

LEAGUE OF NATIONS.

C.H./Malaria/265.

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HEALTH ORGANISATION.

MALARIA COMMISSION.

A CONTRIBUTION TO THE STUDY OF DRUG PROPHYLAXIS BY ATEBRIN,
IN INTENTIONALLY-INDUCED INFECTIONS WITH P.VIVAX AND P.
FALCIPARUM.

Results obtained by various modes of administration
(daily, bi-weekly, and in diminishing doses)

by

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The information contained in the Fourth Report about drug prophylaxis, which is based on field investigations, requires further verification by experimental means, in order to determine more exactly what results can be secured by using atebirin administered in a number of different ways.

The Report states: "A bi-weekly dose of atebirin administered either on successive days or at one or two days' interval gave better results, especially in the Italian and Malayan experiments (subject to the reservations made), than daily doses of 0.05 grm. of atebirin, and slightly better results than quinine in the indicated daily dose".

Certain workers placed great hopes in the prospect of a sufficient retention of atebirin in the organism to allow of a gradual diminution of the later doses in prophylactic treatment.

We have therefore felt that a useful purpose would be served by closer investigation of this point, beginning with laboratory experiments, since tests in the field are subject to fluctuating factors of a complexity too great to allow definite conclusions to emerge.

The reader will find below a summary of the observations made on each patient.

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I. INTENTIONALLY-INDUCED P. FALCIPARUM INFECTION.

A. Drug prophylaxis (malignant tertian): small daily doses
of atebirin (0.06 grm.).

This group of four patients received a single weekly inoculation of P. falciparum sporozoites during three weeks.

The sporozoite count was made by Shute's method.

A daily dose of 0.06 gm. of atebirin was given throughout the 3 weeks. As a rule, the last dose of atebirin was given 7 days after the last inoculation of sporozoites. The total amount of atebirin given was 1.26 gm. The duration of incubation was reckoned from the date of the first inoculation.

The results, as entered on the summary of the observations on our patients, were as follows:

Gr.E. 9/5/38.

Weekly inoculation of *P. falciparum* sporozoites.

Daily dose, 0.06 gm. atebirin; last dose 6 days after last inoculation of sporozoites. Total amount, 1.26 gm.

<u>Week.</u>	<u>Sporozoites</u>	<u>Atebrin</u>	<u>Appearance</u>		<u>Remarks</u>
			<u>Para-sites</u>	<u>Fever</u>	
1st	31,000	0.06 x 7	-	-	-
2nd	35,000	0.06 x 7	+ 10th day	+ 12th day	-
3rd	21,000	0.06 x 7	+	+	Intermittent attacks
4th	-	-	+	+	Subfebrile condition
5th	-	-	+	+	Subfebrile do
6th	-	-	+	+	Subfebrile do
7th	-	-	+	-	-
8th	-	-	+	-	Intermittent parasites.
9th	-	-	-	-	-
10th-16th	-	-	-	-	-

Observations ceased 16/8/38.

R.A. 9/5/38.

Weekly intravenous inoculation of *P. falciparum* sporozoites.

Daily dose, 0.06 gm. atebirin; total amount 1.26 gm.

<u>Week</u>	<u>Sporozoites</u>	<u>Atebrin</u>	<u>Appearance</u>		<u>Remarks</u>
			<u>Para-sites</u>	<u>Fever</u>	
1st	34,200	0.06 x 7	-	-	-
2nd	26,800	0.06 x 7	-	-	-
3rd	21,000	0.06 x 7	-	-	-
4th	-	-	-	-	1 day's fever (?) without parasites
5th	-	-	-	-	-
6th	-	-	-	-	-
7th	-	-	-	-	-
8th	-	-	-	-	-
9th	-	-	+ 57th day	-	Spontaneous disappearance
10th	-	-	+	-	" "
11th-14th	-	-	-	-	-

Observations ceased 11/8/38

A.E. 9/5/38.

Weekly intravenous inoculation of *P. falciparum* sporozoites.
Daily dose, 0.06 gm. atebtrin; total amount, 1.26 gm.

<u>Week</u>	<u>Sporozoites</u>	<u>Atebrin</u>	<u>Appearance</u>		<u>Remarks</u>
			<u>Parasites</u>	<u>Fever</u>	
1st	38,000	0.06 x 7	-	-	
2nd	44,000	0.06 x 7	+ 13th day	+ 13th day	Fever at constant level for four days.
3rd	33,200	0.06 x 7	+	+	Subfebrile condition.
4th	-	-	+	+	Feverish condition.
5th	-	-	+	+	Quotidian attacks.
6th)					
7th)	Patient placed under treatment				
8th-12th	-	-	-	-	

Observations ceased 4/8/38.

L.O. 9/5/38.

Weekly intravenous inoculation of *P. falciparum* sporozoites.
Daily dose, 0.06 gm. atebtrin; total amount, 1.26 gm.

<u>Week</u>	<u>Sporozoites</u>	<u>Atebrin</u>	<u>Appearance</u>		<u>Remarks</u>
			<u>Parasites</u>	<u>Fever</u>	
1st	28,500	0.06 x 7	-	-	
2nd	27,200	0.06 x 7	+ 10th day	+ 11th day	Quotidian attacks
3rd	27,900	0.06 x 7	+	+	"
4th	-	-	+	+	Irregular fever
5th	-	-	+	+	Irregular attack
6th	-	-	+	+	Subfebrile condition
7th	-	-	+	+	" "
8th	-	-	+		Spontaneous disappearance
9th-16th	-	-	-	-	

Observations ceased 20/8/38.

x

x

x

SUMMARY:

The inadequacy of small daily doses of atebtrin in induced *P. falciparum* infections is manifest. Reinfections occurring during the clinical period do not worsen the patient's general condition.

Infection tends to become chronic; the immunisation process does not appear to be impeded.

x

x

x

B. Does the organism retain sufficient atebtrin, during drug prophylaxis, to allow the later doses of atebtrin to be diminished?

1. A group of 4 paralytics was given, for malariatherapy purposes, large bi-weekly intravenous inoculations of sporozoites during 4 weeks. On the same days the patients underwent prophylactic treatment with diminishing doses of atebtrin (from 0.40 x 2 to 0.05 x 2 weekly); the last dose of atebtrin coincided with the last inoculation of sporozoites.

The period of incubation was reckoned from the date of the first sporozoite inoculation; in the "Remarks" column, the reader will also find incubation reckoned as from the date of the last sporozoite inoculation.

V.E. 9/5/38.

Bi-weekly venous inoculation of sporozoites.
Bi-weekly doses of atebtrin; total amount, 1.50 grm.

The first infection and the first administration of atebtrin took place on the same day.

<u>Week</u>	<u>Sporozoites inoculated</u>		<u>Atebtrin</u>		<u>Appearance</u>		<u>Remarks</u>
					<u>Parasites</u>	<u>Fever</u>	
1st	30,400 +	32,400	0.40+	0.40	-	-	
2nd	64,800 +	28,000	0.20+	0.20	-	-	
3rd	24,900 +	35,000	0.10+	0.10	-	-	
4th	32,000 +	21,000	0.05+	0.05	-	-	
5th					-	-	
6th					-	-	
7th					+ 44th day+	46th day	Regular clinical form 19 days after last infection & last dose of atebtrin (0.05 grm.)
8th					+	+	
9th					+	+	
10th-12th					+	-	
13th					+	+	2 tertian attacks.
14th			0.30 x 7		+	-	

Observations ceased 14/8/38.

L.E. 9/5/38.

Bi-weekly sporozoite infection.
Bi-weekly diminishing doses of atebtrin; total amount,
1.50 grm.

<u>Week</u>	<u>Sporozoites inoculated</u>	<u>Atebrin</u>	<u>Appearance Parasites</u>	<u>Fever</u>	<u>Remarks</u>
1st	33,000+ 27,200	0.40+ 0.40			
2nd	49,000+ 24,800	0.20+ 0.20	+ 13th day		Very rare rings. Spontaneous disapp.
			=		
3rd	19,800+ 35,600	0.10+ 0.10			
4th	32,000	0.05+ 0.05	+ 23rd day		" "
			=		
5th			+ 34th day		
			=		
6th					Parasite infection, only a few young forms. No gametocytes up to spontaneous disappearance of parasites.
7th					
8th					
9th-14th					

Observations ceased 20/8/38.

E.N. 9/5/38.

Bi-weekly venous inoculation of sporozoites.
Bi-weekly diminishing doses of atebtrin; total amount,
1.50 grm.

<u>Week</u>	<u>Sporozoites inoculated</u>	<u>Atebrin</u>	<u>Appearance Parasites</u>	<u>Fever</u>	<u>Remarks</u>
1st	50,000+ 32,000	0.40+ 0.40	0	0	The two 0.40 doses were tolerated.
2nd	65,600+ 29,600	0.20+ 0.20	0	0	
3rd	29,600+ 32,800	0.10+ 0.10	+ 15th day	+	Subfebrile condition.
4th	31,600+ 21,000	0.06+ 0.05	+	-	
5th			+	0	
6th			+	+	<u>Regular quotidian form</u>
					10 days after last infection and last dose of atebtrin.
7th			+	+	
		<u>0.30 x 7</u>			
		<u>after 10th</u>			
		<u>attack</u>			
8th			+	-	
9th			-	-	
10th-12th			-	-	

Observations ceased 24/7/38.

Bl.R. - Bi-weekly sporozoite infection.
Bi-weekly diminishing doses of atebtrin; total amount, 1.50 grm.

<u>Week</u>	<u>Sporozoites inoculated</u>		<u>Atebrin</u>		<u>Appearance Parasites Fever</u>		<u>Remarks</u>
1st	46,000+	48,800	0.40+	0.40			
2nd	35,000+	32,500	0.20+	0.20			
3rd	21,300+	32,800	0.10+	0.10	+	15th day + 20th day	A very few rings for one day.
4th	31,600		0.05+	0.05	0		
5th	-----				0		
6th					+	37th day	Regular clinical form 17 days after last infection & 14 days after last dose of atebtrin.
7th			<u>0.30 x 7</u>		+	+	No gametocytes were found in spite of marked resistance by thophozoites (10 days' therapeutic doses of atebtrin - 1.30 x 7).
8th					+		

Observations ceased 17/8/38.

CONCLUSIONS:

Under the conditions governing our experiments, i.e., repeated and heavy infections, the protective effect of atebtrin given in therapeutic doses survives just as long as the prophylactic treatment.

In 3 cases out of 4, the clinical symptoms appear to be the result of the last inoculation of sporozoites, made at a stage when the atebtrin dose had been reduced to an insufficient level (0.05 grm. x 2).

Under conditions of severe reinfection, the hypothesis of an accumulation of atebtrin in the organism sufficient to make up for the subsequent reduced doses is, therefore, not confirmed.

It would not appear that enough of the early, large doses of atebtrin was retained to balance the deficiency in the later doses. The incubation period after the last infection lasted 7 days for parasites and 10 days for attacks.

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II. INTENTIONALLY-INDUCED P. VIVAX INFECTION:

Strain employed: T.B. HOHR (a Horton strain kept temporarily in two countries of different endemicity and at Horton).

A. Group of 4 patients.

Heavy weekly infection by intravenous inoculation of sporozoites for 3 weeks. Atebrin given daily (0.06 gm.) for 21 days; last dose given 6 days after last sporozoite inoculation. Total amount of atebrin, 1.26 gm.

(1) M.T.25/12/37.

<u>Week</u>	<u>Sporozoites</u> c.c.	<u>Atebrin</u>	<u>Appearance</u>		<u>Remarks.</u>
			<u>Parasites</u>	<u>Fever</u>	
1st	17,500	0.06 x 7	-	-	
2nd	23,600	0.06 x 7	-	-	
3rd	12,000	0.06 x 7	-	-	
4th	-	-	-	-	
5th	-	-	-	-	
6th	-	-	-	-	
7th	-	-	+ 45th day	+ 45th day	Quotidian attacks 30 days after last infection.
8th	-	-	+	+	" " "
9th-14th	-	-	Spontaneous dis- appearance		
15th	-	-	+	-	
16th	-	-	+	-	
17th	-	-	+	+	3 quotidian attacks
18th-34th-	-	-	-	-	
			Spontaneous dis- appearance until 21/5/38.		

(2) H.A1. 18/12/37. T.B.HOHR

1st	12,000	0.06 x 7	-	-	
2nd	25,000	0.06 x 7	-	-	
3rd	28,000	0.06 x 7	-	-	
4th	-	-	+ 25th day	-	11 days after last infection
5th	-	-	-	-	
6th	-	-	+	-	Disappearance of parasites on 36th day.
7th	-	-	-	-	
8th	-	-	+	-	
9th	-	-	+	-	
10th	-	-	-	-	
11th	-	-	+	-	Temporary appearance,

Observations ceased 4/3/38

<u>Week</u>	<u>Sporozoites</u> cc.	<u>Atebrin</u>	<u>Appearance</u>		<u>Remarks</u>
			<u>Parasites</u>	<u>Fever</u>	
(3) <u>Sid. Al. 18/12/37.</u>					
1st	6,800	0.06 x 7	-	-	
2nd	12,000	0.06 x 7	-	-	
3rd	21,000	0.06 x 7	-	-	
4th	-	-	+ 28th day	-	14 days after last infection.
5th	-	-	+	-	
6th	-	-	+	+	2 tertian attacks 27 days after last infect.
7th	-	-	+	-	
8th	-	-	-	-	
9th	-	-	+	-	
10th	-	-	+	-	Disappearance of parasites on 68th day.
11th-30th	-	-	-	-	

Observations ceased 10/8/38.

(4) R.E. 18/12/37.

1st	14,720	0.06 x 7	-	-	
2nd	20,000	0.06 x 7	-	-	
3rd	14,000	0.06 x 7	-	-	
4th	-	-	+ 28th day	-	14 days after last last infection.
5th	-	-	+	+	Subfebrile condition 17 days after last infection.
6th	-	-	-	-	Disappearance of parasites on 38th day.
7th-15th	-	-	-	-	

Observations ceased 8/4/38.

Note: Of the 4 patients treated, 3 some time later showed benign clinical symptoms, the 4th only parasite infection. All recovered without further treatment.

B. T.B. HOHR.

Weekly intravenous sporozoite inoculation for 3 weeks.

Bi-weekly doses of atebtrin (0.20 grm.) for 3 weeks; these doses administered on inoculation days and 5 days later, except last dose, which was administered 4 days after last sporozoite inoculation. Total amount of atebtrin, 1,20 grm.

<u>Week</u>	<u>Sporozoites per cub.mm.</u>	<u>Atebrin</u>	<u>Appearance Parasites</u>	<u>Fever</u>	<u>Remarks</u>
(1) <u>T.I. 18/12/37.</u>					
1st	8,000	0.20 x 2	-	-	
2nd	20,600	0.20 x 2	-	-	
3rd	15,200	0.20 x 2	-	-	
4th	-	-	-	-	
5th	-	-	-	-	
6th	-	-	+ 38th day*	-	*25 days after last infection. A single febrile crescent.
7th	-	-	+	-	
8th	-	-	+	+	3 tertian attacks 38 days after last infection.
9th	-	-	+	+	Irregular attacks.
10th	-	-	+	+	" "
11th-17th	-	-	+	?	Patient restless, temperature could not be taken.
18th	-	-	+	+	2 attacks.
19th-29th	-	-	+	0	Intermittent appearance of parasites.

Observations ceased 10/8/38.

C.A. - T.B. HOHR.

1st	9,200	0.20 x 2	-	-	
2nd	9,000	0.20 x 2	-	-	
3rd	11,000	0.20 x 2	-	-	
4th	-	-	-	-	
5th	-	-	+ 34th day*	-	*Intermittent appearance 21 days after last infection.
6th	-	-	+	-	Intermit.apprnce.
7th	-	-	-	-	
8th	-	-	+	-	Continuous apprnce. of parasites.
9th	-	-	+	-	
10th	-	-	-	-	
11th-12th	-	-	+	-	Intermit.apprnce.
13th-18th	-	-	-	-	

Observations ceased 25/4/38.

<u>Week</u> <u>S.M.</u>	<u>Sporozoites</u>	<u>Atebrin</u>	<u>Appearance</u>		<u>Remarks.</u>
			<u>Parasites</u>	<u>Fever</u>	
1st	7,400	0.20 x 2	-	-	
2nd	25,200	0.20 x 2	-	-	
3rd	7,600	0.20 x 2	-	-	
4th	-	-	-	-	
5th	-	-	-	-	
6th	-	-	-	-	
7th	-	-	-	+?	Subfebrile condition
8th	-	-	+60th day*	+	" "
					*39 days after last infection
9th	-	-	±	0	
10th	-	-	-	-	
11th	-	-	-	-	
12th	-	-	+	-	
13th	-	-	+	+87th day.	4 quotidian attacks.
14th	-	-	+	±	Subfebrile condition
15th	-	-	-	-	Spontaneous disappearance
16th	-	-	-	-	
17th-19th	-	-	-	-	

Observations ceased 6/8/38.

(2) I.Gh.18/12/37.

1st	9,000	0.20 x 2	-	-	
2nd	19,500	0.20 x 2	-	-	
3rd	7,000	0.20 x 2	-	-	
4th	-	-	-	-	
5th	-	-	-	-	
6th	-	-	-	-	
7th	-	-	-	-	
8th	-	-	+ 56th day*	-	*44 days after last infection.
9th	-	-	+	+ 57th day.	3 slight attacks 45 days after last infection.
10th	-	-	+	-	
11th	-	-	+	-	
12th	-	-	+	+	2 quotidian attacks
13th	-	-	+	+	3 tertian -do-
14th	-	-	+	+	3 tertian -do-
15th	-	-	+	+	Irregular attacks
16th	-	-	+	-	Subfebrile condition
17th	-	-	-	-	
18th	-	-	±	-	Slight parasitism (intermittent)
19th-31st	-	-	-	-	

Observations ceased 12/8/38.

SUMMARY.- It should be remembered that the last dose of ateb-
brin was given 5 days after the last sporozoite infection.
Of 4 cases treated with bi-weekly doses of 0.20 gm. ateb-
brin, 1 showed purely parasitic infection 34 days after the
first and 21 days after the second infection. The 3 others
showed clinical symptoms after periods of incubation lasting
52, 57, and 87 days respectively, reckoned from the first in-
fection, or 38, 45, and 53 days respectively, reckoned from
the last infection.

In all these cases the clinical form, of a benign
type and tending to the chronic state, was cured spontaneous-
ly without necessitating further treatment.

C.T.B. HOHR.

In this group of patients, infection by means of
weekly intravenous sporozoite inoculation was carried out in
the same manner as on Group B.

Bi-weekly administration of doses of 0.20 gm. of
atebrin was continued 3 weeks longer (from the last infection),
in order to cover a somewhat protracted incubation period.
Total amount of atebirin, 2.40 gm.

<u>Week</u>	<u>Sporozoites</u> per cub.mm.	<u>Atebrin</u>	<u>Appearance</u>		<u>Remarks.</u>
			<u>Parasites</u>	<u>Fever</u>	
<u>M.N. 12/3/38. T.B. HOHR.</u>					
1st	29,200	0.20 x 2	-	-	
2nd	35,500	0.20 x 2	-	-	
3rd	25,000	0.20 x 2	-	-	
4th	-	0.20 x 2	-	-	
5th	-	0.20 x 2	-	-	
6th		0.20 x 2	-	-	
7th					
8th					
<u>Observations ceased 8/5/38.</u>					

B.E. 15/3/38.

1st	35,000	0.20 x 2	-	-	
2nd	45,600	0.20 x 2	-	-	
3rd	25,200	0.20 x 2	?	-	
4th	-	0.20 x 2	-	-	
5th	-	0.20 x 2	-	-	
6th	-	0.20 x 2	-	-	
7th-15th	-	-			
15th-18th	-	-			(119 days
19th			+133rd day.	+132nd day	(after last infection.
20th	-	-	+	+	5 tertian attacks
21st	-	-	+	+	3 quotidian attacks +
22nd	-	-	+	+	3 tertian 2 tertian attacks.

Observations ceased 21/8/38

Atebrin 2.40 gm.

<u>Week</u>	<u>Sporozoites</u>	<u>Atebrin</u>	<u>Appearance.</u>		<u>Remarks.</u>
			<u>Parasites</u>	<u>Fever</u>	
<u>M.P.15/3/38.</u>					
1st	20,000	0.20 x 2	-	-	
2nd	28,000	0.20 x 2	-	-	
3rd	24,400	0.20 x 2	-	-	
4th	-	0.20 x 2	-	-	
5th	-	0.20 x 2	-	-	
6th	-	0.20 x 2	-	-	
7th-15th	-	-	-	-	
15th-22nd	-	-	-	-	

Observations ceased 21/8/38.

<u>C.El.15/3/38 (+Pulmonary tuberculosis) Atebrin 2.40 gm.</u>					
1st	24,400	0.20 x 2	-	-	
2nd	47,600	0.20 x 2	-	+	Pulmonary tuberculosis
3rd	25,000	0.20 x 2	-	-	
4th	-	0.20 x 2	-	-	
5th	-	0.20 x 2	-	-	
6th	-	0.20 x 2	-	+?	
7th	-	-	±	+?	Very few
8th	-	-	-	+?	
9th	-	-	-	+?	
10th-16th	-	-	-	+?	Tubercular fever

Observations ceased 2/7/38.

<u>D.D.15/3/38. Atebrin 2.40 gm.</u>					
1st	39,000	0.20 x 2	-	-	
2nd	26,400	0.20 x 2	-	-	
3rd	24,400	0.20 x 2	-	-	
4th	-	0.20 x 2	-	-	
5th	-	0.20 x 2	-	-	
6th	-	0.20 x 2	-	-	
7th-16th	-	-	-	-	
16th-23rd	-	-	-	-	

Observations ceased 22/7/38.

SUMMARY.- This group of patients confirms the efficacy of bi-weekly prophylactic doses of atebrin, provided treatment is continued for 3 weeks after the last infection. One only of the four patients showed benign clinical symptoms, after 133 days' incubation (119 days after the last infection). These observations also confirm those collected over a long period by many workers, showing the need for continuing the administration of an anti-malarial drug for a certain time after the subject has left the malarial district.

D. - T.B.HOHR.

This group of patients was given 2 intravenous sporozoite inoculations a week for 4 weeks.

The doses of atebtrin were gradually reduced from 0.40 grm. x 2 to 0.05 grm. x 2. The last dose (0.05 grm.) was given the day before the last inoculation. Total amount of atebtrin, 1.50 grm.

The incubation period relating to the last two inoculations therefore fell outside the period of preventive treatment.

Atebrin 1.50 grm.

<u>Week</u> I.E. 25/12/37.	<u>Sporozoites</u>	<u>Atebrin</u>	<u>Appearance</u>		<u>Remarks</u>
			<u>Parasites</u>	<u>Fever</u>	
1st	16,500 + 14,200	0.40 x 2	-	-	
2nd	13,800 + 13,500	0.20 x 2	-	-	
3rd	13,200 + 10,200	0.10 x 2	-	-	
4th	12,000 + 14,000	0.05 x 2	-	-	
5th	-	-	-	+ 35th day	6 days after last infection
6th	-	-	+ 36th day*	+ 37th day	5 quotidian attacks *11 days after last infection
7th	-	-	+	+	7 quotidian attacks
8th	-	-	+	+	Irregular attacks
9th	-	-	+	+	" "
10th	-	-	+	+	7 quotidian attacks
<u>Treatment: Atebrin 0.30 x 7</u>					
11th	-	-	+	-	
12th-17th	-	-	-	-	
18th-23rd	-	-	+	-	
24th-27th	-	-	-	-	
28th-34th	-	-	-	-	

Observations ceased 19/8/38.

D.E. 25/12/37.

Atebrin 1.50 grm.

1st	16,500 + 34,600	0.40 x 2	-	-	
2nd	16,500 + 16,800	0.20 x 2	-	-	
3rd	20,400 + 10,200	0.10 x 2	-	-	
4th	14,700 + 25,600	0.05 x 2	-	-	
5th	-	-	-	-	
6th	-	-	+ 37th day	+ 40th day	Subfebrile condition 10 days after last infection
7th	-	-	+	+	2 tertian attacks
8th	-	-	+	-	
Spontaneous cure					
9th-19th	-	-	-	-	
19th-34th	-	-	-	-	

Observations ceased 5/8/38.

Atebrin 1.50 gm.

<u>Week</u>	<u>Sporozoites</u>	<u>Atebrin</u>	<u>Appearance Parasites</u>	<u>Fever</u>	<u>Remarks</u>
<u>C.C.25/13/37.</u>					
1st	18,000 + 16,200	0.40 x 2	-	-	
2nd	10,600 + 16,400	0.20 x 2	-	-	
3rd	8,600 + 10,200	0.10 x 2	-	-	
4th	17,400 + 35,700	0.05 x 2	-	-	
5th	-	-	+35th day	-	8 days after last infection
6th	-	-	+	+	*7 quotidian attacks 10 days after last infection.
7th	-	-	+	+	
8th	-	-	+	+	2 quotidian attacks, then spontaneous cure.
9th-12th	-	-	-	-	
13th-16th	-	-	-	-	
17th-20th	-	-	-	-	
21st-28th	-	-	-	-	
29th-33rd	-	-	-	-	

Observations ceased 16/8/38.

St. E.25/12/37.

Atebrin 1.50 gm.

1st	17,400 + 46,200	0.40 x 2	-	-	
2nd	17,600 + 12,000	0.20 x 2	-	-	
3rd	13,600 + 9,000	0.10 x 2	-	-	
4th	24,000 + 22,000	0.05 x 2	-	-	
5th	-	-	+35th day*	-	*8 days after last infection
6th	-	-	+	+	Subfebrile condition 15 days after last infection.
7th	-	-	+	+	Irregular attacks
8th	-	-	+	-	
9th	-	-	-	-	
10th	-	-	-	-	
11th	-	-	+	-	Intermittent appearance
12th	-	-	-	-	
13th-28th	-	-	-	-	
29th-31st	-	-	-	-	

Observations ceased 10/8/38.

Atebrin 1.50 gm.

<u>Week</u>	<u>Sporozoites</u>	<u>Atebrin</u>	<u>Appearance</u>		<u>Remarks</u>
			<u>Parasites</u>	<u>Fever</u>	
<u>H.P.25/12/37.</u>					
1st	49,500 + 49,600	0.40 x 2	-	-	
2nd	36,600 + 29,000	0.20 x 2	-	-	
3rd	15,600 + 9,000	0.10 x 2	-	-	
4th	37,500 + 32,500	0.05 x 2	-	-	
5th	-	-	-	-	
6th	-	-	+	+	*Feverish condition 11 days after last infection
7th	-	-	+	-	
8th-14th	-	-	-	-	
15th	-	-	+	-	Irregular appearance
16th	-	-	-	-	

Observations ceased 18/4/38.

SUMMARY: Under the conditions governing the drug prophylaxis experiment made on this group, all the patients without exception showed clinical symptoms of the disease during the sixth week of the treatment. The last two sporozoite inoculations and the two smallest doses of atebrin were administered during the 4th week. Under the conditions laid down in our experiment, the accumulation of large doses of atebrin during the first week was not enough to compensate for the later reduction in the dose. It should once more be pointed out that the incubation period relating to the last two inoculations fell outside the period of treatment.
