CRINODORA (PALUSAN) IN INDIAN STRAINS OF MALARIA

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AFTER the synthesis and successful trials of atebrin in the treatment of malaria, a number of acridine derivatives closely resembling it in chemical composition and properties were prepared. In France, 'quinacrine' was synthesized and in the U.S.S.R. 'acriquine'. Soon after, S. A. Farmaceutici Italia Milano synthesized a similar compound which they called 'Palusan' and later 'Crinodora', the chemical composition of which, as stated by the manufacturers, is the same as that of atebrin. As the supplies of atebrin in India from German sources have been stopped on account of the outbreak of war, we undertook to test this drug in the treatment of infections with Indian strains of malaria, so that, if the acridine derivatives prepared in Italy resembled atebrin closely, use could be made of this source for the supply of another effective antimalarial drug in this country.

The investigation was carried out on a series of 44 patients in the Carmichael Hospital for Tropical Diseases. Most of the patients came from different parts of Bengal where malaria is endemic. The studies were mainly undertaken to determine: (*a*) the effects of the drug on the temperature and other symptoms; (*b*) its effects on the asexual and sexual forms of the parasites, and the time taken for their disappearance from the peripheral blood; (*c*) its effect on the splenic enlargement; (*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. In this paper the results of these trials are summarized.

On admission of patients a thorough physical examination was carried out; the peripheral blood was examined and a rough estimate of the number of parasites, both sexual and asexual, was made. Except in urgent cases, the patients were put on a simple alkaline mixture and the antimalarial treatment was not started until the parasite counts were observed for two or three consecutive days. This gave valuable information regarding the intensity of the infection. If the parasites in the peripheral blood were scanty, these were allowed to increase till the rigors and other symptoms were pronounced, and then the drug was administered. Crinodora (palusan) was given by the mouth in tablet form, one tablet, containing 0.1 gramme, being given three times a day for five consecutive days. No other drug was given except a mild purgative whenever necessary. No restrictions regarding diet were observed. Daily examinations of the blood were carried out for malaria parasites during the course of treatment and a rough estimate of the number of parasites was also made wherever possible. The pulse, blood pressure and respiration were carefully recorded.

After completion of the course the patients were kept in hospital for a fortnight, daily examinations of the blood for parasites being made during this period. Cultural examinations of the blood for malarial parasites were also made where thin and thick films were negative.

TABLE

Race, Sex and Age	Species	Findings of parasites before treatment per 500 leucocytes		Findings of parasites during and after treatment. Parasites per 500 leucocytes								Days of fever after beginning treatment	Remarks
				2nd day		3rd day		4th day		5th day			
		As.*	Sex.	As.	Sex.	As.	Sex.	As.	Sex.	As.	Sex.		
H., M., 22	B T	240	Sc.	200	Sc.	Sc.	0	0	0	0	0	2	
H., M., 23	B T	Sc.	0	Sc.	0	0	0	0	0	0	0	2	
H., F., 5	B T and M T	350	Sc. (B T)	275	Sc. (B T)	Sc.	0	0	0	0	0	2	
H., M., 25	B T	Sc.	Sc.	Sc.	Sc.	0	0	0	0	0	0	2	H. W.
H., M., 12	M T and B T	508 (M T and (B T)	0	316 (M T and B T)	0	220 (M T and B T)	0	128 (M T and B T)	0	Sc. (M T and B T)	0	4	Total dose 1 g. Parasites free next day.
M., M., 62	Q T	Sc.	Sc.	Sc.	Sc.	Sc.	Sc.	Sc.	Sc.	Sc.	Sc.	4	Parasites free next day.

TABLE—*concld.*

Race, Sex and Age	Species	Findings of parasites before treatment per 500 leucocytes		Findings of parasites during and after treatment. Parasites per 500 leucocytes								Days of fever after beginning treatment	Remarks
				2nd day		3rd day		4th day		5th day			
		As.*	Sex.	As.	Sex.	As.	Sex.	As.	Sex.	As.	Sex.		
H., M., 32	M T	Sc.	Sc.	Sc.	Sc.	Sc.	Sc.	0	Sc.	0	Sc.	3	Crescents killed by plasmochin.
H., M., 25	B T	Sc.	0	Sc.	0	Sc.	0	0	0	0	0	1	
H., M., 24	B T	410	Sc.	225	Sc.	Sc.	0	0	0	0	0	2	
H., F., 22	M T	525	0	325	0	110	0	Sc.	0	0	0	3	
A.-I., F., 60	M T	425	0	212	0	110	Sc.	Sc.	Sc.	0	Sc.	3	Crescents persisted.
H., M., 40	M T	325	0	Sc.	0	Sc.	0	0	0	0	0	1	Pains slight in epigastrium.
M., M., 38	M T	625	Sc.	450	Sc.	175	Sc.	Sc.	Sc.	0	0	3	Crescent persisted.
H., M., 33	B T	Sc.	Sc.	Sc.	Sc.	0	0	0	0	0	0	1	
H., M., 17	M T	495	0	329	Sc.	128	Sc.	Sc.	Sc.	0	Sc.	3	Do.
H., M., 41	B T	Sc.	0	Sc.	Sc.	0	0	0	0	0	0	0	
H., M., 49	M T	320	0	130	0	Sc.	0	0	0	0	0	1	
M., M., 52	B T	Sc.	0	Sc.	0	Sc.	0	0	0	0	0	1	
H., M., 15	B T	595	0	320	0	300	0	124	0	Sc.	0	3	Parasite free following day.
A.-I., M., 34	M T	Sc.	0	Sc.	0	Sc.	0	0	0	0	0	1	
M., M., 44	M T	398	0	198	0	118	0	Sc.	0	0	0	2	
H., M., 47	M T	Sc.	0	Sc.	0	Sc.	0	0	0	0	0	1	
M., M., 20	B T	275	Sc.	150	Sc.	Sc.	0	0	0	0	0	..	
H., M., 45	M T	317	0	300	0	150	Sc.	Sc.	Sc.	0	Sc.	..	Crescents disappeared spontaneously after three weeks.
H., M., 30	M T	Sc.	0	0	0	0	0	0	0	0	0	..	
I.Ch., M., 25	B T	425	100	250	90	300	Sc.	Sc.	Sc.	0	0	..	
M., M., 20	M T	320	Sc.	180	Sc.	80	Sc.	Sc.	Sc.	0	Sc.	..	
H., M., 31	M T	Sc.	0	Sc.	0	0	0	0	0	0	0	..	
H., M., 50	B T	310	0	200	0	110	0	Sc.	0	0	0	..	
I.Ch., M., 15	M T	650	Sc.	275	Sc.	Sc.	Sc.	0	Sc.	0	Sc.	Apyrexial	H. W.
H., M., 33	B T	Sc.	Sc.	Sc.	Sc.	0	0	0	0	0	0	„	Colitis.
I.Ch., M., 30	B T	780	Sc.	310	Sc.	Sc.	Sc.	0	0	0	0	3	Anæmia.
H., M., 1	B T	Sc.	Sc.	Sc.	Sc.	Sc.	Sc.	Sc.	Sc.	0	0	2	
M., M., 24	M T	340	0	200	0	85	0	130	0	Sc.	0	4	Parasite free next day.
A.-I., M., 37	M T	258	0	150	0	Sc.	0	Sc.	0	Sc.	0	4	1.8 g. given. Parasite free 6th day.
H., M., 47	B T	374	Sc.	205	0	Sc.	0	Sc.	0	0	0	3	
H., M., 19	B T	Sc.	0	Sc.	0	Sc.	0	0	0	0	0	2	
M., M., 28	M T	278	0	190	0	Sc.	0	Sc.	0	0	0	3	
H., M., 30	M T	Sc.	0	Sc.	0	Sc.	0	0	0	0	0	2	
A.-I., F., 46	M T	421	0	318	0	116	0	Sc.	0	0	0	3	
M., M., 37	B T	Sc.	0	Sc.	0	Sc.	0	0	0	0	0	3	
H., M., 32	M T	Sc.	0	0	0	0	0	0	0	0	0	2	
A.-I., M., 45	M T	Sc.	0	Sc.	0	Sc.	0	Sc.	0	0	0	3	? Blackwater fever.
A.-I., 48	Q T	Sc.	Sc.	Sc.	Sc.	Sc.	Sc.	Sc.	Sc.	Sc.	Sc.	4	2.1 g. given. History of hæmaturia. Parasite free 6th day.

* As. = Asexual forms.

Details of 44 cases are given in the table. A study of the table will show that the temperature in all the three species of parasites usually begins to settle down after 0.6 gramme to 0.9 gramme of the drug has been administered and there is complete disappearance of the parasites

from the peripheral blood after 0.9 gramme to 1.2 gramme, except in quartan infections, where the drug had to be given for two more days to make the blood parasite-free. The drug has no action on the gametocytes of *P. falciparum*.

Rigors are seldom observed after the third day of administration of 'crinodora'. In mild cases of benign tertian infections, if the treatment with 'crinodora' 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.

The blood pressure, pulse rate and respiration were recorded. So far as the blood pressure is concerned, there was a slight lowering, varying from 8 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 'crinodora' has little if any depressing effect on the cardiovascular system in the majority of the patients.

Excretion.—In a series of patients we worked out the excretion of this compound. It is mostly excreted by the kidneys and appears in the urine on the second day after administration and can be detected up to 25 days or longer. Three patients under treatment with 'crinodora' developed a slight yellow colour in the skin which passed away after a few days.

Splenic enlargement.—There was rapid reduction in the size of the spleen to practically its normal size in every case of acute infection, but in long-standing cases, where the spleen was hard, the decrease in size was more gradual and the organ often took a considerable time to come back to its normal size.

Untoward and toxic effects.—In spite of the fact that 'crinodora' persists in the body for a fairly long time no marked untoward symptoms were noticed. One or two cases complained of slight pain or a sensation of uneasiness in the epigastric region. A few of our patients have occasionally complained of loss of appetite while the drug was being given, but the condition passed off with the discontinuance of the medicine.

Summary and conclusions

(1) 'Crinodora (palusan)' is an effective drug in the treatment of Indian strains of malaria. It is usually effective in doses of 0.1 gramme three times a day, the course lasting for five days and making a total of 1.5 gramme of the drug for the cure. The drug has no action on crescents.

(2) The drug behaves in exactly the same way as atebrin and would make an excellent substitute for it now that the supplies from Germany have been cut off.

IDIOPATHIC HYPOCHROMIC ANÆMIA WITH A CASE NOTE

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IDIOPATHIC hypochromic anæmia is a chronic form of anæmia found mostly in middle-aged women; it is associated with epithelial changes in the tongue and in the nails.

Ætiology.—Over 96 per cent of cases occur in women (Wintrobe and Beebe, 1933) and the maximal incidence is between the ages of forty and fifty; the condition is rare below twenty and uncommon above fifty. Repeated pregnancy, as well as excessive loss through menstruation, are responsible for a large number of cases (Davidson *et al.*, 1935).

From experimental evidence Heath, Strauss and Castle (1932) conclude that the main cause of the disease is iron deficiency. In a woman this may be due to a continual drain on the iron reserve of the body during the period of sexual life, deficient intake, and failure of proper absorption on account of hypochlorhydria or achlorhydria, iron being more readily absorbed from an acid medium (Mettier and Minot, 1931).

Although hypochlorhydria or achlorhydria is comparatively more common in women than in men (Davies and Shelley, 1934), they are not infrequently seen in men, whereas idiopathic hypochromic anæmia is rarely seen in men. It is therefore presumed that the low gastric acidity is not the main cause of the anæmia and that it is probably associated with some other, as yet unknown, deficiency of gastric secretion.

Symptomatology.—In addition to the physical signs and symptoms which accompany anæmia, remarkable epithelial changes are common. Epithelial atrophy of the upper part of the alimentary tract is the most frequent finding; the tongue is denuded of papillæ and is often sore and there may be painful fissures at the angles of the mouth.

Occasionally, there is atrophy of the pharyngeal mucosa, which when associated with dysphagia constitutes the Plummer-Vinson syndrome. Mucosal atrophy of the stomach is present in a number of cases and may be seen by means of the gastroscope; this is probably the basis of the hypochlorhydria or achlorhydria which is reported in a large number of cases (Witts, 1931; Davies, 1931; Mills, 1931; Oliver and Wilkinson, 1933). Gastro-intestinal symptoms, such as abdominal pain, anorexia, eructations, a sensation of fullness even after small meals, nausea, and vomiting, are usually present and are probably due to lack of an adequate amount of hydrochloric acid and an excess of mucus which makes the gastric juice very viscid (Davies, *loc. cit.*).

In addition to these changes in the gastro-intestinal tract, alterations in the nails are