Research/Recherche

Metrifonate in the control of urinary schistosomiasis in Zanzibar

A.F. Mgeni,[1] U.M. Kisumku,[2] F.S. McCullough,[3] H. Dixon,[4] S.S. Yoon,[5] & K.E. Mott[6]

Selective population chemotherapy using three doses of metrifonate (7.5 mg/kg body weight each time) at two-week intervals was assessed in an entire community in Kinyasini district in Zanzibar, United Republic of Tanzania. The objectives of the study were to (1) reduce the prevalence of heavy infections (defined as ⩾50 S. haematobium *eggs per 10 ml of urine) by 75% in two years, and (2) reduce the overall prevalence of infection by 50% in two years.*

A total of 4113 people were examined at least once during the two-year period. In the initial survey the highest proportion of infected individuals was in the 10–14-year age group, and in all subsequent surveys in the 5–9-year age group. The age group with the highest proportion of heavily infected individuals was 5–9 years for all surveys. The overall reduction of prevalence of infection from survey 1 to survey 4 was 52.9% and the prevalence of heavy infection was reduced by 62.2%.

The conversion rates (negative to positive in two consecutive surveys) were highest in the longest interval of 12 months and the rates of reversion (positive to negative in two consecutive surveys, without a history of treatment) were highest in the shortest interval of 4 months. Some statistically significant relationships were observed between the number of doses and the egg reduction rates. However, for the egg-negative rates, no statistically significant relationship was observed. In the 4-month interval a 67.6% egg-negative rate was observed among those who took at least one dose; with the 12-month interval a 48.3% egg-negative rate was observed.

Thus, selective population chemotherapy with metrifonate was shown to reduce the prevalence and intensity of infection due to S. haematobium *over a 24-month period.*

Introduction

Advances in diagnostic techniques and chemotherapy now ensure that reduction in disease due to schistosomiasis is within the capabilities of the current health infrastructures of many endemic countries (*1*). The effectiveness of metrifonate, an organo-phosphorus compound with specific anticholinesterase activity against *Schistosoma haematobium*, has recently been reviewed (*2*). Its relatively low cost, lack of toxicity, and high efficacy make it an attractive option for large-scale treatment. However, most of the published studies on the efficacy of metrifonate for *S. haematobium* control have been limited to small groups of school-age children; this age group usually has the highest prevalence and the heaviest infections (*3, 4*). Some studies have examined the efficacy of varying doses of metrifonate; others have used a single dose of 10 mg/kg body weight and achieved a reduction in egg output of at least 90% (*4–6*). A few studies have utilized the WHO-recommended schedule of three doses of 7.5 mg/kg body weight at two-week intervals and achieved a similar reduction in egg count (*7, 8*).

Zanzibar, an island off of the eastern coast of

[1] Health Officer, Schistosomiasis Unit, Ministry of Health, Zanzibar, United Republic of Tanzania.

[2] Director of Preventive Services, Ministry of Health, Zanzibar, United Republic of Tanzania.

[3] Formerly Scientist, Division of Vector Biology and Control, World Health Organization, Geneva, Switzerland.

[4] Chief, Epidemiological and Statistical Methodology, Epidemiological Surveillance and Health Situation and Trend Assessment, World Health Organization, Geneva, Switzerland.

[5] Scientist, Schistosomiasis and other Trematode Infections, Division of Control of Tropical Diseases, World Health Organization, Geneva, Switzerland.

[6] Chief, Schistosomiasis and other Trematode Infections, Division of Control of Tropical Diseases, World Health Organization, Geneva, Switzerland. Requests for reprints should be sent to Dr K.E. Mott at this address.

Reprint No. 5127

Tanzania, was recognized as a highly endemic area of urinary schistosomiasis as early as 1885 (*9*). It was the site of the first clinical trials of metrifonate against *S. haematobium* infection 15 years before this present study (*10, 11*).

This paper describes the results of selective population chemotherapy in an entire community in northern Zanzibar island. Metrifonate was administered in three doses (7.5 mg/kg body weight each time) at intervals of two weeks. The operational aim of the study was to (1) reduce the prevalence of heavy infections (defined as $\geqslant 50$ eggs per 10 ml of urine) by 75% in two years, and (2) reduce the overall prevalence of infection by 50% in two years. The effects of treatment, according to age group, sex, and initial intensity of infection were observed, and the efficacies of complete (three doses) treatment and incomplete treatment were compared.

Methods

Kinyasini district in Zanzibar, United Republic of Tanzania, was selected as the study area. A detailed map (Fig. 1) showing the location of all houses in the district, as well as other relevant geographic features, was prepared and a complete census was undertaken in May 1981. All the residents in the district, who produced urine, were included in the study, each one being assigned a serial number. The four surveys in the study were carried out during a two-year period (July 1981 to July 1983), the census being updated at each survey. The examination and treatment team was composed of a health officer, two assistant health officers, three microscopists, two laboratory assistants and a driver, all from the Ministry of Health.

The presence of *S, haematobium* infection was detected in a specimen of urine collected from each person. When the urine specimens were brought to the examination team, a few drops of 10% formaldehyde were added. Using the Nytrel syringe filtration technique, a 10 ml random aliquot of each well-mixed specimen was examined by a trained microscopist either in a field laboratory or in the central laboratory. Either new or adequately washed Nytrel filters were used at each survey. No quality control was performed during the examinations. If a person was found to be positive, i.e., anyone with at least a single *S. haematobium* egg in the urine, treatment was given based on the WHO-recommended regimen (3 doses of 7.5 mg of metrifonate per kg body weight at 2-week intervals) (*1*).

At each survey, the data on each individual included the district, school, house number, family order number, age, sex, urinary egg count, date of examination, weight, number of tablets of metrifonate per dose, and the number of doses received. Preliminary data check and analysis using hand calculators were completed by the project staff. The data record forms were then forwarded to Geneva for final data processing and analysis by the WHO Epidemiology and Statistical Methodology unit.

There are two distinct seasons for the transmission of schistosomiasis in Zanzibar. The high season, accompanying the rains, lasts from July to August, while the rest of the year can be considered as a low transmission season. The first survey was completed in August 1981, towards the end of the peak transmission season. The second survey was conducted 12 months after the first examination, in August 1982. The third survey was conducted 8 months after the second examination in April 1983, and the last survey was conducted 4 months later, in July 1983, at the beginning of the peak transmission season.

At each survey, subsequent to the first, the total population examined included residents of the area who had participated in previous surveys, and those who had migrated into the study area since the last census. The results of the surveys, therefore, included data from individuals with previous treatments and those who were being treated for the first time. Although this obviates precise comparison of the results of successive surveys, nevertheless reasonable conclusions can still be reached when the analysis is performed on cohorts present during consecutive surveys.

Other interventions were carried out concurrently with chemotherapy including health education and information sessions in Kinyasini school, improvements in the provision of safe water supplies, and molluscicide. Information meetings with the village leaders and the community were held 2–3 times per year during the course of the project. Local religious leaders gave support to the activities of the project by encouraging participation of the community in the surveys. Water improvement projects were carried out by the villagers and several wells were dug during the study period. Two molluscicide applications, using niclosamide, at the main transmission sites (see Fig. 1) were undertaken in January 1983 before the third survey and in June 1983 before the last survey.

Results

A total of 4113 people were examined at least once during the two-year period. The age and sex distribution of the total study population is shown in Table 1. It was assumed that the characteristics of people moving into the area were similar to those leaving the

Fig. 1. **Map of Zanzibar and the Kinyasini project area.**

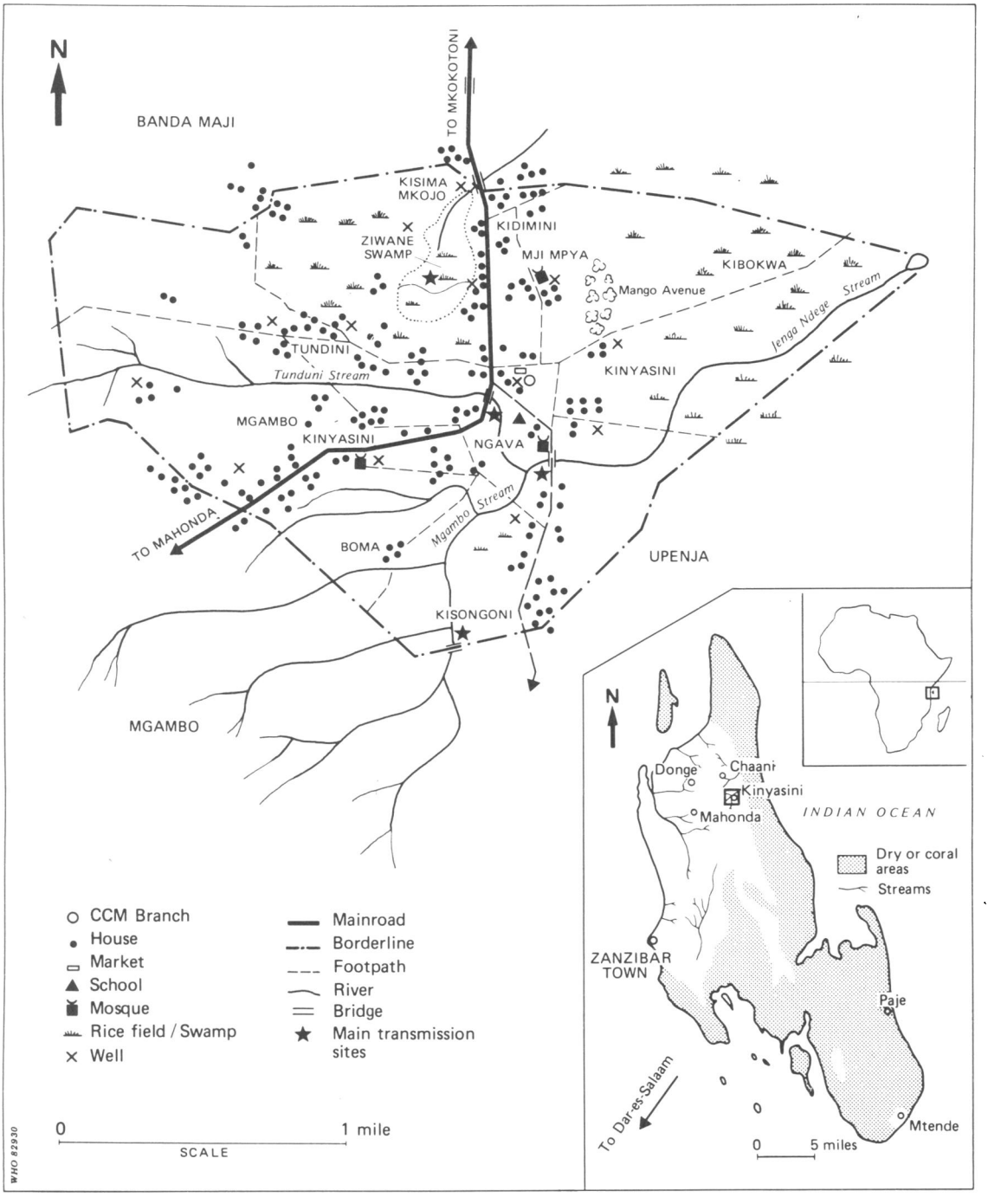

Table 1: **Age and sex distribution of the study population: cumulative summary of four surveys, Zanzibar, 1981–83**

Age group (years)	Male	Female	Total
0–4	334	325	659 (16.0)[a]
5–9	548	563	1111 (27.0)
10–14	404	287	691 (16.8)
15–24	289	319	608 (14.8)
25–44	297	303	600 (14.6)
⩾45	238	206	444 (10.8)
Total	2110	2003	4113

[a] Figures in parentheses are percentages.

Table 2: **Prevalence of *S. haematobium*, Zanzibar, 1981–83**

	No. examined	Egg-positives	Heavy infection[a]
Survey 1	2685	1324 (49.3)[b]	518 (19.3)
Survey 2	1887	751 (39.8)	254 (13.5)
Survey 3	2458	848 (34.5)	269 (10.9)
Survey 4	1719	398 (23.2)	126 (7.3)

[a] Heavy infection: ⩾50 eggs/10 ml of urine.
[b] Figures in parentheses are percentages.

area, i.e., the population structure stayed essentially the same. However, due to migration, the total number of people examined changed from survey to survey. Table 2 shows the number of people examined during each of the surveys, the overall prevalence rates and the prevalence rates for heavy infection (i.e., individuals with ⩾50 eggs/10 ml of urine); the number of people includes those who were new to the surveys.

Surveys

First survey (August 1981). During the first survey 2685 people were examined, of whom 1324 (49.3%) were positive and 518 (19.3%) were heavily infected. The highest prevalence of heavy infections was in the 10–14-year-old age group (203/672: 30.2%). There was no difference in infection between males and females ($P > 0.05$).

Second survey (August 1982). Twelve months after the first survey, 1887 persons were examined; 1420 (75.3%) had been present during the previous survey (survey 1) while 467 (24.7%) were new to the survey. Of the 1887 examined, 751 (39.8%) were infected, and 254 (13.5%) were found to be heavily infected. In this survey the group with the highest percentage of heavy infection was the 5–9-year-old group (104/383: 27.2%).

Third survey (April 1983). Eight months after the second survey 2458 individuals were examined, of whom 1342 (54.6%) had been present during the previous survey (survey 2) and 1116 (45.4%) were either new to the survey, or not present during the previous survey. Of the 2458 examined, 848 (34.5%) were found to be positive, and 269 (10.9%) were found to be heavily infected. The 5–9-year-old age group had the highest percentage of heavily infected individuals (147/687: 21.4%).

Fourth survey (August 1983). A total of 1719 individuals were examined during the fourth survey, held 4 months after the third survey. A total of 1416 (82.4%) had been present during the previous survey (survey 3) and 303 (17.6%) were either new to the survey or not present during the previous survey. Of the 1719 examined, 398 (23.2%) were found to be positive, and 126 (7.3%) were found to be heavily infected. Again, the 5–9-year-old group had the highest proportion of heavily infected individuals (78/541: 14.4%).

With assumptions about the study population stated previously, the overall reduction from survey 1 to survey 4 was 52.9% for the prevalence of positive (from 49.3% at survey 1 to 23.2% at survey 4, Table 2), and 62.2% for the prevalence of heavy infection (from 19.3% at survey 1 to 7.3% at survey 4, Table 2). Similar reductions in prevalence among men and women were observed ($P > 0.05$).

Changes between the surveys

People who were present at one survey, but absent at the previous survey were not included in the further analysis. Thus the data from only those individuals who were present at least on two consecutive surveys were analysed (Table 3) in terms of the overall prevalence rates, the prevalence rates for heavy infection, and the percentage reduction for the two prevalence rates.

Table 3: **Prevalence of *S. haematobium* in cohort present at consecutive surveys: reduction in overall prevalence and prevalence of heavy infection, Zanzibar, 1981–83**

	No. examined[a]	Egg positive		Heavy infection	
		No.	Reduction	No.	Reduction
Survey 2	1420	570 (40.1)[b]	17.8%	191 (13.5)	28.9%
Survey 3	1342	391 (29.1)	26.0%	117 (8.7)	31.0%
Survey 4	1416	303 (21.4)	40.9%	90 (6.4)	45.3%

[a] Number examined includes only those who were present at two consecutive surveys, i.e., the number for survey 2, 1420, includes those who were present at both survey 1 and survey 2.
[b] Figures in parentheses are percentages.

Survey 1 to survey 2. A total of 1420 persons were examined during both the first survey and the second survey 12 months later. Of these 693 (48.8%) were positive and 270 (19.0%) were infected heavily at the time of the first survey. Of the 693 positives from the first survey, 480 (69.3%) had a reduction in intensity of infection, of whom 330 (47.6%) had negative egg output at the second survey. These numbers include the population that was treated as well as those who were not treated after the first survey.

Survey 2 to survey 3. The number of people examined during both the second survey and the third survey 8 months later totalled 1342. Of these, 528 (39.3%) were positive and 169 (12.6%) were heavily infected at the time of the second survey. Of the 528, the intensity of infection was reduced in 395 (74.8%) and 326 (61.7%) had negative egg output by the third survey.

Survey 3 to survey 4. In all, 1416 persons were examined during both the third survey and the final survey 4 months later, of whom 513 (36.2%) were positive and 165 (11.7%) were heavily infected at the third survey. Of those infected, the intensity of infection was reduced in 411 (80.1%), of whom 345 (67.3%) were egg negative at the last survey.

Changes over 24 months (from survey 1 to survey 4). A total of 673 persons were examined in all four surveys; their age distribution is given in Table 4. The cohort was made up of 465 persons who were treated at least once during this period, most of them with at least 1 dose of metrifonate out of the recommended regimen of 3 doses. A total of 208 persons did not receive any treatment; these persons were negative or, if positive, refused treatment.

Out of the 673 persons, 32 (4.8%) were positive at each examination. All 32 individuals received at least one dose of metrifonate during the course of the study. The 5–9-year-old age group had the highest proportion of individuals who remained positive (15/152: 9.9%); only two persons, out of the 32, were 15 years or older.

It was noted that 85 individuals (12.6%) were positive in the first survey, became egg-negative after treatment, and then remained egg-negative throughout the rest of the study. The older age groups (≥15 years of age) had a higher proportion of individuals who were egg-negative and not tested positive compared to the younger age groups. In addition, the intensity of infection among these 85 individuals showed that while 19 (22.4%) of those initially positive were heavily infected, 66 (77.6%) were mild to moderately infected.

Table 4: **Age distribution of cohort examined in all four surveys**

Age group (years)	No.	No. positive in all 4 surveys	Initially positive, then always negative
0–4	112	6 (5.4)[a]	6 (5.4)
5–9	152	15 (9.9)	8 (5.3)
10–14	118	9 (7.6)	13 (11.0)
15–24	70	0 (0.0)	11 (15.7)
25–44	124	1 (0.8)	23 (18.5)
≥45	97	1 (1.0)	24 (24.7)
Total	673	32 (4.8)	85 (12.6)

[a] Figures in parentheses are percentages.

Compliance and conversion/reversion rates

Between 55% and 65% of those eligible for treatment took three doses of metrifonate at each survey (Table 5). The compliance rates at each survey were similar among persons with different levels of infection ($P > 0.05$). Also, there was no statistical difference in the compliance rate between the sexes or among different age groups ($P > 0.05$).

The rates of "conversion" (negative to positive in two consecutive surveys) and "reversion" (positive to negative, without a history of treatment) are summarized in Table 6. The conversion rates were highest (207/727: 28.5%) between survey 1 and survey 2. On the other hand, the reversion rates were highest (13/22: 59.1%) between survey 3 and survey 4.

Effect of treatment and age

Egg reduction rates (positive egg output that was changed to a reduced or negative egg output due to metrifonate chemotherapy), by dose, are summarized in Table 7. Those who took at least one dose of metrifonate during the first survey had a reduction rate of 78.4% (482 of 615), which includes those that became egg-negative. For the second and the third surveys, the reduction rates were 70% (343 of 491) and 80.4% (395 of 491), respectively.

The highest frequency of egg-negative counts after treatment were observed in the older age groups (over 15 years of age) and were found to be statistically significant (Table 8). Interestingly, similar trends in egg-negative rates were observed for the untreated group as well between surveys 2 and 3.

Other interventions

The data collected during the study did not include information on interventions other than chemotherapy which may have affected the level of morbidity in the study population. The impact of the health education activities was not assessed during this study.

Table 5: **Compliance rates for three doses of metrifonate in the study population**

	No. positive	No. who refused treatment	No. of doses received		
			1	2	3
Survey 1	1324	195 (14.7)[a]	97 (7.3)	167 (12.6)	865 (65.3)
Survey 2	751	73 (9.7)	99 (13.2)	165 (22.0)	414 (55.1)
Survey 3	848	69 (8.1)	83 (9.8)	209 (24.6)	487 (57.4)
Survey 4	No treatment records are available				

[a] Figures in parentheses are percentages.

Table 6: **Conversion/reversion of individuals who did not take any treatment**

	Survey 2	Survey 3	Survey 4
Conversion	207/727 (28.5%)	189/814 (23.2%)	135/903 (15.0%)
Proportion with heavy infection[a]	101/207 (48.8%)	42/189 (22.2%)	26/135 (19.3%)
Reversion	33/78 (42.3%)	16/37 (43.2%)	13/22 (59.1%)
Proportion with mild/moderate infection[b]	24/33 (72.7%)	14/16 (87.5%)	12/13 (92.3%)

[a] Heavy infection: ⩾50 eggs/10 ml of urine.
[b] Mild/moderate infection: less than 50 eggs/10 ml of urine.

Table 7: **Egg-reduction rates according to dosage of metrifonate: all infections and heavy infections (⩾50 eggs/10 ml urine)**

	Survey 1–2 (12 months)		Survey 2–3 (8 months)		Survey 3–4 (4 months)	
Doses	No.[a]	%	No.[a]	%	No.[a]	%
All infections:						
0	33	42.3	22	59.5	16	72.7
1	30	57.7	45	70.3	30	78.9
2	80	79.2	93	78.2	93	75.6
3	372	80.5	205	66.6	272	82.4
	$P<0.05$[b]		N. S.[b]		N. S.[b]	
Heavy infections:						
0	19	24.4	4	10.8	2	9.1
1	11	21.2	11	17.2	7	18.4
2	30	29.7	29	24.4	33	26.8
3	152	32.9	89	28.9	85	25.8
	$P<0.05$[b]		$P<0.05$[b]		N. S.[b]	

[a] Numbers include those that are egg-negative.
[b] Chi-square test for binomial trends. N. S. = not significant.

Table 8: **Egg-negative rates for those treated with at least one dose of metrifonate and those untreated**

Age group	Survey 1–2 (12 months)		Survey 2–3 (8 months)		Survey 3–4 (4 months)	
(years)	No.	%	No.	%	No.	%
Treated:						
0–4	24	55.8	30	58.8	25	65.8
5–9	63	34.4	66	43.7	142	58.9
10–14	62	43.4	46	53.5	89	69.0
15–24	47	53.4	61	78.2	35	85.4
25–44	51	63.8	60	82.2	20	100.0
⩾45	50	64.1	47	90.4	21	95.5
Total	297	48.3	310	63.1	332	67.6
		$P<0.001$[a]		$P<0.001$[a]		$P<0.001$[a]
Untreated:						
0–4	0	0.0	2	33.3	2	66.7
5–9	7	43.8	1	14.3	1	25.0
10–14	11	36.7	3	33.3	1	25.0
15–24	3	30.0	3	50.0	6	100.0
25–44	9	69.2	3	75.0	2	66.7
⩾45	3	50.0	4	80.0	1	50.0
Total	33	42.3	16	43.2	13	59.1
		N. S.[a]		$P<0.025$[a]		N. S.[a]

[a] Chi-square test for binomial trends. N. S. = not significant.

No data were collected on the use of the new wells or the change in behaviour attributable to the availability of wells in the study area. However, at the outset of the project there were only three wells in the study area and by August 1983 there were eight. All the new wells were constructed by their owners, who recognized the benefits of washing clothes and drawing water at a distance from the streams. In addition, although molluscicide was carried out twice in 1983, observations on snail host population density, prior to and after application, were not specifically recorded.

Discussion

In this study, selective population chemotherapy with metrifonate was shown to reduce the prevalence and intensity of infection due to *S. haematobium* over a 24-month period in a community on the island of Zanzibar. The operational target of at least 50% reduction in prevalence was achieved. However, heavy infections were reduced by 62% rather than the projected 75%. In all previous reports, metrifonate has been shown to be less efficacious against heavy infections than light infections. The explanations for these observations have ranged from a partial effect of the drugs on the adult worm to the variation in transmission intensity. As noted from the initial trials (*12*) of metrifonate some persons continued to be heavily infected after treatment. Using selective population chemotherapy at 10 mg/kg body weight, selective molluscicide, and modification of the snail habitats by a self-help programme, Rugemalila & Eyakuze observed even higher egg-negative rates (69% at 6 months and 67% at 12 months) in mainland Tanzania (*13*).

The data collected during the study do not lend themselves to rigorous analysis. The study was not designed to obtain information on a cohort in different surveys. The detailed information needed on individuals is difficult to collect and is often beyond the objectives or capabilities of a control programme. Certain comparisons, however, can be made, bearing in mind the limitations of the study design.

The assumption of a high level of reinfection in the study population is supported using the conversion/reversion ratio suggested by Jordan (*14*). We observed an increasing proportion of negative-to-positive conversion as the interval of evaluation increased. This is further substantiated by the parallel increase in proportion of those acquiring heavy infections. On the other hand, the recognized fluctuation in low egg counts over short periods of time is confirmed by the highest rate of reversion at the 4-month interval. As the period of observation got longer, the rates of conversion and reversion became closer. However, this observation must be qualified by stating that the observation periods were conducted at different times of the year, i.e., there may have been an effect on the rates of conversion and reversion due to seasonality of transmission.

The 40% rate of spontaneous occurrence of negative egg counts in untreated persons was similar to that observed by Rugemalila & Eyakuze (*13*). As suggested by them, we observed that these "spontaneous cures" were associated with initially low egg counts and hence were probably due to the short-term variability of urinary egg excretion. In our study area the high rate of reversion to negative egg counts after the 4-month interval may also have been due to low transmission during that period (April to July) and the higher proportion of persons with initially low counts. The timing of chemotherapy to correspond with the projected transmission cycle has been advocated (i.e., treatment should be given ideally immediately after peak transmission) to ensure the longest possible period without reinfection before retreatment. This hypothesis has never been fully tested.

We also observed that the age group with the highest prevalence changed during the course of the study. At the first survey the expected peak in the 10–14-year-old age group was observed. In subsequent surveys, the lowest egg-negative rates and the highest proportion of the heavy infections were observed in the 5–9-year-old age group. This change may be due, in part, to the age-dependent immunity proposed by Wilkins et al., who observed that the prevalence in the 5–9-year-olds in their study had a higher prevalence at 3 and 15 months after treatment with praziquantel and that the geometric mean egg counts ($\log_{10}(n+1)$) were proportionally higher after treatment at the same intervals (*15*). This reinforces the necessity to plan the most appropriate interval to treat children in the early phases of large-scale treatment programmes.

The egg-negative rates, resulting after treatment with metrifonate, increased as the intensity of infection decreased in the course of the study and also as the interval of evaluation decreased. These observations are consistent with those made in endemic areas of *S. haematobium* in Tanzania and elsewhere. Among those that were treated at least once, the egg-negative rates were found to be related to age ($P < 0.001$ for surveys 2 to 4, using the test for binomial trend). Among those that were not treated at all, only survey 3 had a statistically significant relationship between the egg-negative rate and age ($P < 0.05$). Furthermore, even with the full regimen of three doses of metrifonate, some people became more intensely infected in the subsequent survey. The increase in intensity of infection was mostly in the group that was mildly infected (1–9 eggs/10 ml urine) and in the younger age group (between 5 and 14 years of age).

In the cohort which participated throughout all surveys, it was observed that those whose infections were of low intensity at the first survey, tended to remain egg-negative throughout the period of observation. Since most of these persons were in the older age groups, this supports the operational approach of treating adults at intervals of two or more years and targeting school-aged children for more frequent screening and treatment. However, individuals with infections, initially of high intensity, had a less pre-

dictable outcome. This observation has public health relevance in that when operationally and logistically feasible, heavily infected individuals or communities with a high proportion of heavily infected persons (probably greater than 10%) should be reexamined at relatively short intervals and retreated if necessary in the early stages of the control activities.

A number of studies have utilized single-dose metrifonate chemotherapy with success (*6*, *16*), while others have reported a relationship between the number of doses given and the rate of cure; higher cure rates usually correlate with an increased number of doses. In our study, only a weak correlation between efficacy (egg-negative rate and egg-reduction rate) and dosage was found. Davis & Bailey (*12*) stated that there was a non-linear relationship between the number of doses and cure rates. Sato et al. (*7*) have shown that the cure rate and percentage reduction of mean egg output were significantly lower in groups with fewer doses. In this study, however, a statistically significant relationship between the number of doses and efficacy existed only during some of the surveys (Table 7). The number of doses was significantly related to the egg-reduction rates between survey 1 and survey 2 ($P < 0.05$), for both the "all infected" cohort and the "heavily infected" cohort. The "heavily infected" cohort also had a statistically significant relation between doses and egg-reduction rates between survey 2 and survey 3 ($P < 0.05$). There was no statistically significant relationship between the number of doses and the egg-negative rates.

Metrifonate has been widely used because of its low cost and relative lack of adverse side-effects. However, because the recommended treatment with metrifonate requires three doses for the complete regimen, the cost of drug delivery, compared to a single-dose drug (e.g., praziquantel), has been shown to be rather high (*17*). As a method of minimizing the cost of delivery, many researchers have been looking at the efficacy of a reduced number of metrifonate doses given at more frequent intervals. In Burkina Faso, two doses of 7.5 mg/kg body weight were given 2-weeks apart three times in one year to schoolchildren with a resulting 85% cure rate (*18*). This approach has not yet been tested on a large scale and the possible changes in the cost of drug delivery have not been estimated, but they would probably be considerable.

Although the improvements in the water supply were welcomed by the residents, the incorporation of safe water projects within schistosomiasis control programmes need to be analysed in greater detail. Economic as well as epidemiological benefits and costs of water projects must be examined carefully to maximize the benefits of schistosomiasis control programmes.

The effectiveness of molluscicide could not be assessed during this study. As emphasized by previous consultants to the Ministry of Health, molluscicide was not feasible until the geographical limits of transmission sites could be determined.[a] It was assumed that this might be possible after chemotherapy had reduced both prevalence and intensity to low levels and the water contact patterns of those remaining infected or those acquiring new infections could be elucidated. This approach is now being tested on the island of Pemba, north of Zanzibar.

The results of this study have shown that selective mass chemotherapy, using metrifonate, is an effective method of reducing morbidity due to *S. haematobium* infection. Furthermore, the fact that there was a lack of correlation between the number of doses taken and the rate of reduction in intensity in some of the surveys suggests that other factors may be influencing the rate of reduction; if so, they remain to be determined with rigour.

[a] **McCullough, F.S. & Kraft, R.J.G.** *Site visit to Zanzibar.* Unpublished report to the WHO Regional Office for Africa, AFR/SCHIST/34, 1976.

Acknowledgements

The authors are grateful for the support of the Ministry of Health of Zanzibar, especially to Mr Ali Mohamed Shoka, Deputy Minister of Health at the time the project was initiated. All the field work was undertaken by Mr Ameir Khamis, Health Officer, Mr Abdul-Rahaman, Assistant Health Officer, and Mr Issa Haji Ameir, Mr Hassan Ali and Mrs Maulid Soud, microscopists; Mr Hassan Ali and Mrs Dude Mwatabu, laboratory assistants; and Mr Abdullah Shamte and Mr Ame Mussa, drivers. Hamad A.J. Haji of the Ministry of Health and Miss Patricia A. Tschida, U.S. Peace Corps volunteer, assisted the team during some of the surveys.

Financial support was provided by the World Bank/UNDP/WHO Special Programme for Research and Training in Tropical Diseases (TDR). Special thanks are due to Dr A.O. Lucas, Director of TDR at the time, who innovatively and actively supported the idea of this operational project.

Résumé

Le métrifonate dans la lutte contre la bilharziose schistosomiase urinaire à Zanzibar

Cette étude décrit l'efficacité d'une chimiothérapie sélective appliquée à la totalité d'une communauté du district de Kinyasini, à Zanzibar, République-Unie de Tanzanie, en utilisant trois doses de métrifonate (7,5 mg/kg de poids corporel chaque fois), à deux semaines d'intervalle. Le but

de l'étude était de réduire la prévalence des fortes infestations (⩾ 50 œufs de *S. haematobium* pour 10 ml d'urine) de 75% en deux ans, et de réduire la prévalence globale de l'infestation de 50% en deux ans.

Au total, 4113 personnes ont été examinées au moins une fois pendant la période de deux ans. Lors de la première enquête (août 1981), 1324 personnes sur 2685 (49,3%) étaient infestées, et 518 (10,3%) étaient fortement infestées. La prévalence la plus élevée d'infestation a été observée dans le groupe d'âge 10–14 ans. Lors de la seconde enquête (août 1982), 12 mois après la première, 751 personnes sur 1887 (39,8%) étaient infestées, et 254 (13,5%) étaient fortement infestées. Dans cette enquête, le groupe ayant le plus fort pourcentage d'infestation était le groupe 5–9 ans. Lors de la troisième enquête (avril 1983), huit mois après la deuxième, 848 individus sur 2458 (34,5%) étaient infestés et 269 (10,9%) étaient fortement infestés. Le groupe d'âge 5–9 ans était celui ayant le pourcentage le plus élevé d'individus infestés (21,4%). Lors de la quatrième enquête (août 1983), quatre mois après la troisième, 398 individus sur 1719 (23,2%) étaient positifs et 126 (7,3%) étaient fortement infestés. A nouveau, le groupe d'âge 5–9 ans avait la proportion la plus élevée d'individus infestés (14,4%). Dans toutes les enquêtes, le groupe d'âge ayant la proportion la plus élevée d'individus fortement infestés était le groupe 5–9 ans. La réduction globale de la prévalence de l'infestation entre l'enquête 1 et l'enquête 4 était de 52,9% et la prévalence des fortes infestations a été réduite de 62,2%.

Les taux de conversion (négatifs à positifs dans deux enquêtes consécutives) étaient les plus élevés pendant la période la plus longue, de 12 mois, et les taux d'inversion (positifs à négatifs dans deux enquêtes consécutives, sans antécédent de traitement) étaient les plus élevés dans l'intervalle de 4 mois.

Sur 673 personnes suivies pendant la durée de l'étude, 32 (4,8%) sont restées positives pendant l'étude entière; 85 personnes (12,6%) qui étaient positives dans la première enquête sont devenues négatives dans la seconde enquête et le sont restées pendant tout le reste de l'étude.

Certaines relations, statistiquement significatives, ont été observées entre le nombre de doses et les taux de réduction des œufs. Cependant, pour les taux négatifs, aucune relation statistiquement significative n'a été observée. Entre 55% et 65% des sujets justiciables du traitement ont pris trois doses de métrifonate lors de chaque enquête. Chez les personnes qui avaient pris au moins une dose, et pour l'intervalle de 12 mois, un taux de négativité de 48,3% a été observé. Les taux les plus élevés de numération négative d'œufs ont toujours été observés chez des personnes de plus de 15 ans, dans les deux cohortes de personnes traitées et non traitées. Dans cette étude, une chimiothérapie sélective appliquée à l'ensemble d'une population avec du métrifonate s'est montrée efficace pour réduire la prévalence et l'intensité de l'infestation à *S. haematobium* pendant une période de 24 mois.

References

1. WHO Technical Report Series No. 728, 1985. (*The control of schistosomiasis*: report of a WHO Expert Committee).
2. **Feldmeier, H. & Doehring, E.** Clinical experience with metrifonate. *Acta tropica*, **44**: 357–368 (1987).
3. **Tswana, S.A. & Mason, P.R.** Eighteen-month follow-up on the treatment of urinary schistosomiasis with a single dose of metrifonate. *American journal of tropical medicine and hygiene*, **34**: 746–749 (1985).
4. **King, C.H. et al.** Chemotherapy-based control of schistosomiasis haematobia. I. Metrifonate versus praziquantel in control of intensity and prevalence of infection. *American journal of tropical medicine and hygiene*, **39**: 295–305 (1988).
5. **Arap Siongok, T.K. et al.** Quantification of infection with *Schistosoma haematobium* in relation to epidemiology and selective population chemotherapy. II. Mass treatment with a single oral dose of metrifonate. *Journal of infectious diseases*, **133**: 856–858 (1978).
6. **Kholy, A.E. et al.** The effect of a single dose of metrifonate on *Schistosoma haematobium* infection in Egyptian schoolchildren. *American journal of tropical medicine and hygiene*, **33**: 1170–1172 (1984).
7. **Sato, K. et al.** Efficacy of metrifonate in a highly endemic area of urinary schistosomiasis in Kenya. *American journal of tropical medicine and hygiene*, **38**: 81–85 (1988).
8. **Diallo, S. et al.** Efficacité de 3 cures de metrifonate dans le traitement de la bilharziose urinaire au Senegal. *Dakar médical*, **28**: 67–76 (1983).
9. **Petrie, J.** Bilharzia haematobia. *Lancet*, **2**: 133–134 (1903).
10. **Forsyth, D.M. & Rashid, C.** Treatment of urinary schistosomiasis: practice and theory. *Lancet*, **1**: 130–133 (1967).
11. **Forsyth, D.M. & Rashid, C.** Treatment of urinary schistosomiasis with trichlorophane. *Lancet*, **2**: 909–912 (1967).
12. **Davis, A. & Bailey, D.R.** Metrifonate in urinary schistosomiasis. *Bulletin of the World Health Organization*, **41**: 209–224 (1969).
13. **Rugemalila, J.B. & Eyakuze, V.M.** Use of metrifonate for selective population chemotherapy against urinary schistosomiasis in an endemic area of Mwanza, Tanzania. *East African medical journal*, **58**: 37–43 (1981).
14. **Jordan, P.** *Schistosomiasis—the St. Lucia project.* Cambridge, Cambridge University Press, 1985.

15. **Wilkins, H. et al.** Resistance to reinfection after treatment of urinary schistosomiasis. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, **87**: 29–35 (1987).
16. **Pugh, R.N.N. & Teesdale, C.H.** Long-term efficacy of single-dose oral treatment in schistosomiasis haematobium. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, **78**: 55–59 (1984).
17. **Korte, R. et al.** Cost and effectiveness of different approaches to schistosomiasis control in Africa. *Tropical medicine and parasitology*, **37**: 149–152 (1986).
18. **Druilhe, P. et al.** Essai de contrôle de la bilharziose urinaire par 3 cures annuelles de metrifonate. *Annales de la Société belge de Médecine tropicale*, **61**: 99–109 (1981).