Reprinted from
The Journal of the National Malaria Society
Vol. III, No. 2, 1944

RECENT RESEARCH IN PROPHYLAXIS AND TREATMENT OF MALARIA*

REPORT FOR 1942-1943

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The war has made it impossible to receive and review as much literature this year as is usually the case. This being an annual report to the National Malaria Society I have selected, chiefly, those relating to the present emergency. There are no doubt many important reports that have not been available and some that are restrictive or secret in character. For the busy civilian physician and field worker I am sure that the Tropical Diseases Bulletin, even during the war, can serve them well with their concise abstracts. I shall make this report as brief a collection of abstracts as possible from the material at hand.

White (1) in his review, states that the treatment of malaria is a subject of perennial interest and this in itself is an indication that finality has not yet been reached. The relative value of antimalarial drugs in difficult circumstances and the manner in which they can best be employed are matters of outstanding importance at the present time. Java, which produced nine-tenths of the quinine in the world's markets, is in enemy hands. It is interesting to reflect how serious the situation might have been had Japan's aggressive designs been accomplished before Germany's pioneer research work had given us atebrin. He continues by directing our attention to the fact that there is not even uniformity of opinion regarding the manner in which quinine, the oldest and best tried remedy of all, should be administered and still less uniformity of opinion regarding the merits and demerits of the different remedies in the treatment of the acute attack of malaria and in clinical prophylaxis. He attributes some of this unsettled state of mind to the different degrees of malarial endemicity, difference in strains of the malaria parasites and to the different races of mankind. None of the specifics are capable of procuring *therapia sterilisans magna.*

Editorial (2): For a number of years the average consumption of quinine in India has been about 200,000 pounds annually. This is far below real requirements which can be placed, on a conservative estimate, at a million pounds. India supplies 70,000 pounds and imports 130,000 pounds. The present emergency forces the

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*Partial Report of the Committee on Medical Research, National Malaria Society. Presented at the 1943 Meeting of the Society in conjunction with the Southern Medical Association, at Cincinnati.

serious consideration of the League of Nations advice regarding the short course of treatment and permit the patient's immunity full play.

Christopher (3) covered the field of cinchona derivatives and the synthetic drugs. He opposed the intramuscular injection of quinine, the intramuscular injection of atebrin was not so harmful. He feels that in atebrin (mepacrine) we have the only substitute for quinine.

Yorke (4) advocates the conservation of quinine stocks by its economic and efficient use in the treatment of malaria. He believes that nothing is gained by giving more than 20-30 grains of quinine a day in the acute stage. The treatment in use in Liverpool consists of the administration of 30 grains of quinine in solution by mouth, daily for 4 consecutive days and thereafter 20 grains every Saturday and Sunday for 8 weeks, or longer should a relapse occur. If the shortage of quinine stock should become severe the drug should be saved for those acute cases occurring in the unacclimated population.

Yorke (5) prefers quinine therapy but states that atebrin (mepacrine) may be substituted in doses of 0.1 gm. thrice daily for seven days, followed by 0.2 gm. on Saturdays and Sundays for 8 weeks, and preceded, in severe cases, by injections of quinine. During the war it is important to conserve quinine. Mepacrine (atebrin) should be used whenever possible.

Nicol and Shute (6) stress economy in the use of quinine. The amount of quinine necessary for cure varies according to the species of malaria. For *P. vivax* a single dose of five grains will abort an attack, and five grains once daily for 15 days will effect a cure of the febrile attack. Larger doses or extended treatment will not prevent relapses and this applies to patients bitten once by a single infected mosquito or by 100 infected mosquitoes daily for a week. In relapses even smaller quantities will suffice for a cure.

This experience was gained by the use of more than six strains of *P. vivax*. *P. falciparum* infections require 10 grains daily for 10 days, and this dosage is adequate for mixed infections. The so-called anti-relapse treatment is useless. Quinine should not be given after the cure of the first infection until relapse occurs, and then only when the diagnosis has been confirmed by blood examination. These men have had long experience with induced as well as naturally acquired malaria.

Covell (7) calls attention to the necessity of effecting an immediate reduction in the consumption of antimalarial drugs either by modifying our schemes of treatment or by increasing our efforts to reduce the incidence of the disease. It has come to be recognized that massive doses of anti-malarial drugs or the use of them over

long periods of time is not necessary. Relapse is independent of the dosage or duration of treatment. Short courses of treatment, frequently of only a week or even less in length, have therefore become the rule. The use of anti-malarial drugs over long periods when the infection is latent is not merely useless, but may retard the development of the defensive mechanism of the patient, without which the parasite cannot be eradicated from the body. The Fourth General Report of the Malaria Commission of the League of Nations (1937) presents the details regarding modern treatment. There are difficulties in framing a standard scheme of treatment appropriate for all circumstances. Different species of malaria parasites vary in their reaction to treatment and tendency to relapse and different local strains of each parasite show wide variations in this respect. There is a racial difference and people from non-malarial areas differ from those who have lived all of their lives in areas of high endemicity. The treatment offered by the League of Nations Commission was framed with considerable elasticity. The routine is quinine 15 to 20 grains, or atebrin 0.3 gramme, for 5 to 7 days followed in each case by 0.02 gramme plasmoquine daily for 5 days. No drug known, at present, destroys the sporozoits injected by the mosquito, and therefore no drug prevents malarial infection. Quinine or atebrin cut short a clinical attack and destroy the trophozoite stage of the parasite in most instances. No intensification of dosage or length of treatment will effect the radical cure of more than a certain percentage of infections. Plasmochin has no effect on the clinical attack but may reduce the percentage of relapses and may reduce the chances of mosquito infection. The physician's object is rather to tide the patient over the attack. The basic objects of treatment should be the prevention of death and the maintenance of malarious populations in a condition which will enable them to carry on their daily work. As a general guide, it is suggested that routine treatment should be limited to 15 grains quinine or 0.3 gramme atebrin, daily for not more than 5 days provided that clinical symptoms have by that time subsided. This may be followed by 0.02 gramme plasmochin daily for 5 days if available. Since supplies of anti-malarial drugs are at the present time strictly limited, rigid economy in the consumption of such drugs is essential.

Bryant (8) reports his experience with atebrin in the Sudan where *P. falciparum* infections were common and severe. He found that atebrin in doses of 0.3 gm. a day did not control severe malaria and that the drug combined with plasmoquine produced nausea and colic or vomiting. The combined use of atebrin and quinine made his patients feel exceedingly ill. He now uses atebrin in much larger doses than those usually recommended. He found that 0.6

or even 0.9 gm. a day produces no ill effects if plenty of hot, very sweet tea or sugar in some other form is taken. He feels that the parasiticidal action of atebrin is not marked until the renal threshold of the drug has been reached; when the urine becomes bright yellow the temperature falls and improvement in the patient's condition is immediate.

Treatment of a severe case: Atebrin musonate 0.3 gm. is given intramuscularly and 0.3 gm. atebrin by mouth on the first day. If the drug is vomited the injection is repeated after 3 hours. In serious cases a third dose of 0.3 gm. may be given, 0.9 gm. in all on the first day. On the second day 0.6 gm. is given in two doses and if nausea permits an injection of atebrin musonate replaces the first dose. Thus, during the first two days from 1.2 to 1.5 gm. of atebrin are given. Thereafter three tablets (each of 0.1 gm.) a day, in one dose after breakfast, are taken until 24 tablets in all have been given. Many people cannot tolerate more than 20 tablets. This course of atebrin is followed after an interval of four days by quinine, 15 grains a day for four days. After another four-day interval two tablets of plasmoquine simplex (each of 0.01 gm.) three times a day for three or four days, if tolerated, complete the specific treatment.

A constant bitter taste in the mouth and some depression were the only toxic symptoms produced by these large doses of atebrin. Nausea indicates the necessity for terminating treatment or reducing the dose of atebrin towards the end of the course. Plenty of sugar prevents toxic symptoms. Splenomegaly and relapse are uncommon after this treatment.

Self-treatment by laymen in remote stations is encouraged and for this purpose a sheet of instructions is issued.

Meythaler (9) gives his experience on a large scale under war conditions and presumably of restricted quinine supplies. All cases given his method of treatment had to meet the following conditions:

(1) The treatment must be started within two days of the onset.
(2) The infection must be known to be due to a strain of low virulence.
(3) The parasites must be relatively few in number.
(4) The patient must be kept under close observation because of the possibility of a poor response or the development of a more severe type than at first believed.

Atebrin (mepacrine) was given three times a day for seven days in doses of 0.1 gramme each; two days' rest from drugs is allowed and then plasmoquine (pamaquin) is given thrice daily after food, for 3 days, in doses of 0.01 gramme each. For the more se-

vere cases the dose of atebrin was doubled till the temperature became normal. In some, atebrin musonate was given by the intramuscular route in daily doses of 0.3 gramme dissolved in 10 cc. distilled water till the temperature fell to normal. A very severe case on arrival was given 0.3 gramme atebrin musonate by the intramuscular route at once; repeat the dose in ten hours and then continue the injections in fractional doses to the equivalent of 0.3 gramme twice daily until the temperature remains normal.

In 1,500 intravenous injections no serious trouble was experienced and some German clinicians prefer to give intravenous injections for the first few days in all cases of subtertian infection. Meythaler prefers the intramuscular route. The author claims that the relapse rate in benign tertian infections did not exceed 20 per cent. He attributed many of these to insufficient treatment. The author regards atebrin as a perfectly safe drug with practically no contraindications.

Dove (10) is of the opinion that treatment should be determined solely by the symptomatic indications presented and not by the form of malaria. The minimum treatment prescribed for a case of malaria lasts about four weeks and consists of:

1. Atebrin, grains 1½, three times a day, during the febrile period and 4 days thereafter.
2. Quinine, grains 5, four times a day for 7 days.
3. Atebrin, grains 1½, three times daily for 5 days.
4. Quinine, grains 5, three times daily for 5 days.
5. Quinine, grains 5, and plasmoquine grains one-sixth, three times daily for 5 days.

In chronic, frequently relapsing cases the periods 3, 4 and 5 of the treatment are repeated after a ten days' interval. The author never saw a case intolerant of atebrin though quinine idiosyncrasy did occur in some cases. He does not approve of intramuscular or intravenous methods of treatment.

Norman White (Trop. Dis. Bull. Vol. 39, No. 12, page 806) in discussing atebrin feels that we have ample justification for the use of atebrin daily, in a dose not exceeding 0.1 gm., to all susceptible troops exposed to the stress and strain of war in countries where subtertian malaria is prevalent. This method seems desirable over quinine for military needs.

Hill (11) recalls the difficulty in the last war due to subtertian malaria and expressed the opinion that with the aid of the synthetic drugs and quinine it should be possible to improve on the results obtained. He considers under-treatment as the greatest fault. He recommends for the treatment of the acute attack 0.1 gm. of atebrin and 10 grains of quinine three times a day for 7 days. No toxic

signs or symptoms have been noted in 200 cases so treated. In severe cases these doses can be increased with advantage. During the next two days 10 grains of quinine hydrochloride are given three times a day. During the following 5 days 0.01 gm. of plasmoquine and 10 grains of quinine hydrochloride are given three times a day. The plasmoquine part of the treatment might be considered optional, perhaps, for cases treated in the field, but should be compulsory in the hospital. Intravenous treatment is essential at times if lives are to be saved. For anti-relapse treatment for those undergoing excessive strain, it is preferable to give one tablet, 0.1 gm. of atebrin every day. Prolonged trial shows its harmlessness. Yellowing of the skin is of no consequence with troops at war. Statements regarding the toxicity of atebrin have been much exaggerated. Manson-Bahr in discussing Hill's report states that he does not consider the intravenous or intramuscular administration of atebrin as effective as quinine administered in like manner. He also feels that intramuscular injections of quinine can be of very great value. He agreed with Hill that relapses do not occur in persons with atebrin-tinted skins.

Hughes (12) believes that the vast majority of clinical attacks of malaria in adult natives of hyperendemic areas requires no quinine or other specific treatment. The disease runs a mild course and terminates naturally. Europeans in such hyperendemic areas are exposed to very great danger and prophylactic measures with quinine or atebrin should be used. In the treatment of attacks of malaria 30 grains a day are given during the acute stage, and a maintenance dose of about 5 grains a day. Injections of quinine are frequently required and intramuscular injections have advantages. There is no empirical finding to show that intravenous injections are superior to intramuscular injections. In comatose cases the intramuscular injection of quinine together with the intravenous injection of saline and glucose is remarkably successful. In all fever cases treatment should be given promptly. When the European leaves the hyperendemic zone treatment is advisable. For this the author recommends a course of atebrin and quinine to be started 10 days after departure: 2 tablets (each of 0.1 gm.) of atebrin and 2 five grain tablets of quinine daily for 7 days.

Smith (13) relates an experience with malaria on a Cruiser at war. During April and May of 1941 the personnel of a Cruiser, consisting of some 620 officers and men, were subjected nightly to the attacks of anopheline mosquitoes at the height of a malaria season. Experience taught him that it is dangerous to withhold specific treatment until the diagnosis has been confirmed by the microscope. No prophylactic use of quinine or atebrin had been in

use. They developed 159 cases of acute malaria with two fatal cases. No doubt the difficulties were extreme in the management of such an epidemic on board a Cruiser engaged in active war service.

Weed (14) in his discussion of antimalarial drugs refers to the U. S. P. Totaquine now in use: a mixture of alkaloids from the bark of Cinchona succirubra Pavon and other suitable species of Cinchona. It contains not less than 7 per cent and not more than 12 per cent of anhydrous quinine, and a total of not less than 70 per cent and not more than 80 per cent of the anhydrous crystallizable Cinchona alkaloids, the designation *crystallizable alkaloids* referring to cinchonidine, cinchonine, quinidine and quinine. It is recommended the dose be 10 grains three times a day for seven days. He refers also to the therapy routines recommended by the Subcommittee on Tropical Diseases of the National Research Council:

1. Combined Q. A. P. treatment (method of choice):
   (a) Totaquine or quinine sulphate, 10 grains thrice daily after food for 2 or 3 days or until the fever is controlled.
   (b) Atebrin 0.1 gm. thrice daily after meals for the next five days.
   (c) Two days without treatment.
   (d) Plasmoquine 0.01 gm. thrice daily after meals for five days.
2. Atabrine-Plasmoquine Treatment:

Atabrine 0.1 gm. thrice a day after meals for 7 days, then two days' rest followed by 5 days of plasmoquine 0.01 gm. thrice daily after meals.

3. Totaquine or Quinine-Plasmoquine Treatment:

If no atebrin is available give totaquine or quinine as indicated in above for 7 days and during the last two days associate each dose of totaquine or quinine with plasmoquine 0.01 gm. thrice daily.

4. Suppressive Treatment:

Atebrin 0.1 gm. twice daily after food twice a week. Allow two or three days' interval between days of medication. It is recommended that pending more experience atebrin should only be given under the guidance of a physician or public health officer.

Kikuth (15) summarizes the use of atebrin and plasmoquine. Atebrin acts on the asexual forms of all the malaria parasites, but as a casual prophylactic it is just as inactive as quinine. Plasmoquine proved to be an anti-malarial substance of quite a new kind, in that it destroyed the crescents in malignant tertian malaria. It also exhibited another property, in that it lessened the relapse rate

in simple tertian malaria. . . . Unfortunately, however, large doses of plasmoquine are not entirely harmless. Notwithstanding its prophylactic action, casual prophylaxis is still impossible.

Hasselmann (16) described three cases of malaria in the Philippines who were given 0.6 gm. of atebrin during two days and then 0.03 gm. plasmoquine daily for 5 days, most of the doses being given intramuscularly, and who later relapsed with subtertian malaria, although they had remained in a malaria-free district. These cases illustrate the fact that plasmoquine may fail to prevent relapse. In Hasselmann's opinion quinine cannot be replaced by synthetic antimalarial compounds in the tropics. Peter (F. M.) criticizes the treatment as used by Hasselmann and disagrees with his conclusions. (Trop. Dis. Bull. Vol. 40, No. 1, p. 13).

Gamefar (17) is apparently the Italian synthetic product corresponding to plasmoquine and Italchina the Italian substitute for atebrin. The results of experience with these drugs are comparable with those usually expected with plasmoquine and atebrin.

Videla (18) refers to the Ascoli treatment of the chronic malarial spleen and suggests the following method which he has found successful. After quinine treatment, or in the period of full apyrexia, intravenous injections of 10 per cent solution of calcium chloride, in doses of 10 cc., are given daily or on alternate days to a total of 5 injections. Contraction of the spleen is observed within one-half hour of the injection and increases up to 1 hour, but the contraction passes off partially, leaving, at the end of two hours, the spleen permanently reduced to an appreciable extent and splenic pain disappears. These reductions are held to be due to augmentation of splenic tone due to the vaso-constriction induced by the drug.

Schoenback and Spingara (19) report two cases of malaria in drug addicts (heroin) in which the malaria was acquired by the intravenous injection of the drug by means of primitive apparatus shared by a number of addicts without any attempt at disinfection of any kind before or after use. In these cases an eye-dropper with a rubber nipple and a hypodermic needle were used.

A decade before the war the Malaria Commission of the League of Nations recommended the short courses of treatment for those who live in endemic regions. Such considerations were applicable for the most part only to civilians engaged in peace-time pursuits. In this war other considerations predominate. The Army is made up chiefly of young susceptible individuals exposed to the stress and strain of a tropical climate.

It is interesting to note seven of the abstracts in this report all consider atabrine as a safe drug under ordinary dosage yet most all

of them report the toxicity of plasmoquin if given for more than three days in ordinary dosage.

Our personal experience with plasmoquine in doses of 0.01 gram three times a day for 5 days is that one out of 10 will suffer from the toxic effects of the drug. We do not use the drug in the field any more because of this difficulty and also because we do not see that we have gained any benefit from its use as a gametocide nor as assistance in preventing relapses in the field. This may not conform to hospital experience where the drug can be under the control of a good staff of doctors and nurses.

The Chagres River villages (20) of our Santa Rosa Malaria Station have been on bimonthly thick blood film surveys followed by treatment of all found positive for parasites. An inspection trip was made each month between surveys and blood films taken from any who claimed to be sick. These were treated for malaria if parasites were found.

Half of the group in the villages was treated with atabrine (American product) 0.1 gm. three times a day for five days. The other half was treated with quinine sulphate tablets, 18 grains a day for five days. Since we use 3 grain tablets for children, it was easier to double the dose for adults, therefore 18 grains rather than 15 grains a day were given. The atabrine tablets were always broken, at least into two pieces, before administration to insure disintegration. No plasmoquin was used in either group.

The control village situated on a similar arm of Gatun Lake was permitted to use either atabrine or quinine if they cared to use treatment voluntarily but they had to call on some official to see whether they were on the positive list for malaria following each survey. Some of them really treated themselves.

The average bimonthly parasite rates were as follows: Quinine group, 8.9 per cent; atabrine group, 10.9 per cent; control group, 25.6 per cent. The cumulative rates for the year's surveys were respectively 20.9, 30.5 and 45.7 per cent. The relapse rate was lower than usual this year and there was no death due to malaria in any group. No babies from birth to twelve months of age were found positive in the treated groups but 5 out of 14 such babies in the control group were found positive for malaria. It should be stated that the entire isthmian area, whether in controlled regions or not, has shown an unusual decline in malaria since March, 1943 to date (September 1943). Even the hospitals of the area failed to note any increase in malaria in June and July as is usually the case during those months. The concensus of opinion based on the scientific visitors to our region and on the literature received indicates quinine is still the drug of choice if available, atabrine next and totaquine

(U. S. P.) for the less important services. Opinion is divided about the use of plasmoquin but all admit the danger attending its use in the field and nearly all agree that atabrine, in ordinary dosage for treatment or prophylaxis, is harmless.

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