Original Articles

PRONTOSIL IN INDIAN STRAINS OF MALARIA

By R. N. CHOPRA, C.I.E., M.A., M.D., SC.D. (Cantab.), F.R.C.P. (Lond.)
BREVET-COLONEL, I.M.S.
Honorary Physician to the King
B. M. DAS GUPTA
B. SEN, B.SC., M.B.
and
R. T. M. HAYTER, M.B.E.
(*School of Tropical Medicine, Calcutta*)

THE discovery of antimalarial properties in plasmochin and acridine derivatives such as atebrin is undoubtedly a great advance in the therapy of malaria. The untoward symptoms which are occasionally observed, their inability to prevent relapses in a certain percentage of cases and their not having a true prophylactic action, inasmuch as they have no action on the sporozoites injected by the mosquitoes, have however necessitated a vigorous search for drugs which may be free from these disadvantages. A large number of synthetic compounds have therefore been tried in malaria, but so far plasmochin and atebrin have held the field. For the last few years some of the compounds prepared from azo-dyes have been the subject of intensive study on the part of chemists, experimental pathologists and clinicians. Sulphanilamide is the name adopted by the Council of Pharmacy and Chemistry of the American Medical Association as a convenient abbreviation for p-amino-benzene sulphonamide, which has been shown to be the active portion of the molecule of prontosil, a drug which was first introduced by Damagk in 1935. A number of new compounds have since been produced whose activity depends on the presence of this molecule, and which are being extensively used by the medical profession in various infective conditions with remarkable success. These compounds have also been tried in the treatment of malaria and the views which have been expressed with regard to their efficacy in this disease are divergent. For instance, Diaz de León (1937), who was the first to carry out trials in malaria, treated 15 cases with apparently good results. The drug was administered by the mouth excepting in a severe case where he had recourse to an injection of 10 c.cm. of a 5 per cent solution, in addition to the usual administration by the mouth. Hill and Goodwin (1937) in the same year treated 100 cases of malaria with intramuscular injections of prontosil every twelve hours and found that 4 injections sufficed to produce satisfactory results. Read and Pino (1938), however, did not obtain encouraging results. They treated 3 cases of malaria with the initial doses of 6 tablets (1.8 gm.) in 24 hours; afterwards the dosage was reduced to 3 tablets a day. Patients showing gastric symptoms were given intramuscular injections. These workers observed that sulphonamide has antimalarial action of a mild order inasmuch as it has neither a sufficiently definite action on the cycle of schizogony nor has it remarkable properties as a gametocide. Pakenham-Walsh and Rennie (1938) treated a case of induced malaria with prontosil by giving 3 gm. of the drug daily for 3 days. The temperature came down and the parasites disappeared, but a week later, the fever relapsed and the parasite counts were nearly as high as in the original attack.

Das Gupta and Chopra (1938) tested the efficacy of prontosil in monkey malaria. They found that in doses of 0.5 to 1 c.cm., given intramuscularly, the drug failed altogether to check the multiplication of *P. knowlesi* in the rhesus monkey. The disproportionately heavy doses of 3 c.cm., however, proved effective. Trials were then carried out in the Carmichael Hospital for Tropical Diseases on a series of cases of human malaria with a view to seeing how effective the drug was in Indian strains of malaria if administered in such therapeutic doses as are effective in streptococcal infections. In the present paper the results of these trials have been recorded.

The patients were all admitted to the hospital and, with the exception of those showing urgent symptoms, the antimalarial treatment was withheld for a few days in order to select only those cases which did not show any tendency to spontaneous recovery. Approximate estimations of the number of parasites were daily made during this period and the treatment was started when the parasite counts were fairly uniform for two or three days. Daily examinations of the blood for malaria parasites were carried out during the course of treatment and also for a few days after the treatment was completed. The effects of the drug were carefully studied on (*i*) temperature, (*ii*) the sexual and the asexual forms of the parasites and (*iii*) the time taken for the disappearance of the parasites from the peripheral blood. Any untoward effects produced were recorded. Whenever possible, the patients were kept under observation for a fortnight or so after the treatment was completed and the cultural examinations of blood were also carried out in a number of cases to determine if the infection had been eradicated.

In the present series oral administration was the usual procedure but a perusal of the table will show that injections were also given in three cases. We first started with one tablet (0.5 gm.) three times a day for five days and later increased the dose to 2 tablets four times a day. In the one quartan case in this series the drug was continued for seven days. The injections were given intramuscularly in the gluteal region,

TABLE

Number	Race, Sex and Age	Findings of parasites before treatment			Findings of parasites during and after treatment								Duration of fever in days after beginning treatment	Remarks
					2nd day		3rd day		4th day		5th day			
		Species	As.	Sex.	As.	Sex.	As.	Sex.	As.	Sex.	As.	Sex.		
1	M., M., 20	B.T.	(1,000 per 500 W.B.C's).	0	Sc. (200 per 500 W.B.C's).	0	Sc.	0	V.Sc.	0	0	0	3	Five injections of 5 c.c. each of 5 per cent sol. on consecutive days. H.W.+, C.D.+.
		B.T.	(900 per 500 W.B.C's).	0	(150 per 500 W.B.C's).	0	Sc.	0	Sc.	0	Sc.	0	4	Parasites reappeared after three days. Treated with prontosil (orally) 2 tabs. (0.5 gm. each) three times a day for 5 days. Although apyrexial the parasites persisted. Finally treated with atebrin.
2	M., I.Ch., 11	B.T. M.T.	V.Sc.	0	Sc.	Sc.	Sc.	Sc.	V.Sc.	0	Sc.	0	3	Prontosil 3 c.c. i.m. for three days followed by one tab., t.d.s., for 5 days orally. Crescents treated with cilional. Relapsed two weeks after treatment. Finally cured with atebrin.
3	H., M., 28	M.T.	(4 or 5 per field).	0	(2 or 3 per field).	0	(1 per field).	0	Sc.	0	Sc.	0	3	Two tabs. four times a day for 5 days. Rings persisted for 1 day after the treatment was started. Crescents not affected; destroyed with cilional. Kept in hospital for 1 month, no relapse. H.W.+.
4	H., M., 22	M.T.	Sc.	Sc.	Sc.	Sc.	Sc.	Sc.	Sc.	Sc.	0	Sc.	2	Two tabs. four times a day for 5 days. Crescents destroyed with cilional. Observed in the hospital for 3 weeks. No relapse. C.D.+.
5	H., M., 22	M.T.	(Thick film)	Sc.	0	Sc.	0	Sc.	0	Sc.	0	Sc.	1	Two tabs. four times a day for 5 days. Crescents persisted; observed in the hospital for 3 weeks. No relapse.
6	H., M., 16	M.T.	V.Sc.	Sc.	V.Sc.	Sc.	(Thick film).	Sc.	0	Sc.	0	Sc.	Apyrexia	Two tabs. four times a day for 5 days. Crescents persisted; observed in the hospital for 3 weeks. No relapse.
7	M., M., 32	M.T.	+	0	Sc.	0	V.Sc.	0	0	0	0	0	2	Two tabs. four times a day for 5 days; observed for 8 days no relapse.
8	E., M., 41	M.T.	Sc.	Sc.	Sc.	Sc.	(Thick film).	(Thick film).	0	V.Sc.	0	Sc.	3	Two tabs. four times a day for 5 days. Crescents persisted. Relapsed after 20 days. Finally treated with atebrin.
9	M., M., 9	M.T.	Sc.	Sc.	Sc.	Sc.	Sc.	Sc.	0	Sc.	0	Sc.	*Nil*	One tab. three times a day for 5 days. Apyrexial when treatment was started. Crescents persisted. Observed for 20 days; no relapse.

10	*H., M., 23*	*M. T.*	*(6,000 per 500 W. B. C's).*	*0*	*(4,000 per 500 W. B. C's).*	*0*	*Sc.*	*0*	*Sc.*	*0*	*0*	*Sc.*	*4*	*Took 10 grains of quinine on the previous day. Prontosil 5 c.c. (5 per cent) i.m. and 2 tabs., t.d.s., for 2 days and 2 tabs. four times a day for 2 days. Observed for 11 days; no relapse.*
11	A.-I., F., 14	B. T. Q.	Sc.	0	Sc.	Sc.	Sc.	0	0	0	0	0	2	Took 0.3 gm. of atebrin on the previous day. Prontosil 2 tabs. t.d.s., for 5 days. Observed for 16 days. No relapse.
12	H., M., 18	M. T.	Sc.	0	Sc.	0	0	0	0	Sc.	0	Sc.	*Nil*	Prontosil 2 tabs. four times a day for 5 days. Apyrexial when prontosil was started. Crescents persisted.
13	H., M., 28	M. T.	Sc.	Sc.	Sc.	Sc.	Sc.	Sc.	0	Sc.	0	Sc.	1	Prontosil, 2 tabs. four times a day for 5 days. Crescents persisted, observed in the hospital for 13 days; no relapse.
14	I. Ch., M., 19	Q. T.	+	Sc.	+	Sc.	Sc.	Sc.	Sc.	Sc.	Sc.	0	4	Prontosil, 2 tabs. four times a day for 7 days. Parasites persisted for 7 days after treatment. H. W. treated with C_2Cl_4.
15	I. Ch., M., 12	B. T.	+	Sc.	+	0	Sc.	0	0	0	0	0	3	One tab., t.d.s., for 5 days. Relapsed after 2 weeks. Treated finally with atebrin.
16	H., M., 32	B. T. M. T.	+	Sc. (M. T.)	(M.T.)	Sc. (M. T.)	0	Sc.	0	Sc.	0	Sc.	1	Two tabs., t.d.s., for 5 days. Crescents persisted. Filarial lymphangitis.
17	I. Ch., M., 16	M. T.	+	0	+	0	Sc.	0	(Thick film).	0	0	Sc.	1	One tab., t.d.s., for 5 days. Crescents found last day of treatment, treated with cilional. Relapsed after 18 days. Finally treated with atebrin.
18	Buddhist, M., 24	B. T.	Sc.	0	Sc.	0	Sc.	0	Sc.	0	Sc.	0	5	One tab., t.d.s., for 7 days; could not retain; the parasites persisted. Then 2 tabs., t.d.s., for 5 days; could not retain; the parasites persisted. Finally treated with atebrin.
19	H., F., 6	B. T.	Sc.	Sc.	+	Sc.	Sc.	0	0	0	0	0	5	Half a tab. four times a day for 5 days, originally admitted for ichthyosis. Relapsed after 15 days. Finally treated with atebrin.

Abbreviations used:—

M. M. = Mohammedan male.
H. M. = Hindu male.
I. Ch. = Indian Christian.
E. M. = European male.
A. I. = Anglo-Indian.
H. F. = Hindu female.
A. I. F. = Anglo-Indian female.
B. T. = Benign tertian.
M. T. = Malignant tertian.
As. = Asexual.
Sex. = Sexual.
Sc. = Scanty.
V. Sc. = Very scanty.
Q. = Quartan.
H. W. = Hookworm.
i. m. = intramuscular.
C. D. = Wassermann reaction.

the dose being 5 c.cm. of a 5 per cent solution for five consecutive days.

The table shows that prontosil does cause disappearance of the parasites from the peripheral blood; in cases of infection with *P. falciparum* the asexual forms were destroyed within 2 to 6 days but the sexual forms remained unaffected (cases 2, 3, 4, 5, 6, 8, 9, 10, 11, 13, 14, 17 and 18). In infection with *P. vivax* both the asexual and sexual forms disappear from the peripheral blood within 2 to 5 days (cases 1, 2, 12, 16, 17 and 19. Unfortunately only one case of pure quartan infection was admitted during the period of investigation and the effect of prontosil on both the asexual and the sexual forms of this species was found to be much less marked than on the other two infections, the parasites persisting for a comparatively longer period. It is also evident from the table that the patients who were given smaller doses of the drug (0.5 gm. three times a day for five days) were relieved of the symptoms and the blood was negative for malaria parasites, but the patients relapsed during their stay in the hospital. No relapse, however, occurred in those patients who received a higher dose (one gm. four times a day for five days), with the exception of one case who gave the history of long duration. In the present series, prontosil, administered by injection, did not prove to be as effective as when given by the mouth.

The untoward effects which were observed in a certain number of cases during the course of administration of prontosil were of mild character, and beyond slight epigastric distress and flatulence no toxic effects were recorded. One of the patients showed great sensitiveness to the drug and it had to be stopped.

Summary and conclusions

(1) Prontosil in ordinary therapeutic doses (3 to 4 gm. daily for five days) has an undoubted action in causing disappearance of malarial parasites from the peripheral blood and in controlling symptoms of the disease.

(2) It destroys both the asexual and sexual forms of *P. vivax* and *P. malariae* and only the asexual forms of *P. falciparum*. It has no action on the crescents. Its action on *P. malariae* appears to be comparatively slower and less potent.

(3) In smaller doses (1.5 to 2.0 gm. daily for five days) the symptoms of the disease abated and the parasites disappeared from the peripheral blood but recrudescence of the disease occurred within a fortnight.

(4) Prontosil undoubtedly possesses mild antimalarial properties in infections with Indian strains of malaria and is worthy of trial when other antimalarial drugs are not available or are contraindicated.

The series is very small and the conclusions are only tentative.

(*Continued at foot of next column*)

THE CALCIUM AND PHOSPHORUS CONTENT OF STUDENTS' DIETARIES

By K. C. SAHA
K. L. ROY
and
B. C. GUHA
(*From the University College of Science, Calcutta*)

EARLIER work (Pal and Guha, 1937) had indicated the probability that the diet consumed by middle-class people in Calcutta was appreciably deficient in calcium. We sought to obtain further information on this question by investigating the cooked diets consumed by general middle-class students in some of the hostels of Calcutta. Eight hostels were chosen and the cooked diets, consisting of the chief day and evening meals, were analysed to find the average consumption of calcium and phosphorus per head per day. As the bulk of the daily diet was composed of rice, it was considered desirable to estimate the phytin phosphorus of the diet, for phytin phosphorus is not available for nutrition and should be subtracted from the total phosphorus. An aliquot of the total mixed diet, meant for one average individual, was analysed as was done in previous work (Guha, 1934). The figures for calcium (in terms of CaO) and phosphorus are given in table I. The values for phytin phosphorus and total phosphorus obtained on those days, on which both of them were estimated in the same diet, are given in table II. A statistical note on the significance of the results by Mr. K. C. Basak is also given.

Thus the mean values for calcium and phosphorus content per head per day, considering all the hostels and all the days, are 0.636 and 1.01 gm. respectively.

Statistical note

The following two analyses of variance do not show any significant difference in the average calcium oxide and phosphorus contents of the diets of the different hostels.

It will be noticed that in both the cases the mean square within hostels is greater than that between hostels. This shows that the greater part of the variation is due to the daily variation in the amount of CaO and phosphorus in the diet of each hostel.

(*Continued from previous column*)

REFERENCES

Das Gupta, B. M., and Chopra, R. N. (1938). *Indian Med. Gaz.*, Vol. LXXIII, p. 665.

Hill, R. A., and Goodwin, M. H. (1937). *Southern Med. Journ.*, Vol. XXX, p. 1170.

de León, A. D. (1937). *Pub. Health Rep.*, Vol. LII, p. 1460.

Pakenham-Walsh, R., and Rennie, A. T. (1938). *Lancet, ii*, p. 79.

Read, H., and Pino, J. O. (1938). *Arch. Schiffs-u. Trop.-Hyg.*, Vol. XLII, p. 132.