RECENT RESEARCH ON PROPHYLAXIS AND TREATMENT OF MALARIA*
REPORT FOR 1936

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The great volume of printed reports on these subjects since our last meeting makes it necessary to state that I have assumed the responsibility of selecting only a few of the representative reports from different countries for the use of our membership. For those who may want more details and additional reports I respectfully refer them to the League of Nations Malaria Commission and to the Tropical Diseases Bulletin. For the busy field worker I am sure the Bulletin will serve him well with its mass of concise abstracts covering all tropical and subtropical regions.

Quinine is still our drug for the masses and our yardstick to measure the value of other new drugs. Following the plan of last year's report, this review will be given to the new drugs that have received the most extensive field or hospital trials. The field workers in malaria control who are interested in having drug control added to their weapons in the anti-malarial fight will be interested in a recent statement by Watson1 who says, "There is, in my opinion, no antagonism and no competition between the various methods of preventing malaria . . . . in all campaigns antimalarial drugs have a place."

The Ceylon malaria epidemic has held our attention for some time. It is interesting to note that the medical authorities there always keep a reserve supply of quinine equal to ten months requirements and 7,000 pounds were available at the beginning of that epidemic. However, it became necessary to obtain a large supply of other anti-malarial drugs and among the reports on these is one by Briercliffe2 on the use of "atebrin" musonate. It is a comparative test of "atebrin" musonate and quinine made in the hospitals during April, 1935.

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A group of 681 patients was given two intramuscular injections of 0.375 gram of “atebrin” musonate with an interval of 24 hours between them. A second group of 424 patients was treated with two intramuscular injections of 15 grains of quinine followed by quinine given by the mouth. About a quarter of the “atebrin” group and a third of the quinine group complained of pain at the site of the injections; there were two abscesses in the “atebrin” group but none in the quinine group. There were more deaths in the “atebrin” group and 4 of the 17 deaths were attributed directly to “atebrin.”

Between May 20 and May 31, 1935, 1387 persons in malarious villages were treated with “atebrin” injections; 61 suffered from toxic symptoms such as vomiting, collapse and abdominal pains. Mental symptoms, which in most cases lasted for about a week, occurred in 8 patients and one of them died from exhaustion. Pain at the site of injection was complained of by most of the patients, and in 9 abscesses resulted. The data available did not allow definite conclusions to be drawn with respect to the relapse-rate but the belief exists that a full course of “atebrin” by mouth (1.5 gram) has a greater effect in preventing the return of fever than a week’s careful treatment with quinine, and that either of these courses of treatment is better in this respect than two injections of “atebrin” musonate. The majority of patients suffering from malaria do not require treatment by injection with either drug. When, however, treatment by injection is indicated, quinine is to be preferred to “atebrin.”

The temporary mental derangement which may result from the administration of “atebrin” proved a serious objection to its use; in one district, where several hundred people had been treated with oral “atebrin,” at least 15 cases occurred and the use of “atebrin” was abandoned.

Schulemann who has been closely identified with the development and use of “atebrin” and plasmoquin has made an authoritative statement that these two drugs when given together are more apt to cause abdominal pain than when they are given one after the other.

Sesilo and Gilbert tested prophylactic drug treatment in a hyperendemic malarial region using 175 children. 40 of these were under and 135 over 3 years of age, the parasite index at the start was 65.7 per cent. All received the official malaria tablets D. V. G. (each had 240 mg. quinine sulphate and 2 mg. plasmoquin) for one week in therapeutic doses after which the prophylactic trial began of the different test drugs for a period of 15 weeks; then came the end of the treatment, but the blood surveys for the parasite index were continued for 28 weeks in all. There were four groups with 43, 44, 43 and 45 children in each: (1) The use of daily therapeutic doses of D.V.G. malaria tablets for 1 week lowered the parasite index of 65.7 per cent to 4.5 per cent. (2) The children of “atebrin” Group 1 remained wholly parasite free (dosage on 3 days in the week) 3/4 to 1 tablet (50 mg.). (3) Group 2, 1/2 to 2 tablets (100 mg.) quinine hydro-
chlorate, and Group 3, ½ to 2 malaria tablets D.V.G. same period and frequency as Group 1. These were never completely free of parasites, but had a much lower parasite index over the whole 15 weeks than before treatment was begun. (4) Group 4 was given anti-beriberi-vitamin tablets as a control group of no antimalaria treatment. This series had a consistently higher index than Groups 2 and 3, but this was, nevertheless, lower than before the trial began. The index in a neighboring town was 65.2 per cent at the close of these experiments. The stoppage of the experiment was followed by a rise of the parasite index in all the test groups. The expected continued action of "atebrin" for two weeks was not clearly established.

Bonne and Stoker⁵ made experiments on prisoners in Java. There were four groups each with 75 prisoners:

Group 1 received one tablet of "atebrin" (0.1 gram) every evening.

Group 2 received one tablet of quinoplasmine (0.01 gram plasmocin and 0.3 gram of quinine).

Group 3 received two tablets of quinine (0.4 gram).

Group 4 control. No drug given.

The drugs were given for three months, and this was followed by an observation period of two months. The results were as follows: no clinical case developed in the "atebrin" group in three months. Parasites were found only twice at the weekly thickfilm blood examination. Three weeks after the treatment had been stopped, the parasite index was no better than in the control group. There were no toxic symptoms, but at the close of treatment every patient was stained yellow. This raises the question of the cumulative of "atebrin" and the danger of hyperrensitivity to the sun following the deposition of acridine in the skin. The quinoplasmine group had two clinical cases with 44 hospital days. The quinine group had four cases with 50 hospital days, while the control group had 21 cases with 243 hospital days.

Peter,⁶ in a discussion of the clinical testing of malarial remedies, says that "atebrin" differs fundamentally from quinine and plasmochin in its longer retention in the body. It is a dyestuff and its action on the parasites is in all probability a direct one. It has a marked affinity for the parasites to which it becomes firmly bound and on this account the amount required should be regulated by the number of parasites present rather than by the weight of the patient. Foodstuffs with abundant cellulose absorb "atebrin" and thus diminish its effect.

Carman⁷ advises that subtertian infections should be treated immediately. It is vain to hope for the development of immunity against it in European cases. "Atebrin" is as effective as quinine and costs no more. His observations were made in Kenya. He does not believe that Europeans ever develop a useful immunity to subtertian malaria. He finds that quinine and "atebrin" are equally efficient in eliminating parasites, but prefers "atebrin" for hospital use since it requires a shorter course and releases beds earlier so that 14 per cent more patients can utilize the space.

Hicks⁸ calls attention to the fact that "atebrin" munionate is the methyl sulphonic acid salt of "atebrin." Ordinary "atebrin" is the dihydrochloride. "Atebrin" munionate is sold as "Atebrin for Injection" and must
be distinguished from “Atebrin Tablets for Injection,” which consist of the dihydrochloride.

Winckel, discussing malarial therapy in the Psychiatric Clinic at Amsterdam, says that he uses an injection of a small dose (150 mg.) of neoarsphenamine to “damp down the symptoms when they tend to get out of hand.” They have abandoned the use of provocatives of malarial infections such as epinephrine.

Barbosa reports that in La Bozagona, Spain, malaria has been treated by drugs for the five-year period 1930-1934. The general conclusions were that the intensive treatment of patients suffering from tertian infections did not lessen the incidence by this type in the period under consideration. During that period all subtertian infections were given combined quinine and plasmochin and the numbers attacked increased steadily year by year. Such an increase was not seen when quinine alone was used. Consequently, he finds no advantage in giving the combined drugs.

Franchi and Sautel discuss preventive quinine during military maneuvers in a malarious district in the south of Corsica during 1934. They draw particular attention to the wastefulness of this method. If a French soldier contracts malaria he becomes automatically entitled to a pension, even though preventive quinine may have made the clinical symptoms negligible. Large doses must be given if they are to prevent symptoms; the dose used by the French in Macedonia was 10 grains daily. The advantage of preventive quinine is that the soldier can be kept fit for duty over a special period. When the quinine is stopped the patient experiences a sudden attack of malaria without any stage of invasion; the author calls it “decapitated malaria.”

Hill and Olavarria report a three years trial with a short treatment of 1 gram (15.5 grains) of quinine sulphate daily for 4 days in the dispensary at Campo Lugar, a town of 1,200 people in Spain. They think this satisfactory for tertian, but not quite long enough for subtertian infections.

Dawson, Gingrich and Hollar offer the advice that intravenous injections of “atebrin” should be given only in emergency. The injection should be given slowly, and the dose should not exceed 0.1 gram. The toxicity of “atebrin” intravenously is 20 to 40 times greater than that of “atebrin” by mouth.

Vardy gave “atebrin” musonate injections to 50 serious cases. In 32 the patients were cured in 48 hours, in two the drug had no effect and quinine was given while in two others the drug may have had a toxic effect. He states that intramuscular injections are to be preferred over the intravenous method.

Barbosa reports on the use of quinine and “atebrin” in preventing recrudescences after recurrence of benign tertian malaria. He accepts James’ definition of “re-
crudecensce" as a return of fever and parasites within 8 weeks of recovery from the primary attack; a "relapse" as a return between 8 and 24 weeks, and a "recurrence" as a return at some time later than 24 weeks. Barbosa treated 49 cases of benign tertian with quinine and a similar number with "atebrin." In each group there were 12 adults and 37 children. The dosage of "atebrin" was scaled from 0.1 to 0.3 gm. daily according to the age of the patient. Quinine was also graded, the adult dose being 1 gm. daily. Each patient was kept under observation for a period of two months following recovery from the recurrence. Seven (58.3 per cent) of the 12 adults on quinine showed a recrudescence, while the "atebrin" series had five, or 41.6 per cent. Among the children on quinine the rate was 48.6 per cent and for "atebrin" 37.8 per cent. In other words, he believes "atebrin" is more effectual than quinine in preventing recrudescence in benign tertian malaria. "Atebrin" delays the appearance of the recrudescence, the interval being fully twice as long as when treated with quinine.

Kiriłow-Drenowsky, in Bulgaria, presents some observations on a 6-day treatment with "atebrin," "atebrin" and plasmodein simplex, plasmodin Co., quinoplasmodin and quinine. He reports the method of choice to be the "atebrin" plasmodin combination, which gave only 3.7 per cent of relapses. He placed next the "atebrin" treatment alone. Next in order were quinine (25 per cent relapses), quinoplasmodin 33 per cent, and plasmodin Co. 42 per cent relapses.

Hicks and Chand treated 210 prisoners in India suffering from benign tertian and 158 with malignant tertian. The drugs used were (a) quinine, (b) totaquin Type 1 (32 per cent quinine and 11 per cent cinchonine), (c) totaquin Type 2 (19 per cent quinine and 20 per cent cinchonine). The doses, 0.6 gram daily per 70 kg. of body weight in tertian and 1.2 gram daily in subtertian. The drugs were given in tablet form. The patients had spent their lives in an endemic area of India. The results were practically the same, a mean duration of parasites of 1.5 days, and of fever, 2 days. They suggest that a dose of 15 grains once daily for 3 or 4 days would be suitable for the routine treatment of rural populations in the Punjab. This would remove the clinical symptoms, which is all the people demand.

Părvulescu and Boerin made comparative tests with two types of totaquin and with quinine sulphate. The patients were 213 young soldiers. Benign tertian cases were given 9 grains daily for 5 days, subtertian cases received 18 grains daily. Totaquin was less efficient at these doses, but when double the quantity was used they were as effective as quinine.

Marañon, Perez and Russell report on the use of totaquin in the Philippines. Cinchona with an excellent alkaloidal content can be cultivated in the Philippines, and a satisfactory totaquin can be prepared lo-
cally and sold at a seventh of the present price of quin-ine. Refined quinine is an expensive luxury that can be used as treatment only by the rich patient. Tota-quina is an excellent drug for the poor. The produc-
tion and use of totaquina would not interfere with the usual sale of other antimalarial drugs.

Vigoni reports on the use of quinine-Weil in the
Belgian Congo. The formula for this drug is C_{20} H_{24}
O_{2} N_{2} C_{16} H_{11} O_{2}N. It is free from the bitter taste
of quinine. He gave from 10 to 50 centigrams per day,
according to body weight. He concludes that quinine-
Weil (60 per cent quinine base) appears to be very
similar to quinine dihydrochloride in its action. Its
main advantage is absence of the bitter taste of quinine
and milder toxic reaction.

Massias, Bourgin and Nguyen-Van-Tan report ex-
perience with quinacrine and rhodoquine. They report
excellent results without toxic symptoms. The reader is
referred to the article for details.

Chopra, Sen and Ganguli report the use of "tebe-
tren" in India. It resembles quinine, but costs more.
It is a combination of acridine and quinine derivatives
with a derivative of cholic acid. They treated 22 pa-
tients with 3 tablets three times a day for five days
and then continued observations for a fortnight. They
found that it resembles quinine and "atebrin" in action,
but costs more and offers no particular advantage over
them.

Clark and Komp present a sixth year's report on
Chagres River malaria, where field experiments have
been continued with "atebrin" plasmoquine simplex in
one group, quinine-plasmochin simplex in a second group
with a third group for control, but the control has access
to quinine for voluntary use.

The effectiveness of the two drugs are considered
the same, but the people prefer to take "atebrin." We
have had no instances of mental derangement in the
use of "atebrin" for the three years it has been given
a trial. The present year includes 117 adults and 127
children, and many of these have had several courses
of treatment for relapse, and in these cases we give a
seven-day course instead of a five-day course. Plasmo-
chin simplex is given after the "atebrin" course has been
completed. We can keep the parasite index at almost
a constant level of 9 per cent, but there is little hope of
lowering it without additional antimalarial measures
being instituted. Our last year's experience shows that
we cannot prevent an epidemic, but the effects of the
epidemic can be held in control in so far as serious clin-
ical cases are concerned.

The bulk of our malaria this year, as in the past few
years, is confined to the same individuals or families, yet
some of these individuals will average a course of treat-
ment every other month.
It would be impossible in a hyper-endemic area such as the Chagres to apply James' idea of recrudescence, relapse and recurrence, but we feel that the bulk of our cases represent chronic carriers of the disease rather than new infections. A study of babies during the first 12 months of life supports this belief. We were able to get 12 consecutive monthly surveys on 259 people this year. One hundred four (40.1 per cent) were negative throughout the year. One hundred fifty-five (50.8 per cent) were positive at least once during the year and 58 (37.4 per cent) of these positives remained negative after treatment for the remainder of the year, but 97 (62.6 per cent) developed either reinfection or relapse from one to eight times during the year. We think they were chiefly the reappearance of the old infection. The peak of the disease is among persons from 5 to 20 years of age. It is interesting to note that we had in our group this year 68 persons over 60 years of age and 18 of these (26.5 per cent) revealed parasites in their films one or more times and two of them were clinical cases. All of these people have spent their lives in this same area. They, of course, have a very respectable degree of tolerance, but statements regarding immunity to malaria should be given careful thought. We do not fear that drug control over a period of years will deprive people of an opportunity to carry light or chronic infections, although in the past we have shared that opinion. Eradication of a malarial infection and control of one are two very different things. Our antimalarial drugs are wonderful possessions, but they cannot, alone, eradicate all infections. For the past ten years those who practice transfusions have been producing facts and cases of malaria from symptomless carriers of malaria that have extended over periods of years. Bastianelli thinks 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 and discusses the view that, in a hyperendemic district, so-called radical treatment may reduce or prevent resistance to infection.

REFERENCES


