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# REVIEW OF RECENT RESEARCH ON DRUG PROPHYLAXIS AND TREATMENT OF MALARIA*

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This is rendered as a member's report to the Chairman of the Sub-Committee on Medical Research of the National Malaria Committee. The period covered is from August 31, 1937 to September 1, 1938, and it includes only the literature received by our local library and through correspondence. It is impossible to give an abstract of all publications; so the privilege has again been reserved to select a few representative reports from various parts of the world where malaria is a problem.

The field use of drugs seems to be growing in importance and from the standpoint of cost for the mass treatment of the poor, quinine is still the drug of choice. Where the cost of the drug is not important "atabrin" seems to have the call since it is more pleasant to take than quinine. No drug is yet cheap enough to reach all the needs of the poor if they must be depended upon to purchase it for their use.

India[1] still produces somewhat less than half the total amount (about 200,000 lbs.), of quinine salts consumed each year by her people.

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Ignorance and poverty place the drug outside the reach of millions of sufferers from malaria.

For those who believe implicitly in quinine prophylaxis the following report[2] should be of interest. A man had served two years in French Indo-China during which time he was never ill. He took regularly 0.40 gram of quinine a day, increased to 1 gram a day when on duty in the interior of the country. He left Indo-China in May and went to live in a part of France where there is no indigenous malaria. On November 10 he had an attack of tertian malaria. The infection had apparently remained latent for at least five and a half months and from spring to autumn.

As a counter report[3] to this is the record of another young adult who finished his military service in Algeria in August, 1935 and returned to France. He had not been ill during his service. Nine months after his return to France (end of May, 1936) he fell ill with malaria.

In countries where antimalaria drugs[4] are habitually in use it is well to know if there are risks to the nursing child of a mother who is under treatment for malaria.

Terwilliger and Hatcher report that quinine sulphate is found in such small quantities that it would be harmless to the nurseling. Nothing was found in regard to "atabrin" but tests were made on morphine, codeine, salicylic acid, phenolphthalein, barbital, sodium and potassium bromides. Of all of these sodium bromide was the only drug found in sufficient amount to injure a normal breast-fed infant.

A Philippine report[5] on the treatment of 74 adults with totaquina and 152 adults with quinine sulphate seemed to show very little difference in the therapeutic value of the two methods of treatment. The totaquina used was type 1, that is, the total alkaloids extracted from the bark of either *C. succirubus* or *C. robusta*. It was given in doses of 0.5 gram four times a day

and was well tolerated. Quinine sulphate was given in 5 grain doses four times a day.

Gentzkow and Callender[6] give the results of treatment with "atabrin," plasmochin and quinine in 1,696 cases of malaria in the United States Army. Of 967 clinical attacks of *vivax* malaria, 221 (22.9 per cent) recurred; 683 *falciparum* infections gave 34 recurrences (5.0 per cent); 46 *malariae* cases had one relapse (2.2 per cent). Most of the relapses occurred within six months. They conclude that "atabrin" alone failed to prevent recurrences to a greater extent than any other type of treatment. Quinine had somewhat greater relapse-preventing properties than had "atabrin" in *vivax* malaria and markedly greater ones in *falciparum* malaria. Plasmochin given with "atabrin" in the usual manner had a very definite and pronounced effect upon the relapse rate in all types of malaria.

Winchester[7] reports on the prophylactic value of "atabrin." His observations were carried out in 1936 and concerned 426 persons in a prophylactic group and 202 persons in a control group. Both groups were in the same areas. All persons with a history of "chills and fever" or who had parasites in the blood in both groups were given a five day's course of "atabrin," 0.3 gram a day. This was started on May 1. Members of the prophylactic group thereafter took a tablet of "atabrin," 0.05 gram each evening till the end of October. Smaller doses were given the children according to age. Among the controls there were 49 cases of clinical malaria during the season, 24.3 per cent. There was no case of malaria in the prophylactic group. In November the parasite index of the control group was 19.8 per cent. No carrier was found in the prophylactic group. Ninety per cent of the cases observed were *falciparum* infections.

A prophylaxis experiment[8] was carried out in Posada, a small town of 150 houses and a population of 781, in Sardinia. It was a stable popu-

lation, poor, badly housed and indifferently nourished. It was believed that practically everyone had malaria. These people were divided into three groups as nearly as possible. The first group of 235 persons received 0.05 gram of "atabrin" daily, smaller doses for children. The second group of 244 persons received 0.20 gram of "atabrin" twice a week for the adults. The third group of 229 people was a control group. The administration of the drug was continued from May 13, 1935 to the end of October, 1935 and the people were observed until the following April. No symptoms of drug intolerance were observed. Between May and October there were 55 cases of malaria in the "daily group" or 23.4 per cent. The biweekly group revealed 34 cases, 13.9 per cent. The control group had 161 cases or 70.3 per cent. "Atabrin" was more effective against *vivax* than *falciparum*.

Lega[9] reports fifteen cases treated with "atabrin." All of the cases were kept under observation for two and a half years. Ten were tertian cases and five were estivo-autumnal cases. "Atabrin" was given daily for seven days and treatment repeated whenever relapse occurred. The usual daily doses were employed (0.3 gram for adults, 0.15 gram for children). Relapse occurred within the first two months in 4 cases and in 8 cases between the seventh and tenth months. The duration of the tertian infections was estimated at from 10 to 18 months and in the estivo-autumnal cases 8 to 10 months.

Wallace[10] used a mass method of treatment with "atabrin" and plasmochin simplex as the sole method of malaria control. For five successive days two tablets of "atabrin" were given at the morning muster to each adult. In the afternoon one more tablet of "atabrin" and one tablet of plasmochin simplex (0.01 gram) were given. One tablet of plasmochin simplex was given alone on the sixth and seventh days. After this initial intensive treatment a "follow up" treat-

ment, which consisted of a weekly dose of three or four tablets of "atabrin," on one or on two days a week, was started. This was continued in some cases for four months. The malaria rate was reported as practically nil during the period of treatment. Many thousands of coolies were treated and no serious toxic results were noted. No blood surveys for parasites were included in the report. Results, apparently, were based on the clinical cases of malaria that appeared.

Malaria is hyperendemic in a great part of Indo-China.[11] Cases are most numerous at the beginning and end of the rains, July, August and September, and again from December to March inclusive. In practice this amounts to an almost unbroken period of active transmission from July to March. There are places where the infant endemic index remains constantly above 60 per cent. The use of prophylactic synthetic drugs confers great benefits but such benefits are very temporary and are lost completely within two months of the cessation of such treatment. Almost continuous treatment is neither practicable nor desirable. There are a few places that show a marked seasonal prevalence of the disease. In these places the use of synthetic remedies as the sole measure of prophylaxis has given good and lasting results.

"Atabrin" injection results have been compared with the oral use of quinine[12]. Fever disappeared when "atabrin" was used within 48 hours in 87 per cent and with quinine in 77 per cent. All methods of use for "atabrin" are discussed. Special warning is given about the simultaneous use of plasmochin and "atabrin" and also against mass treatment by "atabrin" injections.

Mezincesco[13] *et al.* conclude from field experience that neither the prophylactic treatment with "atabrin" nor with quinine can reduce the number of parasite carriers to zero. While such treatment is in progress clinical cases can almost be held at zero level.

Schechter and Taylor[14] discuss the difficulties of diagnosis in cases where "atabrin" has been used and no history accompanies the case. Mild jaundice, pernicious anemia, carotinemia, Addison's disease, subacute endocarditis, yellow fever and pigment from picric acid such as occurs in trinitrotoluol workers are simulated by "atabrin" pigmentation. They believe that anemia is of importance as a contributory cause of pigmentation. Occasionally the pigmentation is persistent: four cases showed it for 6 weeks, one 8 weeks, one 16 weeks and two for 18 weeks. Tests for "atabrin" in the urine are simple and reliable (see Tropp and Weise, Trop. Dis. Bull., 31:171, 1934).

Sergent's[15] advice still holds good on drug control in malaria:

(a) A drug used for mass treatment must be harmless.

(b) It must be cheap.

(c) It should act on both schizonts and gametes.

(d) No drug yet produced is capable of procuring the *therapia sterilisans magna.*

(e) Mass treatment must perforce be contented if it can procure a non-sterilizing clinical prophylaxis. It is possible to keep labor or expeditionary forces in a state of latent infection and efficiency.

Experience gained in Formosa led Miyahara[16] to consider that "atabrin" was no more effective than quinine in so far as the prevention of relapse was concerned. He reports 62 per cent relapse in *vivax* infection, 23 per cent in *falciparum* and 7 per cent in *malariae* infection.

Ciuca[17] *et al.* dissected out the salivary glands of 16 Anopheles infected with malignant tertian malaria on a slide in a solution of basic quinine, 1 in 2,500. The resultant suspension, 0.5 c.c. was injected intravenously into a patient requiring malaria therapy. The patient contracted malaria after an incubation period of 15 days. The minimum exposure of the sporozoites from the different glands was 30 minutes and it took 30 minutes to dissect the glands. A second

patient received an intravenous injection of a suspension of the sporozoites from 14 salivary glands in a solution of "atabrin," 1 in 2,500. Evidence of infection was observed on the fifteenth day. It would appear that malaria sporozoites are able to withstand the direct application of quinine and of "atabrin" in a concentration of 1 in 2,500.

Chin[18] states that "atabrin" acts chiefly on the central nervous system. For the detailed report on his studies regarding the various organs, the reader is referred to this article.

Hill and Goodwin[19] treated 7 cases of *P. vivax* infections and 93 cases of *P. falciparum* infections with a sulfanilamide compound, "prontosil." In most cases medication was given intramuscularly, 10 c. c. per injection, injections being made every 12 hours. It was seldom necessary to give more than four injections before a clinical cure was evident. Usually within two days after the four injections were given, the patient could return to his job. No relapses were recorded, yet two reinfections occurred 29 to 31 days, respectively, after the completion of the first course of treatment.

This article on sulfonamide compounds[20] deals with the publication of the favorable reports by Diaz de Leon, Van der Wielen, and Hill and Goodwin. These reports included the treatment of 15 cases of tertian malaria, two of quartan malaria and the Hill series of 93 cases of estivo-autumnal malaria and 7 cases of tertian malaria. The reader is referred to the reference list for the source of these publications. It was the opinion of Faget *et al.* that if uniformly good results were obtainable with "prontosil," then sulfanilamide orally should produce an equally favorable response. This opinion was based on the fact that sulfanilamide is the active principle of "prontosil." The authors were surprised when the administration of sulfanilamide failed to cure three cases of malarial fever. A case of

quartan malaria was then treated with "prontosil" according to the methods of Hill and Goodwin. No success attended this treatment. They conclude that the sulfonamide compounds are nonspecific in malaria.

Oganov[21] states that "acriquine" given in doses of 0.4 grain every ten days during a summer period gave perfect prophylactic results in those who took the drug regularly. In those who were irregular in the treatment there was a morbidity rate of 6.4 per cent.

Radvan and Alexandrescu[22] report the use of acaprine in the treatment of ten cases of chronic malarial spleens. They claim very rapid reduction takes place when this drug is used by intramuscular injection following a course of "atabrin" and plasmochin. The dose is apparently 1.5 c.c. of a 5 per cent solution. Usually only one dose is used. Rather severe symptoms appear to develop within an hour but the authors do not consider them of a serious nature.

Berny[23] reports "premaline," a new synthetic drug similar in action to a combination of "quinacrine" and rhodoquine. It is said to act on both the schizonts and gametes. It was used in French Guiana. The parasite index was given as 29.6 per cent at the start of the experiment. No antimalarial measures were used from September to December except the administration of 3 tablets of "premaline" once a week; thereafter, till the 1st of March, 3 tablets were given twice a month. The parasite index fell to zero while in a neighboring post the usual incidence of the disease was present.

Schulemann's[24] "cilional" is reported by Missiroli to be less toxic and a better gametocide than plasmochin. A dose of 2 centigrams a day is recommended. It is intended for use with quinine or "atabrin."

Sioli[25] states that in benign tertian malaria "certuna" is well tolerated and is active. Its

activity differs from the action of quinine, plasmochin and "atabrin" in that a cure with "certuna," even in large doses, is not attained. There is only a temporary suppression of the febrile attacks and parasites.

Observations over a period of 2½ years are reported by Muhlens[26] on "certuna" (Deyer); it is in tablet form for oral administration. Chemically it is, dialkylamino-oxyquinolylaminobutane. It is given in doses of 0.02 gram daily for 5 days. No toxic symptoms were noted. He considers "certuna" superior to plasmochin as a gametocide in estivo-autumnal malaria.

Sargent[27] believes that as long as the infecting parasite remains latent in the body, so long will the body resist reinoculation with the same species of malarial parasite. This resistance ceases when the latent infection is eliminated. It has not yet been demonstrated whether immunity can replace premunition.

(If Sargent's belief is correct then most of the attacks of malaria in a hyperendemic area are due to relapse rather than new infections, a view we are willing to accept.)

Swellengrebel[28] in North Holland, showed that "healthy" parasite carriers are a more important source of anopheline infection than persons actually suffering from malaria and seeking medical aid as a consequence.

Transfusion experience is continually adding evidence that a "healthy" donor not infrequently infects the recipient with malaria. Drug control results cannot be based on clinical attacks. The entire population must be examined to yield all of the facts in regard to the parasite index in any region.

Paul de Kruif[29] has written a fine article on malaria and "atabrin" that should be of help in securing the attention of the public. The success of any campaign against malaria must have the complete support of all of the public

all of the time in any region where malaria is endemic.

For many years we have had an old friend who insists that if he could give every individual in the world 5 grains a day of quinine for a year, malaria could be eradicated!

Paul de Kruif[29] starts his article with the statement that it is no longer a question of whether we can wipe malaria out of the United States, that it becomes the tougher question of, will we? We wish we could share his optimism. There is no doubt that a vast amount of malaria can be controlled with quinine or "atabrin" but there is the symptom free carrier to be kept in mind when you speak of malaria eradication. The most discouraging fact to face is the healthy carrier and relapse victim. We know in several instances, as a result of blood transfusion, that apparently healthy donors who have had no malarial fever for twenty years have given recipients of their blood malarial infections. The general belief is that five years residence in a malaria-free region will end such malarial infections. No one yet knows the answer to this question. Mass treatment or the treatment of carriers selected by microscopic surveys will not eradicate malaria from any tropical region that we have known, regardless of what drugs are used. Either quinine or "atabrin" can relieve symptoms and reduce parasite abundance and prevent deaths. "Atabrin" has the call over quinine only because it is a more pleasant drug to take. The therapeutic values of the two drugs over a five days' course is practically the same. Quinine is cheaper and can be purchased anywhere.

In the lowlands of the tropics malaria is an all the year problem and continuous blanket or mass treatment is not desirable.

Clark and Komp's[30] eighth year's observations on malaria in Chagres river villages that are under drug control show much the same results as

reported last year. The rainfall has been heavier this year yet the parasite rates during the year are lower than at any time since the work started, and the quinine town has a little the advantage of the "atabrin" villages. We have been successful in reducing almost to the vanishing point clinical cases of malaria, but the rate remains, on the average, for monthly surveys, 6½ per cent. Transmission has been low as is shown by the fact that only one infant out of 53 acquired malaria during the year.

REFERENCES


1. Russell, A. J. H.: Quinine Supplies in India. Records of the Malaria Survey of India, **7**:233-244, 1937.
2. Germain, A.; and Morvan, A.: Paludisme a incubation prolongee. Bull. Soc. Path. Exot., **30**:26-28 (Jan. 13) 1937.
3. Morenas, L.; and Brun, J.: Un nouveau cas de paludisme a incubation prolongee. Bull. Soc. Path. Exot., **29**:957-958 (Nov. 18) 1936.
4. Quinine and Atebrine in Breast Milk (Queries and Minor Notes). J.A.M.A., **110**:1388 (April 23) 1938.
5. Ejercito, A.; and Santos, G. O.: The Philippine Totaquina in the Treatment of Human Malaria: Preliminary Report. Mo. Bull. Bureau of Health, Manila, **17**:219-240 (June) 1937.
6. Gentzkow, C. J.; and Callender, G. R.: Malaria in the Panama Canal Department, United States Army: Results of Treatment with Quinine, Atebrine and Plasmochin. Amer. Jour. Hygiene, **28**:174-189 (Sept.) 1938.
7. Winchester, M. E.: Individual Chemoprophylaxis of Malaria: Report of Second Year's Investigation. Sou. Med. Jour., **30**:1172-1174 (Dec.) 1937. First Year's Report Abstracted in Trop. Dis. Bull., **34**:218, 1937.
8. Mosna, E.; and Canalis, A.: Prophylaxis and Treatment of Malaria with Synthetic Drugs: Experiment Coordinated by the Health Committee of the League of Nations. Abstracted in Considerable Detail in Trop. Dis. Bull., **35**:28-29 (Jan.) 1938.
9. Lega, G.; and Casini, G.: Atebrin in the Treatment of Malaria with Special Regard to Relapses. Riv. di Malariologia, **15**:404-413 (Sez. 1) 1936.
10. Wallace, R. B.: The Control of Malaria on Estates by Mass Treatment with Atebrin. Malayan Med. Jour., **11**:187-213 (Dec.) 1936.
11. Farinaud, E.; and Moreau, P.: Present State of the Prevention of Malaria in Indo-China by Administration of Synthetic Drugs: Indications for Their Use; Their Limitations. Bull. Soc. Med-Chirurg. Indochine, **15**:567-582 (June-July) 1937.
12. Siegenbeek Van Henkelom, A.; and Overbeek, J. G.: Treatment of Acute Cases of Malaria by Atebrin Injections. Abstracted in Trop. Dis. Bull., **34**:594-595 (July) 1937.
13. Mezincesco, D.; and Cornelson, D., with the assistance of Lazar, C.; and Busila, L.: League of Nations CH/Malaria/239 (a) August, 1936.
14. Schechter, A. J.; and Taylor, H. M.: Atebrin Pigmentation. Amer. Jour. Med. Sci., **192**:645-650 (Nov.) 1936.
15. Sergent, E.: Guiding Principles of Mass Drug, Malaria Prophylaxis. Arch. Inst. Pasteur d'Algerie, **15**:1-7 (March) 1937.

16. Miyahara, H.: Sutdies in the Treatment of Malaria. XVII. On the Therapeutic Value of Atebrin. Taiwan Igakkai Zasshi: Jour. Med. Assn. Formosa, **37**: in English Summary, p. 91 (Jan.) 1938.
17. Ciuca, M.; Ballif, L.; Chelarescu, M.; Isanos, M.; and Glaser, L.: Action of Quinine and Atebrin on the Sporozoites of *Plasmodium falciparum*. Trans. Roy. Soc. Trop. Med. & Hyg., **31**:235-240 (July 31) 1937.
18. Chin, K.: Pharmacological Action of Atebrin. Abstracted in Trop. Dis. Bull., **34**:595 (July) 1937.
19. Hill, R. A.; and Goudwin, M. H., Jr.: "Prontosil" in Treatment of Malaria. Report of 100 Cases. Sou. Med. Jour., **30**:1170-1171, 1936.
20. Faget, G. H.; Palmer, M. R.; and Sherwood, R. O.: Unsuccessful Treatment of Malaria with Sulfonamide Compounds. Public Health Reports, **53**:1364-1366. (Abstract of an article by the same author entitled "The Unreliability of Sulfanilamide Compounds in the Treatment of Malaria," which appeared in the Hospital News for July 15, 1938.)
21. Oganov, L. I.; Yefimov, I. A.; and Milovzorova, E. I.: Acriquine as an Anti-Malarial Prophylactic. Med. Parasit. & Parasitic Dis., **6**:209-214, 1937.
22. Radvan, I.; and Alexandrescu, D.: Treatment of Malarial Enlargement of the Spleen with Acaprine. Bull. Soc. Path. Exot., **30**:362-366 (May 12) 1937.
23. Berny, P.; and Le Minor, L.: The Prophylaxis of Malaria with Premaline. Bull. Soc. Path. Exot., **30**:367-368 (May 12) 1937.
24. Missiroli, A.; and Mosna, E.: Sterilization of Gametocytes of the Malaria Plasmodium. Riv. di Parasit., Rome, **2**:55-71 (Jan.) 1938.
25. Sioli, F.: Evaluation of the New Malaria Drug, "Certuna," in Inoculation Malaria in Cases of General Paralysis. Klin. Woch., **17**:527-528 (April 9) 1938.
26. Muhlens, P.: Certuna, a New Gametocide in Malignant Tertian Malaria. Deut. Med. Woch., **64**:295-297 (Feb. 25) 1938.
27. Sargent, E.: Immunity or Premunition in Haemocytozoal Diseases, Malaria and Piroplasmosis. Arch. Inst. Pasteur d'Algerie, **14**:413-417 (Dec.) 1936.
28. Swellengrebel, N. H.; de Buck, A.; and Kraan, H.: Further Investigations on "Healthy" Human Carriers of Plasmodium vivax in North Holland. League of Nations, CH/Malaria/240. Geneva, April 18, 1937.
29. de Kruif, Paul: Will We Wipe Out Malaria? Country Gentleman, **108**:7-8 (June) 1938.
30. Clark, H. C.; and Komp, W. H. W.: An Eighth Year's Observations on Malaria in Panama. Amer. Jour. Trop. Med., **19**:33-46 (Jan.) 1939.