Vision.—Right eye = 6/6 H.m. + 0.75. Left eye = 6/6 H.m. + 0.75. Angle of squint 45°. No binocular vision. Movements of the eyeball normal.

Operation.—Resection and advancement of left external rectus, combined with recession of left internal rectus.

Result.—Excellent. Both eyes straight.

Case 8.—A. S., age 17 years, Hindu female. Alternating concomitant convergent squint. History of left eye deviating since childhood.

Vision.—Right eye = 6/12 c̄ + 2.25 D. S. + 1.5 D. cyl. 30° = 6/6. Left eye = 6/18 c̄ + 3.25 D. S. + 1.0 D. cyl. 35° = 6/6. Angle of squint 45°. No binocular vision. Movements of the eyeball normal.

Operation.—Resection and advancement of left external rectus, combined with recession of left internal rectus.

Result.—Satisfactory. Angle of squint reduced to 20°.

Case 9.—M. M., age 4½ years, European boy. Extreme alternating internal strabismus. Angle of deviation 45°. Hypermetropia + 4. History of right eye squinting since he was three years of age. Has been wearing glasses for one year.

Vision.—Right eye = 6/12 c̄ + 3 D. S. = 6/9. Left eye = 6/12 c̄ + 3 D. S. = 6/9.

Operation.—Resection and advancement of right external rectus combined with recession of right internal rectus.

Result.—Excellent. Eyes straight with glasses.

Case 10.—O. A., age 10 years, Anglo-Indian girl. Concomitant convergent strabismus left eye. Angle of deviation 40°. Left eye amblyopic.

Vision.—Right eye = 6/18 c̄ + 3.0 D. S. = 6/6. Left eye = 2/26 c̄ + 4.0 D. S. = 5/60. Movements of the eyeball normal.

Operation.—Resection and advancement of left external rectus combined with recession of right internal rectus.

Result.—Eyes straight.

Case 11.—L. L., age 18 years, European girl. Extreme concomitant divergent squint left eye. History of the left eye deviating outwards since she was a little girl. Movements of the eyeball normal.

Vision.—Right eye = 6/18 c̄ — 1.0 D. S. + 2.0 D. cyl. 90° = 6/6. Left eye = 6/24 c̄ — 1.5 D. S. + 2.0 D. cyl. 90° = 6/6. No binocular vision.

Operation.—Resection and advancement of left internal rectus combined with recession of left external rectus.

Result.—Excellent. Eyes straight.

Case 12.—P. S. G., age 28 years, Bengali Hindu, medical man. Extreme concomitant divergent squint left eye. History of left eye deviating since he was five years of age. Movements of eyeball normal.

Vision.—Right eye = 6/36 c̄ — 1.5 D. S. — 0.75 D. cyl. 30° = 6/6. Left eye = 6/30 c̄ — 2.0 D. S. — 0.5 D. cyl. 150° = 6/6. No binocular vision.

Operation.—Resection and advancement of left internal rectus combined with recession of left external rectus.

Result.—Excellent. Both eyes are straight.

Summary

In Bengal extreme degrees of concomitant squint both convergent and divergent are very common. They can truly be labelled as 'monuments of neglect' for treatment is most satisfactory. The convergent varieties can always be cured and in the case of divergent ones excellent results can be obtained provided the vision is good in each eye.

In eleven of the twelve cases recorded the results were obtained by a single operation on the muscle of one eye.

A COMPARATIVE STUDY OF THE ACTION OF ATEBRIN AND ATEBRIN-PLASMOCHIN COMBINATION ON INDIAN STRAINS OF MALARIA

Part II

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In the attempt to find some drug that will effect a permanent cure in malaria the medical profession in this country has started using combinations of different anti-malarial remedies. Tablets containing these combinations in various proportions have been put on the market by well-known firms and are being extensively used. For instance, plasmochin has been combined with quinine and atebrin in various proportions.

Although the action of plasmochin has been fully investigated by various workers and the drug has finally been shown to act chiefly, in non-toxic doses, on the sexual phase of malignant tertian malaria, a strong belief still exists among the profession that plasmochin possesses marked curative properties in the same way as atebrin or the cinchona alkaloids, and that it is even effective in preventing relapses. This view has been utilized by Messrs. Bayer-Meister Lucius in putting two combinations of atebrin and plasmochin on the market. They have been made in the form of dragées, one containing 0.1 gm. of atebrin and 0.0033 gm. of plasmochin and the other containing the same dose of atebrin but 0.005 gm. of plasmochin. The idea underlying these combinations was that plasmochin by its schizonticidal property would help the action of atebrin considerably and thereby reduce the relapse rate. The dosage of plasmochin has been kept within safe limits so that, if it fails to act on the asexual stage, it will produce its crescenticidal action all the same without producing any untoward effects. Chopra, Gupta and Sen have made a comparative study of the effects of one of these combined preparations (containing 0.0033 gm. of plasmochin) and of atebrin by itself on a series of 54 cases in the Carmichael Hospital for Tropical Diseases and have shown that—

(1) In cases of benign tertian and quartan malaria, the combination is not more effective than atebrin alone in so far as the time of disappearance of the parasites from the blood is concerned. In the case of malignant tertian infection, however, the combination appears to

PLATE XXII

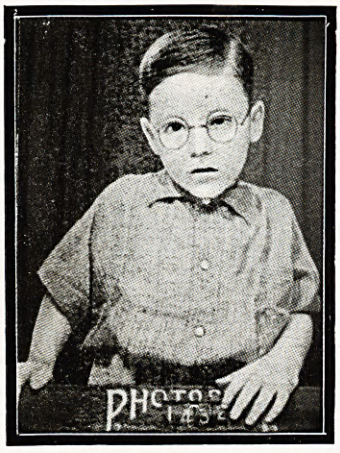
Case 2.

Before operation.

After operation.

Case 3.

Before operation.



After operation.

Case 4.

Before operation.

After operation.

Plate XXIII

Case 5.

Before operation.

After operation.

Case 6.

Before operation.

After operation.

Case 7.

Before operation.

After operation.

be more effective and the parasites disappear more rapidly from the peripheral circulation.

(2) The relapse rate is definitely lower in cases where the combination of the two drugs is used than with atebrin alone, in all forms of infections.

(3) The combination of the two drugs is more toxic than atebrin alone.

In this paper we have embodied the result of our investigation on the effect of the other combination containing 0.005 gm. of plasmochin as compared with atebrin by itself on Indian strains of malaria. The idea was to determine if the higher dose of plasmochin in combination is more effective, so far as the relapse rate is concerned, and whether any toxic effects are produced by such combination. During these studies the effects produced by the drug were particularly observed—

(1) On the sexual and asexual forms of the parasites and the time taken for their complete disappearance from the peripheral blood.

(2) On the relapses.

(3) On the splenic enlargement.

(4) On the function of the liver.

(5) In producing toxic effects.

The investigation was carried out on a series of 45 cases admitted into the Carmichael Hospital for Tropical Diseases and the results were compared with those obtained on a previous series of cases treated with atebrin alone.

Patients suffering from malaria were admitted under the senior author and a thorough physical examination was conducted immediately after admission. Except in urgent cases the anti-malarial treatment was not commenced until the parasites were properly identified and the parasitic counts were fairly constant for two or three febrile days. Daily examination of the 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, they were allowed to increase till the counts were fairly high and the rigor and other symptoms were marked. Whenever possible, sugar tolerance and van den Bergh's tests were done both before and after the course of treatment in order to determine if atebrin and plasmochin, when given in combination, produced any deleterious effect on the functions of the liver.

When all these preliminary investigations were completed the drugs were given by the mouth, one dragée (containing 0.1 gm. of atebrin and 0.005 gm. of plasmochin) three times a day for five consecutive days being the usual doses for an adult. No other drug was given except a mild purgative whenever necessary. As regards diet, only the usual restrictions for a febrile condition were observed. During the course of treatment daily examinations of the blood were carried out and, whenever possible, a rough estimate was also made of the number of parasites per c.mm. of blood.

After the completion of the treatment, the patients were carefully observed in the hospital for at least a fortnight and daily examinations of blood for malarial parasites were conducted during this period. If thick and thin films showed no parasites, cultural examinations of the blood were finally made before the patients were discharged. If routine laboratory examinations revealed any other infection, *e.g.*, dysentery, helminthiasis, etc., these were treated during the period of observation.

Discussion of results

Chopra, Das Gupta and Sen (1933) have studied the effects of atebrin on the Indian strains of malaria and the results obtained in that series have been analysed for purposes of comparison along with those obtained with atebrin-plasmochin dragées in this series.

A perusal of table I will show that the atebrin-plasmochin combination acts both on the asexual and the sexual stages of all the three

TABLE I

A statement showing the species, number of cases treated and the number of days required for complete disappearance of parasites from the peripheral blood after the commencement of the treatment

Species of parasites	Number of cases studied		Complete disappearance of parasites from peripheral blood: On the 3rd day		On the 4th day		On the 5th day		On the 6th day		In more than 6 days	
	A + P	A	A + P	A	A + P	A	A + P	A	A + P	A	A + P	A
Benign tertian	14	11	5	6	6	4	2	1	1	0	0	0
Malignant tertian	20	18	8	2	8	2	2	6	2	2	0	6
Quartan	3	5	0	1	1	4	0	0	1	0	1	0
Mixed benign tertian and malignant tertian.	7	3	0	0	4	1	2	0	1	0	0	2
Mixed benign tertian and quartan ..	1	0	0	0	0	0	0	0	1	0	0	0

A = Atebrin; P = Plasmochin

species and that the time taken for the complete disappearance of *P. falciparum* and *P. vivax* is usually two to four days. A delayed response was, however, obtained in a small percentage of cases, the parasites disappearing five days after the commencement of treatment. In infections with *P. malariæ*, the destruction of parasites was quite slow; 66 per cent of the cases took more than six days for the parasites to disappear from the peripheral blood.

A comparative study of the effects of this combined preparation of atebrin-plasmochin and atebrin alone shows that, in cases of infection with *P. vivax*, the disappearance of the parasites by both methods of treatment is complete in the majority of the cases within four days, whereas with malignant tertian infection the combination removes them in a shorter time than atebrin alone. The reason of this will be obvious from a perusal of table II which shows that atebrin does not act on the crescents and consequently the sexual forms persist even after the course of treatment is over. In quartan malaria, atebrin alone produces even more rapid action than the atebrin and plasmochin combination.

Table II gives an idea of the comparative efficacy of these dragées on the asexual and the sexual forms of the different species. In benign tertian infection, the sexual forms are more rapidly affected than the asexual, but in the case of malignant tertian this treatment produces practically the same effect on both forms. As regards quartan, the number of cases was unfortunately too small to enable us to form any accurate conclusions; the gametocytes seem to disappear more quickly than the asexual forms. The comparatively rapid destruction of the benign tertian gametocytes may be partly explained by their tendency to spontaneous disappearance.

A comparison of the effects of atebrin alone with those of the combination dragées shows that atebrin produces a more rapid action both on the asexual and sexual forms of *P. vivax*, but in the case of *P. falciparum*, although it removes the asexual forms in the majority of cases within a short time, the sexual forms are rarely touched and persist even after the course of treatment is completed. In the case of *P. malariæ*, atebrin alone appears to be as effective or even superior to the combined dragées with regard to their action on both the asexual and sexual forms.

Table III shows that there is no relationship between the parasite count and the number of days required for the complete disappearance of the parasites. A perusal of this table will show that both the drugs behave in more or less the same way with regard to the relationship between the parasite count and their disappearance from the peripheral blood.

Relapses.—Out of a total of 39 cases treated with atebrin alone, 5 apparently relapsed while still under observation in the hospital. Out of 45 cases treated with the combination only 2 (1 *P. falciparum* and 1 *P. vivax*) relapsed. This shows that the relapse rate is 12.5 per cent in the case of atebrin and 4.4 per cent in the case of the combination. The series of cases is very small, but in view of the fact that these trials were carried out under fully-controlled conditions, the results are worthy of note.

Spleen.—So far as the effects on the spleen are concerned a soft spleen rapidly contracts when the patient is put on either treatment and the fever subsides. No difference could be observed in the case of the two treatments in this connection. The hard spleen of chronic malaria showed very little alteration.

Effect on the liver function.—Lævulose tolerance and van den Bergh's tests were performed on a small series of 7 cases. A perusal of table IV will show that out of these 7 cases 4 showed an already defective liver. The function of the liver, in the remaining 3 cases, was found to be normal both before and after the course of treatment.

TABLE II

The comparative efficacy of the drug on sexual and asexual forms of different species

Species of parasites	Sexual forms						Asexual forms					
	Number of cases where present		Number of cases where they disappeared within 4 days		Number of cases where they disappeared in more than 4 days		Number of cases where present		Number of cases where they disappeared in 4 days		Number of cases where they disappeared in more than 4 days	
	A + P	A	A + P	A	A + P	A	A + P	A	A + P	A	A + P	A
Benign tertian	9	7	8	7	1	0	15	11	12	11	3	0
Malignant tertian	10	9	4	1	6	8	21	18	17	18	3	0
Quartan	2	4	1	4	1	0	4	5	0	5	4	0

A = Atebrin; P = Plasmochin

TABLE III

A statement showing the parasite count and the number of days required for disappearance of parasites

Species	With Atebrin + Plasmochin		With Atebrin alone	
	Parasite count on the day of commencement of treatment	Number of days required for complete disappearance of parasites from peripheral blood	Parasite count on the day of commencement of treatment	Number of days required for complete disappearance of parasites from peripheral blood
Benign tertian	(1) 10,000	3 days	(1) 10,020	4 days
	(2) 18,500	2 ,,	(2) 16,820	3 ,,
	(3) 7,500	3 ,,	(3) 30,000	2 ,,
	(4) 5,600	2 ,,	(4) 28,000	1 day
	(5) 21,000	5 ,,	(5) 21,400	3 days
			(6) 9,840	2 ,,
			(7) 10,000	3 ,,
Malignant tertian	(1) 8,000	3 days	(1) 9,240	More than 6 days
	(2) 5,100	2 ,,	(2) 3,840	,, ,, 6 ,,
	(3) 740	2 ,,	(3) 14,200	Only 4 days
	(4) 9,000	4 ,,	(4) 128,000	More than 6 days
	(5) ..	..	(5) 13,000	Only 6 days
Quartan	(1) 650	6 days	(1) 3,520	3 days
			(2) 1,000	3 ,,
			(3) 800	2 ,,
			(4) 2,400	3 ,,

TABLE IV

A statement showing the function of the liver before and after treatment

Species	Liver function tests	
	Before treatment	After treatment
Benign tertian ..	Moderately defective.	Moderately defective.
,, ,, ..	Normal	Normal.
,, ,, ..	,,	,,
Malignant tertian	Slightly defective	Not done.
Quartan ..	Normal	Normal.
Malignant tertian	Slightly defective	Slightly defective.
,, ,,	,, ,,	Normal.

Untoward symptoms.—Untoward symptoms were produced in a large number of the patients of this series. The symptoms were as a rule mild, but in four patients, they were so severe that the treatment with combination dragées had to be stopped. One patient with malignant tertian infection developed the usual toxic effects after eleven doses of atebrin and plasmochin and looked cyanosed and collapsed. Stimulants had to be given and atebrin and plasmochin dragées had to be replaced by quinine. Another case of malignant tertian infection became very restless on the second day of treatment. The patient developed difficulty of breathing and the pulse rate went up to 120 per minute with a temperature of 99°F. The treatment with the combined preparation was stopped and bromides were administered after which the patient improved. He was put on plain atebrin from the following day. In 2 cases of benign tertian infection precordial distress was felt after the use of the combination dragées and they had to be stopped in the middle of the course of treatment. Two patients complained of slight epigastric pain and flatulence but could complete the course of treatment. Yellow pigmentation of a mild character of the whole body was observed in quite a number of the patients. The pigmentation disappeared in the course of a few days in some cases but in the majority slight yellow coloration persisted even up to the time of discharge from the hospital. From a careful study of the three series of patients we have formed the opinion that toxic coloration is somewhat more frequent with the combined preparation than with atebrin alone.

Summary and conclusions

(1) Comparative studies have been carried out in a small series of 45 cases on the therapeutic effects produced by atebrin alone and atebrin-plasmochin dragées (containing atebrin 0.1 gm. and plasmochin 0.005 gm.).

(2) In cases of benign tertian and quartan malaria, the combination of the two drugs is not more effective than atebrin alone in so far as the time of disappearance of the parasites from the blood is concerned. In the case of malignant tertian infection, however, the combination appears to be more effective and the parasites disappear more rapidly from the peripheral circulation.

(*Continued at foot of next page*)

A STABLE SOLUTION OF ANTIMONY FOR THE TREATMENT OF KALA-AZAR

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No apology is needed for an enquiry into the therapeutic efficacy in kala-azar of an antimony compound. During the last two decades advances in the treatment of this condition have turned a 95-per-cent mortality into a 95-per-cent (at least) recovery rate. This is not an unimportant achievement in a disease from which at certain times as many as a million people may suffer in one country alone. Many valuable drugs have been discovered for the treatment of this disease, but none, in our opinion, is superior to neostibosan, which has now had a world-wide trial in this disease for over a decade. Remarkable though its effects are in a case of kala-azar, one would hesitate to predict that it was likely to be the last word in the treatment of this disease. One disadvantage it suffers is that dissolved in distilled water it does not make a very stable solution and it cannot therefore be supplied as a solution, but has to be issued in dry form in sealed ampoules which should be dissolved shortly before use*. There are obvious advantages in having the drug in fluid form ready for immediate administration.

The new compound.—No. 561 is a clear, sterile, colourless solution which is said to be stable. It is a pentavalent compound of antimony and it contains 20 mgm. of antimony (metal) in 1 c.cm. of solution. One c.cm. of a 5-per-cent solution of neostibosan contains 21 mgm. of antimony.

Toxicologically, it is very similar to neostibosan, being slightly less toxic than this compound, milligramme for milligramme of antimony when given subcutaneously, and distinctly less toxic when given intravenously—18.5 c.c. (or 370 mgm. of Sb) per kilogramme is the lethal dose for a mouse, against 6 c.cm. of a 5-per-cent neostibosan solution. Its rate of excretion in the urine is rapid, 68.5 per cent being excreted in the first twenty-four hours against 50 per cent in the case of neostibosan, and therefore the effect is even less likely to be cumulative.

Early trials.—In 1936, we received some samples of this new antimony compound from the Pharmaceutical Department, Bayer, through their representative, Dr. A. G. Brocke, D.SC. We tried this preparation in a series of seven cases. The results were not, on the whole, favourable.

Three of the patients developed pneumonia and died. There was at the time an epidemic of influenza in the hospital; many patients developed pneumonia and others besides these three died. The pneumonia developed after the 1st, 3rd and 5th injections, the maximum doses given were 1 c.cm., 6 c.cm. and 6 c.cm., respectively, and in two instances the injections were given intramuscularly. Taking all these facts into consideration, we consider it unlikely that the pneumonia or the deaths were associated in

*Under favourable conditions we have kept the solution for some days and noticed no increase in toxicity.

(*Continued from previous page*)

(3) With regard to the relationship between the number of parasites and their disappearance from the peripheral circulation, atebrin alone and atebrin-plasmochin dragées behave in the same way.

(4) The relapse rate is somewhat lower in cases where the combination of the two drugs is used than with atebrin alone, in all forms of infection.

(5) There appears to be no difference in the two so far as the reduction of the size of the spleen is concerned.

(6) The combination of the two drugs is more toxic than atebrin alone.

(7) Distinct advantage can be gained by treating cases of malignant tertian infection with the combination dragées, especially when the sexual forms are present. In the case of benign tertian and quartan infections they appear to have no particular advantage.

It is fully realized that the series of cases dealt with in this paper is very small and that the conclusions can only be provisional. We are grateful to Messrs. Bayer-Meister Lucius and Dr. Brocke for supplying the dragées free of charge for these trials.

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