

REVIEW OF RECENT RESEARCH ON MEDICAL PROPHYLAXIS AND TREATMENT OF MALARIA*

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This is a member's report to the Chairman of the Subcommittee on Medical Research of the National Malaria Committee. As is always the case each year, there is so great a volume of published reports that it is impossible to mention them all in this review. I, therefore, exercise the privilege of selecting a few of the available representative reports from different nations where malaria is a great problem. Any member desiring more information can find the large majority of the important reports for the year in the records of the League of Nations Malaria Commission and in the *Tropical Diseases Bulletin*.

Quinine is still our chief drug for malaria due to supply, cost and safety of administration in the field. I shall give it only brief space because I feel sure the Committee desires reference to the synthetic drugs and other new features presented during the year. It is interesting to note that five reports¹ are on record concerning information on the cultivation of cinchona by the East African Agricultural Station of Amani, Tanganyika Territory.

Sinton,² writing on the standardization of mixed preparations of the cinchona alkaloids in relation to Indian conditions, claims that such preparations seem eminently suitable for mass treatment among malarious populations who cannot afford more expensive

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drugs and who cannot easily obtain medical advice. Dunn³ considers quinine the only safe remedy for the mass treatment of malaria. Quinine combined with plasmochin in non-toxic doses for short periods is, however, recommended with a view to reducing the relapse rate and attacking the sexual phase of the parasite of malignant tertian fever when it is present. Dunn gives 22½ grains of quinine daily for seven days. "Atebrin" is considered unsuitable for mass distribution.

Fabry⁵ considers that quinine and "atebrin" have equal value in the treatment of an acute attack of benign tertian malaria infection, but in severe malignant tertian infections, such as are met with in Indo-China, "atebrin" is definitely superior to quinine. The human organism itself and time are the most important factors in recovery and every care should be taken not to damage the former.

Wallace,⁶ in a Malayan report, used mass treatment with "atebrin" as the sole measure of malaria control employed since 1933. For five successive days 2 tablets of "atebrin" were given at the morning muster to each adult. In the afternoon, one more tablet of "atebrin" and one tablet of plasmochin simplex (0.01 gram) were given. One tablet of plasmochin simplex was given alone on the sixth and the seventh days. After this initial intensive treatment a "follow-up" treatment of a weekly dose of three or four tablets of "atebrin" on one or on two days a week was started. This was continued for as long as four months. The rate was practically nil. Many thousands of coolies were treated and no serious toxic effects were noted.

Ziemann,⁷ in discussing war malaria and its results, recommends "atebrin" either 0.05 gram daily or 0.2 gram twice weekly. For permanently clearing a malarial area 0.02 gram plasmochin twice weekly is recommended to prevent development of gametes in the mosquito. Bispham⁸ will read before our society this fall (1937) his final report on the use of "atebrin" in the prophylaxis and treatment of malaria. His investigations were carried out among civilian conservation corps enrollees in the Fourth Corps area during the last three years. He believes that "atebrin" has furnished a solution to the problem of prophylaxis and treatment of malaria as far as infection with *P. vivax* is concerned, but it should not be concluded that "atebrin" is put forward

as a drug which eliminates malarial infection as water does fire. He thinks that 90 per cent of the carriers of *P. vivax* can be cleared of all parasites. He feels that his experience has

"clearly proven that when used as a prophylactic, under supervision, men of susceptible age can live and carry on their various occupations in a highly infected area with a minimum of malarial infection and a maximum of effectiveness."

Untoward actions of the drug were almost never encountered and when encountered were of a transient character.

Rao⁹ claims that mass treatment and prophylaxis with "atebrin" gave good results, but the cost of the program made it impossible to carry on.

Ruge¹⁰ regards "atebrin" as a distinct advance over quinine. For successful prophylaxis, it need be given only twice weekly in doses of 0.1 gram. In badly infected areas it may be combined with 0.01 gram plasmochin twice weekly. It is not yet definitely determined that these two drugs are causal prophylactics. The prophylactic treatment should be started one week before entering the malarial area in order that the drug may reach a certain level in the blood, which prevents the sporozoites from entering the reticulo-endothelial system.

Mezincesco¹¹ finds that "atebrin" and quinine act equally well for prophylactic treatment, but there were many relapses and skin staining was a disadvantage when "atebrin" was used. Transmission occurred during the period of prophylactic treatment.

Amy and Boyd¹² made a study of troops in India, the average strength approximating 55,000. A detailed report is given from 1919 to 1935. They recommend the following standard treatment for troops in India: The patient is put to bed and purged with calomel, followed by epsom salts. Quinine is then given until initial febrile paroxysms are controlled. Quinine is then stopped and "atebrin" is given, 0.3 gram a day for 7 days. The patient is then allowed to get up and receive 0.03 gram of plasmochin a day for a further 5 days. They report fewer cases of relapse where this scheme is used.

Van Henkelom¹³ treated 119 cases of acute malaria by intramuscular injections of "atebrin." Another series of 100 cases were given quinine by mouth. The

"atebrin" series lost their fever in 48 hours in 87 per cent of the cases, while those given quinine in 77 per cent of the cases gave the same results. No cases of "atebrin" poisoning were noted.

Chopra¹⁴ experimented on eight monkeys, *Silenus rhesus*, infected with *P. knowlesi*. "Atebrin" was given either intravenously or intramuscularly. The concentration of the drug in the blood and the parasite count were determined half an hour, 2, 6, 24, 48 and 72 hours after the "atebrin" injections. The highest concentration of the drug in the blood was observed within half an hour of its administration. It could not be found in the blood 24 hours after its injection. The parasite count dropped with the fall in the concentration of the drug. The authors conclude that "atebrin" may have a direct lethal action on *P. knowlesi*. Chopra¹⁵ *et alii* report seven cases of malaria in which "atebrin" or plasmochin, or both, did not give results. The cause was believed to be defective absorption. This may be due to heavy hookworm infection or hypochlorhydria, which is associated with dysentery and colitis, or rapid passage through the small intestine in diarrheas and dysentery.

Bercovitz¹⁶ used "atebrin-musonate" in China and reports no toxic symptoms after the injections and the therapeutic results were excellent. Pregnant women and some children were in the treated series. He used quinine and plasmochin following the 2 injections of "atebrin-musonate" to bring back the general tone of the patient, as well as to take care of any stray parasites not killed by the injections.

Sealig and Singh¹⁷ report that the combined "atebrin-musonate" and "atebrin" treatment is the best for the rapid restoration of fitness for military duty. The method used follows: a subcutaneous injection of 0.75 mg. epinephrine followed half an hour later by an intramuscular injection of 0.375 gram "atebrin-musonate." Twenty-four hours later a five-day course of "atebrin" tablets was started, 0.1 gram three times a day.

Dikshit¹⁸ applied pharmacological tests to plasmochin and records the following:

(a) Tests on protozoa and bacteria show that plasmochin is not very toxic to these. Toxicity tests were also made in cats, dogs, rabbits, guinea-pigs and leeches.

(b) Plasmochin has no antipyretic action of its own. In combination with quinine, however, it produces a quicker action than quinine alone.

(c) Plasmochin reduces the blood pressure by acting directly on the heart and, also, by its action on the vasomotor center.

(d) It depresses the respiration and constricts the bronchioles to a slight degree.

(e) Movements of the gastro-intestinal tract are inhibited. Plasmochin produces a fatty degeneration of the liver cells when given in toxic doses.

(f) There is evidence of general depression of the central nervous system and a moderate stimulant action on the uterus.

Rosa and Maccolini¹⁹ employed plasmochin in the prevention of malaria. They report that of all those who took a full course of treatment only 5.5 per cent contracted malaria, while those who took part of the course showed a rate of 17.2 per cent.

Ciunca *et alii*²⁰ report on the devitalizing effect of a single dose of 0.02 gram of plasmochin upon the gametocytes of subtertian malaria. They claim the dose is effective within 48 hours in most cases, but in practice the dose should be given twice weekly. Their series included 14 cases of natural infection, 5 cases infected by mosquitoes and 7 cases by blood inoculated infection. The blood of all patients was still infective for mosquitoes 4 hours after the administration of plasmochin. After 24 hours, 12 cases infected mosquitoes. After 48 hours, 4 cases were infective, but after the third day only 1 case remained infective.

Rosa and Valli²¹ used "atebrin" and plasmochin as prophylactics in malaria. They held the incidence of malaria considerably below that of the previous year, about one-third as much as the year before. Their term "human bonification" implies intensive treatment of persons before the usual annual outbreak of malaria in highly malarious zones.

Mezincesco and Cornelson²² report on the comparative efficacy of "atebrin" and quinine in malaria prophylaxis as follows:

(1) Neither prophylactic treatment with "atebrin" nor with quinine can reduce the number of parasite carriers to zero.

(2) The parasite index was appreciably reduced, whereas in the control group, which received no preventive treatment, the index remained the same.

(3) As a result of the preventive treatment there were practically no clinical cases during the period of actual treatment in spite of the fairly large number of parasite carriers revealed by the periodic blood tests among the population subjected to the experiments.

Ciuca *et alii*²³ state that as regards direct antifebrile action and the time taken to cause the disappearance of the schizonts, there would seem to be little to choose between quinine and "atebrin." In the same report is a section by Parrot and his coworkers, of the Pasteur Institute, Algeria. They feel that quinine deserves to be rehabilitated as regards its action on gametocytes and that any antimalarial drug endowed with "schizonticidal" properties, *ipso facto*, possesses gametocidal properties in regard to sexual forms in process of development. They warn us that for the treatment of malaria patients, as for the protection of uninfected individuals, which necessarily go together in mass clinical prophylaxis, the exclusive and rational use of a good "schizonticide" is sufficient, and it is in any case better than the exclusive use of a good "gametocide."

Mietzsch, Mauss and Hecht²⁴ tell us that "atebrin" in watery solution decomposes by hydrolysis and this is accelerated by heat. By mouth, watery solutions should not be given later than 12 hours after their preparation.

Hecht²⁵ finds by his method that the liver, lungs, kidneys and spleen in this order took up the "atebrin" strongly, then follow the stomach and intestines, heart, pancreas and genital organs. The muscles, skin and central nervous system take it up very slightly.

Bhattacharjee²⁶ reports a single patient with subtertian malaria who became so violent that four men were needed to hold him in bed. He talked nonsense, kept his eyes closed tightly and resented all attempts to open them. His temperature was between 99.4 and 101° F. He improved rapidly on quinine and in about 24 hours his symptoms had disappeared.

Kang and Garvis²⁷ report a case in which maniacal symptoms developed following the use of "atebrin." The patient was a young, intelligent adult male, with no

personal or family history of mental or nervous trouble, who developed maniacal symptoms two days after the completion of a five-day course of treatment with "atebrin." The total amount of "atebrin" taken was 1.5 grams. The symptoms lasted eight days.

Canet²⁸ says that mass quinine distribution had little value in the rubber plantations. Synthetic drugs gave better results. He feels that a combination of antilarval prophylaxis and mass treatment with synthetic drugs should produce a permanent improvement in the health conditions of the plantations.

Ragiot and Moreau²⁹ describe a severe case of subtertian malaria in which hematuria occurred subsequent to the administration of two intramuscular injections of 1 gram of quinine and 0.5 gram of the same drug by mouth. Injections of French "atebrin" were then given instead of quinine, 0.2 gram in the morning and 0.1 gram in the evening for 4 days. The patient improved quickly, the hematuria stopped at once, the parasites disappeared in three days, and treatment with quinine was then resumed without recurrence of the hematuria. Abundant parasites were in the blood during the occurrence of hematuria and the authors think this may be a point of distinction between hematuria due to quinine and hematuria of blackwater fever in which the parasites disappear from the blood.

Sicault and Messerlin³⁰ present a standard treatment for ordinary cases of malaria that consists of 0.3 gram of French "atebrin" and 0.03 gram of another synthetic daily for 5 days, followed by a continuous treatment of one dose weekly. In very severe cases the initial treatment consisted of the injection of 1.6 grams of quinine daily for the first two days, followed by three days' treatment with synthetic drugs.

Berny and Nicolas³¹ report success in the control of malaria in a prison. Each Sunday everyone was given French "atebrin" 0.30 gram and 0.02 gram of another synthetic. This was kept up for six months. At the end of the period the parasite index was zero and in the neighborhood malaria was very prevalent. There was no sign of drug intolerance and no interference with work.

Rubinstein³² reports on the use of a new drug, "acri-chin." It is an analogue of "atebrin," which was

used against *P. vivax* in general paresis cases for his experiment. The dose was 5 to 8 c. c. of a 3 per cent glucose solution of "acrichin" intravenously daily for a week, the same dose twice daily if given intramuscularly. It was given by mouth, in doses of 0.1 gram, thrice daily for a week. He treated 21 cases and had no relapse and no untoward effects from the drug.

Naegelsbach³³ discusses a preparation of quinine in weakly alkaline solution. Injections are free from the pain usually caused by quinine. One ampule given twice a day is equal to 15 grains of quinine hydrochloride.

Van Nitsen³⁴ presents a copper-containing organic preparation, prepared in the "Meurice" Laboratories of the Union Clinique Belge. It is described as copper oxyquinoline sulphonate of soda; a greenish amorphous powder soluble in water, of neutral reaction and stable in ordinary conditions of temperature and humidity. The daily dose recommended is 0.02 gram per kilogram of body weight for adults. It is given in divided doses in tablet form, each tablet containing 0.20 gram. No symptoms of intolerance have been noted. It is said to be as good as any of the drugs now in use and effective against all species of the parasites.

The modern use of transfusion has given us more and more information on how long and well certain individuals can carry the parasites of malaria without symptoms and after a thorough course of treatment. I shall offer a few references just to show how very unsafe it is to make the statement that a patient is parasite-free. A few drops of blood do not tell us all about the volume of blood in an individual in so far as the presence or absence of a few malarial parasites is concerned.

Wang and Lee³⁵ report that 54 cases of benign tertian malaria and 6 cases of relapsing fever have followed blood transfusions in the Peiping Union Medical College Hospital in the ten-year period 1925-1935, during which 3,700 transfusions were performed. In one case a pregnant recipient was infected with relapsing fever and passed it on to her premature infant, who died of it. Malarial parasites were found in only one of 18 donors incriminated. One donor gave blood to ten people in 1925, and two became infected. He was not used again till 1933, when he infected 3 out of 10

inoculated with his blood. He admitted having a malaria-like fever 20 years before.

Thomas and Keys³⁶ report a donor who had served in India from 1927 to 1933 and who had never shown the parasites of malaria in his blood and had never, so far as he knew, had an attack of malaria. His blood was used for transfusion twice: 18 ounces on the first occasion and 10 ounces on the second. This was done on September 9, 1935, and on September 12, 1935. The recipient developed an attack of malaria (*P. vivax*).

Lorando and Sotiriades³⁷ report 23 cases of malaria in children treated with subcutaneous injections of maternal blood. Three injections of immune maternal blood, combined with small doses of quinine for from 5 to 10 days, are sufficient to effect a clinical cure and to develop an immunity the duration of which, however, has not yet been determined. The authors believe that the antibodies in the immune blood have no direct effect on the parasites, but act through the macrophages of the reticulo-endothelial system. Some authorities, such as Ascoli,³⁸ still believe in the use of epinephrine with antimalarial drugs. Ascoli considers that epinephrine, by reducing the congested portions of the enlarged spleen, destroys the breeding ground of the malarial parasite.

Muhlen³⁹ quotes Broughton-Alcock who, as a result of the examinations of 50,000 persons who had taken part in the World War, said:

"I can with certainty assert that malarial parasites in cases of war malaria do not remain in the blood more than five years after their return home."

[We wonder what transfusions from this group of 50,000 people would show in the recipients after the five years period mentioned.]

Mangiacopra⁴⁰ experimented with spleen extract in the treatment of malaria. He concludes that it has no therapeutic value in acute malaria or in the early stages of chronic malaria. In older chronic infections it can be used with marked benefit. It increases organic immunity, stimulates the reticulo-endothelial system and phagocytosis, improves the blood condition and general nutrition, and effects a marked reduction in the size of the spleen. He, therefore, believes that it is a valuable adjuvant in the treatment of chronic malaria.

It has, moreover, a slight power of reactivating latent infections. A new view has been raised by Toporkov⁴¹ on the localization of malarial parasites during the latent period of infection. He believes they are in the blood stream. The absence of parasites from the peripheral blood stream between attacks is attributed to an extreme diminution in their numbers, when the probability of encountering them in the thick drop film is near zero. This was corroborated by successful infection of general paresis cases with malarial blood which failed to show any parasites in the thick drop blood films examined.

Farinaud⁴² makes a statement with which the writer agrees. He says that in spite of the admitted efficacy of the synthetic remedies in controlling malaria incidence, their prophylactic use is of limited applicability in Indo-China [and other places] where malaria can be considered as hyperendemic for not less than nine months of the year.

Earle and Perez⁴³ conclude that there is no way of predicting the presence of gametocytes in the blood stream. Nothing short of mass treatment could cover an attempt to treat the carriers.

Bastianelli,⁴⁴ in his discussion of the treatment of malaria and immunity, seeks to demonstrate that the current treatment of malaria does not interfere with the immunizing processes that lead to final cure. He emphasizes the time factor necessary for the acquisition of immunity. He discusses the view that, in a hyperendemic district, so-called radical treatment may reduce or prevent resistance to reinfection.

S. P. James⁴⁵ believes that lack of immunity is an important factor in causing an epidemic. Non-immune persons suffering from malaria show gametocytes more frequently and in greater numbers than in immune persons.

Clark and Komp's⁴⁶ seventh year's experience with malaria in the Chagres River villages of Panama is practically the same as reported in 1936. The average monthly parasite index for the "atebrin"-plasmochin towns, quinine-plasmochin towns and the voluntary quinine control area were respectively: 7.4 per cent, 14.4 per cent and 16.2 per cent. The cumulative parasite index for the year, however, is, respectively: 35.0

per cent, 37.0 per cent, and 35.9 per cent. The control area people were very irregular in their appearance on survey days and therefore do not show the high cumulative rate expected of people surveyed each month. The parasite index for age groups is very similar to the record for 1936. The peak was found in those people from 5 to 20 years of age, the greatest rate being 62.5 per cent for those people 10 to 20 years of age who were surveyed in all of the 12 surveys and 50 per cent for those 5 to 10 years of age. The other groups ranged from 30 to 40 per cent. It is again of interest to note that 16 persons over 60 years of age out of 68 examined were positive for parasites, but no clinical case occurred among them this year. These people have spent their lives on the banks of the Chagres River.

Fifty-eight infants born during the year or carried in the records from last year until they were 12 months old, as a special group, reveal the following: 4 positive for parasites in the first nine months of life; four positive for parasites in the 10 to 12 months of life, the general infant rate being 13.5 per cent. This is certainly proof that transmission is going on in the towns where plasmochin is in use. None of the babies regularly surveyed were from the control area. Another indication of transmission in the towns treated with plasmochin is that the mosquito index of infection in our second year's report was 0.48 per cent and for 1937 it is 1.1 per cent. The mosquito parasite index has not fallen with the human parasite index. Transient people and long *A. albimanus* flights may account for this as well as carriers developing between monthly treatment periods. The parasite species (excluding those reported as mixed infections) have the following incidence: *P. falciparum* 82.6 per cent, *P. vivax* 15.7 per cent, and *P. malariae* 1.6 per cent. During the year "crescent carriers" were recorded in *P. falciparum* cases as follows: 42.1 per cent in the "atebrin"-plasmochin towns, 37.8 per cent in the quinine-plasmochin towns, and 31.7 per cent in the control town (voluntary quinine). Clinical malaria is under good control from the viewpoint of an industrial organization, but we consider it suppressed malaria and not eradicated malaria in the people treated. Relapse⁴⁷ this year is practically the same as was reported last year.

The people are greatly improved physically and can

carry on with almost no interruption due to malaria, but the human carriers are there and the mosquito index has not been reduced. We have not yet experienced any cases of mania or mental derangement following the use of "atebrin." I am of the opinion that quinine is just as effective a drug as "atebrin," but unless given under strict supervision, the people in the villages will not take quinine as they will voluntarily take "atebrin."

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