Original Articles

ATEBRIN IN THE TREATMENT OF INDIAN STRAINS OF MALARIA

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FROM the time of the discovery of cinchona up to a few years ago, cinchona bark and the alkaloids obtained from it, particularly quinine, were the only drugs that had been used effectively in the treatment of malarial fevers. These alkaloids, although effective in many respects, are very bitter in taste, have to be given in fairly large quantities, and produce unpleasant by-effects. Besides this, although they destroy the asexual forms of different malarial parasites, they unfortunately have little effect on the sexual forms and no effect whatsoever on the gametocytes of the malignant tertian parasite. In quartan malaria their effect, even on the schizonts, is less powerful and they sometimes fail to relieve the paroxysms. Many other remedies have been introduced from time to time, but none of these have proved effective. The shortage of quinine was especially felt during the Great War and research with the object of finding a synthetic drug that could be used in its place was considerably stimulated. It was therefore a great event when, in 1926, a synthetic compound known as plasmochin (or plasmoquine) was discovered by Professor Schulemann of the Bayer-Meister Lucius research laboratories at Elberfeld. Chemically, this preparation is an amino-quinoline derivative in which a basic aliphatic radicle is united to a quinoline nucleus by a connecting link of nitrogen. This drug could be given in very small doses and has not a very bitter taste. It was at first thought to have a definite curative effect in the treatment of all forms of malaria, but later experience showed that while it was effective in curing benign tertian and quartan malaria, by itself in sub-tertian it was of no therapeutic value because it had no action on the schizonts, and some observers went so far as to say it had a provocative action. It however possessed the remarkable and unique property of destroying the crescents in the peripheral blood. In this type of malaria therefore it was still necessary to use quinine, in fact the two drugs were combined, the quinine for the schizonts and plasmoquine for destroying the crescents, to prevent the patient from acting as a source of infection.

Although the cure of benign tertian and quartan malaria is brought about more effectively by plasmochin than by quinine, the tendency is, in order to obtain the maximum effects, to treat even these two infections with a combination of quinine and plasmochin—quino-plasmochin as it is called. With the two drugs together the relapse rate in benign tertian infections is said to be reduced from the usual 50 per cent to 3 per cent. Plasmochin is also said to have an undoubted prophylactic value whereas quinine has none. With all these qualities, however, it is very toxic and may give rise to severe toxic symptoms and for this reason it is advisable that it should be taken under medical supervision.

Schulemann and his collaborators therefore continued the work with renewed energy towards finding a more effective anti-malarial remedy, and in 1929 synthesized atebrin which originally they called 'erion'. Chemically this preparation is the di-hydrochloride of an alkylamino-alkylamino-acridine derivative. It is a yellow powder with a bitter taste, soluble to 7 per cent in water at 40°C., and like quinine it shows fluorescence under ultra-violet radiation. Since its introduction it has been extensively tried by a large number of workers in every part of the world with good results. This drug is now being largely used by medical practitioners in India, but its detailed effects on the Indian strains of malarial parasites have not been fully investigated, although Napier and Das Gupta (1932), Napier, Butcher and Das Gupta (1932) and Knowles and Das Gupta (1932) carried out detailed studies regarding its action on a small series of cases.

It has been recently shown by James (1932) and others that the action of anti-malarial drugs varies a great deal with different strains of parasites occurring in different parts of the world. James' Madagascar strain failed to react to quino-plasmochin in the same way as other strains, and there are many other examples.

In view of the fact that atebrin is beginning to be considered as effective as quinine and its use is likely to be considerably extended in this country, we took up a detailed study of the effects produced by it in a series of patients in the Carmichael Hospital for Tropical Diseases. In Bengal, malaria is endemic and in certain parts a very virulent type of malignant tertian malaria is prevalent. Our patients came from different parts of the province and probably represented many strains of parasite prevalent here. In this paper we have briefly summarized the results we have obtained by treatment of malaria with this drug. Extensive chemotherapeutic studies have also been carried out on monkey malaria, but these results will be presented in a separate paper.

The studies in connection with human malaria were mainly undertaken to determine :—

(*a*) The effects of the drug on the temperature and other symptoms met with in the disease.

(*b*) Its effects on the sexual and asexual forms of the parasites, and time taken for their disappearance from the peripheral blood.

(*c*) Its effect on the splenic enlargement and relapses.

(*d*) The effect of the drug on the pulse rate, blood pressure, respiration, and generally on the patients, and its excretion from the body.

(*e*) Any untoward effects produced by its administration.

The patients suffering from malaria were admitted under the senior author (R. N. C.) and a thorough physical examination was conducted immediately after admission. The peripheral blood was examined and the number of parasites, both sexual and asexual, per cubic centimetre was determined. Except in urgent cases the anti-malarial treatment was not started until the parasitic counts were fairly constant for two or three consecutive days. The pulse, blood pressure and respiration were carefully recorded. In the meantime the patients were put on a simple alkaline mixture. Daily counts of parasites in the peripheral blood during this period enabled us to watch the progress of the cases and gave us information regarding the intensity of the infection. If the parasites in the peripheral blood were scanty, these were allowed to increase till the count was fairly high, and rigors and other symptoms were produced, before the drug was administered. Atebrin was given by the mouth in tablet form, one tablet containing 0.100 gramme being given three times a day for five consecutive days. No other drug was given except a light purgative whenever necessary. No restrictions regarding diet were observed. Careful daily parasite counts were made while the drug was being administered in one series of 18 patients, but in another series of 20 cases only a rough estimation of the number of parasites in the peripheral blood was made daily.

After completion of the course the patients were carefully observed in the hospital for a fortnight, daily examinations of the blood for parasites and parasitic counts being made. If the thick and thin films were negative, in suspicious cases cultural examinations of the blood for malarial parasites were always made. In addition to the cases reported here in detail, atebrin was given to a number of out-patients and it was on these that some of the by-effects reported below were noted.

In table I the details of 18 cases are given. A study of this table will show that cases of acute infection of all three forms of malaria and some of the relapsing cases, all responded equally well to this drug. Usually the temperature begins to settle down on the second or third day of treatment and on the fourth day there is complete disappearance of the parasites from the peripheral blood. Rigors are seldom observed after the third day of administration of atebrin. In mild cases of benign tertian infections if atebrin treatment is started on the day of the rigor, the next rigor is sometimes manifested in the form of a chilly sensation only, and in cases infected with the quartan type it does not come at all. In relapsing cases the temperature takes longer to settle down than in acute fresh infections.

A study of the table will show that the action of atebrin on the asexual forms of the parasites is gradual and not so rapid as that of quinine. It generally takes 0.6 to 0.9 gramme of the drug (*i.e.*, the administration of 3 tablets for 2 or 3 days) before the asexual forms of benign tertian disappear from the peripheral circulation. Its action on the quartan parasites is as powerful as on the benign tertian (*vide* cases 12, 13, 15 and 17). On the asexual forms of malignant tertian parasites atebrin appears to act just as readily as on the schizonts of benign tertian.

As regards the sexual forms—gametocytes—these were much more slowly acted upon than the asexual forms, the action being marked on the benign tertian and quartan gametocytes, but absent in the case of the malignant tertian gametocytes, as is the case with quinine. That the drug had no effect whatsoever on the sexual forms of malignant tertian parasites—crescents—is clearly indicated by their persistence in cases 2, 4, 9 and 10 after a full course of treatment with the drug. That the drug adversely affected the sexual forms of benign tertian and quartan parasites is obvious from a number of cases in which definite evidence of degeneration could be detected in the gametocytes.

Patient no. 8 was a young child; he vomited his first dose of atebrin, but the drug was continued and he apparently retained the later doses. The fever fell to normal after 60 hours, but subsequently rose again daily to 99° or 99.4°F.; scanty parasites also persisted.

Patient no. 9 is of special interest as he had a very high parasite count and was in danger of going on to the pernicious type. An intravenous injection of 0.1 gramme of atebrin dissolved in 1 cubic centimetre of distilled water was given at once as well as a tablet by the mouth; this was repeated on the two following days. The asexual parasites rapidly decreased in number and the temperature came down. No untoward effects were observed after intravenous administration of the drug and it would appear that the action is more rapid when given by this route.

Patient no. 10 had a mixed infection with benign tertian and malignant tertian and responded to the treatment less readily than in the case of single infections, the schizonts persisting for four days after the administration of atebrin.

Patient no. 11 was treated in the hospital for benign tertian malaria with atebrin 3 months ago, and came in with a fresh malignant tertian infection.

The observations recorded above were corroborated by results obtained in a further series of 20 cases details of which are given in table II. In this series it was not possible to enumerate the parasites daily as in the series given

TABLE I

No.	Race, sex and age	Recent treatment given or not	PARASITE, PARASITE COUNT PER C.MM. AND TEMPERATURE BEFORE TREATMENT				PARASITE COUNT AND TEMPERATURE DURING AND AFTER TREATMENT								Days of fever	REMARKS
			Species	Asexual	Sexual	Temp. F.	2ND DAY		3RD DAY		4TH DAY		5TH DAY			
							Asex.	Sex.	Asex.	Sex.	Asex.	Sex.	Asex.	Sex.		
1	E. M., 50 ..	Yes	B. T.	9,840	180	102.8	6,240	240	1,760	640	0	40	0	0	2	
2	H. M., 27 ..	Yes	M. T.	9,240	0	103.4	240	0	840	Sc.	0	160	0	80	3	Crescents persisted.
3	H. M., 20 ..	No	B. T.	16,340	480	102	9,900	340	800	80	0	0	0	0	2	
4	M. M., 22 ..	No	M. T.	2,400	1,400	100.2	..	..	..	..	0	Sc.	0	Sc.	3	Do.
5	H. M., 16 ..	No	B. T.	30,000		104.6	5,200		0	0	0	0	0	0	2	
6	H. M., 40 ..	No	M. T.	8,800	0	99	6,400	0	..	..	..	..	..	..	..	Absconded.
7	M. M., 30 ..	No	B. T.	28,000		100.4	0	..	..	..	..	..	..	..	2	
8	I. Ch. M., 7 ..	No	M. T.	14,200	..	..	..	..	0	..	Sc.	..	..	..	7	
9	I. Ch. M., 18 ..	No	M. T.	128,000	0	105	..	..	0	Sc.	0	Sc.	0	Sc.	..	Crescents persisted.
10	A. I. M., 20 ..	No	B. T. and M. T.	98,000	1,800	105	15,700	2,400	1,600	1,840	1,020	2,400	0	2,000	4	Do.
11	H. M., 14 ..	Yes	M. T.	12,560	440	104	2,800	480	0	884	0	Sc.	0	Sc.	2	Do.
12	H. F., 18 ..	No	Q.	3,520		100.2	1,440		880		0	..	..	0	3	
13	H. M., 22 ..	No	Q.	1,000		98	560		80		0	..	..	0	3	
14	A. I. M., 26 ..	No	B. T.	21,400	0	100	10,000	Sc.	Sc.	0	0	0	0	0	2	
15	H. F., 18 ..	No	Q.	800		98	420		0	0	0	0	0	0	2	
16	M. M., 35 ..	Yes	B. T.	9,840	0	103	1,200		0	0	0	0	0	0	2	
17	H. M., 27 ..	No	Q.	2,400	0	103	Sc.		Sc.		0	0	0	0	2	
18	M. M., 27 ..	No	B. T.	10,000		104	0	Sc.	0	V. Sc.	0	0	0	0	2	

For abbreviations used *see* table III.

TABLE II

No.	Race, sex and age	Recent treatment given or not	FINDINGS BEFORE TREATMENT				FINDINGS DURING AND AFTER TREATMENT								Days of fever	REMARKS
			Species	Asexual	Sexual	Temp. F.	2ND DAY		3RD DAY		4TH DAY		5TH DAY			
							Asex.	Sex.	Asex.	Sex.	Asex.	Sex.	Asex.	Sex.		
1	H. M., 18 ..	No	B. T. and M. T.	+, Sc.	+, Sc.	103°/98°	Sc.	Sc.	V. Sc.	Cres-cents.	0	Cres-cents.	0	Sc.	3	
2	M. M., 19 ..	Yes	B. T. and M. T.	+	0	..	+	0	Sc.	0	0	0	0	0	3	
3	E. M., 30 ..	Yes	M. T.	Sc.	0	99°	Sc.	0	0	0	0	0	0	0	2	Two courses.
4	A. I. F., 21 ..	No	B. T.	V. Sc.	0	..	V. Sc.	0	0	0	0	0	0	0	2	
5	A. I. M., 11 ..	Yes	B. T.	Sc.	0	99°	Sc.	Sc.	0	0	0	0	0	0	2	
6	E. M., 56 ..	No	M. T.	+	0	101.4°	Sc.	0	Sc.	0	0	0	0	0	3	*See* note.
7	A. I. F., 48 ..	Yes	M. T.	+	..	102°	Sc.	—	Sc.	—	Sc.	0	0	0	2	
8	H. M., 18 ..	No	B. T.	+		104.4°	Sc.		0	0	0	0	0	0	3	
9	H. M., 13 ..	No	M. T.	+		103.6°	Sc.		Sc.		0	0	0	0	2	Two courses.
10	H. M., 35 ..	No	M. T.	+	0	102°	Sc.	0	0	Sc.	0	Sc.	0	Sc.	2	
11	E. M., 25 ..	Yes	M. T.	+	0	103°	+	0	Sc.	0	0	0	0	0	2	Two courses.
12	H. M., 9 ..	No	M. T.	+	960	102.8°	Sc.	++	Sc.	+	0	+	..	+	3	
13	H. M., 11 ..	No	M. T.	+	0	99°	Sc.	Sc.	V. Sc.	Sc.	0	Sc.	0	Sc.	7	
14	H. F., 32 ..	No	Q.	Sc.		100.6°	Sc.	Sc.	Sc.	Sc.	0	0	0	0	2	
15	I. Ch. M., 20 ..	No	M. T.	+	+	103.6°	Sc.	+	V. Sc.	Sc.	0	Sc.	0	Sc.	2	
16	H. M., 18 ..	No	B. T.	++	+	104°	+	+	Sc.		0	0	0	0	2	
17	H. F., 21 ..	No	M. T.	+	0	103°	Sc.	0	Sc.	0	0	0	0	0	2	
18	H. M., 11 ..	No	M. T.	+	0	102.2°	Sc.	0	Sc.	0	0	0	0	0	2	
19	M. M., 30 ..	No	M. T.	Sc.	0	100°	Sc.	0	Sc.	0	0	0	0	0	3	
20	M. M., 35 ..	No	M. T.	Sc.	0	101°	Sc.	0	0	0	0	0	0	0	3	

For abbreviations used see table III.

in table I. The blood was carefully examined daily in every other respect, but only a rough estimate of the number of parasites in the peripheral blood was made. These cases were mostly of the acute type resembling the first series and they reacted in more or less the same way to atebrin.

Cases 3 and 9 in this series are worthy of note. Although the infections were not heavy, these patients did not react to the ordinary five days course of atebrin and very scanty malignant tertian rings could still be detected after the course. A second course of atebrin was given and with it the symptoms subsided and the parasites disappeared from the peripheral circulation. Patient no. 3 improved but left the hospital of his own accord after the second course before his blood could be finally examined. In patient no. 9, the temperature persisted after one course of treatment but subsided after the second course of two tablets twice daily for four days. In patient no. 11 benign tertian rings and trophozoites persisted after a 5-day course of atebrin. The patient was also given a second course but left the hospital before completion of the course. Such cases are difficult to explain. The possible explanation may be that in a low degree of pyrexia the parasites lodge themselves in the internal organs (only a few remaining in the peripheral blood) and are thus less readily acted upon by the drug. In cases 1, 10, 12, 13 and 15 crescents persisted after a full course of atebrin but 0.01 gramme of plasmochin twice daily for two days produced their disappearance. Patient no. 6 felt very depressed and his general condition was low after four days administration of the drug and for two days he had to be put on diffusible stimulants. A number of other patients in the two series complained of a feeling of depression and turned yellowish in colour, but this did not amount to anything serious.

In table III we have put all the chronic cases of malaria with enlargement of spleen which were treated with atebrin. In all these patients besides the usual examinations carried out in the first two series, very careful records were kept of the variations in the size of the spleen, with the treatment. Besides this the effects of the drug on the temperature have been included in the table. A study of this table will show that there was rapid reduction in the size of the spleen to practically its normal size in every case of acute infection. In long-standing cases where the spleen was hard the decrease in size was more gradual and the organ often did not come back to its normal size.

As regards the temperature, it will be seen that the chronic cases did not react so readily to atebrin treatment as the acute cases. In patient no. 3, the temperature persisted even on the 8th day and a second course of atebrin was necessary to bring it down. In patients nos. 4, 5, and 14 the temperature persisted after four days of treatment.

Relapses.—It has been urged that the most valuable property of atebrin is its power to prevent relapses and many workers have borne testimony to this effect. But in our experience quite a number of patients, at least five out of a series of 39, apparently relapsed. It must be pointed out however that, in a malaria endemic area such as this, it is very difficult to be certain whether these were fresh infections or relapses. Two patients relapsed while they were actually under observation in the hospital after the course and parasites of the same species were found in the peripheral blood. (A number of relapses were also reported in the patients treated outside the hospital.) Even though these may not be real relapses but fresh infections, it may be noted that infection took place before the atebrin had been fully excreted from the body of the individual. Although in an endemic area like this, it is difficult to prove in the human patients that relapses actually did occur after a course of atebrin, we have ample evidence in experimental malaria in monkeys (*M. mulatta*) that the drug does not eradicate infection from the body and that relapses are common. In quite a number of these animals after a course of the drug and disappearance of symptoms and parasites from the peripheral circulation, the parasite reappeared usually within two weeks and the animal showed symptoms of the disease.

Prophylactic uses.—Atebrin is claimed to have prophylactic properties and has been used by some workers for this purpose with good results. It is said to have been continued for months without producing any untoward effects in doses of 0.1 gramme daily. It has also been combined with plasmochin for this purpose, 0.1 gramme of atebrin and plasmochin 0.001 gramme being given together daily. The prophylactic value of atebrin is still under investigation, but so far as we can see it has no more true prophylactic action than the cinchona alkaloids.

Blackwater fever.—Atebrin can be given to patients suffering from blackwater fever without ill-effects. It can also be given to patients who are sensitive to quinine and in whom administration of quinine produces hæmoglobinuria.

Pulse rate, blood pressure, respiration, etc.—In a series of nine patients the effects of atebrin on the blood pressure, pulse rate and respiration were recorded. Careful records of these were obtained for a few days preceding the administration of the drug and these were compared with those obtained both when the patients were actually taking atebrin and a few days after the cessation of the drug. So far as possible the readings were taken under exactly the same conditions and at a particular time of the day with due regard to food, posture, temperature, etc.

So far as the blood pressure (systolic and diastolic) is concerned there was a slight lowering varying from 5 to 12 millimetres of mercury in some patients. In others there was no change whatsoever. The pulse rate and respiration also showed no appreciable changes when the patients were under the effect of the drug. From these results one is justified in concluding that atebrin has little, if any, depressing effect on the cardio-vascular system

TABLE III

Number	Race, sex and age	Duration	Spleen in inches below costal margin and temperature before, during and after treatment.									Remarks
			Before treatment		1st Day	2nd Day	3rd Day	4th Day	5th Day	6th Day	After treatment	
1	H. M., 18	3 months	1½	103°/98°	100°/98.4°	99.8°/98°	98.4°/97°	Afebrile	Afebrile	Afebrile	—	
2	H. M., 11	6 „	1¾	101.4°/98°	99°/98.4°	98.8°/98°	98.4°/97°	„	„	„	P	
3	H. M., 13	6 „	3	100°	103.6°/102°	102.6°/99°	98.2°/97.6°	„	„	„	P	100° (8th day).
4	H. M., 9	1 year	U	99°	98°	98.4°/98°	99.2°/97.6°	99°/98°	98.8°/98°	98.8°/98°	1	
5	H. F., 32	3 years	1½	100°/98°	100.6°/98°	98.6°/97°	99.4°/98°	98.4°/97.8°	..	99°/98°	P	
6	H. M., 20	6 days	P	102°	98.4°	101.8°	99°	98°	Afebrile	Afebrile	—	
7	H. M., 35	5 years	4	102°	101°	99°	98.8°	97.8°	98°	98°	2	
8	M. M., 22	2 months	3	103.6°	102.8°	101.6°	98.4°	Afebrile	Afebrile	Afebrile	1	
9	I. Ch. M., 7	5 days	2½	105°	104°	104°	101°	99.4°	99°	99.6°	P	Afebrile from 8th day.
10	I. Ch. M., 20	3 months	2	104.2°/101.6°	103.6°/100.2°	101°/98°	98°/97°	Afebrile	Afebrile	Afebrile	P	
11	H. M., 27	1 year	U	103°/100.4°	..	100°/97.6°	98.4°/97°	„	„	„	1	
12	H. F., 30	6 months	3	105.4°/101.4°	102.4°	99.2°/98°	98°/97°	„	„	„	1	
13	A. I. F., 48	1½ „	1	102°	102°/98.4°	100°/98.4°	99°/98°	99°/98.4°	„	„	P	
14	H. F., 21	1 year	1¼	103°	103°/98.4°	100.4°/99°	101°/99.4°	99°/97.8°	„	„	P	
15	M. M., 19	1½ years	1	101.4°/97°	104°/98°	101.6°/98°	98.4°/97°	Afebrile	„	„	—	
16	M. M., 30	3 days	P	100.4°	98.4°	100°	Afebrile	„	„	„	—	
17	E. M., 25	3 months	P	102°	102°	101°	99°	„	„	„	P	
18	A. I. F., 21	2 „	½	102.8°	102.8°	99°	Afebrile	„	„	„	P	
19	H. M., 27	3 years	P	..	..	103°	„	„	„	„	—	
20	A. I. M., 26	3 weeks	P	103°	..	..	..	..	..	„	—	
21	H. F., 18	2 years	2	100.2°	100.2°	99.8°	Afebrile	Afebrile	Afebrile	„	—	
22	M. M., 35	5 months	1¼	102°	102°	98.4°	99°	„	„	„	—	
23	A. I. M., 11	1 month	P	99°	99°	98.4°	97.4°	„	„	„	—	
24	M. M., 27	7 days	P	104°	104°/98°	98.6°/97.6°	100°/98°	„	„	„	—	
25	H. M., 24	10 months	3	102°	102°/98°	101°/98°	100°/98°	„	„	„	1	
26	H. M.	2 „	½	103°	103°/98°	99°/98°	100°/98°	„	„	„	—	

Abbreviations used:—
E. = European. A. I. = Anglo-Indian. H. = Hindu. M. = Mohammedan or Male. F. = Female. I. Ch. = Indian Christian. B. T. = Benign tertian. M. T. = Malignant tertian. Q. = Quartan. + = Moderate infection. ++ = Heavy infection. Sc. = Scanty. V. Sc. = Very scanty. 0 = No parasites found. P = palpable. U. = Down to umbilicus.

in the majority of the patients. We have given the drug to patients suffering from endocarditis and myocarditis without ill-effects.

Excretion.—In a series of patients we worked out the excretion of the drug. The drug is mostly excreted by the kidney and its presence can be roughly detected in the urine by production of the characteristic yellow colour on addition of an acid. The test suggested by the makers is to extract the alkalized urine with ether, and dissolve the residue resulting from the evaporation of ether extract in strong sulphuric acid, when a yellow colour appears. This latter test is more accurate, and we actually used a modification of it. The urine was first treated with lead acetate to remove all other matter and the lead was removed from the filtrate by the addition of ammonium sulphate. The filtrate was then extracted with ether and tested with acid in the ordinary way. The drug appears in the urine on the second day after administration and can be detected up to 15 or 20 days or even longer. The excretion is not regular and may stop for a day or two and then reappear. Our observations on Indian patients confirm the view that there is some tendency towards cumulation of the drug in the body. Atebrin undoubtedly persists in the body for a much longer period than quinine or plasmochin. If excretion is hindered there is a tendency for the appearance of the dye in the skin which assumes a yellowish tinge.

Untoward and toxic effects.—Atebrin unlike plasmochin is not a very toxic drug. Double the usual dose of 0.3 gramme per day (*i.e.*, 0.6 gramme in 24 hours) can be tolerated, but larger doses may produce gastro-intestinal irritation. In spite of the tendency referred to above of cumulation of the drug in the system we gave two 5-day courses of the drug with a few days interval between without producing any toxic effects, and with therapeutic benefit. Some patients complained of slight pain or a sensation of uneasiness in the epigastric region soon after taking the drug. This generally started on the second or third day and persisted as long as the drug was being administered. The pain was never so severe as that produced by plasmochin. In none of our series did we get the severe abdominal pains described by Green (1932). A number of our patients complained of headache and loss of appetite while the drug was being given, but this also passed off when atebrin was stopped. In some patients a profound feeling of general depression started on the third day of treatment and persisted for several days after the drug was stopped. The patient felt as if he had 'no life in him' and had no desire to make physical exertion and wished to remain lying down. In some of the patients diarrhœa was produced on the second and third days of treatment and persisted while the drug was being given. The diarrhœa was of a mild type and no particular treatment was necessary. It stopped with the cessation of the drug. In a few patients, especially those who were obese, palpitation occurred which was quite distressing but stopped when the drug was discontinued and in one patient cardiozol had to be administered. In one case mental disturbances were reported to have occurred.

A yellow staining of the skin and conjunctiva occurred in several of our patients, but the coloration as a rule was very slight and in none of the patients did it amount to a jaundice-like appearance.

Summary and conclusions

From a study of this series of patients one can draw the following conclusions :—

(1) Atebrin is an effective drug in the treatment of Indian strains of malaria. Its destructive action on the asexual forms of benign tertian, malignant tertian, and quartan types of malaria is about equal, the schizonts disappearing from the peripheral circulation after 0.6 to 0.9 gramme of the drug, *i.e.*, the administration of 3 tablets of 0.1 gramme for 2 or 3 days.

(2) The sexual forms or gametocytes are more slowly acted upon than the asexual forms. The gametocytes of the benign tertian and quartan types are readily destroyed and degenerative changes can be observed in them shortly after the administration of the drug is started. The gametocytes of the malignant tertian type—*i.e.*, crescents—are not touched at all.

(3) The drug is effective in doses of 0.1 gramme three times a day, the course lasting for five days, making a total of 1.5 gramme of the drug for the cure. In the majority of patients such a course is effective, but in a few of the persistent ones it may have to be repeated after a few days interval. The drug can also be effectively given intravenously in doses of 0.1 gramme dissolved in 1 to 2 cubic centimetres of distilled water when the number of parasites in the peripheral blood is large.

(4) In chronic types of malaria the drug is effective and produces a rapid reduction in the size of the spleen.

(5) Atebrin is reported to prevent relapses, but the evidence at our disposal shows that this is not the case with Indian strains of malaria. Its prophylactic value is very similar to that of the cinchona alkaloids.

(6) In blackwater fever and in patients in whom administration of quinine produces hæmoglobinuria atebrin can be safely given.

(7) The blood pressure is lowered in some patients during the administration of the drug, but in the majority there is no effect. The pulse rate and respiration are not markedly affected. It has been used in patients suffering from endocarditis and myocarditis without ill-effects.

(8) The drug is largely excreted in the urine and can be readily detected in it. The excretion is not regular, occurs in fits and starts, and goes on for three weeks or longer. There

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A CASE OF TROPICAL TYPHUS SEROLOGICALLY RELATED TO 'SCRUB TYPHUS' OF THE FEDERATED MALAY STATES

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IN a recent publication, Kundu (1932) described a case of typhus fever contracted in Burma, the clinical diagnosis being confirmed by a strongly positive Weil-Felix reaction with proteus X19. In the conclusions to his paper Kundu refers to the possibility of the tropical typhus which occurs in Malaya overlapping into Burma, and suggested that further investigation in the future would probably reveal the presence in this country of more cases of fever of this type.

Experience in Malaya has shown (Fletcher, 1930) that in that country 'tropical typhus' of two distinct serological varieties is met with. The first of these occurs among the urban population and is designated the 'W' group or 'shop typhus'. The serum of patients suffering from this type of the disease gives a positive agglutination reaction with the ordinary X19 strain of proteus. The other variety, occurring among the rural population, is called the 'K' group or 'scrub typhus' and differs, *inter alia*, from the urban variety in that the serum of the patients does not agglutinate proteus X19 but gives a positive Weil-Felix test with the 'Kingsbury' strain of proteus, proteus XK. To this latter group of typhus-like fevers, according to Fletcher, belongs also tick typhus of India.

Apparently the case described by Kundu corresponds to the 'shop typhus' met with in Malaya.

Cases of 'tick typhus', *i.e.*, typhus-like fevers apparently conveyed by the bite of ticks and probably also of mites, have been reported relatively frequently from India (Megaw and Rao, 1928; Christian, 1932). In such cases the Weil-Felix reaction has been found extremely variable, the majority being negative when proteus X19 is used. The 'Kingsbury' strain, proteus XK, does not appear to have been actually employed in the diagnosis of such cases in India, except in the one case reported by Christian (1932), where the serum of the patient, which gave a negative result in a dilution of 1/25 with the non-motile '0' variant of proteus X19, weakly agglutinated—perhaps in hardly significant titre—the '0' variant of proteus XK. It is therefore not certain to what extent, if any, the typhus-like fevers of India fall into two serological groups corresponding to the 'W' and 'K' groups of similar fevers occurring in Malaya.

So far as we are aware, no cases of tick typhus nor cases of typhus-like fevers corresponding to the 'K' group, or 'scrub typhus', of the Federated Malay States, have hitherto been reported from Burma. The following case, which clinically resembled the one and which laboratory investigation showed to be related to the other, may therefore be of interest, not only as showing that such cases may be met with in Burma but as lending support to Kundu's suggestion regarding the possible identity of these fevers here and in Malaya:

HISTORY AND CLINICAL FEATURES OF THE ILLNESS

Mr. G. F. B., an European, aged 40 years, was admitted under the care of one of us (C. de C. M.) in the Rangoon General Hospital on 27th December, 1932. The previous history was that he was touring in the forests of the Thayetmyo district of Upper Burma

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is a distinct tendency towards cumulative action of the drug in the body.

(9) Atebrin produces certain untoward effects which are not however serious. A profound feeling of general depression occurs in some patients. A slight yellow tinge of the skin and conjunctiva was observed particularly in those patients in whom excretion from the kidney is hindered for some reason. Slight epigastric pain, a feeling of uneasiness in the stomach, headache and loss of appetite and diarrhœa sometimes occur when the drug is being administered. These as a rule stop when the drug is stopped.

(10) The action of atebrin closely resembles that of the cinchona alkaloids and the introduction of this drug is a distinct advance in the treatment of malarial fevers in India. The price at present is too high for its use by the people in general.*

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(* The present price of atebrin is Rs. 49-8 for 300 tablets, that is Rs. 2-8 for one 'treatment' of 15 tablets; of this sum 23 per cent, or 9 annas, is duty. It is hoped that the government will shortly see their way to allow this useful drug to be brought free of duty into India, as at present it is into Ceylon.

A single 'treatment' can be purchased, but the price is a few annas more per 'treatment'. On the other hand the makers are prepared to quote a considerably lower rate for quantities of 5,000 tablets or more.—EDITOR, *I. M. G.*)