RECENT RESEARCH ON THERAPEUTICS OF MALARIA*

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As a member of the Committee on Medical Research, I have been requested by the Chairman to prepare a summary of prophylaxis and treatment, including recent advances and discoveries during the year ending September 1, 1934; and also a summary of the observations on the use of the newer drugs in prophylaxis and treatment. As I have not access to the world's literature, nor the time necessary to read it, a certain selection among those articles of greatest personal interest will be made, in order to enable me to compress my material into reasonable bounds.

The first portion of this report deals with treatment. In this field comparatively little has been done with quinine, the fashion having swung to the newer synthetic drugs. Schwetz[1] attempted to quininize a group of negro infants, 85 per cent of whom had parasites. The attempt was unsuccessful because of poor maternal cooperation, but the number of tertian and quartan parasites was reduced. Barrowman[2] states that in Malaya, on a rubber plantation, the "short quinine" treatment, 30 grains a day for 10 days, is useless either as a means of cure or as a sanitary measure. Lowe,[3] in India, using cinchona febrifuge, treated 29 tertian cases, using 24 grains daily for 7 days, followed by 12 grains daily for another week. No relapses occurred during the following 6 months. C. D. Williams[4] gives 6 grains of intramuscular quinine to severe malaria cases among children in Accra, on the Gold Coast of Africa. Over 300 injections have been given during 2 months with only 2 abscesses. Recovery is almost certain if the child does not succumb to anemia caused by the malaria. In young children, quinine rapidly reduces the size of the spleen.

R. K. Collins,[5] in Bulgaria, advocates the use of a short period of administration of quinine, 15 grains daily for 3 or 4 days, during each clinical attack. This method is applicable in areas where malaria is severe, no antilarval measures are taken, and where it is impossible

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to cure the severe malaria by mass quinine treatment. It maintains the population in a working state, and the danger of recrudescence is only slightly greater than after prolonged treatment. Only about one-fourth the amount of quinine need be used for the same number of cases, as in a prolonged treatment.

Numerous papers deal with the treatment of malaria with atabrine. All seem agreed that the immediate effect of the drug in reducing fever and removing parasites is equal or superior to that of adequate doses of quinine salts, but there is little agreement as to whether the relapse rate is lowered.

Morrow and Wieand[6] treated 30 patients with tertian malaria, men of the United States Navy in Nicaragua, with the usual dosage of atabrine. In addition, they treated 23 with estivo-autumnal malaria with the same dosage of atabrine plus 2 centigrams of plasmochin simplex a day for 5 days. Blood smears became negative after 2½ days, and no recurrences occurred during the short time of observation, but only 20 per cent could be followed for as long as two months.

Barrowman,[2] in Malaya, found a week's treatment with atabrine much more effective and cheaper than 3 weeks' treatment with quinine alone. Manson-Bahr and Walters[7] observed by blood culture and wet-coverslip method the action of atabrine and plasmochin on the parasite of estivo-autumnal malaria. Atabrine showed no action against crescents, but plasmochin in doses of 4 centigrams daily for 5 days caused crescents to disappear entirely.

Soesilo[8] treated a small series of tertian malaria cases with atabrine. After 3 days schizonts and gametocytes disappeared. One case out of 6 relapsed 9 weeks after treatment. All others remained free for a year.

McNabb and Schwartz[9] used atabrine in malaria among United States troops in the Philippines. Fourteen cases, 11 tertian and 3 estivo-autumnal, were successfully treated, as well as a case of blackwater fever. No known relapses have occurred in one case after 4 months and in the remaining cases after 7 to 10 months. On the other hand, Johnson,[10] in the Federated Malay States, treated 49 Europeans with malaria (29 tertian, 17 estivo-autumnal) with atabrine in the usual dosage. The relapse rate was 43 per cent inside of six months. In Asiatics, the relapse rate was not over 10 per cent.

In the work of Komp and myself done in 1933 and just published, some 400 cases of infection with malaria (not necessarily causing symptoms) occurring in a native population in Panama, were treated with atabrine in the usual dosage, 0.3 gm. daily for 5 days, over a period of 8 months. In every case which received such treatment, including numerous severe clinical cases, mostly estivo-autumnal, the blood was completely cleared of asexual parasites. But the number of persons showing positive blood on monthly examinations did not decrease during the 8 months, as more than half of the treated cases showed parasites in the blood again two or three months following treatment. There were 18 persons who showed positive bloods at least three times during the 8 months' period; each of these had received a full course of the drug each time the parasites were discovered. The drug was absolutely free of any toxic effect, and acted promtply and effectively even in severe cases. Because of its lack of unpleasant by-effects, the natives took the drug willingly and the 5-day course made it easy to administer and control.

Causal Prophylaxis and Atabrine.—Several workers tested the use of atabrine as a causal prophylactic, with good results. Soesilo,[11] in the Dutch East Indies, found that 6 out of 21 volunteers contracted malaria after atabrine treatment, while 10 out of 11 controls contracted the disease. The maximum dose, over a period of 4 to 6 days, was 0.2 gram. (This is two-thirds the usual curative dose.)

S. P. James[12] used atabrine, 3 tablets 0.1 gm. for 5 days, as a causal prophylactic in 5 mental patients, none of whom showed tertian malaria infection one month after being bitten by infected mosquitoes, although 5 patients who received 15 grains of quinine for 5 days after infection came down with clinical malaria inside of two weeks.

Kikuth,[13] on the basis of experimental work with birds, considers atabrine not a true causal prophylactic, but that its effect is therapeutic, because this effect develops during the slow excretion of the drug.

Atabrine, if these results can be substantiated, seems much superior to plasmochin for causal prophylaxis because of its lack of toxicity in effective dosage.

PLASMOCHIN

Treatment with this drug was usually in combination with atabrine or with quinine. MacMahon,[14] in Trinidad, treated 50 cases with atabrine and plasmochin compound with good results. He states, as do all others who have

similarly treated malaria, that any complications from the treatment were due to the plasmochin.

Morrow and Wieand,[6] in their paper, already quoted, had 4 cases of abdominal pain in 23 patients taking atabrine and plasmochin, and the same thing occurred in several other cases not included in the series. They also conclude that atabrine enhances the toxicity of plasmochin.

Volcke and Bourguignon,[15] in the Belgian Congo, treated 32 cases of estivo-autumnal malaria in Europeans, using 0.3 gm. atabrine and 0.03 gm. plasmochin daily for 5 days. A "radical, immediate and lasting" cure was obtained in 20 cases, but there were toxic symptoms in 18 cases, more than one-half of all those treated. Most cases were mild, but in some cases there were severe colicky pains that lasted a week or so.

Eckhardt,[16] in Tanganyika Territory, used atabrine and plasmochin intramuscularly in 25 cases, mostly estivo-autumnal, with very good results. The method is simple and as effective as the intravenous route.

A number of workers have attempted to use plasmochin as a prophylactic, either causal or clinical. Wallace,[17] in Malaya, used plasmochin among cooly labor. On all the divisions of the estate where it was used the malaria rate was lower than on the control division. The daily dose of 0.2 gram of plasmochin appeared to be successful in preventing malaria in a division where antilarval measures were suspended. The cost was about 60 cents a head. The effects had vanished two months after treatment was stopped.

Gribben,[18] in Trinidad, gave mass treatment with plasmochin compound, using 2 tablets a week for two successive weeks, a dose of 0.02 gm. of plasmochin and 0.25 gm. (4 grains) of quinine a week. During the month after the treatment there were 66 cases of malaria as against 96 in the same month of the preceding year, a reduction of 31 per cent; at the same time there was an increase of 28 per cent in the malaria in surrounding districts. Unfortunately our work (Clark and Komp,[19] 1932) in Panama, apparently more closely controlled than Gribben's, did not show any such good results with plasmochin in the same dosage used over a period of 8 months.

Missiroli and Marino,[20] in Sardinia, used quinoplasmochin in a hyperendemic area, and found that the percentage of infected mosquitoes fell to zero, while in a control it rose to 2 per cent; the incidence of malaria in the treated villages likewise fell markedly. Treatment for 10 to 20 days during the pre-epidemic period (to sterilize gametocyte carriers) showed no effect on the course of the subsequent epidemic.

Henrard and van Hoof,[21] in the Belgian Congo, attempted a similar control on a coffee estate. They gave 0.02 gm. of plasmochin daily to cooly labor for a little over 3 months. The parasite index fell from 62 per cent to 14 per cent and no gametocytes were found at the end of the treatment. The mosquito infection rate was 13.7 per cent at the beginning and only 3.2 per cent at the end of the treatment. Unfortunately for the experiment, the mosquito rate fell even lower in a control area. Two months after the treatment stopped, the infectivity rate in the treated camp was as high as ever. The failure of the method is ascribed to inability to isolate the area sufficiently to prevent introduced infection. To us, however, it seems more likely to be the result of natural conditions affecting the infection rate of Anopheles. The reduction might easily be an annual seasonal matter, and might have occurred whether or not plasmochin (admittedly given irregularly and inadequately) had been given at all.

In both these last papers as well as in that of Wallace[17] the effects of the treatment with plasmochin had vanished two months after it had been ended.

Hayden[22] treated 125 men of the United States Navy, invalided home with malaria contracted in Nicaragua, with 10 grains of quinine (sulphate?) daily for 8 weeks. Twenty-three and six-tenths per cent of these men had acute recurrences either towards the end of their treatment or just after its completion. Fifty-three other cases were given 10 grains of quinine daily for 3 weeks and 0.02 grams of plasmochin daily, except Sunday, for the first two weeks. The relapse rate was only 5.6 per cent.

This report is defective in several important particulars. No figures concerning the incidence of each type of malaria and the proportion of relapses among them are given; no information as to the length of the follow-up period in the second group is furnished. The fact that so many relapses occurred in the first group points to the possibility that the men did not take their treatment, in spite of the author's assurances to the contrary. Several simple reliable tests for the presence of quinine in the urine are available, but were not used.

New Drugs.—Several new drugs have been used during the past year, none of them apparently being as valuable as atabrine or plasmochin.

Tarajew *et al.*[23] used "plasmocide," a salicylate of methoxyquinoline. In doses of 5 tablets a day of 0.03 gm. each, it was effective in quartan malaria, not so good in tertian, and had no action on the schizonts of estivo-autumnal, although it destroyed the crescents. Some slight toxic symptoms were noted. This seems to be another slightly inferior plasmochin.

Jonkoff and Krassikova[24] tested "plasmocide" for its antigametocidal effects. The infection rate of mosquitoes fed on tertian gametocyte carriers was 72.7 per cent. After 6 doses of 0.015 gm. each, 39 fed mosquitoes proved negative. In estivo-autumnal malaria the rate fell to zero likewise, after the same dosage.

Sicault and Decourt[25] used "574 F" in 17 cases of malaria, but found it toxic in therapeutic dosage. It did not prevent speedy relapse.

Sergent and Vogt[26] treated estivo-autumnal malaria with "rhodoquine U" (915 F). The drug was capricious in its toxic effects and did not prevent relapses.

Sicault and Decourt[27] used rhodoquine (710 F) in treating estivo-autumnal malaria. This drug is similar to plasmochin in its effects. Estivo-autumnal schizonts are not destroyed, but crescents are. Relapses are not prevented. Doses of over 0.08 gm. daily are likely to be toxic.

Krouch,[28] in Tunis, experimented with a shotgun mixture called "gametoxyl." This contains quinine, which makes it uncertain how much of the results should be attributed to the relatively minute amounts of arsenic and dihydroquinamine they contain, or to the daily dosage of from 10 to 14 grains of quinine.

Altogether, no synthetic drug used so far during the last year has proven to be either equal or superior to the two synethetics, atabrine and plasmochin.

Two recent valuable summaries of research in the treatment of malaria have been made by Russell[29] and Craig.[30] That of Craig covers the results of research during the year ending November 15, 1933, but unfortunately no bibliography is appended. Russell's paper has a list of nearly all the important references on atabrine, plasmochin and their combined use to the date of its publication.

Of outstanding interest and importance to all engaged in research on treatment is a short paper by Kligler and Mer[31] on the development of immunity against malaria in young children. He states, on the basis of a large experience, that "the observations made on adults cannot always * * * be applied to children, and a drug the therapeutic efficiency of which has been established for adults may yield disappointing results when tested in the field on a child population." This dictum is so much in accordance with our own results with atabrine that we feel it should be heeded by all who are investigating any sort of drug treatment. Kligler also emphasizes a fact noted many times in our work: that "repeated treatment with accompanying destruction of parasites did not enhance immunity." As a final conclusion, he states that in hyperendemic areas malaria control by drugs depends on the ability of the drug to sterilize the child population or on the continuous administration of the drug during the infective period.

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