affording complete safety i.e. 3 cg. daily, will prevent the parasites to take a foothold in the human body, if it is administered by the time the sporozoites are injected. We have conformed our experiments to JAMES, NICOL and SHUTE's by continuing the prophylactic treatment for 6 full days, the day of infection being the first, commencing it moreover on the eve of that day. In one way our experiments did not comply with practical conditions. Our volunteers and control-cases received unnaturally high doses of sporozoites by allowing them to be bitten by at least 4 infected (and often heavily infected) mosquitoes. Assuming that the larger the quantity of sporozoites injected the more of the drug is needed to destroy them, this circumstance will not fail to influence the interpretation of our results.

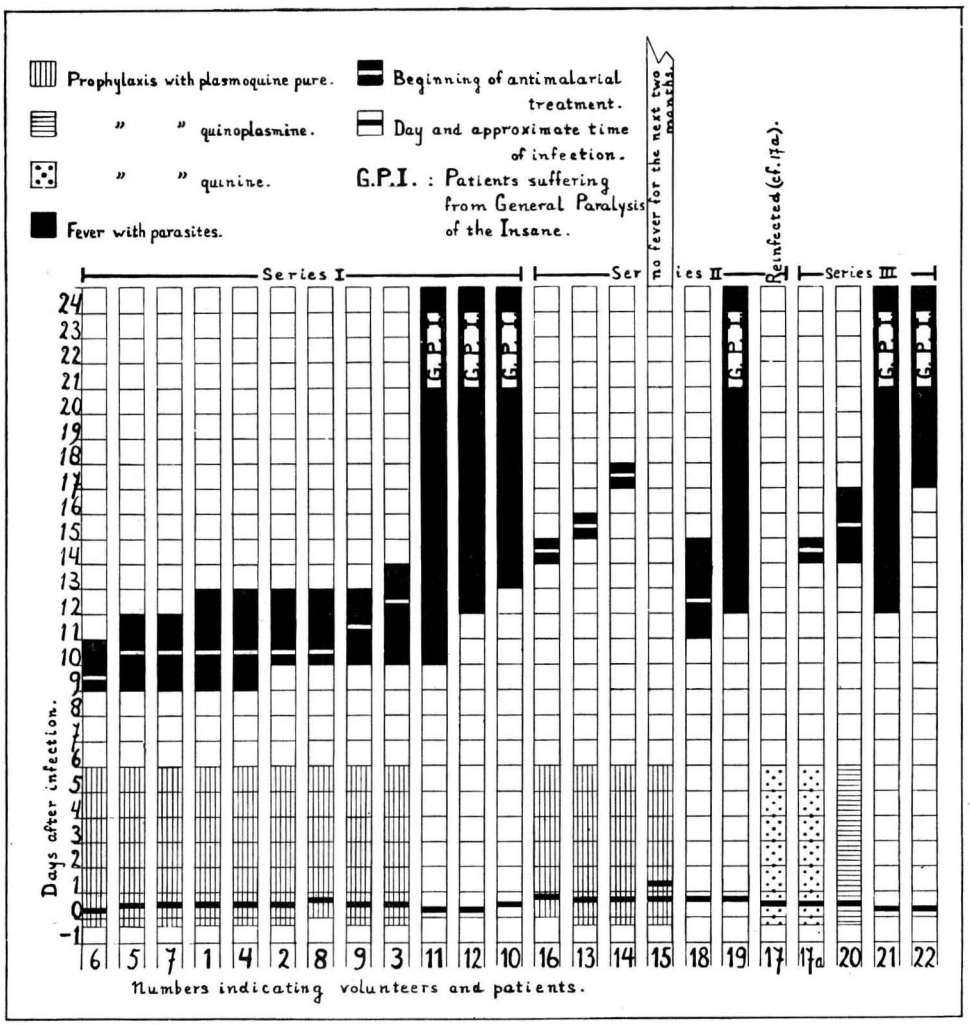
Our experiments were carried out with 16 volunteers, 6 G.P.I. patients serving as controls. They were infected with a strain of benign tertian parasites, we imported from Colonel JAMES' laboratory in Epsom and which originally came from Madagascar. We preferred this one to our home-strain of *Plasmodium vivax*, as its power to infect is more reliable and its period of incubation (a fortnight on an average, against 3 weeks in our home-strain) shorter.

The vector we used was our common short-winged *A. maculipennis*.

We worked with 3 different batches viz. Nos 87, 88 and 91. The incidence of salivary infection and the quantity of sporozoites was in:

Batch 87: 36 mosquitoes, 34 infections (94 %), 14 heavy, 20 moderate, 0 light
„ 88: 45 „ 38 „ (84 %) 0 „ 25 „ 13 „
„ 91: 35 „ 31 „ (88 %) 7 „ 21 „ 3 „

None of the control-cases showed a previous history of malaria. Some of our volunteers did. The difference between the two groups was well marked. Those who never had malaria before all showed KORTEWEG's (1924) "initial fever", i.e. a remittent fever of 3—4 days' duration,




usually with very few parasites. Quinine combined with plasmoquine (1 gm. + 3 cg. a day) was given as soon as fever appeared and parasites had been detected. It was without effect in shortening the initial remittent fever. Only at the time it became frankly intermittent in the control-cases

| N⁰. | Infecting mosquitoes. | | Infected subjects. | | | Details of prophylaxis. | | | | Effect of prophylaxis. | | | Type and treatment of the fever caused by the bite of the mosq. | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Infected with mosquitoes of batch N⁰.: | Bitten by how many mosquitoes? | Volunteer (Vl.) Volunteer and control (Vl.-c.). G.P.I. case, control(G.P.I.-c.) | Had malaria before? How many years ago? | Data of infection. | Which drug? | Daily dose, [1]) | Commenced on: | Stopped on: | Fever commenced on: | How many days after infection? | Parasites found on: | Kortewег's initial fever present? | How many days did it last? | On which day of the fever period treatment was initiated? | How many days the fever continued after the treatment had commenced? (incl. that day). [2]) |
| 1 | 87 | 7 | Vl. | no | 4 Spt. | Plasmoquine | 3 cg. | 3 Spt. | 9 Spt. | 13 Spt. | 9 | 14 Spt. | yes | 4 | 2nd | 3 |
| 2 | 87 | 5 | Vl. | no | 4 Spt. | Plasmoquine | 3 cg. | 3 Spt. | 9 Spt. | 14 Spt. | 10 | 14 Spt. | yes | 3 | 1st | 3 |
| 3 | 87 and 88 | 2 of 87, 3 of 88 | Vl. | no | 4 Spt. | Plasmoquine | 3 cg. | 3 Spt. | 9 Spt. | 14 Spt. | 10 | 16 Spt. | yes | 4 | 3d | 2 |
| 4 | 87 | 7 | Vl. | no | 5 Spt. | Plasmoquine | 3 cg. | 4 Spt. | 10 Spt. | 14 Spt. | 9 | 14 Spt. | yes | 4 | 2nd | 3 |
| 5 | 87 | 5 | Vl. | no | 5 Spt. | Plasmoquine | 3 cg. | 4 Spt. | 10 Spt. | 14 Spt. | 9 | 14 Spt. | yes | 3 | 2nd | 2 |
| 6 | 87 | 6 | Vl. | no | 7 Spt. | Plasmoquine | 2 cg. | 6 Spt. | 12 Spt. | 16 Spt. | 9 | 16 Spt. | yes | 2 | 1st | 2 |
| 7 | 87 | 5 | Vl. | no | 7 Spt. | Plasmoquine | 3 cg. | 6 Spt. | 12 Spt. | 16 Spt. | 9 | 17 Spt. | yes | 3 | 2nd | 2 |
| 8 | 87 | 5 | Vl. | no | 7 Spt. | Plasmoquine | 3 cg. | 7 Spt. | 12 Spt. | 17 Spt. | 10 | 17 Spt. | yes | 3 | 1st | 3 |
| 9 | 87 | 7 | Vl. | no | 9 Spt. | Plasmoquine | 3 cg. | 8 Spt. | 14 Spt. | 19 Spt. | 10 | 19 Spt. | yes | 3 | 2nd | 2 |
| 10 | 87 | 5 | G. P. I.-c. | no | 2 Spt. | — — | — — | — — | — — | 15 Spt. | 13 | 14 Spt. | yes | 4 | — | — |
| 11 | 87 | 8 | G. P. I.-c. | no | 12 Spt. | — — | — — | — — | — — | 22 Spt. | 10 | 23 Spt. | yes | 3 | — | — |
| 12 | 87 | 3 | G. P. I.-c. | no | 22 Spt. | — — | — — | — — | — — | 4 Oct. | 12 | 5 Oct. | yes | 5 | — | — |
| 13 | 88 | 8 | Vl. | one year | 4 Spt. | Plasmoquine | 3 cg. | 3 Spt. | 9 Spt. | 19 Spt. | 15 | 17 Spt. | no | — | — | — |
| 14 | 88 | 6 | Vl. | one year | 4 Spt. | Plasmoquine | 3 cg. | 3 Spt. | 9 Spt. | 21 Spt. | 17 | 21 Spt. | no | — | — | — |
| 15 | 88 | 12 [3]) | Vl. | no | 4 & 5 Spt. | Plasmoquine | 3 cg. | 3 Spt. | 9 Spt. | no..... | .. fever ... | .... nor .... | parasites ..... | ..... till ..... | . November 13th . | — |
| 16 | 88 | 7 | Vl. | two years | 4 Spt. | Plasmoquine | 3 cg. | 4 Spt. | 9 Spt. | 18 Spt. | 14 | 18 Spt. | no | — | — | — |
| 17 | 88 | 6 [4]) | Vl.-c. | two years | 4 Spt. | Quinine bihydrochl. | 0.97 gm. | 3 Spt. | 9 Spt. | no..... | ... fever ... | .... nor .... | parasites ... till .. | Spt. 28, ... then . | ... reinfected ... | .... (see N⁰. 17a). |
| 18 | 88 | 5 | Vl.-c. | no | 7 Spt. | — — | — — | — — | — — | 18 Spt. | 11 | 17 Spt. | yes | 4 | 2nd | 3 |
| 19 | 88 | 9 | G. P. I.-c. | no | 10 Spt. | — — | — — | — — | — — | 22 Spt. | 12 | 21 Spt. | yes | 4 | — | — |
| 20 | 87 and 91 | 1 of 87, 4 of 91 | Vl. | no | 25 Spt. | Quinoplasmine | } 3 cg. Plasm. } 0.9 gm. Quin. | 24 Spt. | 30 Spt. | 9 Oct. | 14 | 8 Oct. | yes | 3 | 2nd | 2 |
| 17a | 91 | 4 | Vl.-c. | two years | 28 Spt. | Quinine bihydrochl. | 0.65 gm. | 27 Spt. | 3 Oct. | 10 Oct. | 12 | 12 Oct. | no | — | — | — |

[1]) In 3 fractions (2 in N⁰. 6) of 1 cg. of plasmoquine (with 0.3 gm. of quinine sulfate in N⁰. 20) or 0.32 gm. of quinine bihydrochloride (in N⁰. 17 and 17a). The first fraction administered on the evening of the day preceding infection, the second one on the day of infection at 8 a.m., 3 hours before the infected mosquitoes were allowed to bite; exc. N⁰. 8, 13, 14, 16 (infected after 3d fraction) and N⁰. 15 (reinfected next day).

[2]) Curative treatment: 1 gm. quinine sulfate + 3 cg. of plasmoquine daily for a fortnight.

[3]) Bitten by 4 mosquitoes on Sept. 4th (two dissected: one moderate and one slight salivary infection) and by 8 on Sept. 5th (five dissected: 3 moderate and one slight salivary infection).

[4]) One dissected: moderate salivary infection.

(who received no antimalarial treatment) it was stopped in the cases under treatment. In our volunteers who had had malaria one or more years ago the fever never was refractory to quinine, not even for one day.

The result of our experiments can be tabulated as follows: (see: annexed table, and graph on p. 1218).

In the first series 9 volunteers (Nos 1—9) and 3 control cases (Nos 10—12) were infected with batch N°. 87 (mosquitoes with 39 % of heavy salivary infections and 55 % of moderate ones). None of them had ever had malaria before. All volunteers had malaria, four had fever 10 days after infection, five 9 days after; the three controls 10, 12 and 13 days after. Consequently there is no evidence of any protective effect of the plasmoquine; the drug seems actually to have shortened the period of incubation. This is not surprising in view of the reported provocative effect of small doses of plasmoquine (FISCHER and WEISE, 1927).

In the second series 4 volunteers (Nos 13—16) and 2 control cases (Nos 18—19) were infected with batch N°. 88 (mosquitoes with no heavy salivary infections and 55 % of moderate ones). Three volunteers (Nos 13, 14 and 16, with a previous history of malaria) had fever 14, 15 and 17 days after infection, the two controls (no previous history of malaria) 11 and 12 days after. Here it would seem that plasmoquine exhibited some slight protective action by prolonging the period of incubation. The fourth volunteer (N°. 15, no previous history of malaria) was effectively protected; he showed neither clinical nor parasitological signs of infection for the next two months after the bite of no less than 12 mosquitoes. We will have to watch him till next summer in order to make sure he is not suffering from malaria with much protracted incubation. At any rate this case N°. 15 negatives the supposition, which may have occurred to some, that the slightly prolonged incubation in volunteers 13, 14 and 16 is due to the effect of plasmoquine on subjects enjoying a certain measure of immunity as a consequence of previous attacks of malaria.

But this supposition seems to apply to one control of this series (N°. 17). He received 0.97 gm. of quinine daily instead of 3 cg. of plasmoquine. In this case the period of incubation was prolonged for at least 24 days. Whether this dose of quinine actually prevented the fever we cannot tell, as this volunteer was subsequently reinfected by batch 91. This time he took 0.65 gm. of quinine daily, which did not protect him as he had malaria 12 days later (Case N°. 17*a*). The full curative dose had, consequently, afforded him at least a certain measure of protection. This is significant as the same dose of quinine (0.9 gm.), combined with 3 cg. of plasmoquine, did not protect case N°. 20. Case N°. 17 showed a previous history of malaria, case N°. 20 had never had malaria before. This suggests that quinine in curative doses has some prophylactic effect but only in persons who have had malaria before. Our experiments confirm previous observations that such persons do not suffer from an initial remittent fever. It was intermittent from the very first and never refractory

to quinine treatment, whereas the initial remittent fever in cases with no previous malaria history had to run its wonted 3—4 days course before quinine could stop it. It seems probable that the lack of protective action of a curative dose of quinine in a subject of the latter type and the inability of the drug in this dosage to cut short the initial remittent fever in such a subject are closely related phenomena.

In the third series 1 volunteer (N°. 20) was infected with batch 91 (mosquitoes with 20 % of heavy salivary infections and 60 % of moderate ones). This is the only case where quinoplasmine was used as a prophylactic which afforded, however, no better protection than plasmoquine pure. This case has been discussed already in the preceding paragraph. Three controls were infected by this batch. One (N°. 17*a*) has likewise been dealt with in the same paragraph ; the others (not mentioned in the table) were G.P.I. cases who had malaria 12 and 17 days after infection.

As a conclusion we may state that our experiments need discourage no one expecting practical results in the field from malaria-prophylaxis with plasmoquine, continued for the whole time the subjects are exposed to infection and in a dosage small enough to warrant reasonable safety. But they show that such a dose of plasmoquine, pure or combined with quinine, administered in the way we have described, cannot be depended upon to prevent an outbreak of fever although it may do so. We repeat, however, what we wrote before viz. that our subjects were bitten by numerous, heavily infected mosquitoes. It is quite likely that the chances of succes would have been far better in the field than in our laboratory.

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