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Prolonged Observation of Schistosoma Mansoni Infections in Patients Subjected to Repeated Courses of Chemotherapy

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Introduction.

In all types of chemotherapeutic trials one reads of persons who are not cured of their infection by the agent being tested. In fact, it is on a favourable ratio of "cured" patients to those who are not cured, that, in the final analysis, the success or otherwise of a new drug is measured.

Rarely does one read of efforts to study why a drug should fail to cure some people of an infection while other people in the same population group are apparently satisfactorily cured. This is, however, a really serious problem encountered in trials of new chemotherapeutic agents against bilharziasis.

A number of factors which might explain this difference in reaction to a drug are fairly well known although the explanation of why these differences should occur, are not clear.

It may be useful to discuss some of these matters briefly:

1. *Dose of Drug*:

Using standard doses of drugs for routine treatment of patients suffering from bilharziasis takes no account of the intensity of the infection which is, presumably, governed by the number of paired worms present in the egg-laying sites. Does the standard dose destroy the ovaries of, say, 100 female worms, halting egg-laying and resulting in the eventual death of the worms, but leave unharmed the ovaries of a further 100 worms? Or does the standard dose merely interfere temporarily with the ovarian function of all 200 female worms which in due course recover their full function and reach their previous egg-laying level? Workers have attributed failure of a drug in a particular case to a heavy infection. Lees (1968) has recorded that in St. Lucia the only subjects who were "parasitologically cured" following a "suppressive management" trial with lucanthone hydrochloride were children with initial *Schistosoma mansoni* egg counts of less than 10 000 eggs in a whole stool and with a few *S. mansoni* worms. In other children, while egg output was reduced all still had active infections.

2. *Age and size of patient*:

Children seem to be able to tolerate schistosomicidal drugs far better than adults. This observation has been recorded with antimonials and the newer agents. Using a "straight line" dose/weight scale usually results in a lower cure rate in children than in adults. In trials with niridazole (Clarke and Blair 1969) a dose/weight scale for children and adults ranged from 40 mg/kg at 20 kg down to 30 mg/kg at 50 kg weight. The latter dose was maintained for persons up to 73 kg weight and the upper dose limit of one gram niridazole twice daily for six days was maintained, even for persons weighing as much as 90 kg or more. Such a dosage scheme, which is widely used in Rhodesia, achieves much better cure rates in children than the officially recommended dose of 25 mg/kg. The drug package size indicates that a maximum of 20 tablets be given at the rate of three tablets a day for six days, however heavy the patient.

In our experience children taking 40 mg/kg tolerate the drug very well, and perhaps, as was suggested in the above quoted paper, an even higher dose level might be more successful. Children have a larger and more efficient liver compared with their body weight, than have adults, and because of this they may be able to metabolise and remove a schistosomicidal drug from the circulation faster and more efficiently.

3. *The difference in cure response between S. haematobium and S. mansoni infections in the same patients*:

It is now a well recognised fact that it is much easier to cure *S. haematobium* infections than *S. mansoni*. The efficiency of the modern drugs is such that follow-up parasitological examinations 6-8 weeks after treatment is hardly necessary as a routine procedure in urinary infections. Either *S. haematobium* worms are more susceptible to drug action than are *S. mansoni* worms, or they are generally located at an egg-laying site which receives a higher blood concentration of the circulating drug. *S. haematobium* female worms produce far larger numbers of eggs than do the females of *S. mansoni*, and this may mean that the reproductive mechanism of the former species is more easily destroyed by drugs.

4. *The potentiation of drug action by acquired resistance of the host*:

The importance of the previous history of the patient in respect of bilharziasis has perhaps not been fully realised in the past. If acquired resistance can play a role in improving the therapeutic efficiency of a drug then presumably persons who have had an infection for a number of years would react more favourably to the administration of a drug. This possibility may also have some bearing in the observed poor therapeutic response to drugs by children.

5. *Treatment given during the invasion (schistosomula) phase*:

When viable eggs are found in the excreta it is sometimes forgotten that at the same time cercariae may have entered the body of the host at a later date and that at the time of treatment these could still be in the schistosomula stage or be young, unmated and sexually immature worms. The exhibition of a drug would not be so likely to affect the viability of the sexually immature females and these might develop to full maturity and mate and lay eggs long after the drug has been removed from the body. This may be an explanation why the initial dose of a drug generally causes a substantial reduction in egg output and an improvement in the patient's well-being, but that eggs continue to be secreted, albeit in much fewer numbers. A more sobering thought is that perhaps the schistosomulae and immature worms not destroyed by the drug may acquire a tolerance of or a resistance to further courses of treatment. It is interesting to note that Diaz-Rivera *et al.* (1957), and more recently Clarke *et al.* (1970) have expressed doubts as to the advisability of treating bilharziasis in the early acute stage. The latter workers have referred to the generally poor results obtained in a series of Katayama syndrome cases of acute *S. mansoni* bilhaziasis who were treated as soon as their infection was diagnosed by finding eggs in the stool.

METHOD.

Two young African males, brothers, Foster and Town Mavida, who were found to have infections with *S. haematobium* and *S. mansoni*, were observed as a daily routine five days a week for eight months in respect of F.M. and 15 weeks in respect of T.M., for the presence, number and hatchability of schistosome eggs before being given specific treatment. During these periods neither subject was exposed to further schistosome infection. F.M. had not received any previous specific therapy for bilharziasis, but T.M. had been given one gram of niridazole once a week for ten weeks followed by a five-week period of observation. They were blood brothers and had previously lived in the same village 100 miles north of Salisbury. Previous observations on F.M. are contained in Blair *et al.* (1969 a and b) and in Blair and Weber (1973) for T.M. The same standard examination and counting of eggs in the mid-day terminal urine was dis-

continued after the first treatment. The initial treatment caused the disappearance of urine eggs in each case. However, irregular checking for eggs in the urine was carried out on both subjects for many months after treatment without any evidence of a remaining active infection being found. The stool examinations which have been described by Blair *et al.* (1969a) involved the examination of two samples a day, five days a week, and an egg estimate and assessment of miracidial hatching was made on each specimen. In order that the results could be compared one with the other a weekly *S. mansoni* egg estimate, which was the total of all eggs in the daily specimens estimated on 0,05 ml of centrifuged deposit, and a weekly miracidia hatching estimate based on the sum of the highest of each of the three days of observation of each specimen, was prepared. Estimates of miracidial hatching after treatments administered to F.M. from 11th July, 1968, to 15th March, 1969, have already been recorded in the paper Blair *et al.* (1969b). In this paper, however, a different method of recording the results was used; namely to record only the maximum miracidial hatch estimate obtained after observation for 50 hours of each sample.

The method employed in the present paper was to record the maximum miracidia hatch rating on *each* of the first, second and subsequent days of observation, and summing these on a weekly basis. This method is thought to give a more sensitive index of miracidia hatching after treatment when eggs and positive hatching observations are few in number.

The results of the long-term follow-up of Foster Mavida:

Table I summarises the weekly egg estimations and miracidial hatchings over 113 weeks from July, 1968, to October, 1970. During the whole period F.M. was away from Salisbury for only two periods — for six weeks over Christmas, 1968, and five weeks in June-July,

Table I.

WEEKLY TOTALS OF EGG ESTIMATION AND MIRACIDIAL HATCHING: FOSTER MAVIDA: JULY, 1968, TO SEPTEMBER, 1970.

Week	Weekly egg estimates	Weekly miracidia hatch	Week	Weekly egg estimates	Weekly miracidia hatch	Week	Weekly egg estimates	Weekly miracidia hatch
10-7-68 hycanthone		Wt. 60 kg 200 mg	25	On vacation six days Christmas		71	10	6
						72	10	9
1	1 320	22	26	400	23	73	30	6
2	1 540	51	2-1-69 hycanthone	Wt. 59,5 kg 200 mg		74	40	18
3	220	23	27	550	41	75	10	11
4	20	16	28	350	28	76	50	14
5	40	19	29	30	17	77-78	Christmas holidays	
6	30	15	30	40	16			
7	60	11	31	120	23	79	40	6
8	80	18	32	300	23	80	20	7
9	320	24	33	310	24	81	0	5
10	100	9	34	270	23	82	40	6
11	260	28	35	330	18	83	20	7
12	340	29	36	60	11	84	30	7
			Niridazole: 1 g twice daily for six days 10-15 March, 1969 Wt. 60 kg			85	0	9
2-10-68 hycanthone		Wt. 59,5 kg 200 mg				86	0	3
						Niridazole: 1 g twice daily for six days 23-28 February, 1970 Wt. 60,9 kg		
13	270	19						
14	460	25						
15	80	16	37	40	4	87-101	0	0
16	10	2	38-40	0	0	102-5	on leave	
17	40	12	41	10	0	106-18	0	0
18	100	17	42	10	0	27-10-70	Wt. 60,9 kg	
19	220	7	43-60	0	0			
20	550	26	61-66	No examinations				
21	480	22	67	0	3			
22	600	32	68	20	5			
23	200	19	69	0	7			
24	360	23	70	20	2			

1970. In 1968 it was feared that he might be re-infected while on vacation at home so he was given detailed instructions to not swim in rivers and not wash except in water which had been heated. On his return from leave it was learnt that since he had left home his village was now supplied with water from a bore-hole, so that it is most unlikely he could have been re-infected. During his home leave in 1970 the weather was at its coldest, so there would be no temptation to swim or bathe in the rivers. The table shows the general trend of the weekly egg and miracidia hatch totals after each treatment. It will be seen that, in fact, there was no week when no eggs were seen and no miracidia hatched after three treatments with hycanthone (Etrenol (R) Winthrop). Complete clearance of eggs and miracidia was not observed until the 38th to 40th week beginning 14 days after the commencement of a six-day course of niridazole (Ambilhar (R) CIBA). Unfortunately, owing to other commitments it was necessary to discontinue for six weeks the regular routine of stool examinations, but in the 67th week a very scanty miracidia hatch total was recorded. In view of the low egg counts and the scanty miracidia hatching recorded it was hoped that F.M.'s infection might die out without further treatment, but a long period of observations indicated that eggs and miracidia continued to be produced at a very low level. A fifth course of treatment, namely a second course of niridazole, was given from 23rd to 28th February, 1970. No eggs or miracidia were seen after the completion of the course to the end of the daily observation period on 9th October, 1970. Thereafter stool specimens were examined for five days (one week) each month, but no eggs were seen or miracidia hatched, for a further five months observation.

It should be recorded that the three hycanthone treatments caused no toxic side effects other than slight nausea in the evening after the second treatment and vomiting after the evening meal on the day of the third injection. During the fourth treatment when niridazole was administered, he had some abdominal pain only, and continued with his duties. During the fifth treatment with niridazole he experienced joint pains and was unable to work on the fourth day of treatment. In July, 1968, his weight was 60 kg and there was little change in weight each week until after the fifth course of treatment. In October, 1970, his weight was 65,6 kg.

It is, perhaps, more interesting to observe the cessation of miracidial hatching after each treatment on a daily basis to see how long after treatment it was to the first day when no miracidia were observed. This can be summarised as follows:

First hycanthone injection — 15 days.

Second hycanthone injection — 16 days.

Third hycanthone injection — no cessation of hatching.

First niridazole — 8 days from commencement of treatment.

Second niridazole — 4 days from commencement of treatment.

The results of the long-term follow-up of Town Mavida:

The results of the follow-up of T.M. are summarised in Table II. During the first ten weeks it will be seen that the administration of one gram of niridazole once a week had little impact on egg output and miracidial hatching except perhaps the reduction of eggs during the fourth week to less than half the usual number. After five more weeks of observation it was clear that the egg output and miracidial hatching had not been much affected by the ten weekly doses of niridazole (Blair and Weber 1973)..

T.M. did not leave Salisbury for the whole time of observation from January, 1969, to December, 1970, so that there was no possibility of re-infection in this case.

There was no week after the first two treatments with hycanthone (Etrenol (R) Winthrop) when no eggs or miracidia were seen. After the third treatment with niridazole from 11th to 16th August it will be seen that no miracidia were seen in the 34th to 39th weeks inclusive, and the weekly egg counts had been very much reduced. However, from the 40th to the 58th week eggs and/or miracidia were seen every week. The fourth treatment again with niridazole, was given from 23rd to 28th February, 1970, and eggs and miracidia were not seen during the 62nd week, but thereafter returned. The fifth treatment with hycanthone was given on 11th May, and supplemented with 100 mg oral hycanthone (Winthrop 24, 933-2) on 19th and 25th May. Only the 73rd and 74th weeks were free from eggs and miracidia hatching. The patient experienced no side-effects at all after the hycanthone injections and the doses of oral hycanthone. During the first two courses of niridazole treatment he had the usual complaints of abdominal tenderness and joint pain, but he also suffered a brisk epistaxis on the third day of each course.

After a prolonged period of observation of 15 months, he was given a sixth and final treatment on 17th August, 1970: this was an intravenous injection of 60 mg (one grain) of sodium antimony tartarate, and on that day a course of treatment with niridazole, one gram twice a day for six days, was started. The treatment was abandoned when he fainted and

REPEATED TREATMENT

Table II.

WEEKLY TOTALS OF EGG ESTIMATION AND MIRACIDIAL HATCHING: TOWN MAVIDA: 13TH JANUARY, 1969, TO 5TH NOVEMBER, 1971.

Week	Weekly egg estimates	Weekly miracidia hatch
1	2 550	59
2	2 770	67
3	1 400	56
4	1 090	48
5	4 840	70
6	3 640	55
7	3 920	55
8	3 150	51
9	2 260	53
10	2 950	62
1 g each Wednesday 1-10 niridazole		
11	2 300	55
12	1 890	34
13	2 240	41
14	1 550	51
15	3 240	63
16	2 930	57
30-4-69 Wt. 62,7 kg hycanthone 190 mg		
17	1 640	56
18	150	18
19	10	1
20	50	17
21	30	12
22	180	36
23	350	34
24	450	34
30-6-69 Wt. 65,9 kg hycanthone 200 mg		
25	590	44
26	370	33
27	10	4
28	20	9
29	100	24
30	140	31
niridazole, 1 g twice daily for six days 11-16 August, 1969 Wt. 67,3 kg		
31	160	26
32	80	15
33	0	2
34-35	0	0
36	10	0
37-39	0	0
40	0	2
41	10	0
42	0	5
43	30	6
44	0	3
45	10	4
46	0	8
47	40	13
48	50	10
49	20	12
50-51	Christmas	
52	30	11
53	0	6
54	40	9
55	60	11
56	0	13
57	10	7
58	20	6
niridazole, 1 g twice daily for six days 23-28 February, 1970		
59	0	6
60	10	5
61	0	1
62	0	0
63	30	3
64	40	13
65	40	9
66	60	15
67	90	14
68	10	14
69	40	21
11-5-70 Wt. 70,0 kg hycanthone 200 mg		
70	10	9
71	100	16
72	10	1
73-74	0	0
75	10	3
76	20	10
77	70	12
78	0	4
79	40	17
80	80	16
81	30	13
82	50	22
83	10	17
84	40	19
85	20	18
86	40	14
87	40	17
88	40	17
89	80	17
90	50	9
91	60	10
92	30	19
93	30	19
94	30	12
95	60	6
96	80	9
97	20	17
98	10	14
99	60	15
100	30	15
16-12-70 Wt. 67,3 kg		

	Average Weekly egg estimates	Average weekly hatch
101-134	40	15
17-8-71	60 mg S.A.T. once and 1 g Niridazole twice daily for 3½ days	
135	0	3
136	0	9
137-146	0	0
10-11-71 Wt. 69,0 kg		

had a convulsion after seven doses. He made a quick recovery and was back at work two days later. The passage of eggs and hatching of miracidia ceased 11 days after the commencement of treatment, and none observed for the rest of the follow-up period.

In January, 1969, his weight was 62,7 kg and reached a peak of 70,9 kg at the end of October, 1969, but a year later in October, 1970, his weight had fallen to 67,3 kg and in August, 1971, his weight was still at this level.

Observation of the cessation of miracidial hatching after each treatment to see how many days elapsed after treatment was given, to the first day when no miracidia were observed, is summarised as follows:

(a) 10 weeks of a single weekly dose of niridazole — no cessation of hatching.
(b) First hycanthone injection — 16 days.
(c) Second hycanthone injection — 18 days.
(d) First niridazole — 14 days from commencement of treatment.
(e) Second niridazole — 7 days from commencement of treatment.
(f) Third hycanthone injection supplemented by two weekly doses of 100 mg each of oral hycanthone — 14 days from injection.
(g) 60 mg SAT and three and a half days niridazole — 11 days after commencement of treatment.

Discussion.

In the case of Foster Mavida, it required five full courses of treatment to cure his *S. mansoni* infection and the daily follow-up examination of his stool specimens for five months show that he is, in fact, cured. In his case, further follow-ups for five days in one week in each month have been continued for a further five months, but it seems unlikely that in the absence of opportunities for re-infection that any further evidence of *S. mansoni* bilharziasis will be found.

In the case of Town Mavida five full courses of treatment have failed to cure his *S. mansoni* infection. The first full course of treatment using a single intramuscular injection of hycanthone on 30th April, 1969, produced a great reduction in egg excretion and miracidia hatching, but despite two further treatments with hycanthone and two of niridazole, he continued to pass a few *S. mansoni* eggs in the stool, and miracidia hatched more frequently. As an example, on the five days, 2nd to 6th August, 1970, two specimens were examined from each morning stool, ten specimens in all. Eggs of *S. mansoni* were seen microscopically in only three specimens, but miracidia were hatched from all of the ten specimens.

It may be of interest to compare the total egg count and miracidia hatch for the first fifteen weeks; prior to the treatment with hycanthone on 30th April, 1969, with the findings for 15 weeks of observation — 7th September to 18th December, 1970. In the first period 42 720 *S. mansoni* eggs were estimated, and miracidial hatchings 877 as compared with only 660 eggs and 210 hatchings in the 86th to 100th weeks of observation. Further observations on the same basis for the 101st to 133rd week, 21st December, 1970, to 6th August, 1971, totalled 1 320 eggs and 493 hatchings. During this time there were only two weeks during which not a single egg was seen, but miracidia were hatched each week, and, in fact, only 29 specimens in a total of 324 stool specimens studied over the period of 33 weeks showed no miracidial hatch. This would seem to indicate that in a period of over a year there has been no improvement whatsoever in the number of eggs passed in the stool or in the amount of miracidial hatchings observed. Furthermore, snails have been infected with miracidia passed by the patient during January, 1971; from these snails Mastomys and hamsters were infected, and numbers of *S. mansoni* adults were recovered on perfusion of these animals proving that his infection is not only still active, but is well able to reproduce a cycle of infection in experimental animals.

This represents a reduction of over 98 per cent. in egg excretion as observed microscopically, and shows that miracidia hatching is a more sensitive and reliable index of continuing *S. mansoni* infection.

Foster Mavida did not show any significant weight gain throughout the 27 months of observation. His brother, Town Mavida, weighed 62,7 kg at the outset and 69,0 kg in November, 1971 — a 10 per cent. weight gain over 27 months.

Summary.

Two brothers infected with *S. haematobium* and *S. mansoni* were observed five days a week for many months during which they were given repeated treatment with hycanthone intramuscularly, and niridazole by mouth. One was cured after five treatments given over a period of 20 months: the second was cured after six treatments given over 27 months — four treatments with hycanthone, and two with niridazole. Supplementary treatment was given on three occasions, sodium antimony tartarate with niridazole once and with hycanthone once, and oral hycanthone supplementing one of the intramuscular hycanthones.

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