Brit. J. Pharmacol. (1949), **4**, 68.

MIRACIL. CLINICAL TRIAL ON PATIENTS INFECTED WITH *SCHISTOSOMA HAEMATOBIUM* AND *S. MANSONI*

BY

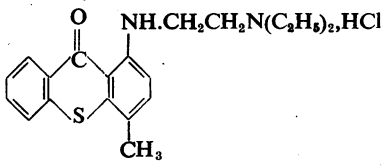
D. M. BLAIR, F. HAWKING, C. V. MEESER, AND W. F. ROSS

From the Public Health Department, Southern Rhodesia, and the National Institute for Medical Research, London, N.W.3

(Received September 19, 1948)

A previous paper (Hawking and Ross, 1948) has described the toxicology, absorption, and excretion of miracil D in monkeys and in healthy volunteers. The present paper records a clinical trial of this compound on patients infected with *Schistosoma haematobium* and/or *S. mansoni*. A preliminary note on these findings was published by Blair, Hawking, and Ross (1947).

Miracil D is the hydrochloride of 1-methyl-4-β-diethylaminoethylaminothioxanthone:



It was synthesized by Mauss, and shown by Kikuth, Gönnert, and Mauss (1946) and Kikuth and Gönnert (1948) to have considerable therapeutic activity for mice and monkeys infected with *S. mansoni*. The compound is administered by mouth. Subcutaneous or intramuscular injection causes considerable local irritation, and when given intravenously the toxicity is much greater than when given orally.

As shown in the previous paper, it is rapidly absorbed from the alimentary canal, and 2¼ hours after a single dose of 0.2 g. to an average man the concentration in the blood rises to about 1 mg. per litre. Only about 7 per cent of the drug is excreted in the urine, and little appears in the faeces; presumably about 90 per cent is degraded in the body. There is little tendency for the drug to accumulate. Deliberate prolonged overdosage in animals produced degenerative changes in the liver and the renal tubules in a few animals, but these were usually much less than would have been expected.

Organization of therapeutic trial

The present investigation was carried out at Salisbury, Southern Rhodesia, beginning in the second half of 1947. Patients with active schistosome infections were selected for the trials. Urines and stools were collected and examined for the presence of eggs and miracidia. The urines were examined by collecting the terminal specimen of urine, centrifuging it, and examining the resultant deposit for eggs. Originally the faeces were examined by collecting material from the outer layers of the stool together with any blood or mucus present and making an emulsion, with pond water, in a 3-in. × 1-in. tube. This emulsion was then filtered through a coffee strainer and transfered to a conical urine glass, further pond water was added, and the whole was allowed to settle. The supernatant was poured off, fresh water was added, and this washing process was repeated several times. Finally the resultant deposit was examined microscopically for the presence of eggs. Later, improved methods of diagnosis were used both for urine and faeces, depending on the hatching out of miracidia from the washed deposit and their identification with a hand-lens under indirect illumination (Gorman, Meeser, Ross, and Blair, 1947; Meeser, Ross, and Blair, 1948). Most of the therapeutic trials were made on young patients who were passing eggs in large numbers; infections in adults are less satisfactory for this purpose, since excretion of eggs is often intermittent.

Previous to treatment each patient was examined clinically and weighed stripped. The age in Africans can be ascertained only approximately. Before commencing treatment a haemoglobin estimation was

made using a Newcomer standard (acid haematin) measured with a Klett-Bio colorimeter; a white blood corpuscle count and a differential leucocyte count were also made. The drug was given as uncoated 100-mg. tablets (kindly made up by Messrs. Burroughs Wellcome and Co.) followed by a drink of water. With patients receiving once-daily doses it was usually given at 2–3 p.m., about two hours after the midday meal, but occasionally it was given at 10 a.m. Doses were not given on Sundays. All doses were given under the personal supervision of one of the writers.

After treatment the patients were followed up at 7-day intervals for at least sixteen weeks. In some of the groups these weekly examinations were interrupted for four weeks by absence during the school holidays. The successful follow-up of so many of the school-children was greatly assisted by the helpful co-operation of Messrs. C. M. Drury and F. G. Loveridge, successive headmasters of the Salisbury African School. At each follow-up a specimen of urine and/or stool was examined by the methods already described. Patients were considered "negative" if there were no eggs, or only calcified eggs were present. Patients were classified according to whether (1) active miracidia could be hatched (A), (2) living eggs were found but no miracidia hatched (E), (3) only dead eggs were present (D), (4) no eggs could be detected (O). A haemoglobin estimation and a white cell count were also made. If the white cell count was altered significantly from the previous count, then a differential cell count was done to obviate the insidious onset of agranulocytosis or any other type of cell change.

Clinical Results

The patients treated may be divided into five series, some of which may be subdivided into groups.

First series of patients

The patients of the first series were divided into five groups. The first group consisted of three adult male Africans employed in the laboratory; their ages were 30–45 years. The second group was made up of ten male African schoolboys; their ages ranged from 14–17 years, average 16 years, and their weights ranged from 40 to 64 kg., average 53 kg. One boy in this group, who felt unwell on the fourth day, stopped treatment after one dose of 50 mg. and three doses of 100 mg. The third group consisted of thirteen male African school-boys; their ages ranged from 14–17 years, average 15½ years, and their weights from 33 to 66 kg., average 54 kg. The fourth group consisted of seventeen Eurafrican (coloured) schoolchildren, thirteen males and four females, whose ages ranged from 10–17 years, with an average of 13 years. As there were considerable differences in weight in this group, a demarcating line of 40 kg. was taken, those over 40 kg. (six boys weighing 41 to 68 kg., average 49 kg.) forming one subgroup, while those less than 40 kg. (seven boys and four girls weighing 30 to 40 kg., average 35 kg.) formed another. The fifth group consisted of one male European, aged 17 years.

Of the forty-four patients under treatment, in the first group two had *S. haematobium* infections and one *S. mansoni*; in the second group, five had *S. haematobium* infections and five had double infections of *S. haematobium* and *S. mansoni*; in the third group, two had *S. mansoni* infections, nine had *S. haematobium* infections, and two had double infections; in the fourth group, fifteen had *S. haematobium* infections and two had double infections; and in the fifth group there was a single *S. haematobium* infection.

The results of treating the first series of patients are shown in Table I.

It must be remembered that in schistosomiasis egg production as discovered by examination of the excreta may frequently be intermittent. During a series of repeat examinations of the same patient negative findings are not uncommon. This may be due to a number of factors, such as ageing, relatively infertile worms ceasing to produce eggs regularly, or advanced damage of bladder and bowel with consequent fibrosis which makes the passage of eggs more difficult. Thus in Group III one case was positive, negative, and then positive, and a second case negative, positive, and again positive at the end of treatment, four weeks later and eight weeks later respectively. Furthermore, although reinfection during the time of the follow-up was unlikely, it was by no means impossible, and after eight weeks cases classified as "relapses" may possibly have been reinfections. These factors make the assessment of cure at any one time difficult. From Table I it can be seen that 12 infections (1 of *S. mansoni* and 11 of *S. haematobium*) were apparently cured—i.e., no miracidia or fresh eggs were found twelve weeks after treatment; but in 9 of these 12 infections the excretion of eggs had initially been light or irregular. The number of patients cured was smaller than the number of infections cured, since 9 patients initially had double infections, and one species might disappear while the other remained. The results of treating these double infections were as follows; among the eight patients followed for twelve weeks, not one remained negative for both infections although three became negative for *S. haematobium* alone and one for *S. mansoni* alone.

TABLE I

SUMMARY OF THE EFFECTS OF TREATMENT BY MIRACIL D (1ST SERIES)

H indicates *S. haematobium*, and M indicates *S. mansoni* infections

Group	No. of patients	Average weight kg.	Doses mg.	No. of patients passing no living ova/No. treated							
				End of treatment		After 4 weeks		After 8 weeks		After 12 weeks	
				H	M	H	M	H	M	H	M
I	3 (2H, 1M)	56.5	50 × 1 100 × 1 150 × 1 200 × 13	2/2	0/1	2/2	0/1	2/2	0/1	2/2	0/1
II	10 (10H, 5M)	53	50 × 1 100 × 13a 300 × 12	1/10 (6/9) *	1/5 (1/4)	3/9 (3/8)	3/4 (3/3)	1/9 (1/8)	2/4 (1/3)	2/9 (3/8)	1/4 (1/3)
III	13 (11H, 4M)	54	50 × 1 200 × 18–22	1/11 (7/9)	1/4 (0/4)	2/11 (2/9)	1/4 (1/4)	3/11 (4/9)	0/4 (0/4)	4/11 (3/9)	0/4 (0/4)
IV	11 (11H, 2M)	35	50 × 1 100 × 6 200 × 13	1/17 (6/16)	0/2 (0/1)	3/17 (3/16)	0/2 (0/1)	3/17 (3/16)	0/2 (0/1)	3/17 (4/16)	0/2 (0/1)
	6 (6H)	49	50 × 1 200 × 19								
V	1 (1H)	59	50 × 1 200 × 18	1/1		1/1		0/1		0/1	
Totals	44 (41H, 12M)			6/41 (19/34)	2/12 (1/9)	11/40 (8/33)	4/11 (4/8) b	9/40 (8/33) b	2/11 (1/8) b	11/40 (10/33) b	1/11 (1/8)

(a) 1 boy infected with *S. haematobium* received only 1 dose of 50 mg. and 3 doses of 100 mg.
(b) 1 patient with a double infection could not be followed up.

*Brackets refer to cases from which hatched miracidia could be obtained.

TABLE II

SUMMARY OF THE EFFECTS OF TREATMENT (2ND SERIES)

Boys given up to 11 daily doses of 0.6 g. during 15 days

A = Miracidia hatched and active. E = Living eggs. D = Dead eggs. O = No eggs or miracidia. M = *S. mansoni*

No.	Age	Total dose		Initial state			Excretion of ova at number of weeks after end of treatment											
		g.	mg./kg.	RBC	Ova	Miracidia	1	2	3	4	5	6	7	8	9	14	15	16
1	13	3.0	77	++	+++	++	E	E	O	D	O	O	O	O	O	O	O	O
2	15	3.6	83	+++	++	+	A	E	A	D	A	A	E	A	A	A	A	A
3	17	3.0	46	+++	++	±	—	O	E	A	E	A	A	O	A	—	—	A
Also *mansoni*						AM	AM				AM			AM				AM
4	15	6.6	150	++	+++	++	D	O	O	O	E	O	O	O	O	O	D	O
5	18	2.4	35	+	+	+	A	D	O	O	O	O	O	O	O	O	O	A
6	17	3.6	61	+++	+++	++++	E	O	O	O	O	O	O	O	O	D	O	A
7	15	3.0	54	++	+++	++	O	D	E	D	O	A	A	A	A	A	A	A
8	15	4.2	91	++++	+++	+++	A	A	A	A	A	A	A	A	A	A	A	A
9	13	4.2	98	+++	++	++	A	O	O	D	O	O	O	O	O	D	O	D
10	14	3.6	84	++++	++++	++++	A	E	O	D	A	D	A	A	A	A	E	A
11	16	3.0	55	++++	++++	+++	A	E	D	D	O	D	A	O	D	O	O	O
12	15	1.8	35	++++	+++	+++	A	A	A	A	A	E	A	O	A	E	E	D
13	15	3.6	69	+++	+++	+++	A	E	—	O	O	E	A	A	A	A	E	A
Proportion not passing living eggs (*haematobium*)							—	6/13	7/13	10/13	7/13	6/13	6/13	6/13	6/13	6/13	5/13	4/13

TABLE III

SUMMARY OF THE EFFECTS OF TREATMENT (3RD SERIES)

Children given 0.3, 0.4, 0.5, 0.6, 0, 0.6, 0.7, 0.7, 0.6, 0.6 g. on successive days (per 45 to 55 kg.). All males except Nos. 16, 17, and 18. Symbols as in Table II

No.	Age	Total dose		Initial state March 31 1948			Excretion of ova at number of weeks after end of treatment														
		g.	mg./kg.	RBC	Ova	Miracidia	1*	2	3	4	5	6	7	8	9	10	11	12	13	14	15
14	15	5.0	104	+++	++	++	A	E	D	D	O	O	D	O	O	O	O	O	O	D	—
15	19	6.0	104	++	++	++	O	O	O	O	O	O	O	O	O	O	O	A	O	A	A
16	13	4.0	90	+	++	++	A					O	O	O	O	O	O	O	O	O	O
17	14	4.0	90	+++	+	+	E					O	O	O	O	O	O	O	O	O	O
18	14	3.5	90	+	+	+	O					O	D	O	O	O	O	O	D	—	O
19	18	5.0	100	++	+	+	E					O	—	O	O	O	O	O	O	O	O
20	15	5.0	93	+++	++	++	A					A	A	E	A	A	A	A	A	A	A
21	14	4.0	97	++++	+++	+++	E					A	O	A	—	E	O	O	A	O	O
22	14	4.0	92	++	++	+	A					O	O	O	D	O	O	O	O	O	O
23	14	4.0	92	++	++	+	A					—	O	—	O	O	O	O	O	O	O
24	15	5.0	98	+	+	+	E					O	O	O	O	O	O	O	O	O	O
25	14	4.4	93	++	++	+	A					O	—	O	D	O	O	O	O	O	O
26	14	3.6	103	++	++	++	A					O	O	D	O	O	O	O	D	E	O
27	15	3.8	79	++++	+++	+++	O					—	—	O	D	O	O	D	O	O	O
28	15	6.0	104	+	+	+	E					—	—	—	—	—	O	A	A	A	A
					+M	+	—					—	—	—	—	—	A	A	A	A	A
29	18	5.3	92	+	+	+	A					D	—	O	D	O	A	O	A	E	A
30	19	3.9	64	+	+	+	O					O	O	O	O	O	O	O	O	O	O
31	18	2.5	40	++	++	++	A					O	O	O	D	O	O	O	O	O	—
Proportion not passing living ova (*haematobium*)							4/18					13/15	11/13	14/16	15/17	15/17	14/18	13/18	13/18	12/18	12/18

* 3 days after last dose

If the results are reckoned in terms of individual patients, and the type of infection is disregarded, then out of forty-three patients treated only eight patients no longer passed eggs twelve weeks after treatment had finished; two of these were in Group I, one in Group II, three in Group III, and two in Group IV. On the other hand, if the cases are judged by the criterion whether or not miracidia could be hatched from the excreta (satisfactory data on this subject are not available for all the patients), it is found that at the end of treatment 19 out of 34 cases of *haematobium* infection had become negative. Two weeks after treatment 15 out of 26 cases were negative; at four weeks after treatment the results by this test (8 negative out of 33) were similar to those judged by the presence or absence of living ova (11 negative out of 40). The results with infections of *S. mansoni* were approximately the same whether judged by the presence of viable eggs or by the hatching of miracidia.

From this series it was concluded that the therapeutic effect of miracil in daily doses of 0.3 g. was not great. However, in view of reports from workers at Cairo that patients could tolerate larger doses of miracil than 0.3 g. daily, and in view of the failure of miracidia to hatch in many of the cases after miracil treatment, further trials were instituted using higher levels of dosage.

Second series of patients

These consisted of thirteen African school-boys, who were given a daily dose of 0.6 g. per day during 15 consecutive days (omitting the 11th, 12th, and 13th days on account of the weekend). Many boys complained of abdominal pain and vomiting (some of which may have been psychological in origin), so that attendance for treatment was irregular and only one of the boys, No. 4, completed the full course. Two of the boys had been treated with miracil six months earlier as part of the first series, No. 2 having received 0.35 g. and No. 5 having received 4.25 g. without any apparent benefit. The details concerning these patients together with the results of treatment are shown in Table II.

In spite of the great irregularity of the dosage, the therapeutic effects of the compound are much more definite than those observed in the first trial. The effects are most marked at three weeks after the end of treatment, at which time 10 out of the 13 boys had ceased to pass living eggs. After this some of the boys began again to show signs of infection. For the purpose of this paper, these cases are interpreted as relapses, although the possibility that some were reinfections cannot be excluded. By the sixteenth week 4 out of the 13 were still free from living eggs; these 4 boys had presumably been cured—i.e., sterilized by the treatment. The therapeutic effect was not in direct proportion to the dose. The boys who were cured had received total doses of 77, 150, 98, and 55 mg. per kg. In other boys—e.g., No. 2 and No. 8—total doses of 83 and 91 mg. per kg. had exerted little or no definite effect on the excretion of living eggs.

Third series of patients

In view of the encouraging early results of this second series of patients, a third series was commenced. The patients were again school-children. A dose schedule for subjects of medium weight (45–55 kg.) was planned as follows: 1st day 0.3 g., 2nd day 0.4 g., 3rd day 0.5 g., 4th and 6th days 0.6 g. (5th day omitted), 7th and 8th days 0.7 g., 9th and 10th days 0.6 g., total 5.0 g. Adjustments were made for patients lighter or heavier than this weight-range. These children took the drug much better than those of the previous series did, even though the average daily dose was greater. They actually received total doses ranging from 40 to 104 mg./kg., average 90 mg./kg.; the average daily dose was about 8–10 mg./kg. The details about these patients and the results of treatment are given in Table III. In addition six similar children (five infected with *S. haematobium* and one with *S. mansoni*) chosen for controls were given placebo tablets of sodium citrate dyed yellow so as to resemble miracil; the details of these are given in Table IV for comparison. At 6 weeks after the end of treatment, 13 out of 15 treated patients who were examined no longer passed live eggs; only 2 of those examined still showed signs of an active infection. Fifteen weeks after treatment 9 out of 18 appeared completely free from infection, and 3 others passed only occasional dead eggs. One patient had never responded to treatment, while the remaining five showed a temporary response but the infection reappeared. One patient (No. 28) who was also infected with *S. mansoni* continued to pass ova in the faeces. The six controls (Table IV) continued to pass large numbers of living eggs throughout the period of observation, apart from the fact that a girl (No. 32) with a double infection of *haematobium* and *mansoni* ceased to pass *mansoni* ova in the faeces.

Fourth series—maximum tolerated doses of miracil

In order to discover the maximum amounts of miracil which could be tolerated, larger doses were given to patients with *haematobium* schistosomiasis who had been put in hospital for some other

TABLE IV

SUMMARY OF THE EXCRETION OF OVA IN SIX UNTREATED CONTROL CHILDREN, CHOSEN AT RANDOM FROM THE THIRD SERIES

Symbols as in Table II

No.	Age and sex	Wt. kg.	Initial state			Excretion of ova at number of weeks after end of treatment											
			RBC	Ova	Miracidia	1	2–5	6	7	8	9	10	11	12	13	14	15
32	13♀	37.5	++	+ +M	+ ++	A OM	—	A	A OM	O	A OM	A	A OM	A	A OM	E	A OM
33	17♂	53	+	+	+	A	—	A	A	A	A	A	A	A	A	A	A
34	14♂	46	+	+	++	E	—	O	A	A	A	—	A	A	A	A	A
35	14♂	46	+	+	+	A	—	A	A	A	A	A	A	A	A	A	A
36	15♂	37	+	+	+	A	—	A	A	A	A	A	A	A	A	A	A
37	16♂	43	—	O +M	+	O AM	—	O —	O OM	O AM	O OM	O AM	O AM	O AM	O AM	O AM	O AM
Proportion not passing living ova						0/6		1/5	1/6	1/6	1/6	0/5	0/6	0/6	0/6	0/6	0/6

reason. As shown in Table V, three patients were given 0.4 g. three times a day for about 9 days (one patient only for 6 days), and three were given 0.6 g. three times daily for 6 days. Only one of these patients, No. 40, showed any toxic effect that might have been due to the drug; he complained of abdominal pain and vomited on the fifth day; the significance of this vomiting is uncertain. Before treatment began, miracidia could be hatched out from the urine of five of these patients. On the last day of their treatments, the urines of two of these five patients were free from eggs; the urines of the other three contained apparently living eggs but the miracidia did not hatch. Another patient, No. 44, was given 0.6 g. twice daily for two days; soon after the first dose on the second morning he vomited. The dose was reduced to 0.4 g. once daily for two days; nausea was felt. On the fifth day he was given 0.3 g. twice and he had nausea and vomited. Four days later the urine still contained eggs but miracidia could not be hatched. Four other patients (Nos. 45–48; not in hospital) were given once-daily doses as shown, which were increased during the five days of treatment to a maximum of 1.6 g. Two of these (46 and 47) had no toxic symptoms at all. One (No. 45) weighing 54 kg. complained of abdominal pain on the 4th and 5th days after doses of 1.2 g. and 1.6 g. respectively; he vomited after the last dose, without bringing up much of the compound. One patient (No. 48; weighing 32 kg.) had abdominal pains, nausea, and vomiting on the 4th and 5th days after doses of 0.8 and 1.0 g. respectively. On the day following treatment miracidia could be hatched from the urines of three out of the four patients. Six of these patients have been followed for 15 weeks; at the end of this period, none passed living ova.

Fifth series of patients

Four miscellaneous patients were treated according to various schedules. The details about these are shown in Table V. In the two European children (Nos. 51 and 52), the skin was stained yellow by the drug. Three of these patients seemed to have been cured; one relapsed (or was reinfected) after 11 weeks.

Toxicity

The patients were questioned daily when given their dose for any toxic effects of the treatment, but with Africans it is generally difficult to evaluate reports of minor symptoms which may be exaggerated or concealed. The symptoms of possible toxicity during this investigation were still more difficult to evaluate because they tended to be more pronounced during the less intense courses than in the more intense ones.

In the first series (treated with 0.2–0.3 g. daily) two boys reported slight or moderate nausea, each on one occasion, but its relation to miracil is uncertain. One fairly old man in Group I suffered more severe symptoms. He began taking miracil on July 21. On Aug. 2 he vomited, and for the next two days there was nausea, lack of appetite, and weakness. On Aug. 4 the drug was stopped (after 12 doses totalling 2.1 g.) but was started again soon after. On Aug. 5 he felt all right; haemoglobin 86 per cent, W.B.C. 4,200 per cu.mm. as at beginning of treatment. On Aug. 7 and 8 nausea, anorexia, and vomiting, but he continued at work these two days. On Aug. 9 he could not come to work; cough, shortness of breath, slight disorientation, pulse rate 96. On Aug. 10 he

TABLE V

SUMMARY OF THE EFFECTS OF TREATMENT (4TH AND 5TH SERIES)

All males except 51 and 52, who were European girls. Symbols as in Table II

No.	Age	Total dose		Schedule, g.	Initial state			Excretion of ova at number of weeks after last dose														Symptoms
		g.	mg./kg.		RBC	Ova	Miracidia	1*	2	3	4	5	6	7	8	9	10	11	12	13	14	15	
								FOURTH SERIES														
38	30	10.4	190	0.4 × 2, 1 day 0.4 × 3, 8 days	++	++	++	O (3)	A	—	A	—	A	O	—	—	—	O	—	—	—	—	None
39	13	10.4	298	0.4 × 2, 1 day 0.4 × 3, 8 days	++	++	+	E (3)	E														None
40	18	6.8	121	0.4 × 3, 6 days	occ.	+ +M	+ +M	E OM (3)	O	—	O	O	O OM	O OM	O OM	O	O	O	O OM	O	O OM	O OM	Pain and vomiting 5th day
41	35	10.8	190	0.6 × 3, 6 days	++	—	—	— (0)															None
42	26	10.8	202	0.6 × 3, 6 days	occ.	+	+	E (0)															None
43	20	10.8	212	0.6 × 3, 6 days	+++	+	—	O (0)	D	D	D	O	O	D	O	O	D	O	O	D	O	D	None
44	25	4.2	74	0.6 × 2, 2 days 0.4 × 1, 2 days 0.3 × 2, 1 day	++	++	++	E (4)	—	—	O	—	O	O	O	O	D	—	O	—	O	O	Nausea and vomiting
45	20	5.8	107	0.6 × 1, 1 day 1.2 × 1, 3 days 1.6 × 1, 1 day	+++	++	++	A (1)	A	E	D	D	O	D	D	D	D	D	—	—	O	O	Abdominal pain 2 days. Vomited last day
46	14	4.6	107	0.6 × 1, 1 day 0.8 × 1, 1 day 1.0 × 1, 2 days 1.2 × 1, 1 day	++	+	+	A (1)	A	A	D	D	D	D									None
47	18	5.8	105	0.6 × 1, 1 day 1.2 × 1, 3 days 1.6 × 1, 1 day	++	+	+	E (1)	E	A	O	O	O	D	O	O	O	O	—	—	O	O	None
48	10	3.6	112	0.4 × 1, 1 day 0.6 × 1, 1 day 0.8 × 1, 2 days 1.0 × 1, 1 day	+++	+++	++	A (1)	A	A	O	O	O	D	O	O	O	D	—	—	D	O	Abdominal pain and nausea 2 days. Slight vomiting 2 days
								FIFTH SERIES														
49	18	6.0	91	0.3 × 2,10 days	++	++	++	O	O	D	D	O	O	O	O	O							
50	7	5.6	154	0.2 × 4, 8 days	++	+	+	A	O	O	O	O	O	D	O	O	O	O	O	O	O	O	
51	8	3.0	97	0.3 × 1, 4 days 0.4 × 1, 3 days 0.3 × 1, 2 days	++	++	+	A	O	—	—	O	—	—	—	—	O	—	O	O	O	O	
52	4	1.8	92	0.2 × 1, 9 days	++	++	++	—	D	D	—	—	—	O	—	O	O	A	A	—	O	D	

*Figures in brackets show days after last dose

began to take food. Aug. 11, all right; chest, nothing abnormal discovered. Aug. 15, haemoglobin 63 per cent, W.B.C. 3,500 per cu.mm. These symptoms may have been due to other causes, although there was no clear evidence of an intercurrent infection, and they cannot be proved to have been due to miracil.

None of the patients treated showed significant changes in the haemoglobin percentage or white cell counts during or after treatment. None complained of tinnitus (Africans might not report it even if present). There were no gross changes in the urine; slight albuminuria or haematuria was masked by the schistosomiasis. The European of the first series, Group V, became distinctly yellow in the skin and conjunctivae while taking the drug, but he had no other symptoms.

In the second series there was a good deal of difficulty in getting the children to take the full doses (0.6 g. once daily); they complained mainly of loss of appetite and abdominal pain and there seems to have been much deliberate absenteeism. The doses were given as 6 tablets each of 100 mg., and this large number of separate pills may have had a bad psychological effect. One boy, No. 4, took 6.6 g. On the last day of his course (Feb. 17) he complained of pain in the abdomen and inability to see clearly. On Feb. 24 he developed an acute generalized pruritus, which was severe during the short time it lasted. The next day he showed a close herpetiform rash on the outstanding margin of his R. trapezius muscle, perhaps an affection of the accessory nerve. In this connexion it may be recalled that Alves and Blair (1946) observed a herpetiform rash over the trapezius muscle in one of 100 Africans treated by their intensive course of sodium antimonyl tartrate. Ritchken and Cantor (1947) noted an association between the administration of a similar intensive course of antimony and the onset of herpes zoster in five of their patients. These cases of herpes and herpetiform rash had been attributed to the antimony, but in view of a similar occurrence during treatment with miracil it is possible that the herpes is really caused by the disintegration products of the dying schistosomes.

In the third series most of the children registered no complaints except loss of appetite; but one child (No. 28) felt ill after the penultimate dose. Another complained of vomiting and of feeling generally weak on the 8th day after beginning treatment, but he took his other doses without incident.

In the fourth series (which received the highest doses) the symptoms of toxicity were restricted to abdominal pain, nausea, and vomiting in some of the patients, and they have already been described. In the fifth series no toxic symptoms were observed.

Concentration of miracil in the blood of patients

Three adult male Africans, who were infected with *S. haematobium* (2) or *S. mansoni* (1) were given miracil D by mouth at 8 a.m. each day for 6 days. Blood was withdrawn at appropriate intervals and the concentration of miracil was determined according to the method of Latner, Coxon, and King (1947) as used in the work of the previous paper. These patients, who were confined to bed, suffered no toxic effects. They left hospital six days after treatment, at which time they were still passing viable eggs. The details of these estimations are shown in Table VI, which should be compared with Table II and Fig. 2 of the paper by Hawking and Ross (1948). The blood concentrations reached in different individuals vary somewhat; allowing for these variations the concentrations obtained in these African patients were similar to those found in the European volunteers. There was no definite tendency of the compound to accumulate in the blood.

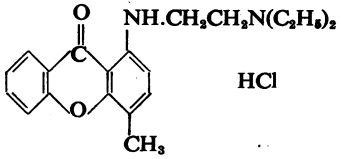
TABLE VI

CONCENTRATIONS OF MIRACIL D IN BLOOD IN MG. PER LITRE

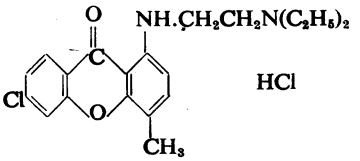
Daily dose mg.	1st day			2nd day		4th day		6th day	
	2½ hr.	6 hr.	24 hr.	2½ hr	24 hr.	2½ hr.	24 hr.	2½ hr.	24 hr.
100	—	0.62	0.42	0.53	0.24	0.32	0.32	0.52	0.28
200	0.33	0.77	0.68	0.82	0.32	0.37	0.52	0.60	0.44
300	0.89	1.20	0.96	1.20	0.90	1.10	0.78	1.40	1.20

Patients treated with miracil A, B, and C

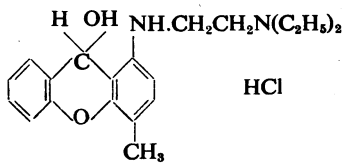
Trials were also carried out on miracils A, B, and C, but as only a small quantity of each compound (less than 10 g.) was available, which had been kindly supplied by Dr. Mauss for another purpose, only one patient could be treated with each.



Miracil A is the hydrochloride of 4-β-diethylaminoethylamino-1-methylxanthone



Miracil B is the hydrochloride of 8-chloro-4-β-diethylaminoethylamino-1-methylxanthone



Miracil C is the hydrochloride of 4-β-diethylaminoethylamino-1-methylxanthydrol

Miracils A and B are xanthones whereas miracil D is a thioxanthone. Miracil C is the dihydro derivative of miracil A; miracil B differs from miracil A in containing a chloro substituent in the second benzene ring.

These compounds were synthesized by Mauss, and their chemotherapeutic activity on experimental schistosomiasis in mice and monkeys was investigated by Kikuth and Gönnert. They found that these compounds are well tolerated by mouth; when given subcutaneously they produce marked local irritation which occasionally leads to necrosis at the site of the injection; when given intravenously they are inactive except miracil D, which is not given by this route for pharmacological reasons. When given orally for the treatment of *mouse schistosomiasis* miracil B is almost four times as active as miracil C and D and more than eight times as active as miracil A. In the treatment of *monkey schistosomiasis* the relative activities are different. Miracil D is the best preparation, miracil B produces an effect only in doses which cause vomiting, and miracil A, which is only slightly active in mice, shows clear-cut activity in monkeys. Miracil C occupies a mid-way position in activity in both mouse and monkey tests.

TABLE VII

TOXICITY TESTS

The toxicity of the miracil compounds, when given orally to mice

Compound	Maximum tolerated dose in mg. per 20 g.	
	Kikuth and Gönnert (single dose)	Sewell (four daily doses)
Miracil A	6.7	5
Miracil B	20	10
Miracil C	10	5
Miracil D	13	5–10

The toxicity of these compounds was kindly determined for us at the National Institute for Medical Research, London, by Mr. P. Sewell, by giving oral doses of 5, 10, and 20 mg./20 g. mouse daily for four successive days. His results are given in Table VII and compared with those of Kikuth and Gönnert, obtained by treating mice with a single oral dose. In view of the small number of mice used, the results obtained are in agreement.

Clinical trial

The patients were young Africans. Each patient is considered individually.

A. Weight 63 kg.; infected with *S. haematobium*; complained of blood in urine before commencing treatment; previously treated with antimony for schistosomiasis in January, 1947. He was treated with 6 daily doses of 100 mg. miracil A by mouth in first week and 6 daily doses of 200 mg. miracil A in second week. Total dose = 1.8 g.

B. Weight 66 kg.; infected with *S. haematobium*; this man had no symptoms at commencement of treatment. He was treated with 5 daily doses of 100 mg. miracil B by mouth in first week and 5 daily doses of 200 mg. miracil B in second week. Total dose = 1.5 g.

C. Weight 66 kg.; infected with *S. haematobium*; this man, who was very dull mentally, complained of vague "falling turns" for past three years. He was treated with 6 daily doses of 100 mg. miracil C by mouth in first week and 6 daily doses of 200 mg. miracil C in second week. Total dose = 1.8 g.

These three patients had viable eggs in their urines when treatment began. They were examined at weekly intervals during treatment, and at 2 weeks, 4 weeks, and 8 weeks after the end of treatment. On each occasion viable eggs were found in the urine. Neither these three patients nor the patients who were treated in determining the blood concentrations showed any toxic effects of the drugs.

Concentrations of miracils A, B, and C in the blood of patients

Adult African patients who were in hospital suffering from some other condition as well as schistosomiasis were used in determining the blood concentrations of these drugs. The concentration of the drug was measured by means of a Spekker photo-electric absorptiometer according to the

TABLE VIII

BLOOD CONCENTRATIONS OF THE MIRACIL COMPOUNDS AFTER A SINGLE ORAL DOSE OF 200 MG.

Compound	Mg. per litre at various times after dose		
	2½ hr.	6 hr.	24 hr.
Miracil A	0.16	0.12	Nil
Miracil B	0.10	0.28	Nil
Miracil C	Nil	Nil	Nil

method of Latner, Coxon, and King (1947) for the estimation of miracil D. It appeared that miracils A, B, and C could be estimated in the same way as miracil D. For each drug the blood concentrations after a single dose of 200 mg. were determined and these are shown in Table VIII. The blood concentrations of miracil A and miracil B were less than those observed after a single dose of miracil D (Hawking and Ross, 1948 ; Table II) if allowance is made for the marked individual variations between different patients. No drug could be detected in the blood of the patient who had received miracil C ; as there was no more miracil C available, this result could not be verified. The blood concentrations of miracils A and B were followed in patients who received daily doses of 100 and 200 mg. for 5 days as shown in Table IX ; the urinary concentration of the drugs was determined on the two days following cessation of treatment. The results are shown in Table IX. The blood concentrations of miracil A and B are lower than those observed in patients treated with miracil D in similar dosage (Hawking and Ross, 1948).

TABLE IX

BLOOD AND URINE CONCENTRATIONS OF MIRACILS A AND B DURING FIVE DAILY DOSES BY MOUTH

Daily dose of compound	Blood concentrations. mg./l.				Urine concentrations. mg./l.	
	1st day		2nd day	5th day	6th day	7th day
	2½ hr.	6 hr.	6 hr.	6 hr.		
Miracil A 100 mg.	0.20	0.10	0.40	0.32	2.0	Nil
Miracil A 200 mg.	0.30	0.46	0.56	0.48	2.7	Nil
Miracil B 100 mg.	0.16	0.04	0.08	0.28	1.2	Nil
Miracil B 200 mg.	0.24	0.10	0.30	0.34	2.1	Trace

Owing to the limited supplies of the compounds which were available the patients observed were too few to yield significant results, but they may provide preliminary indications for further investigations. In these doses no toxic effects and no therapeutic effects were observed. Judging by analogy with miracil D, however, it is probable that much larger doses would have been tolerated and these might have been therapeutically effective.

Discussion

This investigation on the therapeutic value of miracil D is still in progress and it will probably be several years before a reliable evaluation of the compound can be made. The present paper reports the preliminary results which have been obtained for the information and guidance of workers who may be interested in this subject in other parts of the world.

The therapeutic effect of miracil D seems to depend much more on the intensity of the dosage than on its total amount. At 0.2 or 0.3 g. per person (4 mg. per kg.) daily, the therapeutic effect is slight and dubious even though treatment be continued for over three weeks. At 0.5–0.7 g. per person (over 10 mg. per kg.) daily the therapeutic effect is marked, and a high proportion of the patients can be sterilized.

These results may be compared with those reported from Egypt in three papers by Azim, Halawani, and Watson (1948), Watson, Azim, and Halawani (1948), and Halawani, Watson, Nor El-Din, Hafez, and Dawood (1948). They treated patients with doses up to 7.5 g. during 8 days, but permanent cures were not usually produced except by the highest doses ; toxic symptoms seem to have been more pronounced than they were in Rhodesia.

The data about the possible toxicity of the compound are conflicting. One boy (second series) suffered from generalized pruritus and a herpetiform rash after taking 6.6 g. during 15 days ; this may have been due to the drug or to disintegration products of dying schistosomes. One man suffered from intense nausea, with vomiting, profound malaise, cough, and slight disorientation after taking about 14 daily doses totalling about 2.5 g. ; these symptoms may or may not have been due to the drug. Some of the boys in the second series complained of nausea and colic, but many of these symptoms may have been psychological. Of the 11 patients given the biggest doses, seven were all right and five suffered from nausea, vomiting, and abdominal pain ; but in only one patient

were the symptoms severe enough to require reduction of the dose.

Taking the patients as a whole, it may be concluded that nausea, vomiting, and abdominal pain may occur ; but they are not serious and their frequency is not proportional to the dose. It is not certain that the other untoward effects are really due to the drug. All these symptoms of toxicity seem to be idiosyncrasies depending on the patient more than on the size of the dose. No uniform set of toxic symptoms has yet manifested itself. The yellow staining which is seen with light skins is unimportant except from the cosmetic point of view. The insomnia, headache, giddiness, vertigo, excessive sweating, tremor, and twitching observed by Halawani and his colleagues (1948) have not been seen in our patients, nor has there been any evidence of disturbance of the heart. Halawani, Newsome, and Wooton (1947) have shown that the blood concentration of miracil (and presumably also its toxicity and its therapeutic potency) is raised by impairment of kidney function ; most of our patients were vigorous adolescents in whom the kidney function was presumably good.

The ultimate value of a drug depends on the ratio between its therapeutic effectiveness and its toxic effects, but convenience of administration, expense, and the possibilities of alternative treatments have to be taken into consideration. With miracil D evidence has now been obtained that a large proportion of patients infected with *S. haematobium* can be sterilized by doses which are tolerated by the great majority of persons. (The expense of manufacture may, however, be a handicap to widespread use.)

The effect on *S. mansoni* is not clearly indicated by the cases treated to date in S. Rhodesia. In the first series of patients, 11 out of 40 cases of *haematobium* infections were cured, but only 1 out of 11 cases of *mansoni* infections. In the second series, patient 3 had a double infection, neither of which responded. In the third series, patient 28 had a double infection ; *haematobium* ova disappeared temporarily from the excreta, but *mansoni* ova were found at all examinations (figures incomplete). There is a suggestion that *S. mansoni* responds less readily than *S. haematobium*.

Further judgment about the value of miracil must be withheld until greater experience has defined more accurately the maximum tolerated dose, has shown whether dangerous idiosyncrasies exist, and has enabled the therapeutic effect of large doses to be compared accurately with that of antimonials. In any case, miracil is of great scientific importance as showing antischistosome action in a new series of organic compounds, and it has the practical advantage of being effective when given by mouth. A safe drug which could be given orally for the treatment of schistosomiasis would be of very great value in Africa. It could be given in villages to out-patients, and administration could be left to non-skilled hands. If the effectiveness and safety of miracil are confirmed by wider experience, village treatment of schistosomiasis free from the thraldom of an intravenous ritual will at last become a practical possibility.

Summary

1. Miracil D (1-methyl-4-β-diethylaminoethylaminothioxanthone hydrochloride) is a new synthetic remedy for schistosomiasis. It is given by mouth.

2. Forty young persons infected with *S. haematobium* were treated with total doses of approximately 80–100 mg. per kg. during periods of approximately three weeks, mostly as daily doses of 0.2 g. per person (4 mg. per kg.). Twelve weeks later eleven of them were free from infection. Eleven infections with *S. mansoni* (mostly the same patients as those with *S. haematobium*) were similarly treated ; one of them became free from infection.

3. Thirteen boys infected with *S. haematobium* were treated with doses ranging from 35 to 150 mg. per kg. during fifteen days, given (irregularly) as daily doses of 0.6 g. per person. Three weeks after treatment ten out of thirteen no longer passed living ova. Four months later four of the boys appeared permanently cured.

4. Eighteen school-children infected with *S. haematobium* were given total doses of about 90–100 mg. per kg. during ten days, mostly as daily doses of 0.5–0.7 g. per person (about 10 mg. per kg.). Six weeks later fourteen out of sixteen no longer passed living ova ; fifteen weeks later twelve out of eighteen appeared to be permanently cured. Fifteen other patients (many adults) were given amounts up to 1.6 g. daily.

5. In most patients the compound was well tolerated. Symptoms of toxicity consisted mostly of abdominal pain, nausea, and vomiting. They were not directly related to the size of the dose and seemed to depend at least partially on idiosyncrasy of the individual patient.

6. Miracil D appears to exert a valuable therapeutic effect on infections of *S. haematobium* in doses which are well tolerated by most patients.

The dose should be at least 10 mg. per kg. per day. The effect of maximum tolerated doses on infections of *S. mansoni* is not yet known.

7. Three single patients were treated with miracil A, B, and C respectively in total doses of 1.5–1.8 g. during two weeks. No toxic or therapeutic effects were observed at this dosage, which is probably much less than the tolerated one.

8. In patients taking about 3 mg. miracil D per kg. daily, the blood concentration at 2½ hours after the dose was 0.3 to 0.8 mg. per 100 ml. In patients taking miracil A and miracil B, the blood concentrations were similar to (or lower than) those taking miracil D. In a patient given miracil C, the compound could not be detected in the blood.

Grateful acknowledgments are due to Dr. R. M. Morris, medical director, Southern Rhodesia, for access to clinical material and laboratory facilities; to the principals of the schools involved for their kind co-operation; and to Drs. Mauss, W. Kikuth, and R. Gönnert for information and material.

REFERENCES

Abdel Azim, M., Halawani, A., and Watson, J. M. (1948). *Lancet*, **1**, 712.
Alves, W., and Blair, D. M. (1946). *Lancet*, **1**, 9.
Blair, D. M., Hawking, F., and Ross, W. F. (1947). *Lancet*, **2**, 911.
Gorman, S., Meeser, C. V., Ross, W. F., and Blair, D. M. (1947). *S. Afr. med. J.*, **21**, 853.
Halawani, A., Newsome, J., and Wooton, I. (1947). *J. Roy. Egypt. med. Ass.*, **30**, 656.
Halawani, A., Watson, J. M., Nor El-Din, G., Hafez, A., and Dawood, M. (1948). *J. Roy. Egypt. med. Ass.*, **31**, 272.
Hawking, F., and Ross, W. F. (1948). *Brit. J. Pharmacol.*, **3**, 167.
Kikuth, W., and Gönnert, R. (1948). *Ann. trop. Med. Parasit.*, **42**, 256.
Kikuth, W., Gönnert, R., and Mauss, H. (1946). *Naturwissenschaften*, **8**, 253.
Latner, A. L., Coxon, R. V., and King, E. J. (1947). *Trans. Roy. Soc. trop. Med. Hyg.*, **41**, 133.
Meeser, C. V., Ross, W. F., and Blair, D. M. (1948). *J. trop. Med. Hyg.*, **51**, 54.
Ritchken, J., and Cantor, F. (1947). *Clin. Proc.*, **6**, 125.
Watson, J. M., Abdel Azim, M., and Halawani, A. (1948). *Trans. Roy. Soc. trop. Med. Hyg.*, **42**, 37.