alternating with diarrhœa, was a common feature among those patients in whom the skiagrams revealed a condition of loss of tone or a condition of intestinal stasis due to spasmodic contraction of the large gut. Out of the total 80, 23 had looseness of the bowels; as might be expected many of these had colitis and catarrhal condition of the bowels, but quite a number, seven in this series, showed involvement of the appendix and were diagnosed as pathological appendix. Banerji, Chopra and Ray (1936) have fully discussed these cases elsewhere. What we wish to stress here is that in those patients in whom the appendix was not cleared of the opaque meal after 24 hours (sluggish appendix) while the cæcum and ascending colon were empty, a pathological appendix was suspected, and those in which the appendix still retained the meal after 48 hours and longer a definite diagnosis of pathological appendix could be made. These results were confirmed by operation in a number of cases.

Thirty-three patients passed mucus in their stools, being generally those whose stools were diarrhœic, though there were a few who passed streaks of mucus with constipated stools. Mucus was frequently observed in the stools of those in whom the appendix was pathological; it also occurred in those who had colitis and atonic or spastic conditions of the gut. Those who had acute colitis often passed both mucus and blood in their stools. The only case of duodenal ulceration that passed mucus and blood had an *E. histolytica* infection.

Of the patients who gave a history of melæna, one showed signs of duodenal ulceration, which was confirmed by radiological examination. In the other cases, no lesion was detected in the gastro-intestinal tract. The two cases with occult blood had heavy hookworm infections.

Anæmia was a common symptom in this series, 22 patients suffered from it. Of the four patients who showed a rise of temperature above normal while in hospital, two had malaria. The liver was enlarged in five cases of which three had *E. histolytica* infection.

A detailed microscopical and cultural examination of the stools was done in all this series. Five patients were found to be suffering from hookworm infection. *E. histolytica* was found in the stools of eight patients.

The bacterial organisms of doubtful pathogenicity, which were found in the stools by culture, are given below :—

Non-lactose fermenters—

(1)	*Bact. pseudo-carolinus* ..	16
(2)	„ *alkaligenes*	14
(3)	„ *morgani*	4
(4)	*Ps. pyocyanea*	4
(5)	*Bact. asiaticum*	4
(6)	„ *para-asiaticum* ..	4
(7)	„ *pseudo-asiaticum* ..	2

(Continued at foot of next column)

(Continued from previous column)

(8)	*Bact. lunavensis*	1
(9)	„ *metalkaligenes* ..	1
(10)	„ *douglasi*	1
(11)	„ *paratyphosum* ..	1
(12)	„ *pritnitzi*	1

Late lactose fermenters—

(1)	*Bact. belfastiensis*	1
(2)	„ *metadysentericum* ..	2

Others—

(1)	*Strept. fæcalis*	1
(2)	Staphylococci	2
(3)	Monilia	2

Summary

A series of 80 cases with chronic gastro-intestinal disturbances admitted under the senior author were investigated by radiological examination. Many of them originally had dysentery, which was later complicated with other pathological conditions of the bowels. Symptoms were variable, the chief being abdominal pains, distressing flatulence and irregularity of the bowels, which had lasted for prolonged periods and which were not controlled by ordinary methods of treatment. This is the class of case which often comes under the category of functional or neurasthenic. Nothing but a thorough laboratory and radiological examination could have diagnosed these cases. The commonest cause was stasis and atony in 37.5 per cent in this series. Other causes were pathological appendix, duodenal ulceration, and colitis, in the order of frequency. Thirteen patients showed normal appearance of the gastro-intestinal tract.

It was observed that in patients in whom the appendix still retained the barium meal after 24 hours the organ was not normal. In those in which the meal was still retained after 48 hours the appendix was definitely pathological and many of these cases showed constrictions and concretions. These observations were confirmed in a number of patients after operation.

REFERENCE

Banerji, L. M., Chopra, R. N., and Ray, P. N. (1936). Amœbiasis and Appendicitis. *Indian Med. Gaz.*, Vol. LXXI, p. 693.

INDIVIDUAL VARIATIONS IN THE EFFECTIVENESS OF SYNTHETIC ANTIMALARIAL DRUGS (A PRELIMINARY NOTE)

By R. N. CHOPRA, C.I.E., M.A., M.D. (Cantab.), M.R.C.P. (Lond.)
BREVET-COLONEL, I.M.S.
Honorary Physician to H. M. the King
B. SEN, B.SC., M.B.
and
A. C. ROY, M.SC.
(From the Department of Pharmacology, School of Tropical Medicine, Calcutta)

THE disadvantage of treating malignant tertian malaria with quinine or atebrin alone is

that neither of these drugs has any effect on the viability of the gametocytes of *Plasmodium falciparum*. In fact, the administration of quinine in some cases brings about an increase in the number of crescents in the peripheral blood. The necessity for a drug, possessing crescenticidal properties has therefore been felt for a long time. It was thus a great event when the synthesis of plasmochin was carried out by Schulemann and his co-workers in 1926. The literature regarding the action of this drug is enormous and there is no doubt that it produces a marked and rapid destructive action on the gametocytes of *P. falciparum*.

Knowles and Das Gupta (1931) worked out the minimal lethal dose of plasmochin for the gametocytes of the Indian strains of *P. falciparum*. They have shown that a total dosage of 0.04 gm. to 0.06 gm. of the drug is sufficient to eradicate all the sexual forms from the peripheral blood, even when the infestation is a very heavy one. These conclusions have also been borne out by Clemesha (1933). This dosage should be administered by the mouth, giving 0.01 gm. of the drug twice daily for two to three consecutive days. Within 24 hours of administration of plasmochin the gametocytes swell up and become irregular, the chromatin breaks up by karyorrhexis and the crescent stains very badly. In 48 hours, many of the gametocytes present in the film are almost unrecognizable and they finally disappear from the peripheral circulation.

In the literature, few cases of resistance to plasmochin are on record. In the Carmichael Hospital for Tropical Diseases we have had opportunities of treating and observing carefully a large number of patients with *P. falciparum* infection showing gametocytes in their blood, and we have found that the total dosage of 0.04 gm. of plasmochin as a rule succeeded in eradicating the gametocytes altogether from the peripheral blood, however large their number may be. Only in a few instances was a dosage of 0.06 gm. necessary.

We were therefore somewhat surprised when, in a patient recently admitted under the senior author into the Carmichael Hospital for Tropical Diseases and showing a heavy infection with the sexual forms of *P. falciparum*, the crescents persisted even after administration of 0.095 gm. of plasmochin, and a total of 0.135 gm. had to be given before they disappeared from the peripheral blood. This patient belonged to the series in which we were testing the effect of combined atebrin and plasmochin dragées (Bayer) on the Indian strains of malaria, and the details of this case are as follows :

Case I.—S. M. K., aged 31, was admitted into hospital on 3rd September, 1936, with the history of malarial fever off and on for the last three months. He was emaciated, slightly jaundiced and his spleen was palpable about an inch below the costal margin. Examination of the blood revealed the presence of malignant tertian rings and crescents. The laboratory findings and treatment are described below:—

Date	Laboratory findings	Treatment
4-9-36	Scanty M. T. rings and crescents.	
7-9-36	Do.	Atebrin 0.1 gm. and plasmochin 0.005 gm., t.d.s.
8-9-36	Crescents	Do.
9-9-36	Do.	Do.
10-9-36	Do.	Do.
11-9-36	Do.	Do.
12-9-36	Scanty crescents	..
13-9-36	Do.	..
14-9-36	Do.	..
15-9-36	Do.	..
16-9-36	Do.	Plasmochin 0.01 gm., b.d.
17-9-36	Do.	Plasmochin 0.02 gm., b.d
18-9-36	*Nil*	..

Laboratory examination.—Aldehyde test—negative; antimony test—undiluted + and diluted (1/10) —; lævulose tolerance test—normal before and after treatment with the combined preparation of atebrin and plasmochin; van den Bergh test—direct —, indirect ±, before and after treatment. Stool examination showed the presence of *Trichomonas hominis, E. nana* cysts, *Bact. morgani* and *Bact. para-asiaticus*.

The drug was administered by the mouth in the form of tablets each containing 0.1 gm. of atebrin and 0.005 gm. of plasmochin three times a day. The results puzzled us a good deal at first. We then started testing the urine for the presence of these drugs in order to see if any absorption was taking place. There was no difficulty in testing the presence of atebrin but we found the detection of plasmochin was not so easy. In a series of cases in which dragées were given, the urine was tested as a routine for the presence of atebrin, and parasites in the peripheral blood were also examined daily with a view to seeing what effect was being produced on them. Our intention in describing these cases is to bring out the fact that the question of absorption and excretion is an important factor in drug therapy and should never be lost sight of in cases where the expected results are not attained. Plasmochin is a toxic drug and as, in the case described, no such symptoms were noticed even with a dose much higher than the ordinary therapeutic dose, it is likely that the normal absorption of the drug was interfered with.

Case II.—A. U. S., aged 16, was admitted into hospital with the history of malarial fever for three months. He was anæmic and slightly emaciated and the breath

sounds were slightly diminished on the back. He gave a history of chronic irregularity of the bowels and occasional attacks of epistaxis. His spleen was tender and palpable about 2¼ inches below the costal margin. Examination of the blood revealed the presence of scanty malignant tertian rings.

Date	Malaria parasites	Treatment	REMARKS
21-11-36	Scanty M. T. rings.	Atebrin 0.1 gm. and plasmochin 0.005 gm., t.d.s.	
22-11-36	Do.	Do.	
23-11-36	Do.	Do.	
24-11-36	Do.	Do.	
25-11-36	Do.	Do.	Urine shows no atebrin. No effect on temperature.
26-11-36	Do.	Atebrin 0.1 gm., t.d.s.	
27-11-36	Do.	Do.	
28-11-36	Do.	Do.	
29-11-36	Very scanty M. T. rings.	Do.	
30-11-36	No parasites	Do.	Urine: appreciable amounts of atebrin.
1-12-36	Do.	..	Do.

Other laboratory findings.—Hookworm 700 eggs per c.cm.; urobilin present in the urine; van den Bergh indirect +, direct —; R. B. C. 3,300,000; hæmoglobin 62 per cent.

It will be observed that after a full five days' course of the atebrin and plasmochin dragées the asexual forms still persisted and the urine did not show the presence of atebrin. The patient was then put on atebrin by itself to see if the combination was at fault. The drug was detected in his urine in small quantities, and the asexual parasites disappeared from the peripheral circulation. The patient suffered from chronic gastro-intestinal trouble and had hookworm infection. It would appear that whereas the drug from the combination dragées was not absorbed at all in this case, atebrin by itself was absorbed with difficulty.

Case III.—K. N., aged 15, was admitted into hospital with the history of malarial fever for five months. He was anæmic, slightly icteroid and his spleen reached the level of the umbilicus. Examination of the blood showed the presence of a moderate infection of benign tertian malaria.

Date	Malaria parasites	Treatment	REMARKS
25-11-36	B. T. rings, trophozoites.	Atebrin 0.1 gm. and plasmochin 0.005 gm., t.d.s.	
26-11-36	Do.	Do.	
27-11-36	Do.	Do.	
28-11-36	B. T. rings, trophozoites, gametocytes—scanty.	Do.	Urine: no atebrin.
29-11-36	B. T. rings, trophozoites—scanty.	Atebrin 0.1 gm. and plasmochin 0.005 gm.	No effect on temperature.
30-11-36	..	..	Urine: no atebrin.
1-12-36	B. T. rings, trophozoites—scanty.	Atebrin 0.1 gm., t.d.s.	Do.
2-12-36	Do.	Do.	Urine: atebrin in small amount.
3-12-36	Do.	Do.	Urine: atebrin in appreciable amount.
4-12-36	No parasites	Do.	Do.
5-12-36	Do.	Do.	Do.
7-12-36	Do.	..	Do.

Other laboratory findings.—Hookworm less than 100 eggs per c.cm.; urobilin present in urine; van den Bergh indirect +, direct —; Widal: typhoid (H) 25, paratyphoid A (H) + 50; Wassermann reaction moderately positive.

In this patient the usual doses of atebrin and plasmochin in the form of dragées had no effect on the parasites in the blood. No atebrin could be detected in the urine. Even after administration of atebrin alone the absorption of the drug, as judged from excretion in urine, was slight at first. The patient had light hookworm infection and was anæmic.

Case IV.—G. A. G., aged 29, was admitted with the history of malarial fever for two weeks. He suffered from an attack of enteric fever in 1923; his liver was tender, the spleen was palpable about half an inch below the costal margin and a few moist sounds were also audible at the back of the lungs. Examination of the blood showed a scanty malignant tertian infection.

Date	Malaria parasites	Treatment	REMARKS
8-10-36	Scanty M. T. rings.	Atebrin 0.1 gm. and plasmochin 0.005 gm., t.d.s.	
9-10-36	No parasites	Do.	
10-10-36	Do.	Do.	
11-10-36	Do.	Do.	
12-10-36	Do.	Do.	
13-10-36	Very scanty B. T., growing trophozoites.	..	Urine: no atebrin.
14-10-36			
15-10-36			
18-10-36	B. T. rings, growing trophozoites.	Atebrin 0.1 gm., t.d.s.	Urine: appreciable amount of atebrin.
19-10-36	Do. scanty	Do.	
20-10-36	Do.	Do.	
21-10-36	No parasites	Do.	
22-10-36	Do.	Do.	

Other laboratory findings.—R. B. C. 3,490,000; hæmoglobin 70 per cent; Wassermann reaction strongly positive; van den Bergh: indirect—faintly positive, direct—negative.

This patient did not show any gastro-intestinal trouble, yet no atebrin was detected in the urine after administration of the combined dragées for five days. But when plain atebrin was started the urine showed appreciable amounts of the drug.

Case V.—S. C. S., aged 37, was admitted with the history of an attack of malaria about two months back. Eleven days after admission into the hospital, the patient started getting fever and, on examination of his blood, a fair number of malignant tertian rings was found. He was suffering from palpitation and difficulty of breathing and gave a history of occasional attacks of hæmatemesis. His spleen was just palpable.

Date	Malaria parasites	Treatment	Remarks
3-11-36	M. T. rings	Atebrin 0.1 gm. and plasmochin 0.005 gm., t.d.s.	
4-11-36	Do.	Do.	No effect on temperature.
5-11-36	Do.	Atebrin 0.1 gm., t.d.s.	Urine: trace of atebrin.
6-11-36	Do.	Do.	
7-11-36	Very scanty M. T. rings (thick film).	Do.	
8-11-36	No parasites.		

Other laboratory findings.—Hookworm, 3,800 eggs per c.cm.; *E. nana* cysts in stools; urobilin present in urine; van den Bergh: indirect +, direct —.

This patient suffered from a moderate infection with hookworm and showed no atebrin in the urine after administration of the combined dragées for two days. Atebrin by itself was absorbed with difficulty, as only traces were found in the urine, but the parasites disappeared from the peripheral blood on the fourth day.

Case VI.—N., aged 26, gave history of fever for six days only. Blood showed benign tertian infection. He gave a history of chronic constipation.

Date	Malaria parasites	Treatment	Remarks
25-10-36	B. T. rings, growing trophozoites and schizonts.	Atebrin 0.1 gm. and plasmochin 0.005 gm., b.d.	
26-10-36	Do.	Do.	
27-10-36	Do.	Do.	No effect on temperature.
28-10-36	Do.	Quinine.	
29-10-36	Scanty B. T. rings, growing trophozoites.	Do.	
30-10-36	No parasites	Do.	
31-10-36	Do.	Do.	
1-11-36	Do.	Do.	Urine: no atebrin.
3-11-36	Do.	..	Do.
4-11-36	Do.	..	Do.

Other laboratory findings.—Bact. pseudo-carolinus and *Ps. pyocyanea* present.

In this patient the combination dragées had no effect and administration of quinine caused disappearance of the parasites and symptoms were controlled. No atebrin could be detected in the urine. The stools of the patient showed the presence of organisms of the metadysentery group. This is the class of case in which the gastric acidity is usually low and the meal rushes through the small intestine.

Case VII.—H., aged 30, was admitted with the history of malaria—off and on—for three years. He was treated outside with quinine, esanofele, etc., but without much effect. His spleen was just palpable and blood showed scanty benign tertian infection.

Date	Malaria parasites	Treatment	Remarks
	B. T. rings and growing trophozoites—scanty.	Atebrin 0.1 gm. and plasmochin 0.005 gm., t.d.s.	
	Do.	Do.	Urine: atebrin a trace.
	Do.	Do.	Urine: no atebrin.
	Do.	Do.	Urine: just a trace of atebrin.
	Do.	Do.	

Other laboratory findings.—Trichomonas hominis and *Bact. pseudo-carolinus.*

In this patient, after administration of combination dragées, only a minute trace of atebrin could be detected in the urine and the parasites and symptoms persisted. The stools showed the presence of organisms of the metadysentery group. It is the class of case in which the meal rushes through the intestine and the urine only shows a trace of atebrin when it was given either in the form of combination dragées or by itself.

Discussion

Variations in the effectiveness of drugs and relative resistance of certain strains of malarial parasites have been frequently reported. What we wish to show, by describing these cases, is that absorption and excretion of drugs are important factors and should not be lost sight of when expected results are not forthcoming. The same drug, given to two different patients under similar conditions for the same symptoms, has behaved entirely differently, and, on testing the urine, one showed the presence of the drug while the other did not.

The reason of this variability in absorption is not far to seek. An analysis of the records of patients admitted into the Carmichael Hospital for Tropical Diseases during the year 1935 shows that in as many as 60 per cent of the patients the gastro-intestinal tract was involved.

Detailed investigation with the help of laboratory and *x*-ray examinations brought out the fact that approximately 26 per cent suffered from helminthic infections, 28 per cent from catarrhal conditions of the intestines of various origin and the remaining patients from pathological appendix, gastro-duodenal ulcer, pathological gall-bladder, etc. Helminthic parasites, especially hookworm, live in the upper part of the small intestine and a heavy infection may alter the normal physiological processes of absorption in this part (cases II and V). In addition, a large number of patients complained of vague abdominal symptoms without showing any definite laboratory findings for known infective agents. Most of these patients showed a condition of hypo- or hyper-chlorhydria which is very commonly associated with chronic dysenteries and colitis in which the original causal agent, either bacterial or protozoal, is very difficult to detect. The acidity of the stomach is in itself a factor in the absorption of the drug inasmuch as it is often here that the drug is rendered suitable for absorption by disintegration of tablets and conversion of insoluble into soluble compounds.

Another important factor which should not be lost sight of is that the rapid passage of the drug through the small intestine, where absorption of a drug usually takes place, occurs in chronic diarrhœas and dysenteries. *X*-ray examinations by barium meal show that the meal in these cases hurriedly passes through the small intestine and in a few hours, less than five usually, it reaches the pelvic colon, not a trace being left in the small intestines. The drug is thus not allowed time for absorption. Besides these conditions, the mucous membrane of the gastro-intestinal tract is not quite normal in a large percentage of patients in the tropics and peptic ulcers, pathological gall-bladder and appendix are frequently met with. The absorption of drugs in such cases may not be normal.

Summary

The following factors may be responsible for the variability in the absorption of drugs from the gastro-intestinal tract and the practitioner in the tropics should bear them in mind when the expected therapeutic results are not obtained :—

(1) The acute or chronic inflammatory condition of the mucous membrane. It is well known that under such conditions absorption of drugs is modified.

(2) The rapid passage of the meals through the small intestines generally, and upper part of the small intestine particularly, where absorption of these drugs usually takes place.

(3) The hypo-acidity of the stomach which is often met with in chronic dysenteric infections.

(*Continued at foot of next column*)

THE TREATMENT OF PITYRIASIS ROSEA

By P. A. MAPLESTONE, D.S.O., D.SC., M.B., B.S., D.T.M.

and

N. C. DEY, L.M.P., L.T.M.

(*From the Medical Mycology Inquiry, School of Tropical Medicine, Calcutta, partly financed by the Indian Research Fund Association*)

THE ætiology of pityriasis rosea is still unknown and there are several theories as to its cause. The most recent of these is that the disease is caused by a filtrable virus, and as the work described in this paper was undertaken solely with the object of testing this theory it is the only one that will be considered.

Wile (1927), as the result of several years' observation amongst a large body of university students, has produced some facts that suggest that pityriasis rosea is contagious, and after many failures he partially succeeded in transmitting it to himself and three other volunteers. He employed fluid from a blister raised over a typical lesion, in two of the cases it was injected intradermally and in two it was applied to a scarified surface. The eruption produced was very mild and short-lived in every instance but some of the lesions definitely resembled those of pityriasis rosea.

Thomson and Cumings (1931) made a complete pathological investigation of the disease

(*Continued from previous column*)

(4) Lastly, the drug may be administered in the form of tablets which are not properly constituted. Some of the ingredients used may prevent the disintegration of the tablet before reaching the part where absorption of the drug takes place, and in some cases the tablets may not disintegrate at all and may pass through the gut in an unbroken mass. It is open to question whether the atebrin and plasmochin combination in the dragées used renders the absorption of the individual drugs more difficult. It will be observed that, in a number of cases cited, atebrin was not absorbed when the combination dragées were administered, whereas atebrin in the form of tablets by itself was absorbed.

SELECT BIBLIOGRAPHY

Clemesha, W. W. (1933). Brief Note on Results obtained with Antigametocyte Treatment only, without Anti-Larval Measures. *Indian Med. Gaz.*, Vol. LXVIII, p. 199.

Fletcher, W., and Kanagarayer, K. (1927). Plasmochin in the Treatment of Malaria. *Ibid.*, Vol. LXII, p. 499.

Knowles, R., and Das Gupta, B. M. (1931). Clinical Studies in Malaria by Cultural and Enumerative Methods. *Ibid.*, Vol. LXVI, p. 1.

Sinton, J. A., and Bird, W. (1928). Plasmoquine in the Treatment of Malaria. *Indian Journ. Med. Res.*, Vol. XVI, p. 159.

Tropp, C., and Weise, W. (1933). The Excretion of Atebrin in Urine and Fæces. *Arch. Exper. Path. u. Pharm.*, Vol. CLXX, p. 339.