

HEALTH ORGANISATION

TREATMENT OF MALARIA.

STUDY OF THE THERAPEUTICS AND PROPHYLAXIS OF MALARIA BY
SYNTHETIC DRUGS AS COMPARED WITH QUININE.

Fourth General Report of the Malaria Commission.

It will be remembered that in 1933 the Malaria Commission of the League of Nations published its third general report entitled "The Therapeutics of Malaria". This report was based chiefly on the knowledge acquired by a study of experimental malaria.

Two years later the Commission arranged for experiments to be made with the treatment and prophylaxis of malaria, with synthetic drugs and with quinine so as to compare their efficacy. These experiments were conducted according to a plan which had been very carefully prepared beforehand and which involved the use of the same drugs, the same doses and the same technique. They covered 12,288 subjects and were carried out in Algeria, Italy, the Federated Malay States, Roumania and the U.S.S.R. under the direction of Professor Edmond Sergent, Professor Bastianelli, Dr. Neave Kingsbury, Professor Ciuca and Professor Serguieff, respectively.

The Commission has now drawn up the text of its fourth general report on the basis of the lessons to be learnt from these experiments, whilst paying due regard at the same time to the scientific papers that have been otherwise published on the question of the treatment of malaria. This report is the work of a drafting committee consisting of Professor Edmund Sergent, Chairman, Dr. Balfour, Professor Pittaluga and Colonel Sinton. It represents the unanimous views of the Commission. It is entitled "The Treatment of Malaria" and will shortly appear in the Bulletin of the Health Organisation. The annexes will include an account of the experiments, a bibliographical review and the text of the observations made by the various members of the Malaria Commission.

We have pleasure in giving below the conclusions of the report:

1. ACTION OF QUININE AND OF SYNTHETIC PRODUCTS ON
THE DIFFERENT MANIFESTATIONS OF MALARIAL INFECTION.

(a) Quinine.

(1) Action on the trophozoites in primary infections.
A minimum daily dose of 0.50 grm. of quinine hydrochloride

sometimes suffices to cause a temporary disappearance of the trophozoites of P.vivax; but a mean daily dosage of 1 grm. for five to seven days is often necessary to cause the trophozoites to disappear (on an average on the third day) and not to make their reappearance in the peripheral blood until after a latent period of varying length, in the course of the first relapse. In quartan (P.malariae) the same effects are usually obtained. In infections with P.falciparum, the average effective daily dose should be fixed at about 1.30 grm. to produce analogous results. In some countries, it is even necessary to use 2 grm. in order to obtain a rapid effect upon the clinical attack and on the parasites. With the usual dose of 1 grm. the trophozoites generally disappear one day later, on the average, than in the case of P.vivax; sometimes their resistance continues even longer.

(2) Action on the gametocytes of P.vivax and P.malariae. - Quinine, in the doses indicated, exercises its parasitocidal activities on the young forms of P.vivax and P.malariae capable of producing gametocytes, and also on fully-developed gametocytes. On the fully-developed gametocytes of P.falciparum, quinine has only a very slight action; but it also impedes the formation of the pre-gametocytes of this species. It may thus be regarded as directly schizonticidal and indirectly gametocidal in the case of P.falciparum.

(3) On the acute clinical symptoms of primary infection, quinine, in the indicated doses, has a definite action from the third day onwards (second paroxysms of fever) in benign tertian; its action is less reliable or less rapid, according to the strain of P.falciparum concerned, on attacks of malignant tertian, which often continue until the fifth dose (third or fourth paroxysm).

(4) On the frequency of relapses in general, quinine has a clearly marked effect which is, however, influenced by individual factors and by the strain of parasite. The treatment of primary P.vivax or P.malariae infections with quinine in the usual doses (1 grm. daily) is followed by relapses in a proportion of individuals which may be as high as 50%.

(5) The action of quinine on splenomegaly, when suitable treatment is applied in each attack, has proved to be of real efficacy in endemic regions, especially among children. It is but transient, however, if the community concerned is subject to a high proportion of relapses or is exposed to frequent reinfections.

(6) Quinine treatment with the usual doses does not affect the patient's general condition adversely and generally has no depressive or toxic effect, if the period of administration is limited to the strictly necessary number of days. In such a case, there is no good reason for thinking that this treatment hinders the processes of immunisation, but ill effects may occur when treatment is unnecessarily protracted.

(b) Atebrin.

(1) Action on the trophozoites. - Atebrin in daily

doses of 0.30 grm. (for adults) has a slightly more rapid action on P.vivax trophozoites than quinine in the usual dose of 1 grm. The trophozoites disappear on an average after the third dose, and in some cases even after the second. This parasitocidal action appears to continue for a longer period, in that the phase of latency of the disease (absence of clinical symptoms) is established more certainly and lasts somewhat longer after the end of treatment with atebtrin than with quinine. On the trophozoites of P.malariae, the action of atebtrin can be said to be of the same nature. On the trophozoites of P.falciparum, atebtrin is equally in advance of quinine in certain cases; but the differences between the strains of parasite prevent the drawing of uniform conclusions. The trophozoites of P.falciparum disappear from the peripheral blood after the fourth dose of atebtrin in 90% of cases.

(2) The action of atebtrin on the gametocytes is of a similar nature to that of quinine; it has no effect, from the point of view of devitalisation, on the gametocytes of P.falciparum. But the action on gametocytes already present in the blood is perhaps slightly more marked than that of quinine, particularly as regards the gametocytes of P.vivax and P.malariae.

(3) The action on the clinical symptoms of an acute attack is very marked, both in benign tertian and in malignant tertian. In some endemic regions, where there may possibly be special strains of P.falciparum, the therapeutic action of atebtrin is even more energetic on malignant tertian than on benign tertian. But, in other cases, the contrary seems to be true. This is why some practitioners and malariologists in tropical countries prefer to use quinine during the first days of the acute attack and to continue with atebtrin thereafter. In benign tertian the fever nearly always falls after the first three therapeutic doses of atebtrin - that is to say by the second attack. In malignant tertian the fever falls almost invariably by the third attack.

(4) The action of atebtrin on relapses is slightly more effective than that of quinine, especially in the case of benign tertian and of certain strains of malignant tertian.

(5) The spleen rate in communities treated with atebtrin seems to decrease somewhat more slowly than in communities treated with quinine, but the effects of the drug continue to be felt for a longer time during the observation period after the end of the treatment, the decrease in the percentage of enlarged spleens continues longer, and the return of the splenic index figures to their former high level occurs a little later.

(6) The action of atebtrin on the general condition of patients seems to be determined by factors which, after this form of treatment, are still not entirely known - that is to say, by the action of the drug on the organic defences in general and on the processes of immunisation. The yellow coloration of the skin produced by atebtrin is a disadvantage, especially during prolonged prophylactic treatments.

(c) Plasmoquine.

(1) Action on the Trophozoites. - The action of plasmoquine on the trophozoites of P.falciparum is almost nil. It acts to some extent on the trophozoites of P.vivax, and especially on those of P.malariae. With small non-toxic

doses of plasmoquine associated with the usual doses of quinine or atebtrin, better results are sometimes obtained on the trophozoites of P.vivax and even of P.falciparum.

(2) Plasmoquine acts upon the gametocytes of the three species, but especially on those of P.falciparum, which are practically unaffected either by quinine or by atebtrin. In minimum doses of 0.02 grm., plasmoquine devitalises the gametocytes of P.falciparum, and at the same time diminishes their numbers.

(3) There is no advantage in using plasmoquine alone for the treatment of the clinical symptoms of an acute attack in any of the forms of malarial infection.

(4) Plasmoquine has a definite effect upon the frequency of relapses of benign tertian or quartan. In association with quinine or atebtrin, or administered after either of these two drugs, it is to a marked degree effective in preventing relapses in benign tertian (except perhaps in the case of a few particular strains) and quartan, and appears similarly to reduce the frequency of malignant tertian relapses.

(5) We do not possess sufficient data to assess the action of plasmoquine alone, used either therapeutically or prophylactically, upon the state of the spleens in malarial communities, for it is nearly always administered together with other drugs.

(6) The small doses of plasmoquine (0.02 grm. for example) that are now being used, seem to have no serious depressing effect on the general state of the patient. That the prolonged use of plasmoquine may exert some influence on the neoformation of haemoglobin must not be overlooked.

(d) Quinine-atebtrin, Quinine-plasmoquine and Atebtrin-plasmoquine Combinations.

(1) The few experimental observations that have been published give no indication that there is any advantage in combining quinine and atebtrin together for purposes of treatment.* Further clinical research is required in order to determine the effects of these two drugs, when administered one after the other (usually quinine first and atebtrin afterwards) in the treatment of acute attacks of certain kinds of infection, especially P.falciparum.

(2) The combined use of quinine with plasmoquine produces less frequent and less intense toxic symptoms than that of atebtrin with plasmoquine. The association properly so called (that is to say, the simultaneous use) of quinine and plasmoquine (for example, up to 0.02 grm. or even 0.03 grm. of plasmoquine daily for short treatments) therefore does not involve any particular contra-indications. Certain authors recommend however that, whenever possible, the two drugs be administered consecutively. For the treatment of adult groups under observation (soldiers, workers) there is,

* Prof. RODHAIN, in a private communication, states that he has recently obtained beneficial effects by this method.

however, no serious disadvantage to be feared from the simultaneous use of quinine and plasmoquine, which moreover shortens the duration of treatment.

The association of quinine with plasmoquine represents one of the most efficacious methods of treating benign tertian and quartan malaria. Treatment with average doses (1 grm. to 1.30 grm.) of quinine-plus-plasmoquine (even only 0.02 grm. to 0.03 grm. twice a week) greatly reduces (perhaps more than any other method) the number of relapses in benign tertian (except, as already indicated, in the case of certain strains) and in some cases also in malignant tertian.

(3) The simultaneous administration of atebtrin and plasmoquine appears to aggravate the toxicity of each. It is not to be advised, though it is understood to have been used without ill effects in certain communities of adult men. It should in any case not be adopted without medical supervision. Consecutive treatment with atebtrin first and then with plasmoquine in suitable doses (0.30 grm. atebtrin daily for five or seven days followed by 0.02 grm. plasmoquine daily for five days) has no appreciable influence either in reducing the proportion of trophozoites in the blood or on the clinical manifestations. Like the quinine-plus-plasmoquine treatment, this method has, however, the advantage of decreasing and devitalising the gametocytes, especially those of P.falciparum. Moreover from the clinical point of view, it diminishes substantially the number of relapses, both in malignant tertian and, more especially, in benign tertian and quartan.

2. PRACTICAL SUGGESTIONS FOR TREATMENT AND PROPHYLAXIS.

Without presuming to lay down hard and fast rules, and while avoiding any interference with either the personal freedom of the doctor, who has to take the responsibility for the treatment of each case, or the initiative of the malariologists, who have to judge the different circumstances of the local epidemiology in the field, the Commission believes that it is in a position to give certain indications. Account should however first be taken of the following points, on which reservations have been made in the previous pages, with respect, not only to the individual treatment of patients, but generally also to the application of any therapeutic procedure: (1) The varying reactions of the different parasite strains of the same species and of patients to the drugs; (2) the special indications applicable to the parenteral administration of drugs; (3) the drawbacks of the synthetic products (yellow coloration of the skin by atebtrin, toxicity of plasmoquine).

(a) Individual Treatment of Patients.

It is always desirable that the doctor should be in a position to diagnose malaria and to determine the species of parasite concerned, by a microscopic examination of the blood.

, In ordinary cases of P.vivax (benign tertian) infections, it is almost immaterial whether quinine or atabrin is employed for treatment of the attack. Plasmoquine, associated with quinine or atabrin, or administered after these drugs, has no appreciably useful effect on the attacks, but seems to reduce the frequency of subsequent relapses.

The association of plasmoquine with quinine, or its administration after atabrin, is useful in P.falciparum infections, on account of its action on gametocytes and relapses.

(b) Treatment in the Field.

Atabrin, when used for collective treatment in daily doses of 0.30 grm. (for adults) for five to seven days, acts in the same way as quinine in daily doses of 1 grm. to 1.30 grm. for five to seven days or more. There is no reason save financial considerations, why either quinine or atabrin should be preferred. The manner in which collective treatment is conducted will depend upon the intensity of the endemicity, which is itself the resultant of a series of factors: the incidence of malignant tertian infection (P.falciparum), the virulence of the strains, the sensitiveness of the strains to the various drugs, the susceptibility of various population groups, etc.

Collective treatment with quinine or atabrin may usefully be accompanied or followed by plasmoquine treatment, in order to diminish the number of gametocytes and the risk of relapses.

The choice of the basic drug for collective treatment should be left to the public administrations or malariological organisations which undertake or control such treatment, and will be guided by local and economic considerations as well as by the preferences of the medical profession and of the population. It should, however, be remembered that the choice of drug, as well as dosage and duration of therapeutic administration, should, so far as possible, be directed towards the achievement of the real aim of mass treatment. This aim is: (1) to secure the largest number of complete cures in case of malaria (intensive treatment of patients); (2) to reduce to a minimum the risk of anopheline infection, either by direct action upon the gametocytes, or by indirect action on the parasites generally, thereby effecting an eventual reduction in the number of carriers of sexual forms (gametocyte therapy). It would therefore be wise not to rely on plasmoquine alone for this second purpose. These considerations also apply to the choice of the basic drug and the manner of its administration to the community, either directly associated with, or followed by, plasmoquine.

There are, however, large malarial areas, especially in the Tropics, where such mass treatment is impossible of practical application for various reasons, often financial. Under such conditions, it is desirable to provide adequate and easily available treatment for the clinical manifestations of the disease, so that the morbidity, the mortality and the physical incapacitation of the afflicted individuals are diminished. Such treatment has very often

to be placed in the hands of laymen for distribution, and little or no direct medical supervision is possible. In these circumstances, the cinchona alkaloids appear to be the more suitable drugs.

(c) Mass Drug Prophylaxis.

Mass drug prophylaxis has a twofold purpose: (1) to protect the population undergoing prophylactic treatment from the clinical manifestations of endemic malaria, in order that its working capacity and comparative standard of health may be safeguarded without injury to its premunisation, even in areas in which it is exposed to repeated reinfection; (2) to reduce, in due course, the sources from which the local mosquitoes may be infected.

No prophylactic method, unless applied to disciplined communities under stringent supervision, is capable as yet of attaining these two objects. Special stress should be laid upon the desirability - and, at the same time, the difficulty - of promoting the immunisation process in the population, which depends precisely upon the degree of tolerance to infection and upon repeated reinfection. At the same time one wishes to avoid the risks attendant upon the presence and persistence of such latent infections in the community.

Experience has shown, at all events, that very useful results can be obtained with daily doses of quinine (0.40 grm.) administered during the whole of the malaria transmission season, and even for a few weeks longer. This is also true of bi-weekly doses of atebtrin (0.20 grm. = 0.40 grm. per week) administered in certain conditions. With the latter method (bi-weekly atebtrin), which has given encouraging results, further trials would be desirable. The daily dose of 0.05 grm. of atebtrin recommended for prophylactic purposes has proved inadequate. The harmlessness of quinine makes it a suitable drug for administration by subordinate personnel without constant medical supervision, whereas such supervision is essential in the case of atebtrin.

Plasmoquine should not be distributed for prophylactic treatment otherwise than under direct medical control. Its use in mass prophylaxis would be justifiable only if it were administered to a disciplined population, which should be kept under constant medical care. It is useful more especially for the purpose of ultimately reducing the number of gametocyte carriers and arresting the transmission of infection to the anopheles. Plasmoquine is certainly the gametocidal agent par excellence, especially where P.falciparum is concerned. But both quinine and atebtrin also exercise in the latter case a gametocidal action (mainly indirect) by destroying the sexual forms in process of development.

The real efficiency of such methods in the field is, moreover, largely dependent upon a highly important epidemiological factor: namely the children. The proportion of gametocyte carriers is much higher among children than among adults, given the same environmental conditions (village, house, family) in respect of endemicity and anophelism. Children, on the other hand, are more difficult

to subject to regular treatment, and finally, as already pointed out, the doses and form of administration of atebirin and plasmoquine to children cannot yet be regarded as finally settled.

(d) Drug Eradication.

Experience has so far shown that the eradication of malaria from a locality by the curative and prophylactic treatment, with the drugs at present available is practically impossible. To begin with, it is impossible to reach, in sufficient time, all the inhabitants of an area, or even of a small village. Moreover, while curative and prophylactic treatment may greatly diminish the morbidity yet it cannot suppress the parasites in all the carriers.

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In this Report, the Commission has not considered the question of expenditure entailed by treatment and prophylaxis campaigns, which depends upon the price of drugs and the cost of staff. It would, however, emphasise the great importance of this problem - which will probably be studied in detail by the Malaria Commission in the near future - in connection with the choice of drugs to be used for curative or prophylactic mass treatment.

Among those drugs, quinine still ranks first in current practice, by reason of its clinical effectiveness and almost complete absence of toxicity, coupled with the widespread knowledge of its use and dosage. As regards the synthetic products, which have only been used in therapeutics for ten years, the Commission hopes that it has discharged the duty which devolved upon it by giving in this Fourth General Report an account of the present state of our knowledge regarding the possible use of atebrin and plasmoquine in the treatment and prophylaxis of malaria. In certain circumstances, as has been shown above, these drugs - representing a notable scientific advance - possess a very special value.
