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The Medical Director has the honour to communicate herewith a :

NOTE ON THE TREATMENT OF MALARIA WITH QUININE
AND PLASMOQUINE

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This document has been prepared for the meeting of the Study-Committee of the Malaria Commission.

The treatment of malaria by quinine and the synthetic drug plasmoquine has engaged our attention for a number of years. In addition to studying the therapeutic value of these drugs we have investigated their relative merits from the standpoint of prophylactic mass treatment. The present note presents a brief summary of the observations made during this period.

In order to obtain a proper evaluation of the relative merits of the drugs tested, it is necessary to consider their effectiveness under three different heads:

- 1) Their immediate therapeutic effect,
- 2) The incidence of relapses after apparent clinical cure,
- 3) Their effectiveness in mass treatment.

A. Therapeutic value of quinine and other drugs.

Regarding the relative therapeutic efficiency of quinine and plasmoquine our own observations correspond with those of other workers. Our observations on small individual groups as well as in mass treatment have shown:

1) That quinine given in adult doses of two grams per day eliminates the parasites from the circulation after five days treatment.

2) That plasmochine in doses of 0.06 grams per day for five days effects the same result in benign tertian malaria but has a less favourable action on malignant tertian cases. In such cases plasmochine may act as a provocative. Moreover, this dosage of the drug is apt to be toxic and can only be given with caution.

3) A combination of quinine and plasmoquine in adult doses of 1.0 gm, quinine and 0.03 gm. plasmoquine effects a clinical cure in all forms of malaria in three to five days, without any apparent toxic effect.

Consequently, from the standpoint of the immediate therapeutic effect the combination of quinine and plasmoquine (or quinoplasmine) is, in so far as our experience goes, the most effective drug for the treatment of malaria. The combined drug has the added value of rapidly removing the gametes of the various species from the circulation.

B. Post-treatment Relapses.

Of greater importance is the problem of post-treatment relapses. In considering this problem it is essential to deal separately with the children and adult population. The essential difference in the effectiveness of a drug in adults and children respectively has not received adequate attention. Most of the observations on the relative efficacy of anti-plasmodial drugs have been made on adults. In infected areas, however, the greater part of the infected population consists of children under ten. Our experiments have shown that children, and more particularly those below six years of age, are less favourably affected than adults. While the immediate

therapeutic effect may be the same in children as in adults, the cure rate as judged by the post treatment relapses is much lower.

Judged from this angle the problem assumes a different aspect. In our earlier comparative studies on quinine and plasmochine this phase of the problem was not fully considered. In a comparative study on the relative therapeutic efficacy of quinine and quinoplasmine in children below the age of six, quinine gave a clinical cure in 17 out of 18 cases and quinoplasmine in 17 out of 17. The immediate effect was, therefore, approximately the same. After an interval of two months, however, 7 out of the 18 cases treated with quinine alone, and only 2 out of the 17 treated with quinoplasmine relapsed.

Subsequent studies were, therefore, made with quinoplasmine alone. These studies, however, revealed a higher rate of relapse than in the first series. Of 21 children treated (during the same period) 12, or 57 per cent relapsed within two months. The only apparent explanation of the discordant results was that children previously treated did not respond as well to subsequent treatments as did those who had not received any previous treatment. This surmise was confirmed when children of the first series were treated a second time. This time this group also gave a higher rate of relapses; out of 42 children treated, 19 or 45 per cent relapsed in two months.

A summary of these data is shown in Table I.

A further analysis of the data showed that most of the relapses occurred in the ages below six, and that the lower the age the less effective was the drug both from the standpoint of immediate and that of permanent cure. The relative therapeutic efficiency of quinoplasmine in different age groups is shown in Table II. It is apparent that the drug acts differently on

Table I. - Relapse Rate after Treatment (1).

Method of Treatment	Type of Malaria									
	BT : Troph. Gametes		MT : Troph. Gam.		QT : Troph. Gam.		Mixed : Troph. Gam.		Total Posit. : Troph. Gam.	
<u>1st series</u>										
<u>1) Quinine</u>										
No. positive before treatment	3	1	3	1	9	0	3	1	18	3
after treatment	0	0	0	0	0	0	0	1	0	1
2 months (2) later	0	0	2	1	2	0	3	1	7	2
<u>2) Quino-plasmine</u>										
No. positive before treatment	1	1	5	5	6	0	5	4	17	10
after treatment	0	0	0	0	0	0	0	0	0	0
2 months later	0	0	1	0	1	0	0	0	2	0
<u>2nd series</u>										
<u>Quinoplasmine</u>										
No. positive before treatment	8	2	3	0	5	2	5	4	21	8
after treatment	0	0	0	0	0	0	0	0	0	0
2 months after	3	0	1	0	3	0	5	1	12	1
<u>3rd series</u>										
<u>Quinoplasmine</u>										
No. positive before treatment	6		17		16		3		42	
after treatment	1		2		1		0		4	
2 months later	5		7		6		1		19	
<u>Total (3)</u>										
No. positive before treatment	15		25		27		13			
after treatment	1		2		1		0			
No. relapsed	8		9		10		6			
% relapsed	53.0		36.0		37.0		46.0			

(1) All treatments in March
 (2) Final examinations early in May
 (3) Quinoplasmine only.

different groups of children, but is, in general, less effective in children below the age of four than in those above that age.

C. Mass Treatment.

The daily dosage was as follows:

Less than 2 years	0.3 gm.	quinine sulphate	+	0.003 gm.	plasmochine		
2-6 "	0.55 "	"	"	÷ 0.01 "	"	"	"
7-10 "	0.65 "	"	"	÷ 0.015 "	"	"	"
11-14 "	0.75 "	"	"	÷ 0.02 "	"	"	"
above 14 "	0.9 "	"	"	÷ 0.03 "	"	"	"

Pregnant women received only 0.04 gm. plasmochine. The treatment was given twice daily, young children and infants receiving emulsions, the others tablets.

The treatment was continued for six days; treatment on the last day was given only to those individuals who had not received a full course. Lists were kept of all the people treated and the names of those receiving treatment checked daily.

No ill results were noted during the entire course of the treatment.

The observations on selected groups were supported by the result of more extensive experience with mass treatment. This experiment included 782 adults and 475 children. The procedure was the same as in the previous series. The results are summarised in Tables III and IV. Here again the effectiveness of the treatment differed in different places and in adults and children respectively. Immediately after the treatment the incidence of trophozoites and of gametes was higher among children than among adults, and three to four times as high among children below four years of age as among those above that age. It is evident, therefore, that the reports on the efficacy of a given drug will depend in a large measure on the age of the subjects treated.

Table II - Relative Efficacy of Drugs in Different Age Groups

	<u>Age Groups</u>					
	<u>- 2</u>		<u>2 - 4</u>		<u>4 +</u>	
	Before treatment	Relapse No. %	Before treatment	Relapse No. %	Before treatment	Relapse No. %
Quinine	8	2 25.0	6	2 33.0	4	2 50.0
Quino-plasmine	12	2 16.7	4	0 0.0	1	0 0.0
Quino-plasmine	5	3 60.0	8	7 87.5	8	2 25.0
Quino-plasmine	19	11 58.0	16	8 50.0	7	0 0.0

Table III - Summary of Blood Examinations (Mass Treatment) Showing Conditions Before Treatment and Two Weeks after Last Treatment.

<u>Melaha</u>		<u>Adults</u>		<u>Children</u>				
		Men	women	14-10	10-6	6-4	4-2	below 2
Before treatment	No. Exam. % pos.	118 11.0	118 6.7	26 35.0	37 51.0	20 66.0	44 80.0	49 100.0
after treatment	No. Exam. % pos.	67 6.0	79 3.8	24 0.0	41 5.0	21 10.0	41 40.0	50 26.0
Before treatment	No. Exam. % pos.	58 14.0	70 6.0	15 33.0	21 33.0	10 80.0	25 92.0	24 83.0
after treatment	No. Exam. % pos.	31 6.5	40 12.0	12 8.0	16 6.0	13 14.0	24 42.0	11 55.0

Table IV - Incidence of Gamete Carriers among Children and adults Before Treatment and Two Weeks after Last Treatment.

	<u>P l a c e</u>					
	<u>Jahuleh</u>		<u>Melaha</u>		<u>Almanieh</u>	
<u>Children</u>	before	after	before	after	before	after
Total Treated	115	115	256	256	41	41
No. Exam.	104	85	181	177	31	37
percent gametes +	14.4	7.0	14.9	1.1	20.0	5.5
<u>Adults</u>						
Total Treated	192	192	409	409	83	83
No. Exam.	128	71	236	148	50	32
percent gametes +	1.5	0.0	0.0	0.0	0.0	0.0
<u>Total</u>						
population treated	307	307	665	665	124	124
No. Exam.	232	156	417	325	81	69
Percent Gametes +	6.4	2.6	5.0	0.45	6.5	1.8

Although the incidence of parasite and gamete carriers in the child population was markedly reduced by the treatment, at no time during the repeated intermittent treatment was that population free of gamete carriers. This was true of the general child population and of the special group under constant observation. (Details can be found in the publication referred to - Kligler, I.J. and Mer, G., Riv. di. Mal. 10,4., 1931).

With regard to relapses, the results paralleled those immediately after treatment. The incidence of relapses varied with the age group and decreased progressively with increasing age. Children below 2 gave 50 percent relapses while those from 6-10 gave only 20 percent. The children receiving a complete course of treatments gave 35 percent relapse as against nearly 100 percent among those who received only incomplete or irregular treatment.

With regard to the type of malaria, malignant tertian yielded less readily to treatment than any of the other forms. Of a total of 41 cases receiving full repeated treatment, nine cases or about 25 percent failed to respond (all of these were in the age group below four: nine relapses of a total of eighteen cases.)

The results of our studies can, therefore, be summarised as follows:-

Quinoplasmine combines the therapeutic value of quinine and plasmoquine and consequently is a better agent than quinine alone, particularly insofar as gametes are concerned. Earlier studies have shown that a five day course of treatment with this mixture in daily adult doses of 0.03 gm. plasmochine and 1.0 gm. quinine is effective in producing clinical cure and freeing the peripheral circulation of both trophozoites and gametes. Subsequent studies were intended to test the value of repeated

Table V - Gamete Carriers (MT & BT) among Fully Treated Children in Melaha and Jahuleh During the Course of Treatment

Age	Before Treatment			12 days after first treatment			12 days after second treatment			12 days after third treatment			final examination 2 weeks later		
	no. exam	no. ÷	perc. ÷	no. exam	no. ÷	perc. ÷	no. exam	no. ÷	perc. ÷	no. exam	no. ÷	perc. ÷	no. exam	no. ÷	perc. ÷
0-2	51	16	31.0	49	2	4.0	47	0	0.0	48	4	8.3	46	3	6.5
2-4	49	3	6.0	48	0	0.0	44	0	0.0	44	2	4.7	44	1	2.3
4-6	26	4	15.4	25	0	0.0	21	0	0.0	26	0	0.0	23	1	4.3
6-10	46	4	8.7	39	0	0.0	43	0	0.0	43	0	0.0	37	0	0.0
10-14	38	1	2.7	26	0	0.0	23	0	0.0	31	0	0.0	28	0	0.0

Table VI - Relapses in Children after Quinoplasmine Treatment.

a) Sample of Child Population

age	March 1930		Before treatment		March 1931		4 months after treatment	
	No.	Exam.	No.	pos. Perc. pos.	No.	Exam.	No.	pos. Perc. pos.
-2	26		26	100	45		29	51
2-4	21		17	81	44		21	45
4-6	9		9	100	19		4	21
6-10	14		9	64	23		3	13

b) All Children Treated

age	Sept. 1930 before treatment			March 1931 - 4 months after last treatment		
	No.	pos.	Perc. pos.	No.	pos.	Perc. pos.
-2	27	27	96	27	13	50
2-4	26	23	88	26	12	46

c) Those Who Received Full Treatment

age	Sept. 1930			March 1931.		
	No.	pos.	Perc. pos.	No.	pos.	Perc. pos.
-2	18	17	95	18	6	33
2-4	17	15	88	17	5	30

d) Those Who Received Partial Treatment.

	19	17	89	17	15	88
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1) Three courses of five days at intervals of three weeks.

Table VII - Effect of Full Treatment on Varicous Types of Parasites.

Types of Malaria.

<u>Age</u>	No.	MT Gam.	BT Gam.	QT Gam.	Mixed Gam.	Total No.	Total Gam.		
<u>-2</u>									
Before treatment	13	7		6	0	6	4(MT) 25	11	
effect of treatment	6	1		0	0	2	0	8	1
<u>2-4</u>									
before treatment	5	0		10	0	5	2	20	2
effect of treatment	3	0		6(1)	0	2	1	11	1
<u>4-6</u>									
before treatment	6	1		2		1		9	1
effect of treatment	0	0		0		0		0	0
<u>6-10</u>									
before treatment	12	2		3	0	3	1	17	3
effect of treatment	0	0		0	0	0	0	0	0

(1) Relapsed as MT.

intermittent treatment. The first treatment was given at the middle of September a month before the fall activity of A. elutus (the dominant vector in the area) and the last early in November, two weeks before the end of the active prehibernating flight; a total of three treatments was given. The results showed that the measure was effective in reducing the infection rate. Both the incidence of human and mosquito infection was reduced to about one-third of that normal for the area.

At the same time the results showed: 1) That the mixture was far less efficacious in children below four years than in those over four years of age; 2) That while the immediate effect of the treatment was good a considerable number of cases relapsed within two weeks and 4 months after the treatment was terminated; and 3) that repeated treatment tended to decrease the cure rate, probably as a result of the increased resistance of the parasites to the drug.

Further comparative studies of the efficacy of the different drugs in the treatment of children, particularly those below the age of six, is, therefore, necessary before any conclusion can be drawn concerning their relative merits.