**Medicine.** — *Report on a small experimental epidemic of benign tertian malaria started in September 1931 and followed up till January 1933. By N. H. Swelengrebel.* (Communicated by Prof. W. A. Schüffner.)

(Communicated at the meeting of February 25, 1933.)

The object of the present note is to relate the further events of an experiment commenced in September 1931 and which already has formed the subject of two communications 1).

The experiment originally aimed at preventing malaria by small doses of plasmoquine (3 cg. daily) taken by healthy volunteers before, on, and 5 days after infection by the bite of numerous mosquitoes carrying salivary sporozoites. As all volunteers became infected and as we were able to keep the majority under observation, the experiment gradually changed its character. What we actually had done was this: we had started an experimental epidemic of benign tertian malaria, the disadvantage of small numbers being compensated to some extent by the circumstance that all our subjects were infected on known dates and by one and the same strain of parasite, conditions warranting a uniformity of results hardly to be obtained under field conditions.

The drug we had used as a prophylactic had failed us, a fact readily explained by the small dose, the short time it was taken and the unusually heavy infection. But the experimental epidemic once started allowed us to test the curative effect of plasmoquine (combined with quinine) and atebrin in two ways: 1°, individually and 2°, by the aspect and course of this experimental epidemic as a whole.

1. *Individual effect.*

As our 15 volunteers suffered from one to several relapses there were many more "cases" to treat:

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18 with quinine 1 gm. + plasmoquine 3 cg. daily for 2 weeks, 16 relapses (3 relapsed twice, 1 three times.)
5 with quinine 1 gm. + plasmoquine 3 cg. daily for 3 weeks, 1 relapse.
8 with quinine 1 gm. daily for 3-5 days, 5 relapses (1 relapsed three times).
9 with quinine 1 gm. daily for 2-6 weeks, 7 relapses (1 relapsed twice).
9 with atebrin 0.3 gm. daily for 5 days, 7 relapses (1 relapsed twice).
4 with atebrin 0.3 gm. + plasmoquine 3 cg. daily for 5 days, 2 relapses.
1 with two doses of salvarsan (150 and 300 mg.)

Taking together all the cures with quinine + plasmoquine, with quinine alone and with atebrin the result is not exactly encouraging:

23 quinine + plasmoquine cures with 17 relapses.
17 quinine cures with 12 relapses.
13 atebrin (alone or + plasmoquine) cures with 9 relapses.

But the result would have been better, we believe, if we had returned sooner to the full (i.e. the three weeks' instead of the fortnight's) quinine + plasmoquine treatment.

With atebrin the results might have been improved by the addition of a daily dose of 0.03 Gms. of plasmoquine, but the cases treated this way are too few in number to relieve us of the feeling that atebrin was no better than quinine. But even if we should have to accept as a fact the impression that atebrin is not an ideal drug to cure benign tertian malaria, there remain Col. James' 1) indubitable results proving its outstanding qualities as a cure for the most recalcitrant strains of malignant tertian. These qualities combined with the short duration and low price 2) of the treatment and with its life-saving value in cases of blackwater fever, more than suffice to compensate any minor shortcomings with regard to the curative effect on benign tertian malaria.

b. Effect on the type of epidemic (see graph 1 and 2).

The first thing which strikes one is that the bites of infected mosquitoes, inflicted in September, all took immediate effect. There was no protracted incubation except in one case. This seems to contradict our former observations but it really does not. In our investigations on malaria with

2) With regard to this point it would be well to compare the costs of a cure effected by atebrin with a 5-days or 7-days quinine treatment, and not with a „standard-treatment”, which very often exists on paper only.
prolonged incubation\(^1\)) all our volunteers were bitten by one (two in one case) infected mosquito only whereas in this prophylactic experiment their number was 5—12. This circumstance alone seems sufficient to account for the absence of a protracted incubation. Still it is possible that the drug the volunteers were made to swallow at the time of infection, had something to do with it too, as small doses of plasmoquine are known to act as a stimulant to the parasites, a fact which was also brought to our notice by the exceptionally short incubation (9 days) in some of our subjects. But our control cases infected simultaneously with our volunteers and by the same number of mosquitoes did not show a prolonged incubation either and so we conclude that the heavy dose of salivary sporozoites and not a stimulating effect of plasmoquine was the cause of this unusual behaviour in our experimental epidemic.

Our graph No. 1 is strongly suggestive of the correctness of the view that the common Dutch malaria epidemic is composed of nothing but relapses (recurrences, sensu James). Every springcase is a repetition of an usually latent, but occasionally patent, primary manifestation of malaria during the preceding autumn. The patent autumnal primary attacks of our experiment have occasioned a vernal epidemic which is the exact replica of a typical Dutch epidemic: A steep rise in spring, a maximum in summer and a decline which is less abrupt owing to a separate secondary rise in

early autumn. This separate autumnal rise is supposed to be due to a

certain proportion of autumnal infections failing to remain quiescent till

the following spring. But our experiment proves that a series of late

relapses may give rise to a similar autumnal peak.

In order to render the comparison of our experimental epidemic with a

natural one as accurate as possible, we have added Graph 2. This graph

does not represent a complete dutch epidemic but only that portion of it

which starts from primary cases in September and October. It is based on

observations Dr. KORTEWEG continued at Wormerveer for a period of

several years and which he kindly allowed us to make use of. Like in our

experimental epidemic all primary cases are autumnal and the whole of

the summer epidemic is composed of relapses. The resemblance existing
between Graphs 1 and 2 is sufficiently obvious to require no further explanation; the differences amount to no more than a shifting of the summer peak from May to June, the autumnal peak from August—September to October and the peak of primary cases from September to October.

For the present purpose the main point is: the 54 cases of benign tertian malaria composing our experimental epidemic, in 36 of which the treatment was with plasmoquine + quinine (23 cases), plasmoquine + atebrin (4 cases) or atebrin alone (9 cases) have arranged themselves in exactly the same way as they might have been expected to do if treated with quinine only.

c. An additional explanation to account for the unsatisfactory results of our treatment.

For the data underlying the following consideration we are indebted to Dr. Korteweg who provided us with figures indicating, for each month separately, the number of his patients suffering from a primary attack of malaria in that month, and the subsequent history of each patient followed up for the next two years.

Studying these figures, a point struck us as possibly affording an additional explanation of the unsatisfactory results of our treatment with regard to the prevention of relapses. This point is the following:

10. In 242 persons, who had a primary attack of malaria in spring and summer (April—August), 119 had relapses (51%). Out of these 119, 57 (48%) suffered from more than one relapse.

20. In 77 persons, who had a primary attack of malaria in autumn and winter (September—March) the relapse rate was about the same: 38 (49%). But out of these 38, 27 (71%) had more than one relapse.

Unless this is a mere coincidence, it signifies, in Holland, that a person, suffering from a primary attack of malaria in autumn and winter, is more liable to repeated relapses than one whose primary attack occurred in spring or summer. Considering that most malarial infections in Holland are acquired in autumn and winter, this means that the chances to suffer from repeated relapses are the greater the shorter the time between the infection and the primary attack. We may put this conclusion in a different wording by saying that the chances of repeated relapses are the greater the more sporozoites are injected. For Schüffner, Korteweg and Swelengrebel (1929) have shown that a malaria infection, by mosquito bites in autumn, is followed by an attack of malaria after an incubation period of a few weeks only, if the dose of sporozoites injected is a heavy one. but that the attack is retarded for 7—8 months if the infection is brought about by the bite of one mosquito only.

Applying this conclusion to the present experiment, the heavy infection to which our volunteers were subjected appears in the light of a causative
agent obscuring not only the prophylactic but likewise the curative properties of plasmoquine; the same, of course, holds good for atebrin. In our previous communication we have already suggested that this heavy infection might have had the effect to frustrate our attempt at prophylaxis at the commencement and to interfere with our curative efforts at the end of our experiment. It is only after taking cognisance of Dr. KORTEWEG’s field observations that this assumption seems to be better supported.

Conclusion.

Although we are not in a position to contribute to the mass of favourable opinions regarding the curative effect of the new synthetic drugs and, more especially, their power to prevent relapses and to cut short an impending epidemic, we recognise that the positive results obtained by some other investigators may be as true as are our own negative ones. Although we are well aware that our experiment recommends itself by some special features, uniting the advantages of field- and laboratory observations (our volunteers being healthy individuals living under normal conditions) we realise on the other hand that we have been working with a particularly resistant strain of Plasmodium vivax and that we have aggravated the morbid condition resulting from the infection with this strain by exposing our volunteers to an unusually large number of infecting mosquito bites.

Consequently we feel we cannot do better than to repeat the conclusion to which our previous investigations led us, viz. that a system of prophylaxis and treatment, which has definitely proved its great practical value, may occasionally break down under the stress of unusual conditions.