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REVIEW OF RECENT RESEARCH ON
DRUG PROPHYLAXIS AND TREAT-
MENT OF MALARIA*

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This review was prepared as a report to the Sub-Committee on Medical Research and the period covered is from September 3, 1939, to September, 1940. It includes only the examination of the literature available in Panama and contacts with local workers and visiting scientists. Representative reports from various parts of the world have been selected and only those drugs are discussed which show some promise of availability at a reasonable cost.

This year's survey continues to indicate that the popular drugs are quinine, atabrine and plasmochin.

Castellani¹ adds a report on the prophylactic use of quinine in the Italian forces during the Ethiopian campaign. The total force numbered 500,000. Throughout the war there were but 1,241 hospital admissions for primary malaria and 1,093 for relapses. He attributes this low incidence to the use of prophylactic quinine which was rigidly enforced. Each man received 0.6 gram (3 tablets) of quinine bihydrochloride or sulphate each day.

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Pansini² reports on 7,400 Italians invalidated from East Africa to an institutional center in Italy. These patients were received in a period of thirteen and a half months and 3,500 of them had malaria. Attacks occurred in spite of prolonged quinine prophylaxis. *P. vivax* was more commonly observed than *P. falciparum* in the proportion of four or five to one. Most of the patients were discharged after an average stay of 3 months fit for work, but a reduction of the enlarged spleens to normal proportions rarely occurred.

Boyd and Kitchen³ recorded observations on some patients in the Florida State Hospital undergoing malaria therapy. They studied the effect of small amounts of quinine administered on a single day on the subsequent course of infections with *P. vivax* and *P. falciparum*. A single dose of 20 grains of quinine had very little effect on the strains of *falciparum*. A dose of 11 grains or more suppressed paroxysms and induced periods of clinical quiescence, of varying duration, in the large majority of *vivax* cases. A declining trend in parasite density which lasted several days was also noted. Nothing comparable in *falciparum* infections was noted even after a dose of 20 grains.

Teichler⁴ used atabrine prophylactically on 500 natives of East Africa, in a highly malarial district, with atabrine for 3 days, one tablet of 0.1 gram three times a day. On inspection the following week he found that 10 complained of fever, 4 of headache, 1 of giddiness and 1 of weakness. He considers that by giving such short courses he can maintain the health of the labor force.

Kostic and Antic⁵ report the prophylactic use of atabrine in an endemic malaria region in Jugoslavia on 240 prisoners and warders kept under strict surveillance. The observations were made over the whole malaria season, May to October. The people were divided into two groups, of which 86 untreated persons acted as

controls, and 154 people were treated. The ages were all between 21 and 60 years. The drug was given in 0.4 gram doses per week, half of the total being administered on two successive days. At the start of the experiment the percentage showing parasites in the blood was 7.5 and at the end it fell to 0.8 per cent in treated cases. Amongst the controls the percentage of infected cases was fairly constant and rose to 46.7 per cent in August. There were no ill-effects from the use of the drug and all treated cases were able to continue at work.

Canet⁶ believes that synthetic remedies are undoubtedly more effective than quinine. A serious outbreak can be suppressed almost immediately by the administration to a village population of "quinacrine," 0.30 gram a day (adult dose) for three to five days. The working capacity of a labor force can thus be quickly regained, but after a few weeks conditions relapse to their former severity in the absence of a follow-up treatment. In general, administration once a week was found necessary and sufficient. His experience did not show that the association of a gametocide with "quinacrine" served any useful purpose.

Casini⁷ reports three years of experience in Sardinia. His general conclusions are that by atabrine or quinine prophylaxis, especially if this be continued through the inter-epidemic period, accompanied by prompt treatment of all febrile attacks, it is possible to reduce malaria symptoms, spleen rates and parasite rates, and to effect a marked improvement in the health of a population, but it is not possible by these means to eradicate malaria.

Clark, Komp and Jobbins⁸ report the tenth year's experiment in drug control among six Chagres River villages. About half of the people were treated with quinine-plasmochin and the other half with atabrine-plasmochin. Quinine sulphate tablets, 15 grains a day, were given for a period of five days. Atabrine tab-

lets 0.1 gram, three times a day, were administered over a period of five days. In each group, after these courses were given, plasmochin 0.01 gram twice a day for five days was administered.

Monthly thick blood film surveys were used to measure the results and discover those who required treatment. The average monthly parasite rate for the atabrine-plasmochin group was 11.5 per cent and for the quinine-plasmochin group 12.7 per cent. The cumulative parasite rate over a period of 12 months was 55.5 per cent and 57.3 per cent, respectively.

Madden Dam Highway people (control) averaged 32.7 on four surveys while Rio Pescado, a control group, on a similar arm of Gatun Lake to that occupied by the experimental villages, was 65.1 per cent.

The atabrine-plasmochin group was visited by a member of the staff once a week, while the quinine-plasmochin group received but one visit by a staff member. Both places were well attended by native girls and the native river supervisor and boatman.

The cumulative result of 12 consecutive monthly blood film surveys shows that more than half of the two groups were positive for malaria at some time during the year. The relative incidence of new infections, and relapses, is still a debated question. Three facts support the opinion of these workers that most of the positive cases of malaria were due to relapse rather than new infections: (1) the infant rate for the year for initial infections was 2.5 per cent. (2) During the year, the parasite rate in the children (15 years and under) and in adults were almost equal in the drug controlled towns, while in uncontrolled rural villages in endemic centers the children's rate is, usually, almost double that of the adults. (3) Most of the positive blood films were obtained from the same individuals living with the same family and sleeping in the same house. Such individuals perpetuate the disease in their locality and repeated treatment seems

never to eradicate the infection, although good clinical results are obtained. The species of malaria parasites found were *P. falciparum*, 72 per cent; *P. vivax*, 22 per cent; *P. malariae*, 6 per cent.

No deaths due to malaria occurred during the year. Ten years of experience in these towns leaves them with the impression that the drug control method cannot eradicate parasites in all cases and that epidemics cannot be prevented if circumstances occur that produce abundant anopheline mosquitoes. These methods have been successful in keeping the inhabitants fit for duty and in reducing clinical cases of malaria to a very low incidence. They are of the opinion that quinine and atabrine are of equal therapeutic value as antimalaria drugs. Their people prefer atabrine but quinine is much less expensive. They do not believe that plasmochin simplex has played a very important role in reducing transmission and preventing epidemics. They conclude that non-medical personnel can carry out reasonably good drug control measures, without the blood film surveys, if the personnel can be supervised by a qualified physician who is interested in tropical and industrial medicine. Weekly visits by a physician make it possible to recognize and correct the management of other infectious diseases before they spread in an epidemic fashion. Drug control is advised only for the temporary locations of labor camps and small villages where standard methods of malaria control of a permanent nature cannot be established. Expenditures incident to such drug control programs are economically justifiable, and will result in an increased labor efficiency commensurable with the financial outlay required.

Rashina⁹ gives his experience in an attempt to control malaria in a town of 2,000 located near breeding places of a very active vector. At the start of his work the parasitic, splenic and endemic indices were 44.4, 44.7 and 63.7, re-

spectively. All persons found harboring malaria were treated. In the spring all of those who had suffered from malaria in the previous year were treated ("acriquine" 0.1 gram three times a day for five days, with plasmocide 0.03 gram twice a day on the first and third day of treatment). All acute cases were treated in the same way. During the transmission season all persons who had had malaria were given plasmocide 0.03 gram twice a day on the first and fourth day of six-day cycles. The total number of malaria cases in the three years (primary cases, reinfections and relapses) were 661, 438, 233 respectively. Infants under 2 years of age showed a rate for 3 years of 50.4, 17.4 and 4.3 respectively. He concludes, nevertheless, that in view of the location with regard to the mosquito breeding areas that complete control will necessitate the adoption of anti-mosquito measures in addition to the drug treatment.

Malycheva¹⁰ treated two groups of patients with "acriquine." One group was given 0.15 gram twice a day for seven days. The second group used the same doses, but they were given for five days, then an interval of rest for 10 days was followed with the same medication for 3 days, followed again by an interval of 10 days' rest, after which the 3 days' treatment was repeated: eleven days' treatment, in all, over a period of a month. The first group contained 168 patients and the second group 141 patients. The frequency of early relapses was almost the same in the two groups, 33.6 and 35.5 per cent respectively.

Dupoux¹¹ *et al.* report the use of "premaline" in Tunis. They gave the drug twice each month from June 1 to November 1. Those found with parasites were given curative treatment with "premaline." Prophylactic treatment was given to 27,126 in 1937 and to 26,906 in 1938. No anti-mosquito measures were undertaken. At the start of their work the parasite index for children was 21.9 per cent, for adults 17.6 per cent.

At the end of the first year's trial these rates were 3.5 and 2.5 per cent. Patients treated with "premaline" and subsequently submitted to a bi-monthly administration of the drug suffered no relapses.

Niven¹² treated 80 cases with "prontosil" and 68 cases with quinine bihydrochloride. He decided that "prontosil" had some lethal action on plasmodia, but that it was much less efficient than quinine.

Chopra and Basu¹³ fed 511 laboratory-bred *A. stephensi* on five crescent carriers before and after the administration of "prontosil" in various doses. As large a dose as 40 tablets failed to devitalize the crescents which developed to the sporozoite stage in a considerable proportion of the mosquitoes.

Menk and Mohr¹⁴ studied the action of "prontosil rubrum" and "prontosil soluble" in 3 cases of benign malaria and 7 cases of malignant tertian infections. The first drug was given by mouth and the second one by injection. The results with both drugs were unsatisfactory. They state, however, that these results should not interfere with further research on the action of sulphonamide bodies in malaria and that possibly they might be found to have an action on the cycle of the malarial parasite in the reticulo-endothelial cells.

Chopra and Basu¹⁵ report an experiment in which large numbers of *A. stephensi* were fed on three gamete carriers of *P. falciparum* before and after treatment with "cilional." A five days' treatment consisting of "cilional" 0.02 gram with atabrine 0.1 gram three times a day did not prevent the development of the parasites in the mosquitoes.

Marotta¹⁶ concludes after his study of 24 hospital patients under treatment for malaria that adrenalin is without action on the manifestations of malaria, that it does not shorten the disease and does not reinforce the action of qui-

nine. It does not prevent relapses. Intravenous injections produce a contraction of the spleen which lasts from 3 to 4 minutes. No evidence was noted that adrenalin improved the blood or the patient's general condition.

Sinton¹⁷ *et al.* report on "proseptasine," a benzyl derivative of sulfanilamide. In order to learn whether such malaria prophylactic properties as the drug might possess were causal (operative against sporozoites and intermediate forms between sporozoites and trophozoites) the drug was not continued later than the day following the application of infected mosquitoes to the patient. A Rumanian strain of *P. falciparum* was employed. From 15 to 20 infected *A. maculipennis* var. *atroparvus* were applied to each of 8 patients. Three patients each received 7.5 grams of the drug during the 24 hours before infecting bites and an additional 4.5 grams during the subsequent 8 hours. One of these 3 persons was positive on the twelfth day after the bites. An untreated control developed an attack on the eleventh day after the bites. Two patients received 12 grams of the drug during the 24 hours before the infecting bite and an additional 15 grams during the subsequent 32 hours. One of these patients developed fever and parasites 22 days after the infecting bite.

Three patients received 3 grams of the drug three times at four hourly intervals. One was bitten by infected mosquitoes immediately after the last dose, the second 24 hours later, the third 48 hours after the last dose. The first and last of these patients developed acute attacks of malaria after incubation periods of 15 and 16 days respectively. Thus of the 8 patients 5 showed no clinical or parasitologic signs of infection, though they had been under close observation from 4 to 5 months. "Proseptasine" appears to have a true causal prophylactic action against the strain in use of *P. falciparum*. In view of the precautions necessary in the use of sulphon-

amide compounds and the short duration of the prophylactic action observed, the observations have a very limited practical application.

DeCourt,¹⁸ in discussing the pharmacodynamic bases of antiplasmodial measures, recognizes that they possess in varying degrees schizonticidal, gametocidal and anti-sporogenic activities. In addition to these he describes a dysgonic action, a conception that is both parasitologic and clinical. Under the influence of this action schizonts lose almost entirely their power of asexual reproduction and gamete formation. From the clinical point of view, this action is manifested by the absence of morbid phenomena in spite of the presence of schizonts, sometimes numerous, in the blood. His article deals with "quinacrine." The mere presence of this drug in the blood is insufficient to explain dysgonic action. A very small dose given daily is much less potent in this respect than the optimum dose given at much longer intervals, although the total amount of the drug given by the former method may be greater. Thus a dose of 0.1 gram given on 3 or 4 days in the week is less effective than one of 0.3 gram given three times a month. The duration of this dysgonic action is not appreciably prolonged by increasing the optimum dose, even by large amounts. No relationship seems to exist between the curve of dysgonic action and that of the concentration of the drug in the blood or tissues.

Nikolajev¹⁹ records the results of seven years' observations in Leningrad on 11,347 cases of naturally acquired malaria and 200 cases of experimental benign tertian malaria transmitted by mosquitoes. The patients were living in conditions which precluded a chance of reinfection.

The naturally acquired infections were listed as *P. vivax*, 9,464; *P. falciparum*, 719; *P. malariae*, 310. He states that the duration of malaria infections is limited:

P. vivax infections 27 months.

P. falciparum infections 20 months.

P. malariae infections sometimes persist for 3 to 4 years.

He thinks there is no reason to believe that the first two species can survive in the human host for indefinite periods. His experience with induced malaria leads him to conclude that prevalent ideas regarding the influence of season on the course of malaria infections is without foundation.

Gardner and Dexter²⁰ report the case of a woman aged 30 who had never had malaria nor lived in a malarious locality. This patient had a cold abscess incised and to combat postoperative weakness she was given two transfusions of 600 c. c. of whole blood. A month after the first transfusion she had an attack of clinical malaria with quartan parasites in the blood films. The donor of the first transfusion had had quartan malaria 17 years previously while with the Italian Army in Albania. He then returned to the United States and has never made trips farther South than Washington and Baltimore. He had not had attacks of fever for 17 years and no parasites were found in his blood when he was used as a donor. In spite of this the authors believe that the donor gave the patient malaria. The patient recovered under treatment with sulfanilamide, 3.6 grams a day, for 17 days.

Lesné²¹ *et al.* report the case of a 7-months-old infant ill with pneumonia who received an intramuscular injection of its father's blood as a part of its course of treatment. Two months later the child developed quartan malaria. The infant had never been outside of Paris. The father had left the Cameroons 13 years previously. He had suffered from fevers while in the Cameroons. He had had no fever since he returned to France 13 years ago and examination of his blood revealed no parasites.

Most²² reports he had the opportunity, in a period of six years, to observe well over two hundred heroin addicts suffering from *falciparum* malaria contracted as a result of the common use of the hypodermic syringe for intravenous administration of the drug. He speaks of it as an endemic disease in drug addicts of the New York metropolitan area.

Hutton and Shute²³ warn the physician of the risk of transmitting malaria by blood transfusions. Their experience, based chiefly on malaria induced by infected mosquitoes, is as follows:

P. vivax may persist in the blood for 18 months after the primary infection.

P. falciparum will persist for at least 12 months.

P. malariae may persist for many years.

Latent cases of malaria cannot be diagnosed with certainty by any known method. Persons in good health may harbour parasites in sufficient quantity to transmit malaria if they serve as donors for blood transfusions. Keeping a donor's blood for days, or even weeks, at low temperatures will not destroy the plasmodia it may contain. Persons who have lived in places where malaria is endemic should not be used as donors if others are available.

Accinelli Fernandez²⁴ says that in the agricultural lowlands of Peru malaria is a serious labor problem and that malaria under such circumstances should be considered an occupational hazard. He urges the importance of including it in the list of professional diseases in the Workmen's Compensation Acts.

Sinton²⁵ has expressed himself on general principles regarding the treatment of malaria in different conditions:

"When infections are contracted by individuals resident under conditions in which the chances of reinfection, except at comparatively long intervals, are slight,

the treatment of choice is one which produces a *radical cure* of the infection at the earliest possible moment.

"When individuals are resident under conditions where they are exposed to frequent and constant risk of infection, reinfection and superinfection, the object of treatment should be the rapid production of a *clinical cure* of each attack, and *not* a radical cure of the infection.

"When individuals are exposed only temporarily to chances of frequent infection and superinfection, then *clinical prophylaxis* of the disease with an appropriate drug is the treatment of choice."

This seems to the reviewer to be very sound advice.

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