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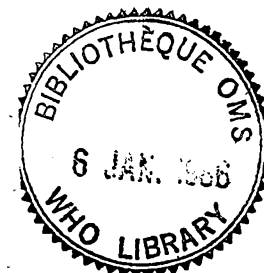
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¹ This study received financial support from the Malaria Applied Field Research component of the UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases.

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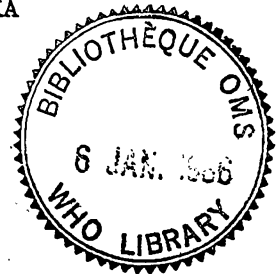
Tanzania

CHLOROQUINE-RESISTANT *PLASMODIUM FALCIPARUM* AT THE TANGANYIKA
PLANTING COMPANY (TPC) SUGAR ESTATE, MOSHI, TANZANIA¹

by

T. K. Mutabingwa,² V. A. E. B. Kilimali² and W. L. Kilama³

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1. INTRODUCTION

When chloroquine was first introduced into clinical use in the 1940s, African Plasmodium falciparum was so innately sensitive to it that the isolated reports of the 1960s alleging resistance to this drug were convincingly refuted by eminent malariologists (Bruce-Chwatt, 1970). However, the first incontrovertible report of African P. falciparum resistance to chloroquine appeared in 1978 (Center for Disease Control, 1978) and since then innumerable cases of resistance were encountered in non-immune visitors including those returning to Europe and North America (Bruce-Chwatt, 1982). There are now conclusive reports of chloroquine resistance in East African semi-immunes based on hospital patient reports and community surveys (Kihamia & Gill, 1982; Onori et al., 1982; Harrison et al., 1983, 1984; Hess et al., 1983; Schwartz et al., 1983).

Since the mid-1970s there have been increasing allegations concerning the inefficacy of chloroquine in the treatment of malaria in some parts of Tanzania. The present study, which was prompted by reports of poor response to chloroquine among patients seen by the medical officers at the Tanganyika Planting Company (TPC) sugar estate near Moshi, northern Tanzania, was undertaken during October 1982.

2. MATERIALS AND METHODS

2.1 Study area

The sugar estate covers 35 000 acres of land situated at the foot of Mt Kilimanjaro at a distance of 25 km from Moshi town, at an altitude of about 700 metres above sea level, and at 3°42' South and 37°15' East. The area has an average annual rainfall of 450 mm, mean annual temperatures of 32°C maximum and 17°C minimum. It has a total population of 11 500 of whom 4500 are employed by the sugar estate and 7000 are spouses and children. The company provides free and comprehensive health care to employees and their families whereas another 3000 people from the surrounding villages are charged minimal fees.

2.2 Selection of cases

Primary-school children ranging in age from 8 to 18 years (mean 12 years) were selected for study from two schools within the estate. Thick blood smears were Giemsa stained at a pH of 7.2 and examined for malaria parasites. Those found with less than 1000 asexual forms of P. falciparum parasites per μ l of blood, and those with a positive urine test (Dill-Glazko method) for the presence of 4-aminoquinolines on day 0, were all excluded from the study.

2.3 In vivo testing

The WHO Standard Field Test, or "7-day test", was used. This test consists of the administration of 25 mg chloroquine base per kg body weight over 3 days (i.e. 10 mg/kg on days 0 and 1, and 5 mg/kg on day 2) with a 7-day observation period, and was given to all children found suitable for testing. Absorption of the first drug dose was confirmed by a second Dill-Glazko test (Lelijveld & Kortman, 1970) which was performed for each selected child on day 1 before the administration of the second dose. Drug ingestion was systematically supervised and to rule out immediate vomiting of the drug the children were kept under observation for a period of not less than 45 minutes after drug ingestion.

In order to minimize possible side effects due to taking chloroquine on an empty stomach, every child under study was given a cup of porridge before administration of the drug.

Thick blood smears were taken from each subject studied, daily for 8 days (i.e. from day 0 to day 7). Each smear was stained with Giemsa and examined for malaria parasites. For each blood smear, asexual malaria parasites were counted against 200 leukocytes. Considering the normal range of white blood cell counts to be 4000-11 000 leukocytes per mm^3 of blood, a middle figure of 8000 leukocytes per mm^3 was applied to all cases. Thus every parasite count obtained per 200 leukocytes was multiplied by $8000/200 = 40$ to get the parasite density per mm^3 of blood. A blood smear was declared negative when 100 microscopic fields failed to reveal any asexual form of P. falciparum.

The individual parasite counts per mm³ of blood were classified according to the following scale described by Bruce-Chwatt (1958):

Parasite count per mm ³	Less than 200	101- 200	201- 400	401- 800	801- 1600	1601- 3200	3201- 6400	6401- 12 800	12 801- 25 600	25 601 and over
Class	1	2	3	4	5	6	7	8	9	10

The parasite density index (PDI) was then calculated by weighting the frequency of individual parasite counts falling within the range of each class by the number of the class. The sum of the weighted frequencies was divided by the total number of positive children (i.e. 91 cases).

2.4 In vitro testing

These tests were carried out according to the instructions for use of the WHO standard micro test kit for the assessment of the response of *P. falciparum* to chloroquine and mefloquine in vitro. A 100 µl of blood from a finger tip prick was drawn into a sterile, heparin treated, capillary tube and injected into a tube containing 900 µl of RPMI 1640 medium supplemented with 7.2% HEPES buffer and 2.4% sodium bicarbonate. Aliquots of 50 µl of the mixture were then transferred to each of the 8 wells for each test column resulting in chloroquine concentrations of 0, 0.2, 0.4, 0.8, 1.14, 1.6, 3.2 and 6.4 x 10⁻⁶ mol/l blood. The plate was then incubated at 37°C for 24 hours. After incubation, thick blood smears were prepared from the contents of the wells, dried, Giemsa-stained and the number of schizonts per 200 parasites counted for each well. When growth in the control wells was 20 schizonts or more per 200 asexual parasites, an inhibition of growth at a chloroquine concentration of 1.14 x 10⁻⁶ or less, indicated susceptibility whereas growth at 1.14 x 10⁻⁶ or above indicated resistance (WHO, 1984).

3. RESULTS

Of a total of 746 schoolchildren from two primary schools who were screened for malaria parasites, 245 (32.8%) were found to be positive and of these 120 (16.1%) were found to be suitable for sensitivity testing. Only 102 children actually presented themselves for the tests and 53 of them underwent both the in vitro and the in vivo tests. Of the 102 children who initially underwent the in vivo drug testing only 91 successfully completed the test. These children whose mean age was 12 years had a mean initial parasite density of 2862/mm³ of blood (geometric mean).

All subjects had a positive Dill-Glazko urine test on day 1 thereby suggesting that the initial drug dose had been absorbed. Of the 53 in vitro tests performed, 42 successfully grew on the culture medium.

In vivo testing

Among the 91 successfully followed up schoolchildren, asexual parasites of *P. falciparum* had not been cleared from the peripheral blood of 12 children by day 7.

The mean parasite clearance time for the 79 cleared cases was 2.9 days (Table 1). There were 21 schoolchildren who had parasites resistant to chloroquine (i.e. 12 resistant at the RII level in the in vivo test, 1 with an early recrudescence resistant at the RI level in vivo, and 8 resistant at the RI level in the in vitro test) and these resistant cases were given quinine and sulfadoxine + pyrimethamine (Fansidar) as alternative drugs (Table 2). Quinine was administered orally at a dose of 10 mg/kg body weight every 8 hours, with only one dose per day being taken under supervision. Sulfadoxine + pyrimethamine was given in a single oral dose according to age, i.e. 1/2 tablet to those under 5 years old, 1 tablet to those 5-9 years old, 2 tablets to those 10-15 years old, and 3 tablets to those over 15 years old. Parasitaemia cleared in all these patients except one who was on quinine and who was

changed to sulfadoxine + pyrimethamine (single dose). This patient was followed by the TPC medical officer and was reported to have been cleared of parasitaemia on the fourth day after administration of sulfadoxine + pyrimethamine. This one patient who failed to clear on quinine could be among those few subjects who should receive quinine for 10-14 days, but, as only one of the three doses of quinine was taken under supervision, it is also possible that the other two doses which had to be taken at home were not in fact taken.

In vitro testing

Of the 42 children who successfully underwent the in vitro micro test, 17 (40.5%) showed schizont maturation at or above 1.14×10^{-6} mol/l which is indicative of chloroquine resistance. The upper limit for schizont maturation was at 1.6×10^{-6} mol/l for 12 isolates and at 6.4×10^{-6} mol/l for 5 isolates.

The concentration response data for chloroquine are given in Table 3 and are graphically displayed in Fig. 1.

4. DISCUSSION

The malaria prevalence of 32.8% observed in this study is appreciably lower than the hyperendemic situation reported by Clyde (1967) for this area. As there is perennial malaria transmission at this irrigated sugar estate, the surprisingly low endemicity is most probably due to the high consumption of chloroquine which is readily and freely available in all dispensaries and which costs very little to buy on the market.

Of the 91 subjects given the full dose of 25 mg/kg chloroquine base, 13 (14.3%) had persisting parasitaemia on day 7. In comparison, Campbell (pers. comm.) found a rate of resistance of 38% on Zanzibar, whereas Onori et al. (1982) at Mto-wa-Mbu and Kouznetsov et al. (1980) at Bagamoyo found no resistant cases at the above chloroquine dosage. The rate of resistance at TPC therefore seems to lie between that on Zanzibar at one extreme and that at Mto-wa-Mbu and Bagamoyo at the other. However, like the Zanzibar results, the in vivo resistance seen within 7 days at TPC was all at the RII level.

Of the 42 isolates successfully tested in vitro, 17 (40.5%) were resistant to chloroquine and, of these, 12 showed schizont maturation at the chloroquine concentration of 3.2×10^{-6} mol/l and 5 at the concentration of 6.4×10^{-6} mol/l. Overall, the 42 in vitro tests reveal a bimodal distribution with 25 cases being sensitive, the remaining 17 cases showing only a high level of resistance and the absence of cases with low or intermediate levels of resistance. When these in vitro results are plotted with those for Mto-wa-Mbu (Onori et al., 1982) and those for Zanzibar (Schwartz et al., 1983), the response of half of the parasite population parallels that of the sensitive population at Mto-wa-Mbu and the response of the other half parallels that of the predominantly resistant population on Zanzibar. Moreover, sensitive parasites were cleared from the blood of patients in an average of 2.9 days (Table 1), a period which is usually characteristic of fully sensitive parasites in East Africa (Lelijveld & Mzoo, 1970).

The separate plotting of sensitive and resistant isolates (Fig. 1) gives a sharper regression line for the sensitive isolates thus indicating their more homogenous response to chloroquine. The regression line for resistant isolates shows a bimodal tendency in that half (like the sensitive isolates) fail to mature at a chloroquine concentration of 0.4×10^{-6} mol/l of blood, with no appreciable change in susceptibility at 1.14×10^{-6} mol/l and 1.6×10^{-6} mol/l, and the other half only partly succumb to concentrations of 3.2 and 6.4×10^{-6} mol/l. The failure of the highest chloroquine concentration of 6.4×10^{-6} mol/l to clear parasitaemia in 5 cases may perhaps be considered to forecast the appearance of well-established resistance. The above analysis suggests that the administration of low chloroquine dosages such as those used in chemosuppression would inhibit the maturation of only a small proportion of the schizonts, while intermediate concentrations of the order of 0.8×10^{-6} mol/l would inhibit the maturation of 98% of the sensitive parasites but of only 41% of the resistant ones. The concentration of 1.14×10^{-6} mol/l for discriminating an RI level of resistance would be expected to inhibit the maturation of all sensitive isolates but only of about 58% of the resistant phenotypes. The high concentration of 3.2×10^{-6} mol/l would only inhibit the maturation of 85% of the schizonts, while the matured parasites would be resistant to chloroquine and would conceivably produce resistant progeny.

Chloroquine resistance at TPC may have evolved initially as a response to the low curative and chemoprophylactic dosages used. For 12 years, from 1966 to 1978, mass chemoprophylaxis within the TPC sugar estate was mandatory and self-medication with chloroquine is still very common. As some parasites broke through the antimalarial barrier, they probably became exposed to treatment with higher concentrations of chloroquine which subsequently selected them for enhanced drug tolerance. Indeed as a result of sensitivity testing data, the treatment of P. falciparum in this part of Africa has been characterized by frequent reassessment of chloroquine curative dosages. Clyde (1961, 1966) reported the failure of 1.5 mg/kg chloroquine to clear P. falciparum in north-eastern Tanzania. Similarly, Pringle & Lane (1966) confirmed the decline in the efficacy of small doses of chloroquine (2.5 mg/kg) in fully clearing P. falciparum parasitaemia, and Lelijveld & Mzoo (1970) found 5 mg/kg to be sufficient. Goosen (1975), Kouznetsov et al. (1980) and Onori et al. (1982) reported that 10 mg/kg chloroquine base could no longer clear all P. falciparum asexual parasites in semi-immune Tanzanians. Clear cases of resistance were reported by Kihamia & Gill (1982) and Schwartz et al. (1983). The dosage required for complete parasite clearance in Tanzania has therefore increased ten-fold over the last three decades.

Alternatively, the resistant parasites in Tanzania could have been introduced from Asian countries just across the Indian Ocean where chloroquine-resistant P. falciparum is rampant. This hypothesis could be investigated by detailed comparative characterization of Tanzanian and Asian resistant isolates.

The emergence and transmission of chloroquine-resistant P. falciparum on the African continent is a matter of grave concern since, for all practical purposes, chloroquine is still the only drug used in both malaria chemotherapy and chemoprophylaxis, and this despite the clearly mounting threat of incipient chloroquine resistance. In retrospect, a wiser option would have been to incorporate a different potent schizontocidal drug (e.g. quinine) for weeding out the persisting asexual parasites, and a gametocytocidal antimalarial for containing the transmission of resistant parasites. Moreover, efficient vector control would have made the situation less critical at least in urban and development areas.

5. CONCLUSION

The presence and spread of P. falciparum chloroquine resistance in Africa is certainly a matter of great concern and there is an urgent need to undertake further studies comparing areas with a history of mass chemoprophylaxis such as the TPC sugar estate and those lacking such programmes. Moreover, the present study emphasizes the need to map and monitor resistance to chloroquine and other antimalarial drugs in this and other areas of Africa and to devise a national policy for the use of antimalarial drugs for treatment, with due consideration to the past and recent history of their use and the level of malaria endemicity. The mapping and monitoring of drug resistance, however, should not per se lead to the introduction of alternative malaria control strategies. In many African conditions one can only aim at the reduction of malaria mortality and morbidity. In order to achieve this, a policy for the rational use of drugs is essential. This means that large-scale chemoprophylaxis schemes should no longer be recommended, while treatment and diagnostic facilities should be made available to the largest possible extent.

In chloroquine-resistant P. falciparum areas, second and third line antimalarials should be readily available in the major health institutions in order to deal satisfactorily with P. falciparum chloroquine-resistant cases.

6. SUMMARY

From 1966 to 1978 the TPC maintained a mass malaria chemoprophylactic programme based on chloroquine. However, after reports of treatment failures to 25 mg chloroquine base per kg body weight, the sensitivity of Plasmodium falciparum to chloroquine at the TPC sugar estate near Moshi, northern Tanzania, was determined. In vivo and in vitro tests utilizing standard methods were carried out on semi-immune asymptomatic primary-school children whose ages ranged from 8 to 18 years, with a mean age of 12 years. These children were selected from a total of 746 schoolchildren who had been screened for malaria parasites and of whom 245 (32.8%) were found to be positive.

In vivo results revealed that 14.3% of the 91 positive cases found suitable for study did not clear on 25 mg/kg chloroquine base and were all resistant at the RII level. The mean parasite clearance time for sensitive cases was 2.9 days.

Of the 42 isolates successfully tested in the in vitro micro test, 25 were sensitive against 17 resistant. An analysis of the rate of inhibition of schizont maturation showed the sensitive isolates to be homogenous in their response, whereas the resistant isolates exhibited a bimodal behaviour reflecting the presence of sensitive and resistant parasites.

All the chloroquine-resistant cases receiving sulfadoxine + pyrimethamine and all but one of those receiving quinine cleared.

An attempt is made at explaining the evolution of chloroquine resistance in Tanzania and suggestions are offered for its management and containment.

ACKNOWLEDGEMENTS

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RESUME

PLASMODIUM FALCIPARUM CHLOROQUINO-RÉSISTANT A LA PLANTATION SUCRIERE DE LA TANGANYIKA PLANTING COMPANY (TPC), MOSHI (TANZANIE)

De 1966 à 1978, la Tanganyika Planting Company (TPC) a poursuivi un programme de chimio-prophylaxie de masse du paludisme par la chloroquine. Mais, à la suite de rapports faisant état d'échecs thérapeutiques à la dose de 25 mg de chloroquine base par kg de poids corporel, on a été amené à déterminer la sensibilité à la chloroquine de Plasmodium falciparum à la plantation sucrière de la TPC située près de Moshi, en Tanzanie septentrionale. Des épreuves in vivo et in vitro, effectuées selon des techniques usuelles, ont été pratiquées chez des écoliers asymptomatiques semi-immuns, âgés de 8 à 18 ans, la moyenne d'âge étant de 12 ans. Ces enfants ont été choisis parmi un total de 746 écoliers qui avaient été soumis à un dépistage du paludisme. L'examen a été positif chez 245 enfants, soit 32,8 %.

Les résultats des épreuves in vivo ont montré qu'il n'y a pas eu élimination du parasite à la dose de 25 mg/kg de chloroquine base chez 14,3 % des 91 cas positifs retenus pour l'étude et pour lesquels une résistance RII a été observée. Le temps moyen d'élimination du parasite chez les cas sensibles était de 2,9 jours.

Sur les 42 isolements examinés avec succès au moyen du microtest in vitro, 25 étaient sensibles contre 17 résistants. Une analyse de l'inhibition de la maturation des schizontes a montré que les isolements sensibles donnaient une réponse homogène, tandis que les isolements résistants avaient un comportement bimodal qui témoigne de l'existence de parasites sensibles et résistants.

Chez tous les cas chloroquino-résistants traités par l'association sulfadoxine + pyriméthamine et chez tous ceux, à l'exception d'un seul, traités par la quinine, le parasite avait été éliminé.

On s'efforce d'expliquer l'évolution de la résistance de Plasmodium falciparum à la chloroquine en Tanzanie et des mesures sont proposées en vue de la combattre et la contenir.

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TABLE 1. EFFICACY OF CHLOROQUINE AT A DOSAGE OF 25 mg (BASE)/kg GIVEN OVER 3 DAYS ON ASYMPTOMATIC INFECTIONS OF P. FALCIPARUM IN SCHOOLCHILDREN AT THE TPC SUGAR ESTATE, MOSHI, TANZANIA

Number examined	91
Mean age in years (range)	12.0 (8-18)
Mean weight in kg (range)	32.0 (20-54)
Mean pre-treatment parasite density per mm ³ (geometric)	2 862
Mean pre-treatment parasite density index	6.1
Daily post-treatment parasite rates (% clearance):	
Day 1	100 (0.0)
2	68.1 (31.9)
3	31.9 (68.1)
4	15.4 (84.6)
5	14.3 (85.7)
6	14.3 (85.7)
7	14.3 (85.7)
% parasitaemias cleared in 7 days (number of children)	85.7 (79)
% parasitaemias not cleared in 7 days (number of children)	13.2 (12)
% parasitaemias recrudesced (number of children)	1.1 (1)
Mean clearance period in days	2.9

TABLE 2. RESPONSE OF CHLOROQUINE-RESISTANT P. FALCIPARUM (P.f.) TO ALTERNATIVE DRUGS AT THE TPC SUGAR ESTATE, MOSHI, TANZANIA

Drug administered	Total No. of patients with resistant P.f. treated	No. cleared by day 7	No. not cleared
Quinine	11	10	1
Fansidar	10	10	0
TOTAL	21	20	1

TABLE 3. RESULTS OF CHLOROQUINE IN VITRO MICRO TESTS IN
P. FALCIPARUM FROM MOSHI, TANZANIA, OCTOBER 1982

Type of isolates	All	Chloroquine sensitive	Chloroquine resistant
No. of isolates tested	42	25	17
% of inhibition of schizont maturation at			
0.2 x 10 ⁻⁶ mol/l	16.9	26.8	5.7
0.4 x 10 ⁻⁶ mol/l	48.6	62.4	31.6
0.8 x 10 ⁻⁶ mol/l	72.3	97.4	39.9
1.14 x 10 ⁻⁶ mol/l	77.4	100.0	48.2
1.6 x 10 ⁻⁶ mol/l	80.2	100.0	54.6
3.2 x 10 ⁻⁶ mol/l	86.9	100.0	70.0
6.4 x 10 ⁻⁶ mol/l	97.4	100.0	94.0
IC ₁	5.53847	7.17749	4.88398
b	1.73743	4.18051	1.65962
EC ₁	0.0224	0.0837	0.0466
EC ₁₀	0.0896	0.1488	0.1985
EC ₅₀	0.4897	0.3014	1.1746
EC ₉₀	2.6769	0.6105	6.9509
EC ₉₅	4.3323	0.7457	11.5063
EC ₉₉	10.6973	1.0857	29.6410
Mean number of schizonts in controls; chloroquine sensitive 68.2 chloroquine resistant 76.0.			

FIG. 1. CHLOROQUINE RESPONSE IN VITRO OF *P. FALCIPARUM*
FROM MOSHI, TANZANIA, OCTOBER 1982

