

Medicine. — *Plasmoquine prophylaxis in benign tertian malaria*¹). By
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W. SCHÜFFNER).

(Communicated at the meeting of June 25, 1932).

In a previous note we described our attempts to prevent the outbreak of fever and the appearance of parasites (benign tertian malaria) in the circulating blood in persons subjected to the bite of infected anopheles, but protected by a six days' course of prophylactic treatment with plasmoquine pure (3 c.g. daily supplemented, in one instance, by 0.9 gr. of quinine) commenced on the evening preceding the infecting bite. These attempts were unsuccessful except in one instance (case N^o. 15). This subject showed neither fever nor parasites for the next 2 months. Still we remarked: "We will have to watch him till next summer in order to make sure he is not suffering from malaria with much protracted incubation". The first object of the present note (which is to be considered as an appendix of our previous one) is to report on the subsequent history of this case:

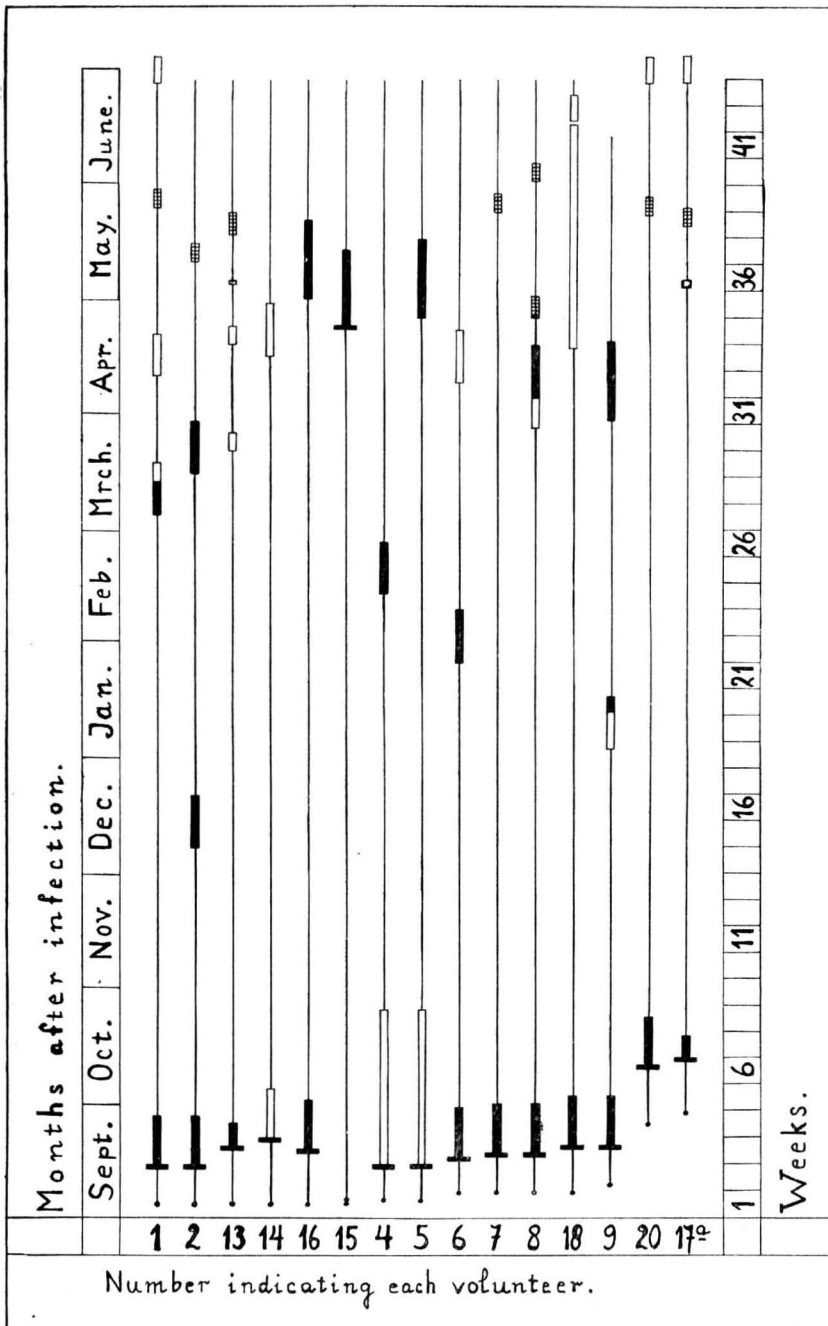
After being bitten by infected mosquitoes on Sept. 4 and 5, 1931, he remained in good health till April 23, 1932. On that day, 7 months 18 days after the infecting bite, he had fever and parasites of benign tertian malaria were found in his blood.

The question arises whether this is simply a case of protracted incubation, as described by JAMES and by SCHÜFFNER, KORTEWEG and SWELLENGREBEL, or whether the long period of incubation is the effect of the prophylactic treatment at the time of the infecting bite. If the latter supposition is correct, we must assume that the period of incubation would have been of normal duration if no prophylactic treatment had been given. Now all 7 control-cases, infected in the beginning of September, had their attack of malaria after the usual lapse of time and the same applies to the other cases, subjected to some kind of prophylaxis. Consequently the infections, caused by the bites of our infected mosquitoes, did not exhibit any tendency to run a course with long incubation and it seems not unreasonable to assume that the one exception to this rule is to be explained by the harmful effect of plasmoquine on the malaria parasites. Still, we prefer to leave this point undecided.

A second question, suggested by the perusal of the accompanying graph, concerns the nature of a malarial attack occurring at the end of a period of protracted incubation. N^o. 15's attack occurred at a time when relapses²) of malaria among our other subjects became more numerous, following upon a period in which they had been rare. Does not this coincidence prove that N^o. 15's malaria is a relapse, like all others supervening at or about the same time, and is not every case of malaria occurring after prolonged

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.

²) We use this word in its general sense and not in the limited sense of JAMES' terminology.



EXPLANATION OF THE GRAPH.

Each subject is represented by a vertical line. The dot (or dots: N^o. 15) at the bottom of each line indicates the date (or dates: N^o. 15) on which the subject was infected with malaria by the bite of mosquitoes. The beginning of the first attack of malaria consequent upon this infection is marked by a short horizontal line. The vertical column on this line indicates the course of treatment of this first attack:

black. Quinine 1 gr. + Plasmoquine 0.03 gr. daily.

white. Quinine 1 gr. daily.

The length of this column shows the time during which treatment was continued (see time-scale on the right).

The columns higher up the vertical lines mark duration and kind of treatment in the successive relapses. The colour of these columns has the same meaning as that of the bottom ones. But near the top relapses are treated with atebrine 3×0.1 gr. daily for 5 days; this is indicated by chequered columns.

incubation to be considered as a relapse, following upon a primary attack so slight as to be overlooked even under experimental conditions? The type of fever in case 15 proves that it was different from the relapses occurring at or about the same time. In the latter ones the fever proved immediately amenable to quinine and was freely intermittent (in so far as a fever showing only on one day can be called by that name). In case 15 it lasted for 4 days as a remittent fever (quinine treatment was commenced on the third day). In other words, it was KORTEWEG's initial fever as we encounter only in subjects suffering from malaria for the first time in their lives. Consequently, case 15's malaria was not a relapse in disguise but a true primary one.

The second object of this note is to draw attention to the fate of our other experimental subjects figuring in the accompanying graph. Although their subsequent histories might seem to be in no way related to the subject matter of this paper (i.e. the effect of prophylaxis by plasmoquine), these histories enable us, we believe, to arrive at a more correct understanding of the result of our experiment. Nine of our volunteers, after having developed the malaria we unsuccessfully endeavoured to prevent, were treated by a fortnightly course of quinine 1 gr. + plasmoquine 3 cg. All of them had relapses. In three (N^o. 2, 6, 9) they occurred within 8—24 weeks after infection ("relapse" according to JAMES' terminology); the other six (N^o. 1, 16, 8, 18, 7, 20) developed relapses after 6—8 months, termed "recurrences" by JAMES. In three instances (N^o. 2, 6, 8) the renewed attacks, treated in the same way, were followed by a third attack after 3 (N^o. 2, 6) and 1 (N^o. 8) months and by a fourth after 1 month and 27 days (N^o. 2). This is a heavy relapse-rate and it becomes the more significant when comparing it with PIEBENGA's experience in Franeker, since the middle of 1930. He successfully prevented relapses of any description in a series of 67 patients, treated by the same dosage and during the same time as our series of subjects. There are, however, two differences between the series:

1. PIEBENGA's were natural infections, our home-strain of benign tertian parasites acting as the virus; ours were artificial infections, the mosquitoes carrying a foreign (JAMES' Madagascar) strain. We know there are several points of difference between the two. Dr. P. C. KORTEWEG¹⁾ found the period of incubation longer in the home strain (three weeks on an average) than in the foreign (12 days). He also found the home-strain less reliable in causing human malaria after infection by means of mosquitoes: 38 % of failures (due, perhaps, to much prolonged incubation) in 66 cases, against 4 % in 52 cases after infection with the foreign strain.

These observations seem to suggest a lesser vitality of our home strain as compared with the foreign one. This decrease of vitality, although not necessarily involving a diminished resistance against all drugs, may be expected to do so in respect of some at least. This would afford some measure of explanation of PIEBENGA's successful prevention of relapses by

¹⁾ Dr. KORTEWEG has kindly permitted us to make use of his report prior to its publication.

plasmoquine treatment, contrasting so strikingly with our own complete failure.

2. The second difference is the number of infected mosquitoes biting the subjects. In PIEBENGA's cases this number is unknown but we may safely assume that it rarely, if ever, was more than one and, at any rate, far inferior to the number of infecting bites inflicted on our volunteers (4—10). It is possible that the vitality of the parasites or the susceptibility of the victims is raised by inoculation of very high doses of sporozoites, to the extent of neutralising the prophylactic effect of plasmoquine and diminishing its curative action in the subsequent primary attacks and relapses.

The same considerations apply to a comparison of our experience with results obtained in North-Holland (Zaan-region) by treating malaria for one week with plasmoquine 3 cg. + quinine 1 gr. a day. These results, although less satisfactory than PIEBENGA's, were far better than ours: 53 % of the cases did not relapse. Finally we should point out that the usual relapse rate of malaria in Holland, after ordinary quinine treatment, hardly exceeds 50 %. In our 15 volunteers it is 100 %.

So we are forced to the conclusion that the malaria our volunteers suffered from was exceptionally refractory to treatment with plasmoquine. Without being able to decide which factors (quantitative or qualitative) caused this state of things, we may assume that they were influencing the experiment from the very beginning. Once this is admitted, it follows that our failure to prevent the primary attack, as well as the relapses, can no longer be regarded as contradictory to statements announcing satisfactory results obtained elsewhere. It only shows that a system of prophylaxis and treatment, which has definitely proved its great practical value, may occasionally break down under the stress of an unusually great number of infected mosquitoes or the prevalence of some strain of parasites of particular vitality.

ERRATUM

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¹⁾ The title of the Dutch paper is: C. P. J. PENNING, *Onderzoek der Bevolking van de Over-Veluwe* 1932.

The footnote printed here as ¹⁾, refers to the name of BERNSTEIN on page 708.