Observations

ON

THE CURE OF MALARIA WITH ATEBRIN

BY

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The production of atebtrin, a drug far more effective than quinine in that it apparently eradicates the malaria parasite in man as a rule after only five days' treatment, is an event in the history of tropical medicine. According to R. Green, malaria research officer of the Institute of Medical Research, Kuala Lumpur, it is not unlikely that in the molecular synthesis of atebtrin the quinoline nucleus (common to both quinine and plasmoquine) has been retained, and that one of the acridine compounds allied to acriflavine has been incorporated. A paper published by Green,¹ together with a synopsis of the German literature on atebtrin and a supply of the drug received from Dr. K. Koenig of Singapore, led me to give this drug a trial on some of the estates under my charge between June and August, 1932. My results² were so favourable that atebtrin, and not quinine, is now the drug in ordinary use for the treatment of malaria on estates served by the Malacca Agricultural Medical Board, comprising an area of nearly 150,000 acres.

PREVENTION OF MALARIA

The primary aim of both the estate medical officer and the planter in Malaya is to prevent malaria by anti-malarial drainage, by oiling of the breeding places of malaria-carrying anophelines, and in some places by the use of mosquito curtains or screening. Though these anti-mosquito measures have proved so valuable that they are being retained even in these days of extreme compulsory economy, a more effective drug than quinine for the radical cure of malaria is indispensable for fuller success.

It has been clearly proved that prophylactic quinine, whether administered daily or at intervals, is a delusion and a snare: no amount of quinine will prevent the development of malaria in a person who has been newly infected. This practice has been entirely abandoned on Malacca estates. Quinine owes its past reputation as a prophylactic to the fact that many of those dosed with it were in fact actually infected with undiagnosed malaria: in such cases it was very useful. For the cure of malaria quinine, though for centuries the best drug available, involves a lengthy and debilitating course of treatment, followed by a high relapse rate. Atebrin, combined with plasmoquine if the malaria is subtertian in type, and reinforced in certain grave cases with quinine administered by injection, appears to effect a complete cure within less than one week in 95 per cent. of cases treated.

THE PROBLEM IN MALACCA

The population with which my colleagues and I deal consists of over 19,000 rubber estate labourers and dependants, and of the staff—European and Asiatic—with their households, numbering over 800, who control the estates. The following figures show the recent incidence of malaria among labourers and dependants, who are known as the labour population.

Most of those appearing under the heading "Out-patients" are relapse patients who, after a chill, have one or two days' fever; in this category are also included a number of the primary cases occurring on Asiatic estates where there are no hospitals. Grave cases on these estates are generally sent into Government hospitals, as evidenced by the few deaths among malaria cases

treated as out-patients—four in 1931 and three in 1932. The majority of European estates, on which over two-thirds of the labour population, including the great majority of Southern Indians, work, have their own hospitals. The weekly use of antimalarial oil to spray anopheline breeding grounds within the danger zone of

Year	Average Labour Population	Cases of Malaria		Deaths from Malaria
		Out-patients	In-patients	
1931	21,553	1,877	934	35 (4 in lines)
1932	19,511	1,364	545	21 (3 in lines)

the coolie lines is almost universal on such estates, where a good deal of antimalarial drainage has also been done in the past. (Antimalarial oiling is the exception rather than the rule on Asiatic-owned estates.) Owing to the widespread reduction in labour forces, many sickly coolies have also been repatriated.

The result of these two factors, combined with early and effective treatment of the sick, is shown by a spleen rate of only 4.2 per cent. among 9,722 Southern Indians examined at the last half-yearly musters on European estates. The spleen rate among a thousand-odd Southern Indians employed on Asiatic estates was, however, over 20 per cent. About 1,400 Chinese work on European-owned estates, and the spleen rate among those examined was 4.27 per cent.; while on Asiatic estates, where some 4,300 Chinese are employed, it was 8.34 per cent. About 1,200 Malays work as estate labourers; nearly all these live in their own kampongs, to which they return daily. As is natural, the spleen rates for these workers were almost identical on European and Asiatic estates, being 12.8 per cent. on the former and 11.64 per cent. on the latter. Many Malays have acquired a partial immunity due to repeated attacks of malaria in childhood; this is probably the reason why their spleen rates are so much less than those of Tamils working on Asiatic-owned estates. The high spleen rate among the Southern Indians on Asiatic estates reveals the lot of the careless labourer who, unprotected by oiling, does not avail himself of a mosquito curtain. The Chinese coolie, on the other hand, uses a mosquito curtain, has more stamina, feeds better, and knows how to look after himself. The result is that, placed in the same position as the Tamil, he shows less than half the spleen rate.

TREATMENT OF MALARIA WITH ATEBRIN

For the actual treatment of malaria reliance has hitherto been placed on that old and tried remedy quinine. On European estates the sufferer from primary malaria has received full doses in hospital for perhaps ten days, followed by smaller doses, for perhaps three weeks, in the lines. He has been given more quinine when at labour inspections he has been found to possess an enlarged spleen. And yet, with all this dosing, it is well known that over 50 per cent. of sufferers so treated relapse and have further attacks of malaria, in some cases repeatedly, and for years after the original infection. There are several notable disadvantages attending the use of quinine—such as the long continuance of the treatment, the difficulty of carrying this out, the lowering effect on the vitality of its continued administration, the great liability to relapse, and, finally, the expense.

Beginning the trial of atebtrin in June, 1932, I have found that it has apparently brought about a permanent cure in the great majority of 153 malaria cases treated by me between that month and the end of the year. Two of my colleagues, Dr. I. D. Stubbs and Dr. Foo Hee Seng, who started to use the drug in August, 1932, have had

similar results among 163 cases treated by them. Our combined figures are:

Total Cases Treated	Type of Malaria				Relapses
	Subtertian	Benign Tertian	Quartan	Unclassified	
317	98	114	5	100	11

Eighteen of the ninety-eight patients under the heading "Subtertian" were cases of mixed infection, showing benign tertian parasites as well. In four subtertian cases, in which cerebral symptoms appeared, I administered from two to six doses of quinine bihydrochloride intramuscularly, with one death. The "unclassified" patients were mainly on estates where no microscope was available, but were clinically cases of malaria. The figures for relapse up to the end of March, 1933—that is, over nine months after the first case and three months after the last case was treated—are eleven. The relapses usually occurred within two months of the first treatment, the types of malaria in which these were noted being subtertian (three), benign tertian (two), unclassified (six).

Relapse Rate

There is little movement among labour forces at present, and it has therefore been possible to keep in touch with the great majority of those treated. Deducting, however, the liberal allowance of 20 per cent. from the total 317 patients treated, on account of persons since lost sight of, there remain 253 treated and still under observation, with eleven relapses—a relapse rate of 4.34 per cent. All persons once treated with atebtrin and having further malarial attacks have been counted as relapses, though some may have been fresh infections. Of the eighteen cases of mixed infection, eleven occurred on one division, where there was a violent outbreak of malaria due to a temporary failure in oiling—thirty-eight out of a population of sixty-seven being affected within one month. Microscopical findings were: fourteen subtertian (of whom eleven showed benign tertian parasites also) and twenty-four benign tertian. In spite of so many double infections, there has not been a single relapse on this division, though seven months have passed since treatment was given.

Death Rates

A comparison of the labour death rates among those treated in hospital with quinine and with atebtrin respectively is of interest. In 1931, 934 cases of malaria were treated in hospital, all with quinine: 10 grains of the sulphate or bihydrochloride were given in solution three times daily for nine or ten days, followed usually by small doses of quinine in the lines for three weeks. Deaths numbered thirty-one; death rate, 3.31 per cent. In 1932, 288 patients were treated in hospital with quinine, of whom fourteen died; death rate, 4.85 per cent. Of the 317 patients who received atebtrin, 257 were treated in hospital, with four deaths—a death rate of 1.55 per cent. Both the relapse rate and the mortality rate, therefore, favour atebtrin treatment. Of the labour population, averaging 19,511 last year, two-thirds were Southern Indians—mostly Tamils—less than one-third were Chinese, and about 1,200 were Malays; 85 per cent. of those treated with atebtrin were Tamils.

Staff Treated

In addition to labour, eight Europeans, including two ladies, and ten members of the Asiatic staff were treated for malaria with atebtrin in the last half of the year 1932. All found it easy to take, and experienced a sense of well-being after it. None has so far relapsed.

Particulars of Treatment

A course of atebtrin lasts as a rule for five days only. The daily amount administered is 0.3 gram ($4\frac{1}{2}$ grains) for adults and for children over 11, 0.1 to 0.2 gram ($1\frac{1}{2}$ to 3 grains) for children of 5 to 10 years, and 0.035 to 0.1 gram ($1/2$ to $1\frac{1}{2}$ grains) for children of 1 to 4 years, and is given in three divided doses. In addition, plasmoquine is prescribed in subtertian cases only, also for five days—0.03 gram ($1/2$ grain) daily for adults in three divided doses; children of 11 receive only half this dose of plasmoquine, and younger children proportionately less. The bowels are kept freely open throughout. The tablets of atebtrin and plasmoquine are crushed and taken with a drink of water half an hour before meals. Most patients are also dosed with oil of chenopodium to remove their ankylostomes, and those who need it have santolin to relieve them of round-worms. At the conclusion of the treatment patients are placed on an iron and arsenic tonic. No quinine has been given with atebtrin by me, except by injection in a few severe cases.

ADVANTAGES OF ATEBRIN

The points in favour of the use of atebtrin in place of quinine are:

1. The fever is usually reduced as quickly as with quinine: it is uncommon to find a temperature above 99° F. after forty-eight hours' treatment. In two cases only did fever persist as long as the fifth day; for these atebtrin was continued for eight days.
2. With the exception of subtertian gametocytes, it is rare to find malarial parasites in the blood after the second day of treatment. No parasites of any description were found in the blood of any hospital case on the conclusion of treatment.
3. The treatment is short, simple, and effective—one $1\frac{1}{2}$ -grain tablet three times a day for five days only, as against a prolonged course of quinine.
4. The drug is not unpleasant to take, and is not depressing. It is well tolerated, even by pregnant women and young children and in blackwater fever, and also by persons suffering as well from other diseases such as pneumonia and influenza.
5. Relapses are rare after atebtrin, while with quinine the relapse rate is high.
6. The cost of a course of atebtrin (fifteen tablets) is about 75 cents (1s. 9d.), that is, less than the cost of a course of quinine—one ounce, about \$1 (2s. 4d.)—not to speak of the cost of treating the frequent relapses when quinine is used.
7. In malaria of the benign tertian and quartan types atebtrin only is necessary.
8. When malaria is subtertian in type it is necessary to give a five-days' course of plasmoquine in addition to atebtrin (cost about 43 cents, 1s.), but this is also needed when quinine is employed, as subtertian gametocytes are unaffected by either quinine or atebtrin.
3. Last, but not least, atebtrin is a powerful preventive of malaria in the sense that most of those treated with it, being cured, are rid of the infection and completely non-infective to their fellows. It may well prove that the regular use of atebtrin—plus plasmoquine in subtertian cases—for the cure of malaria will lessen the amount spent on antimalarial drainage and oiling.

LIMITATIONS OF ATEBRIN

Are there any serious disadvantages in the use of atebtrin? So far as my experience goes, "No." A few patients have colicky pains about the last day of treatment, and a few show a temporary yellow discoloration of the skin and conjunctiva, due not to jaundice, but to the fact that atebtrin contains a yellow dye. No form of the drug suitable for injection is yet available; consequently, in very severe cases of malaria, it is advisable to administer one or several doses of quinine, generally by intramuscular injection. Some medical men, though now using atebtrin for malaria, are prescribing quinine during the first two days of treatment. This may be quite sound, but personally I have as far as possible employed

atebrin alone in order to test fully the value of that drug without quinine.

In a progress report issued locally in November, 1932, R. Green³ states that both benign tertian and quartan parasites, including gametocytes, disappear from the blood more quickly with atebrin than with quinine. In subtertian malaria the rings disappear either with quinine or with atebrin in about three days. The febrile period in all types is slightly shorter with atebrin than with quinine, but, pending the cessation of febrile symptoms, the temperature among some of the subtertian cases seems to remain on the whole somewhat higher, and the patient to be more prostrate, than with quinine. The subtertian infection varies from the very mild case to the fulminating case, attended with fatal results whatever the form of therapy. In the small but certain proportion of subtertian cases which show alarming symptoms, Green regards it as at present advisable to administer quinine for two or three days as a preliminary to atebrin.

Green's Relapse Rates

Among forty-three patients who had 30 grains of quinine bihydrochloride a day for seven days, and were under observation for a maximum of forty-six days, Green's record is:

	Total cases	Relapses
Benign tertian	12	6
Subtertian	13	5
Quartan	18	5

Among forty-eight cases receiving a six-days' course of atebrin, and kept under observation for a maximum of eighty days (seventeen being benign tertian, twenty-three subtertian, and eight quartan), Green observed one relapse—a benign tertian case on the thirty-second day after treatment.

ATEBRIN IN SPLENOMEGALY WITHOUT MALARIA SYMPTOMS

On the presumption that an enlarged spleen indicates a latent malaria infection, it has been usual to give a course of quinine to all newly engaged local coolies with enlarged spleens, and to all coolies and dependants found in a similar state at periodic examinations of labour forces. Towards the end of 1932 I gave instead a five days' course of atebrin to forty-nine such cases; the first twenty-five were admitted to hospital, the other twenty-four were treated in the field. None of these has since developed malaria.

During the present year I am prescribing for the majority of patients with enlarged spleens a course of atebrin in the lines without taking them off work: one tablet is administered in the morning and two in the afternoon. A careful record is being kept: no further atebrin and no quinine will be administered to these cases—even if the spleen continues enlarged—unless an attack of malaria occurs.

CONCLUSION

The treatment of malaria with atebrin is short, simple, and economical. Most sufferers appear to be cured within a week. The consistent use of this drug should effect a great and permanent diminution of malaria among labour forces by sterilizing most of the reservoirs of infection.

I am grateful to Dr. Green for valuable information, and to my colleagues for their records.

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TREATMENT OF MALARIA BY PLASMOQUINE AND QUININE

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TRINIDAD

A remedy that will invariably cure malaria after a single course of treatment has yet to be found, unless the new preparation, atebrin, which is still on its trial, proves superior in this respect to the drugs at present in use. In the Tropics the assessment of the value of anti-malarial treatment is generally rendered difficult owing to the frequent presence of other diseases, the often poor living conditions of the patient, the difficulty of giving a prolonged course of treatment, and the liability to re-infection. In temperate climates patients are often lost sight of after treatment owing to their return to the Tropics, and in the event of a relapse they may fail to return to the prescriber of the original course of treatment. Control over any lengthy period is therefore the exception, while most of the cases treated must inevitably be cases of relapse. It therefore appeared to me that a high percentage of "cures" obtained with a standardized course of treatment under unusually well-controlled conditions might be of some general interest.

Malaria in Trinidad is the largest single cause of death. In 1931 this disease was responsible for 734 deaths out of a total of 5,374 (Registrar-General's Report for Trinidad and Tobago, 1931), and it must accordingly be assumed that the disease here is of a moderately severe type. All the cases in the accompanying table are those of members of the staff (including dependants) of an oil company operating in Trinidad. These form only a small percentage of the total cases of malaria treated, the disease being far more common among the labourers; but, for reasons stated above, the latter are unsuitable for the purpose of this paper. The total number of staff and dependants in this company is approximately 200, living in several widely scattered "fields" in the south of the island. All cases of illness occurring on these "fields" are bound to be reported to me, and thus no case of relapse could fail to come to my notice. The living conditions of these people are good. Comfortable mosquito-proof bungalows are provided, none of which is situated in a malarial area, and infection with this disease is therefore only accidental. Other tropical conditions are rarely found among them, and the general health is excellent. While all three varieties of malaria parasite are found in Trinidad, quartan infection is in my experience unusual, while benign and subtertian are almost equally common, though each predominates in its respective areas.

In the cases shown in Table I the attacks have generally been severe, with maximum temperatures of 103° to 105° F., the fever lasting three to four days. In no case has the fever persisted longer than the fifth day of treatment or risen again subsequently. I have for long been of the opinion that fever which did not respond to suitable treatment within five days was due to some cause other than malaria, providing the drugs administered were being absorbed. In nearly all cases the fever was of a remittent type, the regular intermittent fever frequently associated with relapses being notably absent. This was to be expected in a series where most of the cases were primary. In no case was an injection of quinine found necessary. I limit such injections entirely to cases in which administration of drugs by mouth is impossible owing to intractable vomiting, delirium, or coma. The treatment prescribed has been in use for over three years, and is the outcome of a trial of a number of different combinations of quinine, plasmoquine, and arsenic. No case of