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REVIEW OF RECENT RESEARCH ON DRUG PROPHYLAXIS AND TREATMENT OF MALARIA

(A Report to the National Malaria Society)

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This review was prepared at the request of the Committee on Medical Research and the period covered is from September, 1941 to September, 1942. It includes only the examination of the literature available in Panama and attention must be called to the fact that the present emergency has greatly reduced the number of articles published on the subject. Priorities on supplies and shipment also limit the receipt of records. At the close of the war we shall, no doubt, be flooded with reports on the management of malaria. More investigations in chemotherapy are certainly indicated and this war may provide some new approaches to the problem.

The United States Public Health Reports (1) calls attention to the compelling necessity for increasing knowledge of the prophylaxis and treatment of malaria. Molitor (2) states that we seem justified at present in limiting discussions of effective antimalarials to the quinine, plasmochin and atabrine group but that the ideal antimalarial still has to be found. Up to date only the synthetic compounds belonging to the sulfanilamide group have offered some promise. He calls attention to the fact that almost none of the hundreds of alkaloids and glucosides isolated from tropical plants has been subjected to a pharmacological analysis which today could be regarded as adequate. It may therefore be justified to expect unforeseen and valuable results from a thorough investigation of this field.

The British Army (3) fully realizes that cases of malaria may be expected in men who return from service overseas in malarious countries and that a high proportion of those seen have been suffering from the dangerous malignant tertian variety. They use a standard treatment as follows:

Days 1 and 2:—

Quinine bisulphate or quinine hydrochloride, grains 10 in solution, in one fluid ounce of water, by mouth, three times in 24 hours.

Days 3, 4, 5, 6 and 7:—

Mepacrine hydrochloride, 0.1 gramme tablet, three times a day, swallowed whole with a draught of water, after food.

Days 8 and 9:—

No antimalarial drug treatment.

Days 10, 11, 12, 13 and 14:—

Pamaquin, 0.01 gramme tablet, three times a day, after food.

Mepacrine is the British equivalent of atabrine, Pamaquin that of plasmoquine.

Dauncey (4) advocates the intramuscular injection of quinine in the treatment of malaria. The site for the injection that he selects is the upper part of the middle third of the outer aspect of the thigh; here one can feel the needle pierce the fascia lata. The most effective time to give the treatment is from one hour to half an hour before the temperature begins to rise. His aim is to get the maximum concentration of quinine in the blood while the merozoites are scattered in the blood stream. He believes that one well timed injection of five grains of quinine is sufficient to cure the acute symptoms. By this form of treatment a large amount of quinine can be saved and the patient spared a long course of unpleasant treatment.

The annual report of the Federated Malay States continues to show a preference for quinine over the new drugs that have been given a trial.

In southern parts of China (6) the root-bark of an indigenous tree has been used for the past thirty years to prepare an antimalarial drug. The scientific name given the three is *Fraxinus malacophylla* Hemsley. For convenience the tree has been called the sinine tree. The drug sinine is said to be just as good as quinine for all kinds of malaria. A four days course of treatment is said to kill all parasites. Very little is known about the drug but the tree is abundant and widely distributed. The chunine tree of the same region is also said to produce a similar useful drug (chunine).

Condorelli (7) reports an interesting case of purpura haemorrhagica in a case of malaria under treatment with quinine. A man aged 27 was serving in Abyssinia in 1935. For a time he was on prophylactic quinine daily and showed no sign of intolerance to the drug. In spite of his routine prophylaxis he fell ill with malaria. The attack was not severe but it was accompanied by profuse epistaxis and a generalized petechial rash. He made a rapid recovery under other treatment. In 1936 he returned to Italy and in 1939 he again fell ill with malaria. It was a sharp attack. There was no haemorrhagic phenomena until two days later when he was given an injection of 1 gm. of quinine. Half an hour after this treatment profuse epistaxis, bleeding from the guns, a diffuse petechial rash all over the body, intense subconjunctival haemorrhage in both eyes, intense haematuria, and a large haematoma at the site of the injection. He was dangerously ill but eventually recovered. Later he was given an experimental injection of 0.5 gm. of quinine and the haemorrhagic

phenomena again appeared together with a rise in temperature. A month later a similar dose of quinine caused a slight rise of temperature but no haemorrhagic symptoms. Four and a half months later quinine caused a slight chill but no haemorrhagic symptoms.

Lamprell (8) states that atebrin lowered the incidence of clinical malaria to a greater extent than did quinine. Atebrin in addition had the great practical advantage of being popular with the people whether as treatment for an attack or for prophylaxis. The expenditure on atebrin was about seven times as great as on quinine.

Rose (9) advocates a daily prophylactic dose of 0.06 gm. of atabrine and has had tablets of this prepared. He is not prepared at this time to give definite figures of the results obtained.

A report (10) from the Federated Malay States includes eighty cases that were treated with "Prontosil album," a proprietary sulphanilamide. The series contained the following infections: *P. falciparum* 34, *P. vivax* 38 and *P. malariae* 8. The dosage was 3.0 grm. daily, given in two doses of 1.5 grm. Results were controlled by treating a parallel series of sixty-eight cases with quinine bihydrochloride given at 2.0 grm, a day for every hundred pounds of body weight. Mosquitoes fed on "crescent" carriers after seven day treatment with "Prontosil" were readily infected. It was concluded that: (I) Prontosil is not so efficient as quinine in acute *P. falciparum* malaria; (II) "Prontosil" is still less effective in acute *P. vivax* malaria; (III) "Prontosil" is not an effective gametocide either in *P. falciparum* or *P. vivax* malaria. The drug has no place in the practical treatment of malaria from its low efficiency and high cost.

Schwartz (11) reports the use of Sulfathiazole to terminate artificially induced malaria in nine patients. Relapses occured in 5 of these cases. The action of the drug is slower than that observed with quinine according to his experience.

De Leon (12) reports the intravenous use of Ambesid, a sulphanilamide preparation. In acute attacks of *P. falciparum* infections it is a good substitute for atebrin when intravenous treatment is indicated.

Coggeshall, Maier and Best (13) treated 17 patients suffering from malaria in Gorgas Hospital with promin and 13 with sulphadiazine. They conclude that there are no reasons for giving either drug in preference to quinine or atebrin for the treatment of malaria, but that both may be looked on as important substitutes.

Mapharside (14) is a trivalent arsenical preparation that has been used to some extent in therapeutic malaria. Niven reports its use on 20 *falciparum*, 9 *malariae* and 20 *vivax* infections using an equal control number in the *falciparum* and *vivax* infec-

tions treated with quinine. The mapharside treatment consisted in the administration of two intravenous injections, with an interval of from five to seven days, of 0.04 and 0.06 gm. respectively. He concludes that its use should be limited to the treatment of therapeutic *vivax* infections.

The Imperial Chemical Industries Limited (15) have synthesized a substance, pamaquin, which is believed to be identical with plasmoquine (Bayer). The biological tests confirm this view.

A description of thrombopenic purpura caused by chinin in a Chinese boy 17 years old has been recorded by Siegenbeek van Henkelom (16).

Thoroughman (17) reports the experiences of a hospital on the use of donors in Soochow, Kiangsu, China. Malaria is endemic in Soochow. The donors were for the most part coolies. One hundred and four patients gave no history of recent malaria and no parasites were found in their bloods. The blood films of the donors (coolies) were also negative, yet 45 of these 104 patients developed malaria within a period of 20 days following the transfusion. Twenty-five of the patients had *P. vivax* parasites and 12 *P. falciparum* parasites while the species were not determined in 8 patients. The attacks were easily controlled by quinine. There was no case among 34 patients who received prophylactic quinine for three days after transfusion.

Marks (18) reports an accidental quartan malaria infection in a two-months-old infant. This child received three intramuscular injections of whole blood while under treatment in a hospital in Miami, Florida. The donors of the blood were the father of the infant and a laboratory technician. Neither of the donors had any history of malaria nor did their blood films reveal any parasites. The mother also gave no history or findings of malaria. He concludes that the child had no opportunity to acquire malaria in the natural way and one of the donors was responsible for the accidental transmission.

Gordon (19) reports a case of malaria that was accidentally transmitted by a transfusion of stored blood. A boy of seven years received three transfusions of stored blood for the relief of anemia secondary to sepsis. Forty-four days after the first transfusion and 33 after the last, he developed recurrent fever. Quartan parasites were found in the blood films. The boy lived in a district where malaria was unknown. Two donors were involved. One never had been in a malarial region while the other, had lived in Italy and had a history of malarial attacks in the past. The Italian's blood revealed a

few quartan parasites. His blood had been stored only two days before being used for the transfusion. Gordon believes that a donor's blood should be stored for a period of not less than eight days before using it for transfusion. The general opinion is now held that such donors can be safely used for the production of serum and plasma.

Castelli (20) of the Military Hospital of Padua, offers such information on the question of relapse in soldiers from the Italian Campaign in Africa. Between January, 1937 and August, 1939 eighty-eight patients were admitted suffering from relapse of malaria acquired in the military service in East Africa. The author concludes that relapses are rare after 15 months from the date of infection, and exceptional after two years. *P.vivax* was responsible for a ten-fold greater number of these relapses than was *P. falciparum* though the latter had the highest incidence in primary cases in Africa. No patients were admitted during the period named with *P. malariae*.

Granett (21) gives results of comparative tests of established repellent substances and a recently developed proprietary synthetic organic chemical mixture containing diethylene glycol monobutyl ether acetate, diethylene glycol monoethyl ether, ethyl alcohol, corn oil and perfume. This was developed from tests of nearly 1000 compounds and mixtures. It is superior to citronella and 42 representative proprietary products in lasting power.

Russell and Knipe (22) record a second year's experience with a spray killing mosquito method. As in the former year's work they used 19 parts of kerosene and 1 part pyrocide 20. They used this spray outside of the houses under the eaves as well as inside the house and each house was treated in this manner twice a week. The amount of spraying mixture used was 0.3 litre per 10,000 cubic feet sprayed. The method is effective in greatly reducing malaria transmission and the cost is less than antimalarial work would be in the same area.

Investigations (23) were carried out in Moscow on the possibility of destroying Anophelines in buildings by the light mist or aerosol resulting from the evaporation of Anabasine by heat. One method of obtaining it was to pour a water solution of anabasine sulphate on to quick-lime. The correct proportion was found to be 1 part anabasine sulphate and 1 part water to 6 parts lime. The minimum concentration of anabasine in air that killed all Anophelines in 8 minutes was 0.2 oz. per 1,000 cu. ft. and the rate at which anabasine sulphate must be used to give this is 1-oz. per 1,000 cu. ft. It is said to be better and cheaper than hydrocyanic acid gas and is harmless to fowls, rabbits, food-stuffs and germinating seed.

The Gorgas Memorial Laboratory (24) has continued its observations in its Santa Rosa Station with the following changes in effect from September, 1941 to August, 1942:

1. No plasmochin simplex was used.
2. The quinine group received 18 grains of the sulphate tablets a day for five days. The dosage for children being reduced to suit age and size.
3. The atabrine group was treated with the Winthrop Chemical Company's Dihydrochloride tablets 0.1 gm. three times a day for five days.
4. Blood film surveys were conducted bimonthly instead of monthly although a medical inspection was made of each village in the months when no survey was conducted.
5. Two control areas were surveyed monthly and offered voluntary treatment with quinine without supervision. One of these controls was on the lake shore and the other in the hills 3 miles distant.

The Parasite Rates for the four Groups follow:

Groups in Experiment	Monthly or Bimonthly Ave. Rate	Cumulative for the Year
Quinine (6 surveys)	12.1	25.9
Atabrine (6 surveys)	15.4	32.2
Lake Shore control (12 surveys)	25.8	43.2
Hill village control (11 surveys)	7.4	19.9

From the months of April to and including August there were many returning inhabitants who had been employed for some months with labor forces constructing highways, etc. When these people left their homes they averaged 5 to 8 percent positive, when they returned the rate was 20 to 30 percent according to their home villages. This raised the rates above the old levels more than the reduction of the surveys to a bimonthly period. From a therapeutic viewpoint we still consider quinine and atabrine to be equally effective. The people will take atabrine in a voluntary manner much better than they do quinine. We can, however, treat 5 cases with quinine for the cost of 1 case with atabrine. There were 48 babies, from birth to 12 months, examined in these towns. Twenty-five in the treated towns and twenty-three in the control towns. None of the 48 babies were positive for malaria in the first 12 months of life. At eighteen months there were two positives. One in the atabrine

group and one in the control town. Most of our community malaria rates are due to chronic malaria and to relapse. It is still apparent that we need a good gametocide that can be safely given over long periods of time in the field by non-medical attendants.

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