

The sexual parasites are destroyed by small doses after a few days' administration and therefore the main function of the drug is to prevent dissemination of the disease by mosquitoes.

Plasmochin is a toxic drug and does not bear repetition too often without producing serious toxic effects.

It has been shown that 0.02 gramme of plasmochin daily for a two or at most three-days' course causes disappearance of the crescents in the peripheral blood in cases of Indian strains of malaria and prolonged use is unnecessary and dangerous.

Neither plasmochin nor atebtrin should be used for prolonged periods for prophylactic purposes.

Patients should not be allowed to use these drugs except under direct medical supervision.

There is some evidence to show that combining atebtrin with plasmochin increases the toxicity of the latter.

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## ATEBRIN IN THE TREATMENT OF MALARIA IN RAILWAY EMPLOYEES

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FROM the time of the discovery of cinchona up to 1926 when Professor Schulemann found a more effective anti-malarial remedy in a synthetic compound known as plasmochin, the only drugs that had been used effectively in the treatment of malarial fever were cinchona bark and the alkaloids obtained from it, particularly quinine.

Plasmochin had little therapeutic value in the treatment of subtertian malaria, having no action on the schizonts of *P. falciparum*, but it possessed the unique property of destroying the crescents or sexual forms. This drug had a certain value in the cure of benign tertian and quartan malaria and, to augment its curative effect, it became the practice to combine quinine with plasmochin in treating all types of malaria. Plasmochin, however, required medical supervision for its administration as it was found to be toxic and likely to give rise to severe untoward symptoms.

The introduction of atebtrin in 1929 by Schulemann and his collaborators marked a definite advance on the old and tried remedy, quinine, the newer preparation plasmochin and on the combined quinine and plasmochin treatment.

The treatment by atebtrin has been reported on by many workers to be short, simple, and effective. Such a treatment appeared to us to be most suitable for cases amongst the staff on a railway where the 'sick-man-days' lost to railway administrations due to malaria is such a burden, both financially and by loss of efficiency.

We are herein summarizing the results of a study of the effects of treatment of malaria by atebtrin and plasmochin on over 300 patients living under conditions that generally appertain to all Indian railways. In nearly all cases the patients were treated as outpatients.

The Eastern Bengal Railway traverses parts of Bengal where malaria is endemic, the cases ranging from the very mild to fulminating ones attended with fatal results. Our patients may therefore be taken to represent infection with many strains of parasites prevalent in Bengal.

The studies in this connection were undertaken mainly to determine:—

- (1) the best method of administration of the drug;
- (2) its effect on the parasites—sexual and asexual;
- (3) its effect on the temperature and other symptoms in malaria;

(4) its effect on the splenic enlargement and relapses;

(5) any untoward symptoms caused by its administration.

*Grouping.*—The patients were placed in the following three groups :—

- (1) Persons with parasites in the blood.
- (2) Persons with enlarged spleens and previous history of malaria, but with no parasites in the blood.
- (3) Persons with neither enlarged spleen nor parasites, but with definite previous history of malaria.

*Administration of treatment.*—Each group was further divided in two batches :—

(A) One batch was given atebirin only for the first five days and then plasmochin for the next five days; thus a period of ten days was required for the full course of treatment;

(B) the other batch was given atebirin and plasmochin together during the first five days; thus the period of treatment was reduced to only five days.

The dosage of these drugs was as follows :—

A. For those given atebirin for the first five days and plasmochin for the next five days.

*Adults.*—One tablet of atebirin ( $1\frac{1}{2}$  grains) three times a day for the first five days, *i.e.*, a daily dose of  $4\frac{1}{2}$  grains.

One tablet of plasmochin ( $1/6$ th grain) three times daily for the next five days, *i.e.*, a daily dose of  $\frac{1}{2}$  grain of plasmochin per day.

*Children from 1 to 5 years.*—One tablet of atebirin ( $1\frac{1}{2}$  grains) in three divided doses per day for the first five days.

One tablet of plasmochin ( $1/6$ th grain) in three divided doses per day for the next five days.

*Children from 6 to 12 years.*—One tablet of atebirin ( $1\frac{1}{2}$  grains) twice daily per day for the first five days, making a total quantity of three grains of atebirin per day.

One tablet of plasmochin ( $1/6$ th grain) twice daily per day making a total of  $1/3$ rd grain of plasmochin per day.

B. For those given atebirin and plasmochin together during the five-day course.

*Adults.*—One tablet of atebirin ( $1\frac{1}{2}$  grains) and one tablet of plasmochin ( $1/6$ th grain) in the morning, a similar dose being repeated in the afternoon and evening. Thus each adult had three tablets of atebirin and three tablets of plasmochin per day, *i.e.*, a total quantity of  $4\frac{1}{2}$  grains of atebirin and  $\frac{1}{2}$  grain of plasmochin.

*Children from 1 to 5 years.*—One-third of an atebirin tablet, *i.e.*,  $\frac{1}{2}$  grain, and one-third of a plasmochin tablet, *i.e.*,  $1/18$ th grain, in the morning, a similar dose being repeated in the afternoon and evening. Each child in this group therefore received  $1\frac{1}{2}$  grains of atebirin and  $1/6$ th grain of plasmochin per day.

*Children from 6 to 12 years.*—One tablet of atebirin ( $1\frac{1}{2}$  grains) and one tablet of plasmochin ( $1/6$ th grain) in the morning, a similar dose being repeated in the evening. Thus each child in this group received 3 grains of atebirin and  $1/3$ rd grain of plasmochin per day.

Children over 12 years were given the same doses as adults. Children under 1 year were not given any atebirin or plasmochin and are not included in this report.

*Methods adopted.*—Atebrin was given by the mouth after food either in tablet or powder form. As it leaves no lasting bitter taste in the mouth, it is readily taken by children.

The observations recorded covered a period of eighteen months from January 1933 to June 1934 and include a total of 334 patients. The patients taken up for treatment underwent a thorough physical examination, the peripheral blood was examined and the number of parasites both sexual and asexual per cubic centimetre was determined. Careful daily parasite counts were made in one series of 17 cases. In the rest, the blood was examined before treatment, on the fourth day of treatment and after treatment. A special dispenser was deputed to see that the prescribed doses were swallowed in his presence and in no case were the drugs given to the patients to be taken in the absence of the dispenser. No other drug was given except a purgative, when necessary, and no restrictions regarding diet were observed.

As all the patients were railway employees or their dependents, living in the railway colonies, they were under close observation after the completion of the course of treatment and in a large number of cases it was possible to make fortnightly examinations of the blood after the end of treatment. Though plasmochin has its special value in destroying the gametocytes of subtertian malaria, we made it a rule to give both atebirin and plasmochin in all forms of malaria for reasons to be explained later.

*Results of treatment.*—In group I, there were 143 cases with positive parasite findings—118 subtertian, 14 quartan, 10 benign tertian, and one mixed subtertian and quartan; out of these, 114 were given atebirin and plasmochin separately (group I-A), while 29 others received atebirin and plasmochin together (group I-B).

A study of this group shows that cases of all three forms of malaria responded equally well. The temperature usually came down on the second or third day of treatment, and on the fifth day there was complete disappearance of the parasites from the peripheral blood. After the fourth day of administration of atebirin, rigors were seldom observed. Atebrin caused a gradual reduction in the number of asexual parasites though in some cases (in 4 out of 17 cases in which daily counts were made—of group I-A) the asexual forms increased on the second or third day before finally disappearing on the fifth day. Very little difference was noted in the temperature records whether the case was treated with atebirin alone, or in conjunction with plasmochin, as the temperature came down within 48 to 56 hours in every case, showing thereby that atebirin adversely affects the asexual forms of all species of malaria parasite equally well.

On the sexual forms, atebirin has a slower action. Gametocytes of benign tertian and quartan disappear much more quickly than subtertian, while those of subtertian persisted even on the fifth day (in three cases of group

I-A). In some cases of subtertian, the gametocytes had however disappeared on the second or third day. It is therefore possible that atebirin may have some delayed action on the gametocytes of subtertian as they were noted to disappear by the eighth day in the three cases in which they had persisted up to the fifth.

Of the 66 chronic cases with enlarged spleen and without parasites in the blood (group II), there was rapid and perceptible reduction in the size of the spleen in 56 cases. Most of the spleens of two and three fingers were reduced to practically normal size. In two cases of group II-A which had six- and five-finger spleens, respectively, these were reduced to normal size, but the decrease in size was more gradual in long-standing cases and the spleen did not decrease to its normal size. The remaining ten cases in this series of 66 showed no reduction in the spleen size.

In chronic cases, the action on the temperature curve is less marked than in acute ones.

Group III consists of cases diagnosed only clinically, *i.e.*, there were neither parasites in the blood nor enlargement of the spleen, but there was a definite history of clinical malaria. These responded equally well to the treatment, the only noticeable difference being that in some cases the temperature persisted for a longer time than is usual in cases with positive parasite findings. It is probable that several of these clinical cases are chronic in nature, and as such the effect on the temperature was less marked than in acute cases with parasites.

*Relapses.*—On the Eastern Bengal Railway a relapse is considered as a return of febrile symptoms with parasites in the blood within a period of 12 months since the attack for which the treatment was undertaken. Although the figures, as far as the relapse rate is concerned, are obtained from the staffs of stations under malaria control, the control is not such as to absolutely exclude reinfection. Therefore the relapse rate figure is probably too high.

Of the 334 cases, 50 have 'relapsed' giving a 'relapse' rate of 14.9 per cent. Two cases in group I-A and one in group I-B relapsed within a month of the completion of treatment. All the patients who relapsed are from some of the most notoriously malarious places in Bengal, *viz.*, the Dooars and Terai of Bengal. Some of the cases occurred in 'running' staffs, *i.e.*, staffs not confined to one station, but engaged on travelling duties.

Though it is difficult to exclude the possibility of fresh infection, it should be noted, however, that the three cases of relapse cited above occurred within a month of the completion of treatment. Even granting that they may not be real relapses but fresh infections, such infection must have taken place before the atebirin had been fully excreted from the body, as the

drug can be detected in the urine up to 20 days or even longer. The data in our possession are yet too meagre at present to pronounce any definite opinion on the question of relapses after atebirin. We have this year instituted a systematic treatment with these drugs in the Calcutta Medical District of the Eastern Bengal Railway and are collecting statistics that might enable us to understand this aspect better.

It so happened that in November 1933 there was an accidental shortage of plasmochin and 22 cases (20 malignant tertian and 2 benign tertian not included in the series here reported) were treated with atebirin only. Curiously enough the two benign tertian cases have relapsed although none of the benign tertian cases of the 143 patients treated with atebirin in conjunction with plasmochin (group A) have relapsed so far. This suggests that even in benign tertian cases atebirin and plasmochin administration is better than giving atebirin alone. It is anticipated that the relapse rate will be still less with the two drugs than with one alone.

It may not be out of place to point out that although one can rely on a trained medical subordinate to spot a malarial parasite, such reliance cannot always be placed on his ability to spot the species of the parasite. On a railway system, patients are scattered, being at different places, and the identification of malarial parasites has perforce to be made by medical subordinates of varying grades of ability. In view of the fact that the inclusion or non-inclusion of plasmochin in the treatment depends on the correct identification of the subtertian parasites, and that there is a great possibility of errors in this direction, and in view of the probable decreased relapse rate in benign tertian cases if plasmochin is also given, there would seem to be sufficient justification for treating all cases of malaria with atebirin in conjunction with plasmochin, on railway systems at any rate.

*Untoward and toxic symptoms.*—Such symptoms when they occurred consisted of varying degrees of gastric pain, vomiting and yellow pigmentation of the skin. Of the 334 patients treated, 258 received atebirin and plasmochin separately, *i.e.*, atebirin for the first five days followed by plasmochin for the next five days. Of these 258, fifteen cases exhibited the following symptoms:—

- Five complained of slight pigmentation of skin.
- Six complained of slight gastric pain.
- One complained of moderately severe gastric pain.
- Three complained of severe gastric pain and yellow pigmentation of skin.

None of these symptoms was of any consequence. The severe gastric pain complained of disappeared after a liberal dose of sodium bicarbonate with tincture of hyoscyamus. On the percentage basis it may thus be stated that 5.8 per cent of those treated with atebirin and

plasmochin separately exhibited untoward or toxic symptoms. The remaining 76 cases received atebirin and plasmochin together during the five days' course, *i.e.*, atebirin and plasmochin were swallowed at the same time according to the dosage. In this series 16 persons, or 21.05 per cent, exhibited untoward symptoms. Of these one had extremely severe gastric pain, vomiting and slight collapse, while the others complained of gastric pain of moderate to slight intensity and pigmentation of the skin.

Pregnant women bear the drugs well. Persons exhibiting a high degree of idiosyncrasy to quinine can take these drugs without any discomfort. One patient could not tolerate a grain of quinine and was a constant sufferer from malaria; she was given atebirin and plasmochin together for five days more than a year ago, and ever since has been keeping well.

*Cost of treatment.*—The actual cost of one course of atebirin and plasmochin for an adult is Re. 1-11-8. As against this, the cost of one course of quinine treatment for three weeks is Re. 1-11-4½; but from the view-point of the saving in hospital costs, and reduction in the time lost by the patient, it is certainly a cheaper method of treatment than quinine.

#### *Summary and conclusions*

1. Atebrin and plasmochin are effective in the treatment of malaria due to all strains of plasmodium in Bengal.
2. It is uncommon to find a temperature above 99°F. after 48 hours' treatment.
3. With the exception of subtertian gametocytes it is rare to find malarial parasites in the blood after the third day of treatment.
4. In subtertian malaria plasmochin also should be given owing to its specific action on the subtertian gametocytes.
5. In the absence of absolute certainty regarding the species of parasite, it is beneficial to use atebirin with plasmochin in all forms of malaria.
6. Atebrin produces a rapid reduction in the size of the spleen.
7. People exhibiting idiosyncrasy to quinine tolerate atebirin with plasmochin well.
8. Atebrin given alone occasionally produces certain untoward symptoms which are seldom serious.
9. Atebrin and plasmochin given together cause untoward symptoms in a larger percentage of cases and the symptoms are more severe.
10. It is safer to give atebirin for the first five days followed by plasmochin for the next five days.
11. The cost of treatment is on the whole less than treatment with quinine.

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### NOTES ON AN EXPERIMENT ON THE PROPHYLACTIC AND CURATIVE VALUE OF ATEBRIN AND PLASMOCHIN THERAPY IN A TEA GARDEN IN ASSAM\*

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*Introduction.*—Malaria is a serious problem in all industrial concerns in India, especially in the tea industry. It is responsible for the loss of many working days, especially at a time when a tea garden can hardly afford it, not to speak of children's deaths, anamia, loss of vitality and weakening of the power of resistance to other diseases. The necessity of malaria control is appreciated by all, but it is a very difficult problem to face. Moreover it is probably not realized by many that in order to form an accurate opinion regarding the practicability of permanent malaria control in any given locality, mature judgment, wide experience and a thorough knowledge of anti-malarial measures are required. Also the ability of the authorities concerned to provide large funds for it and the cost of maintaining it subsequent to its adoption have to be considered. Hence in many tea estates temporary anti-malarial measures are adopted of which drug prophylaxis is one. For about the last seven years plasmochin, and for about two years atebirin, have gained prominence in this respect and many papers have appeared as to the value of these drugs from various parts of the world with such varying results that we decided to make an experiment ourselves and form an opinion of our own as to the efficacy of these drugs as prophylactic and therapeutic agents in this locality. Bokpara Tea Estate of the Budla Beta Tea Company, Limited, was selected for this experiment and Colonel H. C. Garbett, C.I.E., V.D., superintendent of the company, kindly obtained the sanction of Rs. 1,000 for this purpose.

\*Read at a meeting of the Assam Frontier and Budla Beta Medical Society held on 11th October, 1934.

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The treatment of malaria with atebirin and plasmochin is a distinct advance. The treatment is simple, short and economical. The consistent use of this drug should effect a considerable reduction in the number of malaria cases and the consequent loss of working days due to this disease on Indian railways.