

LEAGUE OF NATIONS

C.H./Malaria/229.

Geneva, October 1st, 1935.

MALARIA COMMISSION.

The Secretary of the Malaria Commission
has the honour to communicate herewith the following

NOTE ON THE PROGRESS OF STUDIES ON TOTAQUINA AND ITS USE.

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The third number of Volume III of the Quarterly Bulletin of the Health Organisation contained a report on "The Therapeutic Efficacy of Totaquina in Human Malaria". This report gave the results of a series of co-ordinated experiments with the same products, and under the auspices of the Malaria Commission, in nine different countries.

The number of cases studied was 1,144; 1,055 had been treated with one of the five samples of totaquina used for these experiments, and 89, as controls, with quinine sulphate.

Other articles on totaquina have since appeared in the medical press. The works of FLYE SAINTE MARIE, of PARVULESCU, CONSTANTINESCU and BOERIU, of André SERGENT and VOGT, of SLATINEANU, CIUCA, BALTEANU, ALEXA, FRANCKE and RUGINA, are detailed surveys of their therapeutic experiments, the relevant case records having been sent to the Health Section for consideration in the report.

A number of further experiments in totaquina treatment had also been undertaken in various institutes, following the Commission's programme of research, but the documentation relating to them, or part of it, had not reached the Section when the report was written, and consequently could not be included. This applies to the material regarding the observations made in China, India, Japan and Malaya.

YAO and YUNG SUN (1934) studied the comparative efficacy of several treatments in 281 cases of malaria, mostly in very young subjects (under 12 years of age), of whom 152 were treated either with totaquina type I (Burroughs Wellcome) or with type II (Turin "A"). (Only some of these cases were considered in our report, as most of the case-records did not arrive until it had been completed).

As five different types of treatment were employed, certain groups of cases were thus formed, too small to have any statistical value.

The method of administering totaquina was that recommended by the Commission, namely, five days of treatment at 0.60 per day in cases of benign tertian and at 1.20 in malignant tertian or quartan (doses for adults). This treatment was compared with an atebirin treatment at the rate of 0.15 or 0.30 per day for five days, with a quinine sulphate treatment at the rate of 0.69 or 1.17 per day, or with a treatment in which quinoplasmine was administered in a dose of three tablets per day without distinction in all forms of malaria.

The authors' conclusion is that all the drugs had much the same action on the temperature, though the action was slower in cases of malignant tertian. Totaquina I, however, seems to give the best results (24 cases), while totaquina II (23 cases) and atebirin (28 cases) proved less effective.

Regarding the disappearance of asexual parasites, the author considered that the three drugs were about equally effective in malignant tertian, while in cases of benign tertian, quinine and atebirin seemed superior. It is to be noted, however, that the effect of quinine was studied in only 4 cases, and that of atebirin in 7. Out of 56 cases of benign tertian treated with one or the other type of totaquina, 62.5% showed no more parasites at the end of a five-day treatment.

For the reduction of the spleen, quinoplasmine is apparently the most effective (only 4 cases of benign tertian and 12 of malignant tertian), being followed in order of value by totaquina I, atebirin, quinine, and totaquina II.

The only toxic symptoms recorded are cases of vomiting, and these were not very common. The rates were as follows: atebirin, 5.55%; totaquina I, 3.89%; totaquina II, 1.37% of the cases treated.

The results show, in the authors' opinion, that the two types of totaquina are slightly inferior to quinine in all three forms of malaria, but especially in benign tertian. Type II is inferior to type I.

LIU (1934), of the Nanking Central Hospital, confines himself to considering the parasitocidal action of atebirin, quinoplasmine, totaquina, and malarcan. His work relates to 104 patients, but no conclusions can be drawn from the published details.

Totaquina was used in only 21 cases of benign tertian and 5 of malignant tertian (sometimes type I and sometimes type II). The author concludes, however, that totaquina does not give uniform results in benign tertian and seems completely ineffective in malignant tertian. The only two deaths mentioned in medical literature in patients treated with totaquina are among these same 26 cases; one died after two days' treatment with totaquina I (case of

benign tertian), and the other died while under treatment after four attacks (case of malignant tertian).*

FIELD, at Kuala Lumpur, used only totaquina II (Howard's). Only 158 case records reached the Health Section in time to be considered in the report. The experiments were continued until 417 cases had been covered. An extract from field's work has been circulated to the Malaria Commission (C.H./Malaria/214).

The drug was administered in larger doses than at the other experimental centres, most of the adults being given from 1 to 2 grammes a day. We see no need to reproduce Field's conclusions here, as they have been examined and confirmed by FLETCHER in our report in the following terms:

* According to the details kindly supplied by Dr. CHEER, Chief of the Medical Department of the Hospital, the first case was a girl aged twelve who was admitted to the Hospital on the fourth day of the disease (July 31st, 1933). Her medical history was negative, even for malaria. On her third day in hospital (August 2nd) she showed an infection of Pl. vivax, and the Leucocytes, which numbered 8000 at the time of her admission, had increased to 15,400. The number of parasites was 1098 per cub. mm.; the temperature was 41.2°. On August 1st, in consequence of the rigidity of the neck - which, however, was not accompanied by Kernig's symptoms - a lumbar puncture was performed, but revealed no micro-organisms under the microscope. On the fifth day in hospital, i.e., the ninth day of the disease (August 5th), the patient died during a final attack of fever, with a temperature of 40.2°; pulse 106. Parasites were present in the blood at the last examination, which was made the day before her death. While she was in hospital, the temperature, though preserving the characteristics of a tertian, never fell as low as 37°; however, it reached 41° on August 1st, 3rd and 5th. The patient had been given, in all, 24 tablets of totaquina I during the last three days; a certain quantity of the drug had been vomited.

The second case was that of a woman of twenty-nine who had apparently had malaria in childhood; After being ill for twelve days with, it is understood, a quotidian fever, she was taken to hospital on August 14th. Her blood showed parasites of Pl. falciparum and 3,000,000 red blood corpuscles. Throughout her stay in hospital, parasites were always present; on August 14th there were 2548; on the 15th, 1988 of Pl. malariae and 284 of Pl. falciparum; and on the 16th, 432 of Pl. falciparum per cub. mm. On August 17th - the fifteenth day of the disease - the patient died. Pulse 100. During her four days in hospital, the temperature reached 38.8° on the first day, fell to 36.6° on the second, again rose to 39° on the third, and, after a brief remission, rose to 40.8° before death, parasites being still present in the blood. On the patient's first day in hospital, 0.60 of totaquina every four hours had been prescribed. The patient received a total of 9.60 grammes of this drug, followed by three tablets of atebria and quinoplasmine.

"The results obtained were excellent, and, speaking with a long experience of the two hospitals where these tests were made and of the types of patients which are treated there, I can say without hesitation that they are as good as those obtained with quinine given in the same doses. The records do not show that the larger dose has any definite advantage over the smaller; but Dr. Field, as the result of treating a larger series of patients, concludes that the optimum dose lies between the two."

KAORU MORISHITA, malarialogist at the Government Research Institute in Formosa, has sent the Section the clinical material of an experiment he conducted in 1934 with totaquina Type I. The drug in question was the Madras product, which had been supplied to him through the Central Sanitary Bureau at Tokio, to which it had been sent by the Section. The study covers fifty-one cases. Twenty-three of these were treated at the Institute for Experimental Malaria Therapy at Taihaku, in the north of the island, which is under the Government Research Institute, and the remainder were treated in the south of the island, either at the Government hospital at Tainan or at the hospital at Heito.

The doses administered were proportionate to the midpoint value of the different weight-groups, being based on the doses recommended by the Commission for an adult weighing 70 kg., viz., 0.60 g. of totaquina in cases of benign tertian and 1.20 in cases of subtertian or quartan.

A glance at the posological table adopted by Morishita will show that much weaker doses were used for this experiment than for the other experiments considered in the report. For instance, a patient suffering from benign tertian and weighing 50 kg. was given only 0.375 gr. a day.

For benign tertian:

<u>Body-weight in kg.</u>	<u>"Standard" body-weight in kg.</u>	<u>Dose of drug.</u>
7 - 22	14.5	0.125 g.
22.1 - 36	29.1	0.250
36.1 - 51	43.7	0.375
51.1 - 68	58.3	0.500
66.1 - 80	72.9	0.625
80.1 - 95	87.5	0.750

For subtertian and quartan.

<u>Body-weight in kg.</u>	<u>"Standard" body-weight in kg.</u>	<u>Dose of drug.</u>
4 - 11	7.3	0.125 g.
11.1 - 18	14.6	0.250
18.1 - 26	21.9	0.375
26.1 - 33	29.2	0.500
33.1 - 40	36.5	0.625
40.1 - 47	43.8	0.750
47.1 - 55	51.1	0.875
55.1 - 62	58.4	1.000
62.1 - 69	65.7	1.125
69.1 - 77	73.0	1.250
77.1 - 84	80.4	1.375
84.1 - 91	87.7	1.500

The drug was administered in tablets. The blood-examinations carried out according to the Commission's instructions, always before the drug had been administered, also included a count of the various forms of parasite. We are not informed of any control case treated with quinine.

Benign Tertian.

24 cases were studied, most of them being relapses. The action of the drug on the fever can be taken into consideration in only 15 cases, as the remainder either did not present that symptom at the beginning of the treatment or there was no temperature-chart available. In none of these 15 cases did the fever persist after three days of treatment.* After three daily doses of the drug, the asexual forms also disappeared from the circulation in 22 cases out of 24 (in 7 cases after 1 dose, in 9 after 2 doses, and in 6 after 3 doses). In one case of primary infection in a girl aged 18, weighing 48 kg., and receiving 0.735 g. of totaquina a day, trophozoites did not disappear until the sixth day - i.e. after 5 doses of the drug. In another case (relapse), trophozoites were still present on the sixth day. This was a man aged 21, weighing 47 kg., who had received the same doses as the previous case.

Gametocytes of Pl. vivax, which were present in 17 cases, disappeared after 3 doses (in 7 cases after the first dose, in 7 after the second, and in 3 after the third).

Quartan.

This form was represented by only two cases - one a primary infection, which took 4 doses to eliminate fever and trophozoites; the other a relapse, in which parasites, both sexual and asexual, disappeared after 3 doses, the fever having already yielded after 2 doses.

In one case of a mixed infection - benign tertian and quartan - the fever disappeared after 2 doses of the drug. The trophozoites of Pl. vivax also disappeared after 2 doses, but the trophozoites and gametocytes of Pl. malariae did not disappear until the fifth day.

Sub-tertian.

13 cases were treated. Nearly all these were relapses or reinfections, only one case being found to be a primary infection.

The action on the fever can be studied in only 7 cases. In 3 cases the fever disappeared after 1 dose, in 1 case after 2, in 2 cases after 3, and in only 1 case after 4 doses.* The elimination of the asexual forms in no case required more than 4 doses (it was completed in 5 cases after 1 dose, in 1 case after 2, in 4 cases after 3, and in 2 cases, including the case of primary infection, after 4 doses. There was also one case in which the trophozoites disappeared on an uncertain date - after the third or fourth dose).

* See also annexed Table.

There is no need to dwell upon the failure of the drug to act upon the gametocytes of Pl. Falciparum which were still present on the fifth or sixth day, as these were found in only two cases out of the total of 13.

Mixed Infection.

11 cases of mixed tertian were treated. Out of 5 cases in which the course of the fever could be studied, it disappeared in 4 cases after a single dose, while in the fifth case a sub-febrile temperature persisted even after the final dose, notwithstanding the disappearance of the parasites after the second dose.*

The asexual forms had all disappeared after the fourth dose (in 8 cases after the second dose, in 2 cases after the third).

Gametocytes of Pl. vivax were observed in 7 cases; in 2 cases they disappeared after the first dose, in 3 cases after the second, in 1 case after the third, and in 1 case after the fourth. In one case which harboured gametocytes of both forms of infection, those of Pl. vivax disappeared after the first dose, while those of Pl. falciparum were still present after the fifth dose.

Toxic Symptoms.

Despite the small doses of totaquina administered, toxic symptoms appeared in 33 cases. The commonest was buzzing in the ears (20 cases); there were also nausea (19 cases), vomiting (11 cases), diarrhoea (10 cases), albuminuria (10 cases), visual disturbances (9 cases), and dizziness (6 cases).

In the great majority of cases (80 per cent), these symptoms were present on the first day of the treatment, frequently disappearing during the period of observation (42 per cent); in a few cases they persisted until the end of the treatment, but they never seem to have been sufficiently severe to cause the doctors to break off the treatment. In 20 per cent of cases these symptoms represented only a transitory phenomenon, lasting a day or two, coming on during the treatment and disappearing before its completion.

The table that follows shows graphically all the toxic phenomena mentioned on the case records. Except as regards buzzing in the ears, and perhaps visual disturbances, there is a strong impression that these symptoms are due to the disease rather than to the drugs employed.

* See annexed Table.

Tierce maligne & infections mixtes : 27 cas. Tierce maligne.										Tierce bénigne : 24 cas.																																		
Tierce maligne.					Tierce bénigne + T. mal.					Tierce bénigne.					Tierce bénigne.																													
Tainan					Heito					Taihoku					Taihoku					Tainan																								
Tainan					Heito					Taihoku					Taihoku					Tainan																								
Nausee					Vomissements					Diarrhee					Albuminurie					Troubles visuels					Bourdonnements d'oreilles					Vertiges					Fievre avant pendant le traitement									
1 2 3 4 5					1 2 3 4 5					1 2 3 4 5					1 2 3 4 5					1 2 3 4 5					1 2 3 4 5					1 2 3 4 5					1 2 3 4 5					1 2 3 4 5				
Treated at:					Treated at:					Treated at:					Treated at:					Treated at:					Treated at:					Treated at:					Treated at:									
Subtertian					Ben. Tert. + Subtertian					Subtertian					Subtertian					Subtertian					Subtertian					Subtertian					Subtertian					Subtertian				
Subtertian Malaria & Mixed Infections: 27 cases.					Subtertian Malaria & Mixed Infections: 27 cases.					Subtertian Malaria & Mixed Infections: 27 cases.					Subtertian Malaria & Mixed Infections: 27 cases.					Subtertian Malaria & Mixed Infections: 27 cases.					Subtertian Malaria & Mixed Infections: 27 cases.					Subtertian Malaria & Mixed Infections: 27 cases.					Subtertian Malaria & Mixed Infections: 27 cases.					Subtertian Malaria & Mixed Infections: 27 cases.				
Benign Tertian: 24 cases.					Benign Tertian: 24 cases.					Benign Tertian: 24 cases.					Benign Tertian: 24 cases.					Benign Tertian: 24 cases.					Benign Tertian: 24 cases.					Benign Tertian: 24 cases.					Benign Tertian: 24 cases.					Benign Tertian: 24 cases.				

Essais cliniques avec la Totaquina à Formosa

Présence de fièvre et des symptômes toxiques au cours de la période d'observation.

1,2,3,4,5: jours de traitement.

Clinical Tests with Totaquina in Formosa:

Presence of fever and toxic symptoms during the observation period.

1,2,3,4,5: days of treatment.

Further Observation of Certain Cases.

All the cases treated at the Taihoku Institute (23) were kept under observation in mosquito-proof wards for eight weeks. During that period parasitic relapses were recorded: out of the 10 cases of benign tertian, 5 relapses between the eighth and the twentieth day after the cessation of the treatment. Out of 10 cases of mixed tertian, 9 relapses - 5 of Pl. vivax between the fifth and twelfth days, and 4 of Pl. falciparum between the third and tenth days.

In the one case of sub-tertian kept under observation, a relapse occurred on the sixth day.

In the case of benign tertian and quartan, the latter form reappeared on the eleventh day. In the case of quartan, a relapse was observed on the twenty-ninth day, but was due to Pl. vivax and not to Pl. malariae.

A publication by HICKS and DIWAN CHAND (1935) describes the experiments conducted under the direction of the Malaria Survey of India, regarding which we did not receive details in time for examination in our report.

The authors treated 210 cases of benign tertian, 158 of sub-tertian, and 1 of mixed infection. They used either totaquina I or totaquina II, both prepared by the Madras Government Cinchona Department, the content of which was as follows:

1. Type I.

This product, identical with the "Madras I" used in the experiments considered in our report, contained a total of 74 per cent* of crystallisable alkaloids - a proportion which, as the authors observe, approximately corresponds to that of basic quinine in quinine sulphate. The amorphous alkaloids did not exceed 15 per cent.

2. Type II.

Its composition was as follows:

Quinine	19 per cent.
Quinidine	4 " "
Cinchonine ...	20 " "
Cinchonidine ..	26 " "

Total of crystallisable alkaloids	69 per cent
Amorphous alkaloids	19 " "

The treatment was applied in accordance with the Malaria Commission's instructions, to prisoners in the Central gaol and the Borstal Institution at Lahore. The treatment was

* According to the factory analysis. 77 per cent according to the Wellcome Chemical Research Laboratories' analysis.

broken off when the patient had been free from parasites for two days and from fever for one day at least. This difference as compared with the method of administering the drug for five days was to a certain extent offset by a very exact application of the scale of doses recommended by the Commission.

All the subjects were over 16 years of age. As they had always been exposed to malaria, there was no case of primary infection among them. As soon as malaria had been diagnosed, 2 grains of calomel were administered; a second blood-examination and a parasites - count were carried out by Sinton's method; and the drug - either quinine sulphate or totaquina I or II, according to the order in which the patients came up - was then administered in a single daily dose.

The authors observed no appreciable difference between the efficacy of the two types of totaquina and that of quinine. The only "significant" difference from the statistical standpoint would seem to be in favour of Totaquina II, with which the asexual forms disappeared more rapidly than with the other drugs in cases of sub-tertian.

The toxic symptoms are difficult to establish, as the prisoners tend to complain collectively in order to stay longer in hospital. Only cases of vomiting and dizziness were observed, the former being apparently due to the disease rather than to the drugs; they lasted a little longer after the administration of the two types of totaquina than after quinine. Totaquina II, on the other hand, caused fewer cases of dizziness than quinine or Totaquina I. Table 4 in the authors' publications, which we reproduce below together with Table 5 of the report on Totaquina, indicates that the two types of totaquina were more effective in the experiments of Hicks and Diwan Chand than in those of which the aggregate results are considered in the report published in the Quarterly Bulletin.

The authors consider that the optimum dose for a population having a degree of immunity comparable to that of their patients is 1 gramme once daily for three or four days - consequently less than the dose recommended by FIELD. This dose is sufficient to prevent many deaths and to eliminate the clinical symptoms.

* * *

	Number of cases con- sidered	F E V E R				Number of cases con- sidered	SCHIZONTS AND TROPHOZOITES Percentage in which schizonts and trophozoites disappeared after doses:
		1.	2.	3.	4.		
<u>Pl. vivax</u>							
Totaquina I (Q.B. (H.D.C.	139 48	43 44	83.5 92	95.5 98	98.5 100	175 69	40 38 85.5 93 96 100
Totaquina II (Q.B. (H.D.C.	198 36	46 67	72 94	92 97	96 100	290 72	24.5 50 65.5 93 85.5 99 94.5 100
Quinine (Q.B. (H.D.C.	35 41	48.5 54	94 95	100 100	100 100	42 69	40.5 48 81 99 98 99 98 100
<u>Pl. falciparum</u>							
Totaquina I (Q.B. (H.D.C.	122 42	41.5 33	80 81	93 95	96.5 100	155 53	28 43 64.5 81 84 98 91 100
Totaquina II (Q.B. (H.D.C.	234 31	33 29	62 77	79 100	89 100	261 51	20.5 57 53 96 72 98 85.5 100
Quinine (Q.B. (H.D.C.	32 44	34 30	78 77	97 95	100 100	32 54	28 37 53 87 94 98 100 100

Q.B. = figures from Table 5 of the Report published in the Quarterly Bulletin of the Health Organisation, Vol. III, No. 3.

H.D.C. = figures from Table 4, of Hicks and Diwan Chand's work.

Several health administrations have considered using totaquina against malaria in their respective countries. The Italian Supreme Council of Public Health, on July 14th, 1934, authorized the sale of totaquina, "a preparation having an action almost equal to that of salts of quinine". In Roumania, the Malaria Commission of the Ministry of Health has decided to use totaquina in malaria control.

The health authorities of two other European countries have displayed considerable interest in the question and expressed the desire to try the drug as a remedy for malaria.

In India, the Madras Government Cinchona Department manufactured 1,596 kg. 672 of totaquina in 1933.

In Mauritius, the Health Department has adopted totaquina as one of the remedies for malaria control, and has fixed its price. To facilitate its distribution among the public, the Department has requested the Chinese traders to stock totaquina in their stores. The drug can also be sold in any shop; the retail price is fixed at 10 rupees for 1,000 tablets of 0.324, or 30.86 rupees per kg.

In a recent article, P.F. RUSSELL states that researches conducted by the Bureaux of Science, Forestry and Prisons jointly with the Rockefeller Foundation have shown that an excellent totaquina could be prepared in the Philippines and sold at one-seventh of the price of quinine, while still leaving a sufficient margin of profit for the planters, manufacturers, and vendors. The Philippine market alone could take 33 tons without setting up any competition with the quantities of quinine and synthetic drugs now imported. Totaquina, says the author, is less bitter than quinine; it is equally effective, and produces no disagreeable symptoms. He adds that this totaquina might also find a market in South China, and perhaps even in the United States.

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