REVIEW OF RECENT RESEARCH ON DRUG PROPHYLAXIS AND TREATMENT OF MALARIA*
A REPORT TO THE NATIONAL MALARIA COMMITTEE

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This is rendered as a member’s annual report to the Chairman of the Subcommittee on Medical Research of the National Malaria Committee. The period covered is from September 1, 1938, to September 20, 1939, and the review includes only the literature received by our own local library and through correspondence as well as through contacts with local isthmian malarologists and scientific visitors passing through this region. Representative reports from various parts of the world have been used. Where the cost of the drug is not important and where mass treatment of the poor is not considered, “atabrin” seems to be the drug of choice. The consensus of opinion this year seems to indicate that some cases of malaria and malaria carriers cannot have their malarial infections “eradicated” by any form or length of treatment. Some of the newer forms of treatment will first be abstracted.

De Nunnol employed antimony tartrate, a 1 per cent solution in distilled water intravenously, on alternate

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days beginning with a dose of from 6 to 10 c. c. and increased by 2 c. c. to a maximum of 14 c. c. The total amount received by each patient was from 120 to 200 c. c. The number of patients in whose blood gametocytes developed were: 4 of the 6 untreated controls (66.6 per cent), 7 of the 12 treated with quinine (58.3 per cent), and 4 of the 40 treated with antimony tartrate (10 per cent). He concludes that after small doses of antimony tartrate the patient cannot infect mosquitoes.

Diaz de Leon² treated 15 cases of benign tertian malaria with sulfanilamide with completely satisfactory results. It was given in tablet form, except for a case that received one intramuscular injection. He considers sulfanilamide an effective specific drug for vivax infections.

Niven³ treated 80 unselected cases of acute malaria in Kuala Lumpur with sulfanilamide (34 *falciparum*, 38 *vivax* and 8 *malariae* infections). As a control, 68 cases (30 *falciparum* and 38 *vivax*) were treated with quinine. Sulfanilamide, 3 grains a day, in two doses, for 7 days, was found to be less efficient than quinine. Five of the *falciparum* cases showed parasites at the end of the treatment, and 15 of *vivax* were still positive. Mosquitoes fed on four crescent carriers at the end of treatment were readily infected.

Read and Pino⁴ believe that the sulfonamide preparations used in the treatment of tertian malaria have a poor specific antimalarial action because they have neither a sufficiently definite schizontocidal action nor a noteworthy gametocide action.

Farinaud⁵ treated 322 school children that were malaria parasite carriers in Madagascar with "quinacrine" for five days followed by rhodoquine for 3 days. Some of the children received only one treatment, while others received a second course of treatment three months after the first. The blood was re-examined 15 days to a month after the completion of treatment. The percentage of children free of parasites after one course of treatment was 71 to 76 per cent and in those given two courses of treatment 94 to 96 per cent. A few children were refractory to treatment, but no gamete carriers were found following treatment. Dr. J. Lавergne, in discussing this report, stated that the synthetic drugs give better results than quinine.

Fastovskala and Chenderowitch⁶ report on the use of two Soviet synthetic drugs and conclude that they are in every way as effective as quinine and can be recommended for mass treatment.

Tibourskaja⁷ reports from Moscow the use of quinoline as a gametocide. In *vivax* infections 0.03 gram thrice daily eliminated subsequent infection of mosquitoes that were fed on the patient 24 hours after the
last dose was given. In three \textit{falciparum} cases daily doses of 0.09, 0.06 and 0.03 gram, respectively, produced a complete gamostatic effect. The duration of the gamostatic effect in \textit{vivax} infections following 0.03 gram thrice daily was 5 days.

Dupoux, Marini and Barthas\textsuperscript{8} carried out a mass prophylaxis in one of the most intensely malarious regions of Tunis. The experiment included 27,097 persons, of whom 10,021 were children from 0 to 12 years of age. The only drug used was "premaline" in tablet form. A tablet of this drug contains "quinacrine" 0.10 gram, rhodoquine 0.005 gram, and "praequine" 0.005 gram. The experiment started June 1, 1936, and the administration of the drug was continued till November 15, 1936. The tablets were given at intervals of ten days during the first month; thereafter twice a month. Adults were given three tablets and children proportionately smaller doses. Clinical relapses were very rare and even those who revealed some parasites were able to follow their daily occupations. Symptoms of intolerance were rare. The cost of the experiment worked out at 20 francs per head. This was only half the cost that daily quinine administration would have incurred. Twenty-one nurses administered the drug. The authors were enthusiastic about the results.

Ascoli's\textsuperscript{9} method of treatment is well tabulated, on a series of nine reports, and those interested in further details regarding the treatment can secure references from the following table: (See next page)
<table>
<thead>
<tr>
<th>Page</th>
<th>Author</th>
<th>Treated</th>
<th>Results and Remarks</th>
</tr>
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<tbody>
<tr>
<td>35</td>
<td>Marciali, et al.</td>
<td>15</td>
<td>Splenomegaly in children. Satisfactory</td>
</tr>
<tr>
<td>565</td>
<td>Monaco, et al.</td>
<td>6</td>
<td>Very satisfactory in all</td>
</tr>
<tr>
<td>566</td>
<td>Acanfora</td>
<td>5</td>
<td>Chronic. Very satisfactory in all</td>
</tr>
<tr>
<td>568</td>
<td>Pizzillo</td>
<td>6</td>
<td>Acute, epinephrine with quinine. Very satisfactory in quinine-resistant infections</td>
</tr>
<tr>
<td>893</td>
<td>Miletari</td>
<td>70</td>
<td>Great value in splenomegaly and on patient's general condition</td>
</tr>
<tr>
<td>893</td>
<td>Mosna</td>
<td>9</td>
<td>Chronic splenomegaly. Good</td>
</tr>
<tr>
<td>893</td>
<td>Bell</td>
<td>6</td>
<td>Good results in all</td>
</tr>
<tr>
<td>895</td>
<td>Nucciotti</td>
<td>10</td>
<td>Primary attack treated with quinine, epinephrine. Several relapses</td>
</tr>
<tr>
<td>895</td>
<td>Nucciotti</td>
<td>6</td>
<td>Epinephrine, no effect on crescents</td>
</tr>
</tbody>
</table>
It would appear from this that the results of epinephrine treatment were usually good.

Field's\textsuperscript{10} monograph contains an historical resume of cinchona and the progressive steps in the development of antimalarial drugs and offers the present resources for treating and preventing malaria by this means. The book is printed at Kuala Lumpur by the F. M. S. Government Press. The price is not mentioned.

Barbosa\textsuperscript{11} records the results of treatment in 175 persons with primary infections and of 139 persons with reinfections of \textit{P. vivax}. The treatment used comprised quinine alone, quinine and plasmochin, and "atabrin" and plasmochin. He concludes that treatment should not be prolonged more than seven or eight days. "Atabrin" associated with plasmochin is the choice in treatment to prevent relapse. He believes relapses of \textit{falciparum} infections more frequent among children below 4 years of age than in later age groups.

Kalmus and Kostic\textsuperscript{12} (Yugoslavia) report the action of plasmochin in reducing the number of relapses. See the following table:

<table>
<thead>
<tr>
<th>Mode of Treatment</th>
<th>Quinine Sulphate</th>
<th>Quinine and Plasmochin Co.</th>
<th>Quinoplasmochin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cases</td>
<td>196</td>
<td>57</td>
<td>105</td>
</tr>
<tr>
<td>First relapse</td>
<td>51</td>
<td>4</td>
<td>7</td>
</tr>
<tr>
<td>Second relapse</td>
<td>8</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Third relapse</td>
<td>4</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Fourth relapse</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Fifth relapse</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Missiroli and Mosna\textsuperscript{13} report on Schulemann's drug "cilional." It belongs to the plasmochin series of preparations and has the composition dialkylamino-alkylamino-oxy-quinoline. A dose of 2 centigrams a day for six days is a suitable therapeutic dose. Its action on the gametes of \textit{P. falciparum} is quite as potent as that of plasmochin and in doses far less than any that produce toxic symptoms.

Overbeek and Gilbert\textsuperscript{14} compare "atabrin" and quinine. Of 100 cases of benign tertian malaria, 53 were treated with "atabrin," 0.3 gram a day for five days, and 47 with quinine, 1.3 grams a day for seven days. There was no significant difference between the rates of action of the two drugs on the parasite, but three weeks after treatment 34 per cent of the quinine group harbored parasites as compared with 5.6 per cent of the "atabrin" group. One of the "atabrin" cases revealed an acute mental disorder which lasted fourteen
days. A month later a second attack of malaria occurred: anxiety and mental confusion followed the use of 0.3 gram of “atabrin.” The treatment was continued for three days, but fever and parasites persisted. The administration of 1 gram of quinine reduced the temperature to normal and the patient became more quiet.

Miyahara’s experience gained in Formosa by treating 30 cases of malaria with “atabrin,” 0.3 gram a day for five days, led the author to consider “atabrin” no more effective than quinine in so far as the prevention of relapses is concerned. The parasite relapse rate was determined by the frequent examination of the blood, thick film method, during eight weeks following the end of treatment. The relapse rates follow: 62 per cent in the vivax cases, 12 per cent in the falciparum cases, and 7 per cent in the malariae cases.

Field, Niven and Guest used “atabrin” musonate on a group of 284 patients (187 falciparum, 84 vivax and 13 malariae). This series was compared with a quinine group of 271 cases (184 falciparum, 77 vivax and 10 malariae). Each group was divided into two series so that intramuscular and oral methods could be observed. They concluded that as a falciparum gametocide “atabrin” musonate had no advantage over quinine. In spite of the efficacy of “atabrin” musonate in controlling attacks of malaria, the routine is not advised, since oral therapy is the method of choice in the majority of cases.

Rey reports an experiment in an endemic area to sterilize carriers. The drug used was “atabrin” composition in tablet form. Each tablet contains 0.1 gram “atabrin” and 0.005 gram plasmochin. It was administered on five consecutive days in one daily dose without regard to the time of day or interval from meals. The daily dosage was as follows:

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infants</td>
<td>½ tablet</td>
</tr>
<tr>
<td>1-3 years</td>
<td>½ to 1 tablet</td>
</tr>
<tr>
<td>3-5 years</td>
<td>1 to 1½ tablets</td>
</tr>
<tr>
<td>6-10 years</td>
<td>1½ to 2½ tablets</td>
</tr>
<tr>
<td>Over 10 years</td>
<td>3 tablets</td>
</tr>
</tbody>
</table>

Over a period of 8 months in 686 treated cases there was a relapse rate of 12 per cent in benign tertian malaria.

Sinton describes some interesting changes that appeared to occur in gametocytes (crescents) during treatment with “atabrin” and suggests injury that might make them non-infective for the mosquito. Feeding experiments later showed that gametocytes even with little or no pigment in them could develop in the mosquito host.
Winchester reports further experience in Georgia on the prophylactic use of "atabrin" and states that all of his cases showing parasites were of the *falciparum* species. Results were so encouraging as a control measure that he has decided to continue the method. No toxic symptoms caused by the use of the drug were encountered.

Bisham states that if "atabrin" be used as prophylactic, soldiers can live and carry on their various activities in a highly infected area with a minimum of malarial infection and a maximum of effectiveness. Extremely few unpleasant reactions to "atabrin" occurred and these were of transient character.

Chopra and Basu in Calcutta, tested the effect of varying doses of antimalarial drugs on the infectivity of gametocyte carriers for mosquitoes. Laboratory bred *A. stephensi*, 4,665 in number, were used. Cinchona febrifuge, quinine sulphate, "malarcan," "tebetren," "atabrin," plasmochin and "gametochin" were the drugs tested. All failed, with the exception of plasmochin, to prevent the development of crescents in *A. stephensi*. Plasmochin in doses of 0.02 gram was effective in preventing this development.

Ciucu and his staff report some malaria drug control experiments in both field and hospital practice. Four schizonticides were used (quinine, aristoquine, "atabrin" and "acriqueine") and one gametocide (plasmochin). All three species of malaria parasites were represented among the cases treated. They report that the therapeutic efficacy of the drugs in the treatment of an attack were about equal, but that aristoquine was less effective than the others. They recommend, however, "atabrin" followed by plasmochin, each drug to have a five-day course. They think it unnecessary to administer daily doses of plasmochin in *falciparum* infections. A single dose of 0.02 gram, repeated every five days in the rare cases in which crescents persist, is sufficient to devitalize gametocytes. Children under 1 year of age do not tolerate "atabrin."

Gentzkow and Callender believe that "atabrin" alone has failed to prevent relapses to a greater extent than any other of the treatments tried. Quinine, in large and long-continued doses, was somewhat more effective in preventing relapse in *vivax* infections than is "atabrin" and markedly so in *falciparum* infections. Plasmochin given with or following "atabrin" has a pronounced effect upon the relapse rate in all types of malaria.

Chopra treated four patients harboring *falciparum* gametocytes with "cilunal." A total dose of 0.35 to 0.4 gram was administered in doses of 0.03 gram three times a day. This seemed to be sufficient to eradicate the gametocytes of *P. falciparum*. The opinion was
offered, however, that plasmochin was preferable to "cilional." A smaller dose of the former is effective (0.02 gram daily for three days).

Sinton\textsuperscript{25} tested the potentialities of "certuna" as a true causal prophylactic of \textit{falciparum} malaria. Five patients were used in the experiment. The drug was well tolerated, but it failed in all five cases to prevent infection.

Muhlen\textsuperscript{26} used "certuna" over a period of 2½ years in 113 cases of malaria. This drug is put up in tablets for oral administration. Chemically it is dialkylamino-oxy-quinolylaminobutane. When it was given in doses of 0.02 gram daily for 5 days he did not observe any toxic signs such as cyanosis or the formation of methemoglobin. He considers "certuna" superior to plasmochin as a gametocide in malignant tertian malaria.

Sioli\textsuperscript{27} concludes from his use of "certuna" in inoculation malaria (benign tertian) that it is well tolerated and active, but that its activity differs from the action of quinine, plasmochin and "atabrin" in that a cure with "certuna," even in large doses, is not attained. It produces only a temporary suppression of the febrile attacks and parasites. He believes that the drug needs extensive trials in the field by tropical practitioners before its value can be determined.

Brachtel\textsuperscript{28} reports some cases of malaria with remarkably long latent periods, with the object of drawing attention to the possibility of malaria in atypical febrile attacks. Latency period varied from 7 months to 1 year and in a single case 7 years.

Shute\textsuperscript{29} discusses a series of non-immune persons who showed very long periods of latency and long-term relapse periods following treatment.

The summary of the experimental work of Ciuca and his co-workers\textsuperscript{30} using "atabrin" follows:

(a) Of 4 subjects inoculated three times with sporozoites of \textit{P. falciparum} (M. T. R. 78) and kept under the protection of a weekly dose of 0.30 gram of "atabrin" for 6 weeks, two showed clinical symptoms from 1 to 2 weeks after administration of the last dose of "atabrin." One showed a very mild frustrated infection. The remaining one did not show evidence of parasites in the blood during a 20-week period of observation. The control cases, inoculated once, showed clinical symptoms after a period of incubation lasting from 9 to 11 days.

(b) Of 6 subjects who were inoculated with sporozoites of \textit{P. falciparum} (B. T. HOHR) and similarly treated, 3 showed clinical symptoms, but after varying intervals: the first one week after the last dose of "ata-
brin," two others after 6 weeks; the remaining three, a very mild frustrated infection during the period of administration itself. Of the three control cases inoculated with sporozoites once (and not given treatment), 2 showed clinical symptoms after a period of incubation lasting from 9 to 13 days; the third was immune and showed neither fever nor parasites.

In the circumstances governing our experiment, that is, repeated infections, the clinical protection afforded by "atabrin" was generally effective throughout the period of administration. The weekly "atabrin" method does not prevent infection by parasites.

The clinical symptoms began at varying intervals, starting from the first week after administration of the last dose of "atabrin."

The sporozoites of *P. falciparum* (M. T. R. 78) appear to be more sensitive to the action of "atabrin" than those of *P. vivax* (B. T. HOHR), and this confirmed findings reported previously (document C. H./Malaria/264).

If we compare the results obtained by the weekly method with those of the biweekly method (C. H./Malaria/265) the latter, which gives a total of 0.40 grain of "atabrin" instead of 0.30 grain, appears the better of the two. No prophylactic method applied to experimentally induced malaria succeeds in "eradicating" the infection.

As regards possible application in the field, both methods might achieve clinical protection provided the number of reinfections did not exceed the range and relative efficacy of each.

Swellengrebel and de Buck, after discussing malaria in the Netherlands and various methods of control, state that drugs have helped by eliminating the malaria patient as a source of anopheline infection, but there remain the healthy carriers against whom drugs are of no avail.

Clark and Komp's ninth year's observations on malaria in Chagres River villages that are under drug control show much the same results as reported last year except for the last two months (July and August) of the year. The rainfall was extremely light this year and for a long time before the August survey all Madden Lake water was impounded and none escaped over
the dam. The only river current by the villages was due to the discharge of water through the hydro-electric plant at the dam and the few small branches of the Chagres below the dam. This condition caused all floating vegetation to collect and remain in the river near the villages and anopheline breeding occurred on a scale that we have not seen since 1935, when a similar condition occurred at Madden Dam. Our malaria parasite rates in the river bank towns were five times as high as they have been for a very long period of time. Even though the drug has been in effect steadily, it did not prevent an epidemic. As soon as a normal river current is again established and floating vegetation is carried away, we believe that the anopheline density will subside to normal and that our village rates will also fall rapidly. Only one baby in 65 revealed a malarial infection during the year and this one was positive in its seventh and eighth months. The main increase in the parasite index during July and August was noted in the adults.

Treatment very often has to be placed in the hands of laymen and in these circumstances quinine is the safest and, for us, the cheapest drug for general use in rural regions and labor camps. Quinine is still our most important drug because of its clinical effectiveness and almost complete safety coupled with the years’ widespread knowledge of its use and dosage. “Atabrine” is the drug of choice where expense need not be considered and where some form of supervision of treatment can be placed in effect.

REFERENCES


