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# Field Trials with CIBA 32644-Ba in Rhodesia

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The work reported here was carried out with three objectives in view:

1. To conduct a field trial of CIBA 32644-Ba in a group of patients with double infections, *S. haematobium* (Sh) in the urine and *S. mansoni* (Sm) in the stool.
2. To test the drug in a number of patients treated individually.
3. To study toxic side effects in both groups.

## *Field trial at Chipoli, Shamva, 70 miles north of Salisbury*

The Chipoli Estate was selected as the site of the trial because the incidence of both Sh and Sm infections and also, by Rhodesian standards, the intensity of infection are high in this area. The population is very stable, most of them having spent their lives there and, in addition, the operator of the estate offered very good facilities and co-operation.

Urine examinations were made in the usual way and following our practice (BARRETT, BLAIR, CLARKE, and GARNETT, 1964), egg-counts were done in a one-hour specimen of urine taken in the late morning.

The technique is as follows:

The specimen is allowed to sediment for 30 minutes, after which all but 15 ml is pipetted off. These 15 ml are then centrifuged for 1 minute at 1,000 rpm. All but the bottom 0.5 ml of deposit is drawn off. The deposit is agitated, 0.05 ml transferred to a microslide, and all eggs counted. If no eggs are seen, then a large drop is searched. An Sh egg-count per hour is determined. In each series of examinations a miracidial hatching technique is applied to one fresh specimen of urine. The stool specimen in 10% formalin is treated with Teepol, strained through fine wire gauze, and sedimented

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twice; the deposit is transferred to a centrifuge tube and centrifuged, after 1 ml ether has been added. The supernatant is decanted. A drop of the deposit is examined with an X4 scanning lens and a count of eggs made on a 1 to 5+ assessment (see below). Hatching of Sm eggs was carried out only at the 2nd- and 3rd-month follow-ups.

Pre-treatment examinations were made on the Monday, Wednesday and Friday of the week preceding treatment, which was carried out from 23rd to 27th February, 1965. Patients were given 25 mg/kg CIBA 32644-Ba daily in two divided doses, for 5 days. Body-weight was measured on an accurate bathroom scale. Follow-up examinations were carried out one, two, and three months after the conclusion of treatment, on three successive days of the week. Miracidial hatching tests were only attempted on one specimen at the 2nd and 3rd follow-up. A number of the cases were submitted to only one follow-up examination, on 14th July, 1965, 19 weeks after the conclusion of treatment, on 27th February, 1965. Miracidial hatching techniques were applied to both stool and urine specimens.

Treatment was given to 74 patients at Chipoli, and 19 other persons were selected at random to act as untreated controls. The patients in the trial continued to perform their daily duties throughout. No attempt was made to undertake any biochemical or other tests, such as electrocardiograms or X-rays of the chest.

A simple clinical examination was made of chest and heart, and liver enlargement and tenderness were assessed.

Three months after treatment the situation was as shown in Tables 1 and 2.

TABLE 1

*Description of cases available for follow-up at three months*

	Treated cases	Controls
4-10 years	31	9
11-20 years	26	7
21 years and over	12	1
	69	17

*Weight gain:* Over three months there was an obvious weight gain in both treated cases and controls, and an improvement in the general condition (skin tone, etc.) of all treated patients. Excluding women of child-bearing age, the 59 treated cases showed an average weight gain of 4.1 lbs and the 13 controls a gain of

TABLE 2

*Assessment of infestation three months after treatment*

Category (see footnote)	Treated cases		Controls	
	Sh. in urine	Sm. in stool	Sh. in urine	Sm. in stool
I	36	3	—	—
II	30	46	—	4
III	3	8	—	—
IV	—	3	3	4
V	—	9	14	9
Total	69	69	17	17

Prior to treatment all cases were equivalent to Category V.

TABLE 3

*Assessment of infestation 4<sup>1</sup>/<sub>2</sub> months after treatment*

Category (see footnote)	Treated cases		Controls	
	Sh. in urine	Sm. in stool	Sh. in urine	Sm. in stool
I	42	16	—	1
II	10	18	1	2
III	1	1	3	2
IV	1	11	1	1
V	1	9	7	6
Total	55	55	12	12

*Footnote to Tables 2 and 3*

Category I: no eggs, no miracidia hatched.

Category II: dead "black" eggs, great reduction in number, no miracidia hatched.

Category III: few eggs, no hatching of active miracidia, but some activity in ciliary movement, or movement of miracidia seen within the unhatched eggs.

Category IV: significant reduction in number of eggs, but miracidia still hatching and active.

Category V: no reduction in number of eggs, miracidia hatched and active.

5.4 lbs. Two treated cases had surprising gains from 50 to 59 lbs, and from 97 to 111 lbs.

Details on a number of individual cases are given in Table 4:

One case (the first mentioned in Table 4) was followed up in much more detail than was possible with others. This little boy with a double infection was given the drug over four days only. He had an Sm (++) infection and Sh (+) in the stool. No Sm

TABLE 4

*Details of individual cases treated*

Treatment					
Total dosage	Duration (days)	Patient's weight in lbs.	Infection	Last living eggs seen	Category
<i>1. Africans</i>					
125 mg/kg	4	33	Sh. Sm.	at 18 days	Urine II Stool I at 77 days
125 mg/kg	5	135	Sh.	at 14 days	Urine I at 83 days
125 mg/kg	10	138	Sm.	No living eggs Few dead	Stool II at 167 days
125 mg/kg	10	126	Sm.	No living eggs Dead eggs seen on two occasions	Stool II at 138 days
125 mg/kg	10	156	Sh.	No living eggs Dead eggs	Urine I at 163 days
150 mg/kg	5	170	Sm.	No eggs	Stool I at 98 days
<i>2. Europeans</i>					
100 mg/kg	5 (one dose a day)	165	Sm.	No eggs	Stool I at 100 days
125 mg/kg	5	211	Sm.	No eggs	Stool I at 105 days
125 mg/kg	5	98	Sh.	Dead eggs soon after treatment no eggs since	Urine I at 109 days

eggs have been seen at all after treatment, although stool specimens were examined on 17 occasions. Pre-treatment Sh egg output (average of 3 examinations on successive days) was 2,500 eggs per hour taken at the time of peak output. On the first day of treatment the output rose to 16,500 eggs per hour in the urine. It was

noted that hatching in the dark-coloured urine took place, but miracidia did not swim. Immature forms were seen lying beside their shells. The egg-count fell to 7,270 per hour on the last day of treatment. Miracidia, hatched and active, were not seen until 10 days after treatment when the count was down to 860 per hour and more than 50% were "black" and dead. Four days later miracidia hatching ceased; 40 days after treatment there were 580 eggs per hour, all "black" and dead. The indications are that this boy is cured, but it is interesting to note that he continues to pass 300 to 400 blackened "dead" eggs in his urine at each hourly specimen examined, and will no doubt continue to do so for months to come.

A European, the owner of Chipoli Estate, who had a history of urinary bilharziasis since 1935 and who is constantly exposed to re-infection, was not found to be actively passing eggs in stool and urine. Nevertheless his skin-test (*S. mansoni* adult worm antigen) was strongly positive, as was the fluorescent antibody reaction. He weighed 230 lbs (104 kg) and took 125 mg/kg during 5 days, a total of 13.5 grams. He continued his hard physical work throughout and took the whole course of the tablets. He felt a little drowsy on the 2nd and 3rd days. On the 4th and 5th days he felt rather flushed and thought he might have a temperature; at night he woke with a headache. He had a strong, musty, body odour while taking the drug and noted that his facial hair grew rapidly. He was constrained to shave three times a day during treatment and twice a day for a further 10 days.

*Side effects:* The drug is remarkably free from significant side effects and many patients questioned after the completion of treatment had no complaints. Of the patients treated in the main trial, all but one continued their full employment as estate workers. The one exception was off work for a single day, and he had a long history of repeated minor illnesses. Since his treatment he has had no absences from work. However, 22 patients volunteered minor complaints such as "feeling hot", "aches in joints", "sore head" and "sore stomach". The following comments may also be of interest:

1. *Sleepiness:* This was noted in most of the European patients, and one African woman in the main trial fell asleep on the way home and seems to have been asleep for some hours. On the other hand insomnia was not reported, in contrast to the experience with miracid drugs.

2. *Body odour:* This was reported without prompting by three individual European patients. We sampled the odour in one case

ourselves. It was a rather heavy musty odour, not quite that of an unwashed man. It disappeared soon after treatment ceased.

3. *Increased beard growth*: This was reported by one man, the 104 kg patient described above.

4. *Vomiting*: This was not reported much. Two individual African patients vomited at night on the 2nd or 3rd day of treatment.

5. *Diarrhoea*: One patient in addition to vomiting had diarrhoea on the second night of his treatment (the last patient in Table 4, 1).

6. *Appetite*: This drug, unlike the miracils, does not seem to affect the appetite.

In general, complaints of side effects were mostly from adults, who were being given bigger total doses. Children and lighter persons generally showed no side effects.

### *Conclusions and Summary*

Taking our categories I and II as cures, CIBA 32644-Ba cured 66/69 cases of *S. haematobium* and cured 49/69 (the same patients) of *S. mansoni* infections. The patients continued their work and occupations throughout treatment and no toxic side effects of any consequence or relevance were noted. The post-treatment improvement in general condition was marked, and it is surprising that although the patients continued to live in this hyper-endemic area of the disease during the 3-month observation period no re-infections, with either species, seem to have taken place.

Four and a half months after treatment, judged by the same criteria of cure as were adopted at the 3-month follow-up, 52/55 cases of *S. haematobium* and 34/55 (the same patients) cases of *S. mansoni* showed apparent cure of their infestations. At the final summing up, only three children, two of whom started the trial with low hourly *S. haematobium* egg counts, continued, despite treatment, to produce hatching miracidia. In the case of *S. mansoni* infestations the cure rate is not as good as with *S. haematobium* in the same subjects. It is, however, encouraging to note that *S. mansoni* eggs seem to take longer to disappear from the stool than *S. haematobium* eggs from the urine. This is shown by the fact that upon stool examination 3/66 cases were in category I at 3 months whilst at 4½ months the proportion in this category had risen to 16/55.

A study of the categories in the control series demonstrates that in any long-term follow-up of cases, due regard must be given to the part played in overcoming the disease by the effects of the development of "resistance" by the patient against his infestation.

*Conclusions et résumé*

Si les catégories I et II sont considérées comme des guérisons (I : pas d'œufs, éclosion miracidienne négative ; II : présence d'œufs morts uniquement, éclosion miracidienne négative), le CIBA 32644-Ba guérit 66/69 cas d'infestation à *S. haematobium* et 49/69 cas d'infestation à *S. mansoni*. Les malades ont vécu normalement, continuant leur travail et leur occupation habituelle durant tout le traitement ; aucun effet toxique d'importance ne fut observé. L'amélioration clinique après traitement fut généralement nette, et les auteurs furent surpris de n'avoir observé aucune réinfestation chez les malades traités depuis 3 mois et vivant dans une région hyperendémique.

4½ mois après le traitement et sur les mêmes critères parasitologiques, 52/55 cas d'infestations à *S. haematobium* et 34/55 cas d'infestations à *S. mansoni* (mêmes malades) ont montré une guérison parasitologique de leur parasitose. En fin de compte, seuls 3 enfants restèrent positifs pour *S. haematobium*. Le taux de guérison n'est pas aussi bon pour *S. mansoni* que pour *S. haematobium*, chez les mêmes malades traités pour une double infestation. Les œufs de *S. mansoni* prennent plus longtemps à disparaître des selles que ceux de *S. haematobium* des urines. Ceci est mis en évidence par le fait que 3/66 cas de *S. mansoni* étaient en catégorie I au contrôle de 3 mois, alors qu'au contrôle de 4½ mois le taux était monté à 16/55 cas.

L'étude des taux comparatifs des différentes catégories suivant la durée du contrôle, démontre qu'une « résistance » à l'infestation pourrait se développer chez les malades traités.

*Reference*

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