THE IMPORTANCE OF CHLOROQUINE RESISTANT MALARIA IN SINGAPORE IN 1969

By M.J. Colbourne, M.R.C.P., W.P. Fung, M.R.A.C.P.

and

F. Paul, F.R.C.P.

(Faculty of Medicine, University of Singapore)

INTRODUCTION

For the past few years between two and three hundred cases of malaria are notified every year in Singapore. The great majority are infected outside Singapore, especially in Southern Johore. A small number, probably less than fifty each year, are infected on the small islands that are part of the Republic but not of the main Island. Since 1964, when there was a small epidemic of about 40 cases (Chew, 1968) there has been little, if any, transmission of malaria on the main island itself.

For many years the drug of choice for treatment of malaria in Singapore has been chloroquine. The finding of *P. falciparum* malaria resistant to chloroquine in Perlis in the north of Malaysia (Montgomery, 1963) sounded a warning, reinforced by the discovery of its occurrence in Southern Johore in 1968 (McKelvey); the confirmation of resistance in a soldier infected on Pulau Tekong, an island a few miles to the North East of Singapore showed that the routine of malaria treatment in Singapore might require re-examination (Ng, Fung, Colbourne and Gilles, 1969).

The trial to be described in this paper had the objective of discovering the extent of chloroquine resistance amongst cases of *P. falciparum* malaria treated in Singapore and of assessing the need for any change of treatment.

METHOD

The method adopted was to identify cases of *P. falciparum* malaria admitted to hospital in Singapore, to determine, as far as possible, their place of infection, to treat them with a standard course of antimalarial drugs and then observe them for 28 days to detect any recurrence of parasitaemia.

The patients consisted of admissions to the paediatric and some of the medical wards of the Outram Road General Hospital, Singapore. As soon as a patient was diagnosed as suffering from malaria, or a blood film was unexpectedly found positive for malaria parasites, the Department of Social Medicine and Public Health of the University of Singapore was informed. If the blood film contained asexual parasites of *P. falciparum*, either alone or in combination with other species, the patient was included in the trial. The staff of the department undertook the collection and examination of blood films while the patient was in hospital and the follow-up of the patient after discharge. The clinicians undertook the treatment of the patients and the retreatment of those in whom parasitaemia recurred. Tests for the presence of chloroquine in the urine were undertaken by the Singapore Government Biochemistry Department in the General Hospital, using Wilson and Edeson's test (1954).

The methods used have been described in a previous paper (Ng *et al*, 1969). In brief, they were as follows. Thick and thin blood films stained with Giemsa were examined for at least 200 fields of the thick film before being declared negative. Parasite densities were determined by counting parasites against leucocytes in the thick film and converting to parasites per cu. mm. Blood film examination was carried out daily while the patient was in hospital and at least once weekly after discharge, up to the 28th day after the commencement of treatment. Initial treatment consisted of:—1st day—10 mg. chloroquine base per kilo body weight; 2nd day—10 mg.; 3rd day—5 mg.

On the third day of treatment the patient's urine was examined for chloroquine (In all cases the results of the test indicated that the drug had been absorbed).

If parasitaemia persisted with asexual forms of *P. falciparum* or these forms recurred within 28 days after the commencement of treatment, the case was classified as resistant to chloroquine according to the schedule of resistance recommended by W.H.O. (1968).

Patients who were found to be resistant were treated at the discretion of the clinician. (It is not the intention of this communication to assess the value of alternative treatments; on the whole, Fanasil and pyrimethamine were satisfactory, though one patient had a recurrence of parasitaemia 11 days after such treatment and one took eight days to become parasite free).

It will be noted that the patients included in this trial were all hospital admissions but they do not comprise all the patients admitted to hospital in Singapore suffering from malaria during the period of the trial. It is not considered that the selection of these particular wards in this particular hospital introduced any bias.

It is possible that some cases were treated by general practitioners without reference to hospital and it is possible that such a group would include a higher proportion who showed no resistance; perhaps practitioners may refer to hospital only those malaria patients that have not responded to routine treatment. There was no evidence that this had occurred in this series.

Some practitioners started chloroquine treatment before admission of the patient to hospital; in such cases the treatment was repeated according to the agreed schedule; there was, therefore, no chance of under-dosage with chloroquine through relying on reports of treatment before admission to hospital.

RESULTS

During the period of the trial, from April to August 1969, 3,931 patients were admitted to the participating wards; of these 31 were diagnosed as malaria either clinically or as the result of a blood film taken routinely. Blood examination showed 16 to be infected with *P. falciparum* alone, 9 with *P. vivax* alone, and 3 with a mixed infection of *falciparum* and *vivax*. Three patients in whom no malarial parasites were found were excluded from the trial.

Epidemiological investigation into the movements of the patients prior to the onset of clinical symptoms suggested the following sites of infection (Table I).

TABLE I

	P. falciparum	P. vivax	Total
Malaysia (mainly Southern Johore)	8	6	14
Pulau Tekong Island (between Singapore and Johore)	5	—	5
Other small islands off Singapore	2	—	2
Singapore main island	1	—	1
Indonesia	2	2	4
Doubtful (one probably as a result of blood transfusion)	1	1	2
	19	9	28

Of the 19 *P. falciparum* infections eight were followed up completely and they did not visit areas where reinfection was considered possible during the follow-up. Four exhibited "R.I." resistance (W.H.O., 1968) with recrudescence on the 11th, 21st, 22nd and 24th days after the commencement of treatment. Four showed no evidence of resistance during the 28 days follow-up.

Of the four cases of resistance, three were probably infected in Pulau Tekong, and one in Southern Johore; of the four susceptibles, two were infected in Malaysia, one in Indonesia and one in a small island to the south of Singapore.

Four other patients were followed up completely, but the possibility of reinfection could not be excluded. Two, both from Pulau Tekong, had a recrudescence on the 17th and 28th day respectively; these could have been reinfected, though the chance of them being reinfected on Pulau Tekong on the few days after discharge was very low indeed.

The other two visited Malaysia regularly during the follow-up period but remained parasite free; however, these both admitted taking antimalarial drugs irregularly during this period.

Four patients were lost to follow-up; three returned to Malaysia, and one, an illegal immigrant, was deported to Indonesia. One soldier was absent without leave, after having been followed up for 25 days. One patient was admitted in coma and was given intravenous quinine, as it was not thought clinically justifiable to use chloroquine alone if resistance was possible.

A patient who developed a *P. falciparum* infection after blood transfusion during open-heart surgery was not included in this series of natural infections. In fact, a few rings of *P. falciparum* (160 per cu. mm.) were seen on the 10th day after chloroquine treatment; he was retreated with chloroquine and no asexual parasites were found in 15 blood films taken over the next four weeks.

These were the results that had been obtained by the middle of August 1969. About half the cases of *falciparum* malaria admitted to hospital were shown to be resistant to chloroquine. These resistant cases were mainly infected in Pulau Tekong. It should be noted, however, that the follow-up of the cases infected in Malaysia was very incomplete.

On 13th August 1969, the situation was discussed with the general practitioner working on Pulau Tekong; he felt that in the circumstances he could not continue to treat cases of malaria with chloroquine alone and he did not think it was justifiable to continue to insist that patients with uncomplicated malaria be admitted and kept under observation in the General Hospital in Singapore. He pointed out the considerable expense and inconvenience caused.

These comments were certainly justified and, as it had also proved difficult to follow up completely the majority of the patients infected in Malaysia and Indonesia, the trial was terminated on 23rd August, 1969.

DISCUSSION

Has this investigation achieved its objectives of discovering the amount of resistance in Singapore?

P. falciparum resistance to chloroquine certainly occurs in patients with malaria treated in Singapore.

In our series, about 1% of the patients admitted to the participating wards were suffering from malaria and more than half were infected with *P. falciparum*. The proportion of these infections resistant to chloroquine according to the W.H.O. classification cannot be stated as precisely as had been hoped. (It must be remembered that this classification is an arbitrary one; the limit of 28 days is convenient but the distinction between relapse and recrudescence due to resistance is not clear-cut).

We found it difficult to maintain a follow-up even for 28 days, particularly for patients infected in Malaysia and Indonesia. This difference in ease of follow-up would confuse the results if the amount of resistance was different in different localities. Follow-up for at least 28 days is essential as we found that in five of the six patients in whom we diagnosed resistance, parasites reappeared in the third and fourth weeks. We found that half of the patients were resistant (if we take six out of twelve patients as showing resistance the range at the 95% level of probability is between 22% and 72%).

For the reasons discussed above, it did not seem likely that continuation of the trial would produce any more useful results.

This amount of resistance agrees with the findings of McKelvey (1969) who found that 33 of 66 British servicemen infected with *P. falciparum* in various parts of (West) Malaysia were resistant to chloroquine at the "R.I." or "R.II." level.

With the information at present available, can any conclusion be reached about the most suitable treatment for patients in Singapore found to be infected with *P. falciparum*?

This problem must be answered for the individual patient by the clinician, but it would seem hazardous to rely on chloroquine alone for the treatment of a patient in or from Singapore, suffering from cerebral malaria. If we accept that such a seriously ill patient should be given the minimum quantity of antimalarial drugs, then quinine, parenterally, seems to be the most appropriate treatment.

For the less severely ill patient, there are other considerations. If he is given chloroquine alone, his symptoms will be relieved but he has a good chance of a recurrence in a few weeks' time. If, as is not unlikely, this recurrence is treated by a different practitioner, the relapse is likely to be repeated.

In similar situations elsewhere—Thailand (Harinasuta, 1969) and Vietnam (Waterhouse and Riggenbach, 1967)—multiple therapy has been used to obtain quick relief from symptoms and to reduce the chance of recrudescence.

A combination of chloroquine, pyrimethamine and a long acting sulphonamide would seem the most suitable though recurrences after such treatment may still occur.

SUMMARY

Of 3,931 patients admitted to hospital in Singapore during 1969, 19 were found to be suffering from *P. falciparum* malaria.

8 patients were followed up satisfactorily for 28 days and 4 were found resistant to chloroquine at the "R.I." level.

It is suggested that chloroquine alone is no longer a suitable treatment for *P. falciparum* malaria diagnosed in Singapore.

ACKNOWLEDGEMENTS

We wish to acknowledge with thanks the technical assistance of Mr. C. C. Tay of the Department of Social Medicine and Public Health, University of Singapore.

REFERENCES

1. Chew, P.K. (1968): Singapore Med. J. 9.
2. Harinasuta, T., Viravan, C. and Reid, H.A. (1967): Lancet, i, 1117.
3. McKelvey, T.P.H., Lundie, A.R.T., Williams, E.D.H., Moore, H.S. and Worsley, D.E. (1968): Brit. Med. J., iv, 703.
4. McKelvey, T.P.H. (1969): Proc. 4th Singapore-Malaysia Congress of Medicine, Singapore.
5. Montgomery, R. and Eyles, D.E. (1963): Trans. R. Soc. Trop. Med. Hyg., 57, 409.
6. Ng, W.C., Fung, W.P., Colbourne, M.J. and Gilles, H.M. (1969): Ann. Trop. Med. Parasit., 63,313.
7. Waterhouse, B.E. and Riggenbach, R.D. (1967): J. Amer. Med. Ass. 202, 683.
8. Wilson, T. and Edeson, J.F.O. (1954): Med. J. Malaya, 9, 115.
9. W.H.O. (1968): Tech. Rep. Scr. No. 382.