RELAPSING BENIGN TERTIAN MALARIA TREATED WITH PALUDRINE

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TRIALS with 'Paludrine' in benign tertian (B.T.) malaria were carried out under the direction of the War Office and the malaria committee of the Medical Research Council at Colchester Military Hospital, beginning in July, 1945.

The following three different courses of treatment were used, each being given in strict rotation :

(1) Paludrine 0·05 g. daily for ten days.
(2) Paludrine 0·5 g. daily for ten days.
(3) Quinine gr. 30, pamaquin 0·03 g. daily for ten days.

Patients were carefully selected ; for example, those who had been given any treatment before admission to hospital were excluded. In every case there was a previous history of malaria, the vast majority having been proved by blood slide. Between July, 1945, and March, 1946, 324 cases, 108 of each series, were treated.

Blood slides, thick and thin, were taken when the patients arrived in the ward, and in the event of these showing *Plasmodium vivax*, and provided the cases were in other ways suitable, treatment was begun next morning. Above each bed was hung a specially prepared coloured chart on which the nurse responsible entered and signed for each dose of drug given. Every precaution was therefore taken to guard against possible errors in treatment. Each patient was allotted a serial number, and full particulars were entered on a special form devised by the malaria committee. In view of the difficulty of tracing patients after leaving hospital, these particulars included the patient's unit regiment, home address, and " age and service group." This was well rewarded in the final follow-up.

The drugs were given in divided doses, the paludrine twice a day, the quinine-pamaquin three times daily after food ; none of the paludrine cases showed any digestive symptoms.

Patients were confined to bed until they had been afebrile for forty-eight hours, a temperature of over 99° F being considered pyrexial. After the patients had been allowed out of bed, their activities were in no way restricted ; and, apart from ensuring an adequate fluid intake, no special precautions were taken throughout the stay in hospital.

Blood films were examined on the eighth, ninth, and tenth days of treatment in the first 240 cases ; but, owing to shortage of laboratory staff, this was later discontinued. The results of these investigations showed all except one patient to be negative for asexual parasites. This one patient was being treated on the quinine-pamaquin course, and on the ninth day of treatment scanty B.T. rings were seen. Subsequent follow-up showed that this patient was free from relapse after six months.

Patients were normally discharged from hospital on the day following completion of treatment, when they were given two prepaid postcards for return to me. On these was printed a form asking for details in the event of a relapse. Each patient was also asked, in the event of no relapse, to return the first card after three months and the second after six months. Less than 20% of the patients used the cards for the purpose for which they were intended.

RESULTS OF TREATMENT

Immediate.—There was a rapid response to all forms of treatment, and little difference in results was seen in the three series. The number of days of pyrexia were as follows :

Course	Average no. of days of pyrexia after start of treatment
Paludrine (0·05 g.)	1·49
Paludrine (0·5 g.)	1·47
Quinine-pamaquin	0·98

Remote.—Six months after discharge from hospital each patient was sent a standard form asking for information regarding further relapses. If this report indicated a clinical relapse, a second questionnaire, about rigors, periodicity of symptoms, duration, and treatment, was sent. From this information the cases were divided into proved relapses, clinical relapses, and no relapses. As the investigations progressed, an increasing number of patients fell into the doubtful category, owing to many of them being demobilised and therefore no longer entitled to treatment in a military hospital.

The response to follow-up was remarkably good, and many patients replied at the first request. Just over 450 letters were required to trace the 324 cases. Every patient in the series has been followed up, and only one has been excluded from the final analysis (table I). This patient had a further attack of B.T. malaria in Cairo, where it was considered he might have been reinfected.

TABLE I—REMOTE RESULTS OF TREATMENT

Course	No. of cases	Free from relapses	One proved relapse	Two or more proved relapses	Clinical relapse	% relapsed	
						All cases	Proved cases
Paludrine (0·05 g.)	108	62	26	7	13	42·6	30·5
Paludrine (0·5 g.)	107	60	23	2	22	43·9	23·3
Quinine-pamaquin	108	91	9	1	7	15·6	9·2

The standard quinine-pamaquin treatment has been used as a control in this investigation. The results obtained here may therefore be compared with previous findings, which show relapse-rates of 10·3% proved cases,[1] 11·3% proved cases, and 16·5% total relapses.[2] There is therefore no significant difference in the quinine-pamaquin results, and those obtained with paludrine may be reasonably concluded to be equally accurate.

FACTORS POSSIBLY INFLUENCING RELAPSE-RATE

Captivity.—Of the total series, 89 cases (27·4%) were patients who had been prisoners-of-war in the Far East. Since the relapse-rate of these might be expected to differ from the normal cases, owing to most of them having had very inadequate treatment and very frequent attacks while prisoners, they have been analysed separately (table II). The relapse-rate is higher than in the other cases ; but, since the distribution of prisoner-of-war cases shows almost equal division between the total paludrine and quinine-pamaquin series, it is justifiable

1. Malaria Committee of Medical Research Council, report M.L.E. 30, 1945.
2. Johnstone, R. D. C. *Ann. trop. Med. Parasit.* 1946 (in the press).

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TABLE II—RELAPSE-RATE AMONG PRISONERS-OF-WAR AND OTHERS

Course	Total	Free from relapse	Proved re-lapses	Clinical re-lapses	% relapsed	
					All cases	Proved cases
Far East prisoners-of-war						
Paludrine (0·05 g.)	25	12	8	5	52·0	32·0
Paludrine (0·5 g.)	35	13	8	14	62·8	22·8
Quinine-pamaquin	29	20	5	4	31·0	17·2
Other cases						
Paludrine (0·05 g.)	83	50	25	8	39·7	30·1
Paludrine (0·5 g.)	72	47	17	8	34·7	23·6
Quinine-pamaquin	79	71	5	3	10·1	6·3

to include them in the totals provided it is realised that the total relapse-rate is thereby increased.

Return to England.—As relapses are more definite and more likely during the first few months after return to England, the time interval between arrival in U.K. and admission to hospital has been compared in the different series:

Course	*Average months in U.K.*	*Maximum*
Paludrine (0·05 g.) ..	.. 3·26 ..	11 months
Paludrine (0·5 g.) ..	.. 3·31 ..	1 year
Quinine-pamaquin ..	.. 3·13 ..	9 months

There is no bias in favour of any of the three treatments.

Probable Area of Infection.—Since different strains of *P. vivax* may possibly cause relapses at different intervals, the probable area of infection has been compared:

Course	*India-Burma*	*Mediterranean area*	*Far East*	*Others*
Paludrine (average for both courses) ..	65·5 ..	10·5 ..	30 ..	1·5
Quinine-pamaquin ..	64 ..	14 ..	29 ..	1

The probable area of infection does not seem to have influenced the relapse-rate in the different series.

INTERVALS BETWEEN RELAPSES

The interval between treatment and proved relapse has been assessed as follows:

Course	*Average no. of days between treatment and proved relapse*
Paludrine (0·05 g.)	65·1
Paludrine (0·5 g.)	53·0
Quinine-pamaquin	43·7

These findings are open to much criticism, as there is no doubt that some patients took occasional and inadequate doses of mepacrine after leaving hospital, though they were advised not to do so. As a result, it is probable that the relapse period in these cases was prolonged.

SUMMARY

Paludrine has been used in the treatment of 216 cases of relapsing B.T. malaria, while 108 control cases have received the standard quinine-pamaquin treatment.

A six-month follow-up has been obtained in all these cases, and the results show a relapse-rate associated with both dosages of paludrine over double that associated with quinine-pamaquin.

No appreciable difference has been noted between the results of small or large doses of paludrine.

This investigation does not include all the relapses, because the period does not cover sufficient time after treatment, it being generally agreed that a second but small peak of relapses is to be expected in the 250–300 day period. Thus one case treated on paludrine (0·5 g.) is here given as "no relapse," having had his first relapse 240 days after leaving hospital.

Quinine-pamaquin treatment probably causes the temperature to fall to normal slightly quicker than does paludrine.

There is a suggestion that paludrine given in a ten-day course causes a longer period of freedom from relapse than does quinine-pamaquin, in spite of the high relapse-rate.

Paludrine given in a ten-day course is effective in treating acute attacks of B.T. malaria but in no way compares with the standard quinine-pamaquin treatment in controlling further relapses.

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MYELITIS AFTER ANTIRABIC VACCINE

REPORT OF A FATAL CASE

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THE pathogenesis of paralyses following treatment with antirabic vaccine is not yet understood. In the case reported here a necropsy was done.

CASE-RECORD

Clinical.—A Sudanese soldier, aged 25, was bitten on the left hand and right ankle by a stray dog on Sept. 3, 1944. It is not known whether the dog was rabid or not.

Treatment with antirabic vaccine was started immediately. A killed carbolised vaccine was used, made from sheep's brain according to the method of Semple, a 2% emulsion being used. Injections were given subcutaneously into the abdominal wall in daily doses of 5 c.cm. each. Between Sept. 3 and Sept. 10 seven daily injections were given.

The patient then defaulted and next came under medical care on Oct. 31, when he said that the dog was mad, and it was decided to give him a further complete course of antirabic vaccine. Between Oct. 31 and Nov. 14 he was given thirteen daily injections as before. Treatment was then stopped. On Nov. 18, four days after his last injection, he complained of pain and twitching in his left upper arm and shoulder. He was immediately sent into hospital.

On examination there was fibrillary twitching in the muscles of his left upper arm and shoulder girdle. Temperature was 102° F, and a blood-count showed white cells 9600 (polymorphs 45%, lymphocytes 44%, mononuclears 9%, eosinophils 2%). His condition remained unchanged until Nov. 20, when it was found that he could not dorsiflex his left wrist.

On Nov. 21 neck rigidity and head-retraction developed, and there was complete flaccid paralysis of his left arm. Kernig's sign was positive. Temperature 99·2° F, pulse-rate 140 per minute, respirations 40 per minute. Nothing abnormal found in chest and abdomen. The white-cell count was 6400 per c.mm. (polymorphs 52%, lymphocytes 42%, mononuclears 4%, eosinophils 2%). Lumbar puncture was attempted but failed owing to the difficulty in flexing his back.

On Nov. 22, the day of his death, he presented a picture of acute distress. Temperature 100° F, pulse-rate 130 per minute, respirations 45 per minute. Head-retraction present. The fibrillary twitching had ceased in his left paralysed arm but was seen in his right arm and in the chest and abdominal muscles of both sides. He had violent uncontrollable spasms of the occipitofrontalis muscle and the muscles of the right upper lip, and had repeated attacks of retching. A profuse mucoid discharge came from his mouth and nose. His mental processes were unimpaired. He spoke intelligently and complained of pain in the left clavicular region but could not articulate properly and had difficulty in swallowing.