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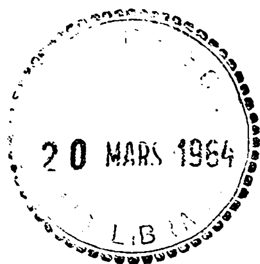

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SUPPRESSION OF MALARIA IN TANGANYIKA USING MEDICATED SALT[1]

by

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1. INTRODUCTION

Attempts to suppress malaria by the use of chloroquine or pyrimethamine mixed with common salt, ingested as part of the normal diet, have been made in some countries where the disease is endemic and other methods of eradication impracticable. In parts of Brazil, Pinotti (1954) and Pinotti et al. (1955) used chloroquine mixed with salt, the concentration of base usually being 0.3%. This treatment, whereby adults taking 10-15 g of salt daily received during each week 210-315 mg of chloroquine base, was intended to cover the entire Amazon region (Pinotti, 1959).

In West Irian in 1959, pyrimethamine was added to salt and distributed free of charge through official channels; but within three months the development of resistance on the part of Plasmodium falciparum made it necessary to change to chloroquine (Meuwissen, 1961). The same problem arose in 1960 in Cambodia, where salt medicated with pyrimethamine and supplied officially free of charge had to be replaced in a year with chloroquinized salt, at successive concentrations of 0.3%, 0.6% (objectionable because of bitter taste), and again 0.3%. In British Guiana the addition of chloroquine in 0.43% concentration to all salt supplies proceeding inland was proposed by Giglioli (1959), this project being commenced in 1961. Chloroquine mixed with salt has been distributed through ordinary commercial channels to some 30 000 people in northern Ghana, where malaria is holoendemic.

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As a result of experience gained in laboratory and field, it appears that where dietary salt consumption among adults is in the region of 10 g daily the optimal proportion of chloroquine is 0.3% (World Health Organization Technical Report Series, 1961, No. 226). Pinotti et al. (1955) reported that daily doses of chloroquine containing 30 (but not 10) mg base given for 1-3 months freed patients of P. malariae or P. vivax parasitaemias. Infection by the latter parasite was suppressed with salt containing chloroquine in the amount of 300 mg base weekly in trials among non-immunes conducted by Coatney et al. (1958). At this dosage, the principal problems that have arisen are, first, the tendency of chloroquine to leach out of the mixture when stored under humid conditions and, secondly, the fact that small children and particularly breast-fed infants, who have the highest parasite rates, may receive little or no salt. In the trial which is the subject of this report, the former difficulty has been met to some extent by the use of a commercial brand of chloroquine coated with cetyl-stearyl alcohol to protect it from moisture. No particular action, such as direct drug administration in the form of tablets, was taken to ensure treatment of infants.

2. METHOD

Selection of the site. The site for the medicated salt project in Tanganyika was selected to comply with the requirements that the incidence of malaria should be typical of that prevailing in the country, that is, holoendemic, and that the entire supply of common salt should be susceptible to control and medication before being sold to a co-operative population through normal commercial channels at no extra cost. Sites fulfilling the second condition are rare, which suggests that the use of medicated salt by itself as a method of malaria eradication is unlikely to be widely successful. One area in Tanganyika, however, though smaller than was desirable but otherwise meeting the requirements, exists in the northern (Arusha) region. The compact settlement of Mto wa Mbu ("Mosquito River") contains some 2200 permanent residents, almost all of Bantu stock, together with several hundred transients mostly nomadic Masai. It is situated at the northern end of Lake Manyara, and is isolated to the south and south-west by this lake and the uninhabited game reserve of the same name, to the north and east by arid scrubland, and immediately to the west by the sheer wall of the Rift rising some 5000 ft (1500 m). Mto wa Mbu itself is at an altitude of 3200 ft (975 m), and is connected by an all-weather road to the regional capital Arusha 70 miles (113 km) to the north-east. In the settlement is a small primary school, and a dispensary which serves the whole district.

Incidence and transmission of malaria. The residents of Mto wa Mbu are, with few exceptions, Bantu of lowland tribes who have acquired in youth a marked degree of immunity to malaria. Some first-generation immigrants from above the Rift wall, where malaria is seasonal or absent, are initially less immune, as are the nomadic Masai who erect temporary camps on the periphery of the settlement. The prevalence of malaria at Mto wa Mbu prior to use of medicated salt is shown in Table 1.

TABLE 1. PREVALENCE OF MALARIA PARASITES AT MTO WA MBU PRIOR TO MEDICATION OF SALT

Human age-groups	Number of people examined	Crude parasite rate	Parasite density index	Relative species prevalence (1)		
				P. falciparum	*P. malariae*	*P. vivax & ovale*
0-11 months	34	64.7	5.1	95.5	18.2	9.1
12-23 months	74	68.9	5.3	98.0	39.2	9.8
2-5 years	91	76.9	4.0	100.0	51.4	11.4
6-10 years	180	71.7	3.1	97.7	24.8	1.6
11-15 years	84	65.5	2.3	100.0	9.1	0.0
16 years & older	243	24.7	1.4	98.3	6.7	0.0

Note: (1) This is the percentage of each species in relation to total positive cases (there were many mixed infections).

The parasite rates and parasite density indices (Bruce-Chwatt, 1958) among different age-groups, characteristic of the holoendemic pattern found in the lowlands of Tanganyika, showed only a negligible seasonal variation. A more considerable variation in the sporozoite rate depending upon the emergence during and after the rainy season of large numbers of young mosquitos made it necessary to restrict gland dissections to gravid *Anopheles gambiae* and *funestus* (Gillies, 1954). Of the other anophelines found at Mto wa Mbu, only *A. pharoensis* might have been a vector of malaria but despite repeated dissections has not been incriminated. The sporozoite rate of gravid *A. gambiae* prior to use of medicated salt was 3.1% (484 dissections), and of *A. funestus* 5.9% (273): thus the combined rate was 4.1%.

Supply and consumption of common salt. The common salt consumed at Mto wa Mbu is supplied to the four shops there through a single wholesale merchant in Arusha. It varies in particle size from small granules to lumps of half a centimetre in diameter, is grey in colour, and though sun dried tends to be moist; some of it is soda-salt from Lake Magadi in Kenya and some sea salt. It is normally dispatched to the retail traders by road in unlined jute sacks each containing 80-100 kg, and may stand for two months in the shop before being sold. The average monthly consumption, as measured by sales over a two-year period, has proved to be 501 kg, approximately 90% being purchased by permanent residents and all used for dietary purposes. It is estimated that each of the 1600 adults at Mto wa Mbu consumed 7.8 g of salt daily, and each of the children 4.5 g, although the latter quantity varies with age, breast-fed infants receiving none and children up to two years of age very little.

Provision of medicated salt. Sacks of salt provided by the wholesale merchant in Arusha were taken to the local health office where the lumpy salt was manually crushed under hygienic conditions. By a process of layering and shovelling, the salt was then mixed with a preparation of chloroquine diphosphate coated with cetyl-stearyl alcohol ("Comosal", Imperial Chemical Industries Ltd.), the object being to obtain a drug concentration in salt of 0.3% of base. Random samples were taken after each mixing for chemical analysis. The medicated salt was then returned in the same sacks, now specially marked, to the wholesale merchant to await transportation to Mto wa Mbu where it was sold at the prevailing price of untreated salt. This operation required to be carried out at intervals of four to five months by a staff of one supervisor and four labourers, who in a period of 30 hours mixed some 2500 kg of medicated salt. During the whole 18 months of the project covered by this report, a total of 10 284 kg of medicated salt was provided from four mixing sessions, the cost of labour and supervision being £ 100 (US$ 280), of mixing equipment such as shovels and sieves £ 25 (US$ 70), and of chloroquine premix delivered at Arusha £ 450 (US$ 1260).

In order to accustom the conservative population of Mto wa Mbu to the use of the finer grade of salt required for medication, for some time prior to introduction of medicated salt the lumps of salt forming existing supplies were crushed, at first being halved in size, then after two months quartered, and finally reduced to the small

particles that would be supplied when medicated. This procedure, together with the wide publicity given to the project and its health aspects, ensured acceptance of the medicated salt when it came into use in December 1961, since which time the project has proved to have a lasting popularity quite unlike short-lived campaigns of larviciding, residual spraying and direct drug treatment attempted at Mto wa Mbu in the past.

Analysis of the medicated salt. Throughout the project samples of medicated salt have been analysed for moisture and chloroquine content. Two samples of the commercial premix as received from England were examined and found to be close to standard. In addition, analyses were made of samples (a) taken from freshly mixed salt at Arusha at each of the mixing sessions, prior to despatch to Mto wa Mbu, and (b) taken from sacks or purchased incognito at various times at the shops in Mto wa Mbu.

With regard to samples (a), the moisture content per cent. w/w (loss at 105° C) varied from 1.8 to 3.1 with the exception of a group of four samples in which a much higher content was found. The chloroquine base content in grams per cent. w/w (calculated to molecular weight 319.9 on dry basis) varied from 0.27 to 0.36; the majority of the samples, irrespective of duration of the mixing process (from 30 to 60 minutes) or of position in a sack that had been standing for four days, proved to be as close to expectation as 0.29 to 0.31 g % w/w.

With regard to samples (b), the findings were as follows:

(1) Five samples were taken from different levels of sacks of the first mixing session (when Magadi soda-salt was used almost exclusively); these sacks of medicated salt had stood for three and four months in three shops at Mto wa Mbu prior to sampling. The moisture content was found to vary from 0.4 to 2.2% and the chloroquine base - from 0.28 to 0.33%, close to expectation. One additional sample from this mix, purchased over the counter as a remnant 15 months later, had a moisture content of 0.3% and chloroquine 0.27%.

(2) Subsequently, analyses were made of medicated salt from the second and third mixing sessions (when only sea salt, mostly imported from Aden, was used). The sacks with one exception had stood for up to four months at Mto wa Mbu

before being sampled. The moisture content of 7 samples taken directly from different levels in the sacks stored in three shops, and of 7 samples purchased over the counter from display trays, varied from 1.0 to 2.0%. Chloroquine contents proved to be 0.11 (from the bottom of a sack inadvertently stored for 11 months), 0.18, 0.19, 0.19, 0.19, 0.20, 0.21, 0.21, 0.22, 0.22, 0.22, 0.23, 0.23, 0.24 g % - the mean of 0.20 g % representing only two-thirds of the expected concentration of chloroquine in the salt being sold.

In addition, two samples taken from a small tin in the fourth shop, after the project had been running for 10 months, were found negative for moisture and chl chloroquine: this dried relic of stock from before the project was withdrawn.

(3) Finally, analyses were made late in the project of medicated salt from the fourth mixing session (sea salt from Aden). Polythene lined bags were introduced towards the end of this period, and the remaining salt of the fourth mix which had been dispatched to Mto wa Mbu in the usual unlined jute sacks was transferred into these bags after two months. Samples of the salt dealt with in this manner were bought over the counter from three shops at Mto wa Mbu, and had moisture contents of 6.3, 6.9 and 7.3%; the chloroquine was 0.17, 0.23 and 0.24 g %, again only two-thirds of expectation.

This consistent loss of one-third chloroquine content after the salt from the second, third and fourth mixes had reached Mto wa Mbu has posed a serious problem that is still being investigated. It is clear from most careful inquiry that the salt after mixing is not being diluted by wholesaler or retailers nor would there be incentive or profit in so doing. That the medicated salt is not being exported to shops in neighbouring settlements is demonstrated by analyses of samples purchased at Karatu (15 miles or 24 km west of Mto wa Mbu) and Makuyuni (20 miles or 32 km east); no chloroquine was found in these samples although the project had been running for 17 months.

Although interval sampling from top, centre and bottom of stored sacks has shown that the chloroquine concentration is no greater at lower than at upper levels, suggesting that the loss is not attributable to ordinary vertical leaching,

nevertheless two findings strengthen the case against leaching; an alternative explanation, chemical degradation of chloroquine by sea salt (as opposed to Magadi soda salt of the first mix), is most unlikely. The first finding was that the jute of an empty sack that had contained medicated salt for 11 months, without a polythene liner, had adsorbed no less than 52 grams of chloroquine base (one-sixth of what had been put in when the sack was filled). And it has been noted that the brine running from unlined jute sacks or pooled in the bottom of polythene liner bags contains a very high proportion of the drug.

3. RESULTS

Parasitological and entomological examinations were carried out at intervals of three and four months following the introduction of medicated salt at Mto wa Mbu. The collection of urine for chloroquine estimation, made at the beginning of the trial, had to be discontinued because it proved extremely unpopular. Attendances for "fever" at the local dispensary were recorded.

Parasite rates. The crude parasite rates found after three, six, nine, 14 and 18 months of treatment with medicated salt are shown in Table 2. As will be appreciated by those with African experience, it proved extremely difficult to be certain that every person examined was a true resident of Mto wa Mbu, or had not recently been away visiting surrounding areas where malaria was unabated.

Parasite densities are not recorded because of the small number of persons remaining infected. Despite the presence of parasites of all species prior to provision of medicated salt, the infections indicated in Table 2 were attributable to *P. falciparum*; with the following exceptions: at six months, scanty *P.vivax* in a 12-year-old boy newly arrived in Mto wa Mbu, and at 18 months, *P. malariae* in a child aged 12 months. A proportional increase in gametocytes was observed at three and six months; some were doubtless relics of infections the asexual stages of which had yielded to chloroquine, while others may have represented a response to what would initially have been a sub-therapeutic dosage in some people.

It is apparent in Table 2 that the parasite rates among children aged less than two years fell more slowly than did those of older people, the low levels found among the latter at three months of treatment only being reached by small children

at nine months. Thereafter, examination sometimes revealed one or two infections in a particular age-group, and none in another, but no consistent pattern was apparent.

TABLE 2. PARASITE RATES AT INTERVALS FOLLOWING INTRODUCTION OF MEDICATED SALT

Human age-groups	Months after introduction of medicated salt				
	3 months	6 months	9 months	14 months	18 months
0-11 months:					
Number examined	22	21	21	36	35
Parasite rate	22.7	19.0	4.8	0.0	2.9
12-23 months:					
Number examined	42	27	30	53	42
Parasite rate	7.1	18.5	0.0	1.9	2.4
2-5 years:					
Number examined	58	48	31	74	67
Parasite rate	0.0	2.1	3.2	1.4	4.5
6-10 years:					
Number examined	112	61	133	104	79
Parasite rate	4.5	3.3	2.3	1.0	1.3
11-15 years:					
Number examined	107	49	56	74	64
Parasite rate	3.7	8.2	0.0	1.4	3.1
16 and older:					
Number examined	196	301	124	263	262
Parasite rate	7.1	2.0	2.4	0.8	2.3

Sporozoite rates. At three, six, nine, 14 and 18 months the respective numbers of gland dissections of Anopheles gambiae and funestus caught by pyrethrum spraying of houses in the centre of Mto wa Mbu were 368, 110, 170, 236, and 300.

No sporozoites were found in any of these examinations, despite the rate that had prevailed prior to the introduction of medicated salt.

Urinary excretion of chloroquine. The collection of specimens of urine for estimation of chloroquine content conflicted with strongly-held superstitions, and proved so unpopular that it had to be terminated after a few months lest the main objectives of the trial be jeopardized. The estimations were made by another organization, and may be summarized as follows:

(1) Period two-three months following provision of medicated salt: no specimens from infants were examined, but in the age group 12-24 months one contained a very small amount of chloroquine and one was negative. Among older people, 14 were negative, 11 contained very small amounts (up to 0.4 mg of chloroquine in 100 ml urine), and 69 contained 0.5 mg or more;

(2) period four-six months: no specimens from infants were examined. In the age-group 12-24 months, one contained a very small amount of chloroquine and three were negative. Among older people, 25 were negative, 10 contained very small and 113 larger amounts.

Dispensary attendances. The small dispensary at Mto wa Mbu serves an area considerably larger than that covered by medicated salt, and many of the attendances for "fever" and other conditions are by strangers visiting the settlement or residents returning from visits elsewhere. Attempts to distinguish with accuracy between these different categories of people at the dispensary have proven impracticable, but it is probable that about one-third of the first attendances are by aliens. The percentage of "fever" cases to those of all diseases may be summarized from the records:

(1) Period of twelve months immediately preceding provision of medicated salt: average monthly percentage of "fever" cases was 30.4 (the range being 25.0-39.5 and the last month before introduction of medicated salt, December 1961, 27.0);

(2) three-month periods during consumption of medicated salt; the average monthly percentage of "fever" cases was as follows:

January-March 1962	13.9
April-June 1962	13.3
July-September 1962	14.4
October-December 1962	14.8
January-March 1963	15.4
April-June 1963	14.7

(During the first month after introduction of medicated salt, January 1962, it was 12.3%.)

The average monthly first attendances for all diseases at the dispensary were 1961 - 1100 to 1350; 1962 - 750 to 850 and 1963 - 860 to 950.

Although the well-known limitations of dispensary records will be borne in mind in evaluating these data, it is apparent that a sudden sharp decline by about half in the number of cases of "fever" occurred within a month of the provision of medicated salt. Much of this "fever" is of course not malaria. Because adults form the bulk of the migrants coming from unprotected areas, it might be expected that the proportion of cases of "fever" reported at the dispensary would be highest in this age-group; but that there is no such clearly defined division is shown by the following records, where the first column is the monthly percentage of "fever" cases among adults, the second among schoolchildren, and the third among pre-school children:

October-December 1961	30.5	41.4	32.6
- provision of medicated salt -			
January-March 1962	16.2	14.7	7.1
April-June 1962	13.8	12.8	11.3
July-September 1962	15.1	12.5	14.5
October-December 1962	14.3	17.7	11.3
January-March 1963	16.7	11.3	17.0

4. DISCUSSION

In a field trial such as this, where an important objective is the assessment of a method which, whilst combating endemic disease, will interfere as little as possible with the daily routine, habits and commerce of a population, it is rarely possible to carry out all the scientific investigations that may seem desirable. Suspicions, and resulting evasions, are easily aroused by persistent questioning of a peasant population regarding recent absences from home - in the case of the inhabitants of Mto wa Mbu visits the surrounding malarious areas - and by insistence on procedures that run counter to deeply-held prejudice, such as the provision of urine specimens in the absence of obvious genito-urinary disease. Indeed, because the success of a medical campaign under field conditions is often directly related to lack of interference with the subjects, medicated salt offers advantages over more direct methods of attack. Provided the basic requirements of the method are fulfilled, namely control of all salt entering the area and a normal dietary intake on the part of the population, the use of medicated salt as an antimalarial agent has proved administratively and technically simpler, less expensive, and far more popular than attack on the disease through elimination of vectors or treatment of individuals. Such has been the experience at Mto wa Mbu, where in the past larviciding, residual spraying and direct suppressive chemotherapy have been tried out without success. But it must be stressed that areas where commercial supplies of salt can be controlled as fully as this are exceptional.

Although the results of the medicated salt trial at Mto wa Mbu have been sufficiently good to suggest that there was a reduction of the sporozoite rate to zero and that this had a considerable effect on the transmission of malaria, two problems remain unsolved, the loss of potency of chloroquine mixed with salt and the persistence of a few cases of malaria in the settlement. The former is being investigated chemically; with regard to the erratic and scanty persistence of malaria parasites, four possibilities must be considered:

(1) Those people with parasitaemia may not have received enough medicated salt in their diet to clear the parasites. Within the first six months of the trial this would certainly account for the gradual rather than abrupt

subsidence of parasite rates among infants who, being breast fed, received no chloroquine except as given for fever at the dispensary, and among weaned children aged less than two years whose diet is customarily unsalted. This may also explain the occasional case found in the early stages of the trial among older people whose initial infections may have been responding tardily.

(2) The occasional cases of parasitaemia found in later months might have been attributed to the diminution by one third of the potency of chloroquine in the salt stored at Mto wa Mbu, as shown by chemical analysis. However, this diminution would result in the actual weekly adult dose falling from 164 to 109 mg base, still substantially greater than the dosage found sufficient to protect Bantu having the advanced degree of immunity of those at Mto wa Mbu (Clyde, 1961). Only if the consumption of salt decreased by half would the dosage of chloroquine become sub-therapeutic, but this did not occur: total salt sales remained fairly constant throughout the trial.

(3) In view of recent findings in other countries it was necessary to consider if parasitaemia might have persisted because of the presence of P. falciparum resistant to chloroquine. Two of the infected cases found at 14 months were given direct oral treatment with chloroquine tablets (age one year, 150 mg base and age seven years, 300 mg), and the parasites were cleared promptly.

(4) The most likely explanation is that most of these infections were acquired outside Mto wa Mbu. Not only is it difficult to be sure that every single individual of the many who assemble for examination is a resident, but the latter also visit back and forth to neighbouring villages where hyperendemic malaria is unchallenged and medicated salt not eaten. It may seem that it would be simple to elicit this information. It is not.

The presence of parasitaemia at all times up to 18 months following the introduction of medicated salt at Mto wa Mbu is considered, therefore, to be attributable to two factors: during the first few months the lag in elimination of pre-treatment infections, and subsequently the occasional presence of exogenous infections among people newly returned to the settlement from visits elsewhere.

5. CONCLUSIONS

Administration of chloroquine diphosphate in the form of medicated salt to the population of Mto wa Mbu has resulted in a decrease of the sporozoite rate from 4.1% to zero and this may indicate a trend leading to eventual interruption of malaria transmission in this formerly holoendemic area. Although the sporozoite rate became negative within a few weeks of distribution of the medicated salt through ordinary commercial channels, parasitaemia was very occasionally found among residents of the settlement throughout the first 18 months of the trial. The irregular pattern of infections suggested, however, that most if not all were being contracted elsewhere. These encouraging clinical results were achieved despite the known lack of salt in the diet of very small children, and despite a loss amounting to one-third of the chloroquine content after mixing with salt and storing. Because of this loss, the reasons for which are being investigated, the actual amount of chloroquine base being eaten each week in the diet of the Mto wa Mbu adult may be as low as 109 mg and not the 164 mg which the mixing concentration of 0.3 per cent. was expected to yield.

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