

LEAGUE OF NATIONS

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HEALTH ORGANISATION.

Malaria Commission.

The Medical Director has the honour to communicate here-
with a :

REPORT ON A SMALL EXPERIMENTAL EPIDEMIC OF BENIGN
TERTIAN MALARIA BEGUN IN SEPTEMBER 1931 and CONTINUED
UNTIL JANUARY 1933.

by Professor N.H. Swellengrebel, Amsterdam.

This document has been prepared for the meeting of the
Study Committee of the Malaria Commission.

The object of the present note is to show the further
developments of an experiment begun in September 1931 and which
has already formed the subject of two communications.*

The experiment originally aimed at preventing malaria by
small doses of plasmoquine (3 cg. daily) taken by healthy

* Swellengrebel and de Buck. Prophylactic use of plasmoquine in
a dosage warranting reasonable safety
for routine treatment.--

Prof. Roy. Acad. of Sc. Amsterdam,
XXXIV, 1931, No. 8, pp. 1216 - 1220.

Ibid.

Plasmoquine prophylaxis in benign
tertian malaria.-- Eod.Loc. XXXV,
1932, No. 6, pp. 912 - 914.

volunteers before, at the time of, and 5 days after, infection by the bite of numerous mosquitoes carrying salivary sporozoites. As all these subjects became infected and as we were able to keep the majority under observation, the experiment gradually changed in character. What we actually did was this: we started an experimental epidemic of benign tertian malaria, the disadvantage of small numbers being compensated to some extent by the fact that all our subjects were infected on specific dates and by the same strain of parasite - conditions which warranted a uniformity of results hardly to be obtained under field conditions.

The drug we had used as a prophylactic had failed - a fact readily explained by the small dose, the short period of dosage, and the unusually heavy infection. But once the experimental epidemic was started we were able to test the curative effect of plasmoquine (combined with quinine) and atebirin in two ways: (a) individually, and (b) by the aspect and course of this experimental epidemic as a whole.

(a) Individual effect (see graph 1).

As our 15 subjects suffered from one or several relapses, there were many more "cases" to treat;

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.).

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Taking together all the cures with quinine + plasmoquine, with quinine alone, and with atebrin, the result is not exactly encouraging and hardly favourable to synthetic compounds:

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 is better than it looks at first sight and would, we believe, have been more satisfactory if we had returned sooner to the full quinine + plasmoquine treatment (i.e. three weeks instead of a fortnight). Unfortunately, it took us some time to realise that a remedy which is perfectly satisfactory and which eliminates relapses when one is dealing

with the Dutch strain of benign tertian malaria, is quite useless in infections caused by Col. James' Madagascar strain of the same species of parasite. Since the latter first opened our eyes to the havoc which the introduction of new strains of malaria parasites belonging to the same species as the indigenous plasmodia may cause in a country, we have all been familiar with that idea -- theoretically. But it is quite another matter when one has an opportunity to observe its truth with one's own eyes.

With atebryn the results might have been improved by the addition of a daily dose of 0.03 gms. of plasmoguinine, but the cases thus treated are too few in number to enable us to state that atebryn is no better than quinine. But even if we are forced to admit that atebryn is not an ideal drug for the cure of benign tertian malaria, there still remain Col. James' results unquestionably 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*

* With regard to this point it would be well to compare the costs of a cure effected by atebryn with a 5-days; or 7-days' quinine treatment, and not with a "standard-treatment", which very often exists on paper only.

of the treatment and with its life-saving value in cases of blackwater fever, more than compensate for any disappointing results with regard to the curative effect on benign tertian malaria.

b. Effect on the type of epidemic

(see graph 2).

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 in effect does not do so. In our investigations on malaria with prolonged incubation¹⁾ all our volunteers were bitten by one (two in one case) infected mosquito only, whereas in this prophylactic experiment the number was 4-8. This fact alone seems sufficient to account for the absence of a protracted incubation. Nevertheless it is possible that the drug the subject had to swallow at the time of infection had also something to do with it, 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 we conclude therefore that the heavy dose of salivary sporozoites and not the stimulating effect of plasmoquine was the cause of this unusual occurrence in our experimental epidemic.

1). Schüffner, Korteweg and Swellengrebel. Proefondervindelyke malaria met lange latentie. Nederl. Tydschr. v. Geneesk. LXXIII, 1929, No. 40, pp. 4622-4629.

Graph No.2 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 spring case is a repetition of a usually latent, but occasionally patent, primary manifestation of malaria during the preceding autumn. The patent autumnal primary attacks observed in our experiment have occasioned a vernal epidemic which corresponds exactly to a typical Dutch epidemic, not preceded by autumnal malaria: A steep rise in spring, a maximum in May and a decline which is less abrupt owing to a separate secondary rise in early autumn. This separate autumnal rise occasionally shows in natural Dutch epidemics. It is supposed to be due to a certain proportion of autumnal infections failing to remain latent till the following spring. But our experiment proves that a series of late relapses may give rise to a similar autumnal peak.

For the present purpose the main point is that out of 54 cases of benign tertian malaria which made up our experimental epidemic, 36 cases (of which 23 were treated with plasmoguinine + quinine, 4 with plasmoguinine + atebryn and 9 with atebryn alone) have reacted to treatment in exactly the same way as they might have been expected to do if treated with quinine only.

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 check an impending epidemic, we

recognise that the positive results obtained by some other investigators may be as true as are our own negative ones. While our experiment has the advantage of some special circumstances, including the benefits of both field and laboratory observations (our subjects 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 subjects 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.

Explanatory note to the following graphs.

Graph 1

Every square represents one case.

Black squares: first manifestations of malaria after the
infecting mosquito bites in September 1931.

White squares: relapses.

Graph 2.

Every horizontal line represents one volunteer; the black
dots along it represent the separate (primary or
secondary) manifestation of malaria from which he (or
she) suffered. The marks attached to each dot signify
the kind of treatment:

no mark: quinine

a cross: plasmoquine

a vertical line on top: atebrin

a vertical line at the bottom: Other treatment.

N.B. The lines marking subjects No.3 and 12 (from the
top) should not have been prolonged till the end as
No.3 left for India in May and No.12 died in July.

