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Effect of CIBA 32644-Ba on *Schistosoma haematobium*

A. DAVIS *

The difficulties attending the use of the antimonial or the thioxanthone drugs in the treatment of human bilharziasis are too well known to merit further comment. Despite intensive search, few alternative compounds have survived screening programmes and clinical trials.

This note describes our first impressions of CIBA 32644-Ba, a new non-antimonial schistosomicide, in the treatment of urinary bilharziasis caused by *Schistosoma haematobium*.

Material and Methods

Initially, twelve patients were treated, of varying ages, weights, and degrees of infection. Eight were adult African males, one an adult African female, one an African child aged four years, and two were European children aged five and nine years.

The methods used have been described in detail elsewhere (DAVIS, 1964). Following physical examination and a chest skiagram, patients with urinary bilharziasis were investigated for associated parasitic infections by standard techniques, and quantitative examinations of urinary egg output were made at least twice before, and daily during treatment.

All urine passed during a period of four hours from 10 a.m. to 2 p.m., the time of maximum egg output, was collected and thoroughly mixed to ensure a Poisson distribution of eggs. Briefly, the method of urine examination involved hatching of a random 10 ml specimen drawn from the four-hour collection. Miracidia were simultaneously fixed and stained with alcohol and eosin and, following centrifugation and withdrawal of supernatant, the final

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0.1 ml was counted as a cover-slip preparation under the 16 mm objective.

The results were expressed as a fraction. The numerator was the number of hatched miracidia, and the denominator was the number of dead eggs which were old and discoloured (B), or those eggs which retained body outline but were not discoloured and failed to hatch (N). Empty egg-shells were not counted. The sum of the numerator and the denominator was the total number of eggs in a random 10 ml sample from a well-mixed four-hour urine specimen at the time of maximal egg output. This procedure has yielded consistently high counts compared with other methods of egg recovery, with a heterogeneity factor well below significance level.

During follow-up, when few eggs were expected, the examination of urines was made by sedimentation for thirty minutes in a conical glass container, after which 10 ml from the bottom of the container was withdrawn and processed as above. This ensured the demonstration of any eggs in the specimen. All follow-up urines were collected between 12 noon and 3 p.m.

Follow-up results were expressed as:

C = Cure. No miracidia or eggs in any one specimen taken over three consecutive days.

P.C. = Possible cure. For three consecutive days no miracidia in any one specimen, but dead eggs were seen.

F = Failure. This meant the presence of hatched miracidia in any specimen, precautions having been taken to guard against contamination.

Results were classified on an all-or-none basis, i.e. to qualify as a cure, three follow-up specimens on consecutive days must have been completely negative. Even the presence of one dead egg in one urine was sufficient to transfer the case to the category of possible cure. Similarly, the presence of one hatched miracidium placed the case in the failed category, and further examinations confirmed this finding.

Results

The first four patients treated will be described in detail to demonstrate the salient points, after which brief reference will be made to the others.

Patient 1

An adult male African with a seven-month history of haematuria; no previous treatment; no physical signs; weight 54 kg; normal chest X ray;

Hb = 96% (M.R.C. grey wedge, 14.6 g Hb/100 ml blood = 100%); blood urea 17 mg/100 ml.

Diagnosis: *S. haematobium* infection; Hookworm; Ascariasis.

Pretreatment urine egg count 1 = 406/29B. i.e. total of 435 and 221 eggs
per random 10 ml from a 4 hour collection 10 a.m.–2 p.m.

Pretreatment urine egg count 2 = 162/59B. i.e. total of 435 and 221 eggs
per random 10 ml from a 4 hour collection 10 a.m.–2 p.m.

Treated with CIBA 32644-Ba 1.25 g daily orally in two divided doses, i.e. 23 mg/kg body weight/day, for eight days, at a total dose of 10.0 g.

No subjective side effects occurred during treatment, but sinus tachycardia varying from 90 to 120 per minute was noted from the third to the eighth day.

Diminished amplitude of $T_{V\ 5,6}$ without inversion occurred on the eighth day and persisted for three days after treatment. No other electrocardiographic changes were noted. The serum glutamic-oxalacetic transaminase (S.G.O.T.) rose from 10 units before treatment to 20 units after treatment, and the serum glutamic-pyruvic transaminase (S.G.P.T.) rose similarly from 10 to 28 units. These values were, however, within normal limits, and other liver function tests remained unchanged. The white-cell count before treatment was 8,000 per cu.mm, differential—neutrophils 18%, lymphocytes 40%, eosinophils 40%, monocytes 2%.

On the first day after treatment the white-cell count was 22,800 per cu. mm, neutrophils 22%, lymphocytes 31%, eosinophils 47%, and on the second day after treatment it was 24,000 per cu.mm, with neutrophils 21%, lymphocytes 32%, and eosinophils 47%.

Daily urinary egg counts were:

Day 3 of treatment 465/21B, i.e. 486/random 10 ml of a 4 h coll. 10 a.m.–2 p.m.

Day 4 of treatment 304/49(10N), i.e. 353/random 10 ml of a 4 h coll. 10 a.m.–2 p.m.

Day 5 of treatment 221/34(10N), i.e. 255/random 10 ml of a 4 h coll. 10 a.m.–2 p.m.

Day 6 of treatment 245/24(10N), i.e. 269/random 10 ml of a 4 h coll. 10 a.m.–2 p.m.

Day 1 post treatment 221/75(15N), i.e. 296/random 10 ml of a 4 h coll. 10 a.m.–2 p.m.

Day 2 post treatment 138/64(10N), i.e. 202/random 10 ml of a 4 h coll. 10 a.m.–2 p.m.

Day 3 post treatment 288/110

(mainly B), i.e. 398/random 10 ml of a 4 h coll. 10 a.m.–2 p.m.

The urine became orange-brown in colour on the evening of the first day and remained discoloured throughout treatment. Normal colour was resumed on the fourth post-treatment day.

Follow-up: fifteen days after treatment there was little symptomatic improvement, but a random urine egg count was 0/8 (4N, 4B) with red cells present. Thus, hatching miracidia had disappeared from the urine, although the count twelve days before had been 288/110 per random 10 ml.

Urinary egg counts after treatment:

57 days after treatment = 0/3B per 10 ml of a sedimented urine taken 12–3.

58 days after treatment = 0/4B per 10 ml of a sedimented urine taken 12–3.

59 days after treatment = 0/3B per 10 ml of a sedimented urine taken 12–3.

Pus cells were present in all specimens but no red cells. Category possible cure.

92 days after treatment = 0/3B per 10 ml of a sedimented urine taken 12–3.

93 days after treatment = 0/9B per 10 ml of a sedimented urine taken 12–3.

94 days after treatment = 0/2B per 10 ml of a sedimented urine taken 12–3.

Red cells present once. Category possible cure.

177 days after treatment = 0/26B per 10 ml of a sedimented urine taken 12-3.

178 days after treatment = 0/16B per 10 ml of a sedimented urine taken 12-3.

179 days after treatment = 0/1B per 10 ml of a sedimented urine taken 12-3.

No red or white cells. Category possible cure. Reinfection risk likely.

This patient typified the major features of the initially treated group—good tolerance, rise in S.G.O.T., S.G.P.T. and W.B.C. during treatment, slight changes in the electrocardiogram, no effect on egg output for the first eleven days, but disappearance of hatching eggs from the excreta within a fortnight of treatment. Follow-up showed a possible cure at two, three and six months after treatment. Persistent urinary debris, and intermittent excretion of black eggs, albeit in small numbers, denied a cure in the absolute sense, although improvement was apparent.

Patient 2

An adult African male aged 18 years, weighing 49 kg, with pretreatment urinary egg counts of 133/30B and 36/29(20B), i.e. totals of 163 and 65 eggs per random 10 ml of urine. Hookworm infection was also present.

He was treated at a dose of 25.5 mg/kg/day for seven days, the total dose being 8.75 g.

Slight nausea was noted on the fifth and sixth day but there was no vomiting. There was no tachycardia. Diminished amplitude of $T_{S1,2,3}$, $V_{5,6}$ without inversion occurred after the fifth day. Tolerance was good.

Daily urinary egg counts were:

Day 2 of treatment 74/45B, i.e. 119/random 10 ml of a 4 h coll. 10 a.m.-2 p.m.

Day 3 of treatment 49/9(5N), i.e. 58/random 10 ml of a 4 h coll. 10 a.m.-2 p.m.

Day 4 of treatment 36/20(10N), i.e. 56/random 10 ml of a 4 h coll. 10 a.m.-2 p.m.

Day 6 of treatment 35/20B, i.e. 55/random 10 ml of a 4 h coll. 10 a.m.-2 p.m.

Follow-up urinary egg counts were:

105 days after treatment = 0/17B per 10 ml of a sedimented urine taken 12-3.

106 days after treatment = 0/26B per 10 ml of a sedimented urine taken 12-3.

107 days after treatment = 0/25B per 10 ml of a sedimented urine taken 12-3.

Red cells in scanty numbers were present in all specimens. The patient was symptom free. Category possible cure. Reinfection risk was unlikely.

Patient 3

An adult African female weighing 42 kg in whom investigation revealed the presence of *S. haematobium*, *Plasmodium falciparum*, ova of hookworm, *Ascaris lumbricoides* and *Trichuris trichiura*. Hb% was 57 and chest X ray normal.

Pretreatment urinary egg counts per random 10 ml were 2123, 2337, 3090 and 2285 on consecutive days.

After treatment with chloroquine sulphate followed by bephenium hydroxynaphthoate she commenced CIBA 32644-Ba but discharged herself the next day with a urinary egg count of 1925 ova per 10 ml having taken 1 g of the drug. She attended one month later and it was surprising to find a urinary egg count of only 470 per 10 ml. The patient said that she had had no treatment in the intervening period and, if true, this may indicate a suppressant action from a single days dosage. She was then treated as an out-patient with a dose of 24 mg/kg/day for six days, a total dose of 6.06 g. Tolerance was good,

no side effects being noted or observed. No effect on urinary egg output was seen during treatment.

Urinary egg counts after treatment were:

37 days after treatment = 0/3B per 10 ml of a sedimented urine taken 12-3.

38 days after treatment = 0/0 per 10 ml of a sedimented urine taken 12-3.

39 days after treatment = 0/6B per 10 ml of a sedimented urine taken 12-3.

Red and white cells were present in all specimens. Category possible cure.

On follow-up at 119, 120 and 124 days after treatment, urine counts were 0/1B on each occasion. At this time she complained of amenorrhoea and had the signs of an eight-week pregnancy. She had been married for three years with no previous pregnancies. Category possible cure. Reinfection risk a possibility.

Patient 4

An adult African male with a five-month history of constant haematuria. Physical examination showed hepatosplenomegaly and weight 78 kg. Investigations revealed trophozoites and gametocytes of *P. malariae*, Hb 66%, and pretreatment urinary egg counts of 2086, 5575 and 5650 ova per random 10 ml of a four-hour collection on three consecutive days.

After chloroquine treatment he was given CIBA 32644-Ba at a dose of 25.6 mg/kg/day for seven days, a total dose of 14 g.

No subjective side effects occurred but there was a slight rise in temperature on the fourth to the sixth day and a sinus tachycardia of 100 per minute on the fifth, sixth and seventh day. A mild leucocytosis occurred after treatment and $T_{V_{1-6}}$ were inverted to a maximum of 2 mm two days after treatment.

On the sixth, seventh and eighth day urinary egg counts dropped to 1450, 2225 and 1300 per random 10 ml but in view of the extremely high counts before treatment and their known variability from day to day no significance was attached to this observation.

Urinary egg counts after treatment were:

19 days after treatment = 0/7B per 10 ml of a sedimented urine taken 12-3.

20 days after treatment = 0/1N per 10 ml of a sedimented urine taken 12-3.

21 days after treatment = 0/60B per 10 ml of a sedimented urine taken 12-3.

Red and white cells were present in all specimens.

47 days after treatment = 0/80B per 10 ml of a sedimented urine taken 12-3.

48 days after treatment = 0/10B per 10 ml of a sedimented urine taken 12-3.

49 days after treatment = 0/27B per 10 ml of a sedimented urine taken 12-3.

Category possible cure.

82 days after treatment = 0/2B per 10 ml of a sedimented urine taken 12-3.

83 days after treatment = 0/19B per 10 ml of a sedimented urine taken 12-3.

84 days after treatment = 0/0 per 10 ml of a sedimented urine taken 12-3.

Category possible cure.

174 days after treatment = 0/11B per 10 ml of a sedimented urine taken 12-3.

175 days after treatment = 0/0 per 10 ml of a sedimented urine taken 12-3.

Category possible cure. Reinfection risk highly likely.

The next five patients were all male African adults of weights within the range 44-66 kg. Four had *S. haematobium* infection solely and one was admitted with lobar pneumonia and urinary bilharziasis.

Three were treated with a dose of 23 mg/kg/day for seven days, one with 26 mg/kg/day for seven days, and one with 24 mg/kg/day for five days.

Two patients vomited once during treatment. Three had no subjective side effects. Three showed an increase in heart rate during treatment without other symptoms. Three patients showed a rise in the white-cell count after treatment but with little change in the differential pattern. No change in the white cell count was seen in the other two patients. Four patients had daily electrocardiograms. One showed no change. In one T wave inversion in V₁₋₃ appeared on the second post-treatment day resembling the pattern seen during antimonial treatment. One showed diminished amplitude of T_{V_{5,6}} and one showed diminished amplitude of T in the standard leads and inversion of T_{V_{1,2}}, both on the last day of treatment. In no case was there marked change in the urinary egg count during treatment.

Follow-up results are given below:

Patient 5

Pretreatment total egg counts per random 10 ml from a four-hour urine collection taken 10 a.m. to 2 p.m. were 2778, 554 and 392.

Urinary egg counts after treatment were:

19 days after treatment = 5/84(4N) per 10 ml of a sedimented urine taken 12-3.
 20 days after treatment = 2/51B per 10 ml of a sedimented urine taken 12-3.
 21 days after treatment = 0/175 per 10 ml of a sedimented urine taken 12-3.

Red and white cells were present in all specimens.

47 days after treatment = 0/1B per 10 ml of a sedimented urine taken 12-3.
 48 days after treatment = 0/1B per 10 ml of a sedimented urine taken 12-3.
 49 days after treatment = 0/17B per 10 ml of a sedimented urine taken 12-3.

Category possible cure.

82 days after treatment = 0/1B per 10 ml of a sedimented urine taken 12-3.
 83 days after treatment = 0/3B per 10 ml of a sedimented urine taken 12-3.
 84 days after treatment = 0/0 per 10 ml of a sedimented urine taken 12-3.

Category possible cure.

174 days after treatment = 0/0 per 10 ml of a sedimented urine taken 12-3.
 175 days after treatment = 0/0 per 10 ml of a sedimented urine taken 12-3.

Category cure. Reinfection risk likely.

Patient 6

Pretreatment total egg counts of 67, 129, 48 ova per random 10 ml from a four-hour urine collection taken 10 a.m. to 2 p.m.

Urinary egg counts after treatment were:

19 days after treatment = 0/2B per 10 ml of a sedimented urine taken 12-3.
 20 days after treatment = 0/0 per 10 ml of a sedimented urine taken 12-3.
 21 days after treatment = 0/0 per 10 ml of a sedimented urine taken 12-3.
 47 days after treatment = 0/0 per 10 ml of a sedimented urine taken 12-3.
 48 days after treatment = 0/0 per 10 ml of a sedimented urine taken 12-3.
 49 days after treatment = 0/0 per 10 ml of a sedimented urine taken 12-3.

Category cure.

82 days after treatment = 0/0 per 10 ml of a sedimented urine taken 12-3.
 83 days after treatment = 0/0 per 10 ml of a sedimented urine taken 12-3.
 84 days after treatment = 0/0 per 10 ml of a sedimented urine taken 12-3.

Category cure.

174 days after treatment = 0/1B per 10 ml of a sedimented urine taken 12-3.

175 days after treatment = 0/2B per 10 ml of a sedimented urine taken 12-3.

176 days after treatment = 0/0 per 10 ml of a sedimented urine taken 12-3.

Category possible cure. Reinfection risk likely.

Patient 7

Pretreatment total urinary egg counts per random 10 ml from a four-hour urine collection taken 10 a.m. to 2 p.m. were 555, 318, 400, 515, 445 on consecutive days.

Urinary egg counts after treatment were:

10 days after treatment = 12/23(8N) per 10 ml of a sedimented urine taken 12-3.

11 days after treatment = 0/0 per 10 ml of a sedimented urine taken 12-3.

13 days after treatment = 3/4B per 10 ml of a sedimented urine taken 12-3.

38 days after treatment = 0/18(2N) per 10 ml of a sedimented urine taken 12-3.

39 days after treatment = 0/17B per 10 ml of a sedimented urine taken 12-3.

40 days after treatment = 0/2B per 10 ml of a sedimented urine taken 12-3.

Category possible cure.

66 days after treatment = 0/0 per 10 ml of a sedimented urine taken 12-3.

67 days after treatment = 0/3B per 10 ml of a sedimented urine taken 12-3.

Category possible cure.

90 days after treatment = 0/5B per 10 ml of a sedimented urine taken 12-3.

91 days after treatment = 0/11B per 10 ml of a sedimented urine taken 12-3.

92 days after treatment = 0/6B per 10 ml of a sedimented urine taken 12-3.

Category possible cure.

173 days after treatment = 0/4B per 10 ml of a sedimented urine taken 12-3.

174 days after treatment = 0/3B per 10 ml of a sedimented urine taken 12-3.

175 days after treatment = 0/1B per 10 ml of a sedimented urine taken 12-3.

Category possible cure. Reinfection risk likely.

Patient 8

Pretreatment total urinary egg counts per random 10 ml from a four-hour collection taken 10 a.m. to 2 p.m. were 890, 569, 313 on consecutive days.

Urinary egg counts after treatment were:

29 days after treatment = 0/3B per 10 ml of a sedimented urine taken 12-3.

30 days after treatment = 0/1B per 10 ml of a sedimented urine taken 12-3.

31 days after treatment = 0/0 per 10 ml of a sedimented urine taken 12-3.

32 days after treatment = 0/1B per 10 ml of a sedimented urine taken 12-3.

Category possible cure.

56 days after treatment = 0/0 per 10 ml of a sedimented urine taken 12-3.

57 days after treatment = 0/3B per 10 ml of a sedimented urine taken 12-3.

58 days after treatment = 0/4B per 10 ml of a sedimented urine taken 12-3.

Category possible cure.

84 days after treatment = 0/90B per 10 ml of a sedimented urine taken 12-3.

85 days after treatment = 0/30B per 10 ml of a sedimented urine taken 12-3.

86 days after treatment = 0/18B per 10 ml of a sedimented urine taken 12-3.

Category possible cure. Reinfection risk likely.

Patient 9

Pretreatment total urinary egg counts per random 10 ml from a four-hour urine collection taken 10 a.m. to 2 p.m. were 59 and 75.

Urinary egg counts after treatment were:

89 days after treatment = 0/3(2N) per 10 ml of a sedimented urine taken 12-3.

90 days after treatment = 0/1B per 10 ml of a sedimented urine taken 12-3.

91 days after treatment = 0/0 per 10 ml of a sedimented urine taken 12-3.

Category possible cure. Reinfection risk unlikely.

Patients 10, 11 and 12 were children aged 4, 5 and 9 years who were all treated with 25 mg/kg/day for seven days. Tolerance in all was good although one boy had mild central abdominal pain lasting for a few hours on the fourth day. All completed the course of treatment.

At the time of treatment two European children had widespread superficial ulceration of the legs caused by coral abrasions, a common condition on the East African coast. Treatment with CIBA 32644-Ba appeared to have no adverse local effect as healing proceeded normally during schistosomicidal treatment. Follow-up is proceeding.

Discussion

In children and adults with single and multiple parasitic infections the drug, which was given in two divided doses daily by mouth, was well tolerated. This is in marked contrast to previous schistosomicides, metallic or non-metallic. Clinico-pathological findings during treatment were similar to those described by LAMBERT (1964) in the initial trials, and it seems possible that the post-treatment leucocytosis may be a phagocytic response to dying or immobilised whole-worm material. It would be interesting to compare the post-treatment leucocyte response, the cure rate, and the degree of infection as judged by egg counts, to see if a correlation exists.

Minor T wave changes occurred in the majority of treated patients but other electrocardiographic complexes were normal. T wave changes occur in a variety of conditions, both specific and non-specific, and flattening or inversion may be provoked by hypoxia, hypothermia, electrolyte imbalance, metabolic derangements, myocardial or pericardial disease, vascular conditions, intoxications, or the use of therapeutic drugs. The changes observed in the present series were similar in some respects to those seen during antimonial treatment but were less marked. It would be reasonable to ascribe them to the effect of the drug but their exact causal mechanism is obscure. Their clinical significance, if any, should become clearer after the treatment of many more patients and further elucidation of their pathogenesis. An increase in heart rate was seen during treatment in about half of the patients treated.

The urinary egg-counts showed little change during the period of treatment but there was a striking reduction in viable egg output between 14 and 21 days after treatment. Patient 4 was particularly impressive in this respect, a pretreatment urinary egg count of over 5,000 per random 10 ml fell to 0/7, 0/1 and 0/60 at 19, 20 and 21 days after treatment. There can be little doubt of the profound initial effect of the drug on viable egg excretion in urinary bilharziasis.

TABLE 1

Short term follow-up of 97 cases of urinary bilharziasis given 530 MGM of metallic trivalent antimony in 15 days by one of three preparations

	Category			Drug A	Drug B	Drug C	Total
	1 month	2 months	3 months	58 pat.	24 pat.	15 pat.	97
Group 1	C	C	C	7	2	7	16
Group 2	F	F	F	4	0	0	4
Group 3	An F in the first two months. Regard as definite failure			6	1	0	7
Group 3 A	An F in the third month only, i.e. a possible reinfection immediately on discharge. Regard as drug failure			4	0	0	4
Group 4	P.C.	P.C.	P.C.	11	8	1	20
Group 5	Any combination of C and P.C. in the first 3 months but excluding a failure			21	11	4	36
Group 6	1 month	2 months	3 months	5	2	3	10
Incomplete details given	C	C	Lost				
	C	Lost	Lost				
	Lost	Lost	Lost				
	Lost	P.C.	P.C.				
	P.C.	P.C.	Lost				
	Lost	P.C.	P.C.				
	Lost	Lost	Lost				
	Lost	C	C				
	Lost	Lost	Lost				
	C	P.C.	Lost				
				58	24	15	97
	C = cure. No miracidia or eggs in three consecutive specimens. P.C. = possible cure. Dead eggs only found. F = failure. Hatched miracidia in any specimen.						

During follow-up it seemed that urinary debris, red-cell and white-cell excretion continued for a longer period than in comparable patients treated with antimonials. This may be related to an additional bacteriostatic action of antimony on superimposed bladder flora. Clinically the drug produced a less dramatic remission of symptoms than in antimonial treated cases.

Although all patients so far followed up over a three or a six month period continued to excrete black eggs there were no outright failures. Follow-up results, and particularly the continued detection of black eggs in patients in an endemic area after treatment, may be difficult to interpret due to the factors of pre-infection and re-infection. The following results, obtained during a post-treatment study of 97 cases given a curative course of one of three antimonial drugs for urinary bilharziasis, may be of some relevance in this respect.

In only 31 of 97 patients (Groups 1, 2, 3) was it possible in an endemic area to reach a clear-cut decision on cure or failure. Fifty-six of 97 patients (Groups 4, 5) excreted black eggs, the majority in very small numbers, throughout, or at some time during the first three months after conventionally curative treatment. From a community viewpoint such cases are harmless, but it may be impossible to decide in an individual case whether true cure has been attained. There are two schools of thought on parasitological criteria of cure in bilharziasis. The first believes that no eggs at all should be excreted to satisfy the term cure. The second believes that intermittent excretion of black eggs after treatment is not necessarily evidence of failure. An expert committee on bilharziasis

TABLE 2

*Long term follow-up of Group 4, Table 1
Patients passing black eggs at each examination for three months
after curative antimony treatment*

	Category 1—3 months			Category at 6 months				Category at 1 year			
	P.C.	P.C.	P.C.	C	P.C.	F	Lost	C	P.C.	F	Lost
Drug A	11			0	8	1	2	1	5	1	4
Drug B	8			2	4	1	1	1	0	4	3
Drug C	1			1	0	0	0	0	0	0	1
Total	20			3	12	2	3	2	5	5	8

C = cure. No miracidia or eggs in three consecutive specimens.
P.C. = possible cure. Dead eggs only found.
F = failure. Hatched miracidia in any specimen.

TABLE 3
Long term follow-up of Group 5, Table 1
Patients passing black eggs at some time during the first three months
after curative antimony treatment

	Category 1—3 months Any combination of C and P.C. but excluding a failure	Category at 6 months				Category at 1 year			
		C	P.C.	F	Lost	C	P.C.	F	Lost
Drug A	21	8	9	1	3	11	2	2	6
Drug B	11	6	2	0	3	2	2	0	7
Drug C	4	1	0	0	3	0	0	0	4
Total	36	15	11	1	9	13	4	2	17

C = cure. No miracidia or eggs in three consecutive specimens.
P.C. = possible cure. Dead eggs only found.
F = failure. Hatched miracidia in any specimen.

(W.H.O., 1953) stated . . . "It is well known that dead eggs can be shed into urine or stool for months after cure." Obviously proponents of the latter criterion produce better "cure rates" than those who hold that only complete absence of eggs during follow-up means a cure. In an attempt to clarify the meaning of excretion of black eggs following curative treatment in an endemic area these 56 patients were followed at six months and at one year. The results are shown in Tables 2, 3, and 4.

Of the 20 cases who passed black eggs at each follow-up during the first three months after curative treatment, two were failures i.e. produced viable miracidia, at six months, and five at one year.

Of the 36 cases who passed black eggs at some time during the first three months after curative treatment one was a failure at six months, and two at a year.

TABLE 4
Addition of Tables 2 and 3

The category of 56 patients passing black eggs in early follow-up after curative antimony treatment	C	P.C.	F	Lost or to be followed
<i>at six months was</i>	18	23	3	12
<i>and at 1 year was</i>	15	9	7	25

C = cure. No miracidia or eggs in three consecutive specimens.
P.C. = possible cure. Dead eggs only found.
F = failure. Hatched miracidia in any specimen.

Summing the two groups and regarding them as cases who passed black eggs throughout or at some time during early follow-up, the following figures were obtained.

Thus at six months only 3 of 44 patients completely followed up became failures, and at one year there were 7 failures in the 31 fully documented patients.

At six months even if all the lost cases were regarded as failures and added to the known failures, the total failure rate would be much less (ratio 41 :15) than those who were either excreting no eggs or continuing to excrete black eggs.

These figures support the concept that black eggs can be shed for months after curative treatment and such eggs do not necessarily mean impending relapse.

At one year the figures were also hopeful but there were too many cases lost for a dogmatic conclusion to be reached. In any event the chances of re-exposure in peasant populations in an endemic area during one year after curative treatment are so high that it was surprising to find only 7 of 31 followed cases positive and in some of these re-infection, as distinct from relapse was the cause.

In the 16 cases in Table 1 who were classified as cures at each of the first three monthly follow-ups (each consisting of three examinations), the results at six months were:

	Cure	Possible cure	Failure	Lost or follow-up proceeding
	7	3	2	4
and at 1 year	5	0	2	9

Thus even those who had the best early follow-up results were not grossly dissimilar in progress at six months to those passing black eggs in early follow-up.

Although the results expose the limitations of long term follow-up in the presence of re-exposure risk it is suggested that, in an endemic area, only a small proportion of those patients passing black eggs in small numbers after curative antimony treatment will relapse at six months. The initial follow-up results with the CIBA preparation should be viewed in this light.

Summary and Conclusions

In a small number of patients with urinary bilharziasis treated with CIBA 32644-Ba tolerance was good. Six of nine patients who had daily electrocardiograms showed minor T wave changes after

treatment. There was no change in urinary egg excretion rates during treatment but there was a striking reduction in egg excretion at times varying from 14 to 21 days after treatment when viable eggs disappeared from the urine.

On follow-up over three or six months there were no outright failures although all cases continued to pass very small numbers of black eggs. Evidence derived from continued follow-up of antimonial treated cases in an endemic area suggested that only a small proportion of those patients passing black eggs after curative treatment would relapse in the first six months.

The finding of black eggs after treatment does little to minimize the potentialities of the drug in the management of urinary bilharzial disease. Larger trials, both in hospital and in the field, are indicated to assess its use in the treatment, suppression and control of urinary bilharziasis in the individual and in the community. Further observations on its effect on the electrocardiogram are needed.

Résumé et conclusions

Chez un petit nombre de malades souffrant de bilharziose urinaire, la tolérance au CIBA 32644-Ba fut bonne. 6 sur 9 malades, chez qui l'ECG a été pratiqué chaque jour, présentèrent des modifications légères de l'onde T après le traitement. Il n'y eut aucun changement du nombre d'œufs éliminés pendant le traitement, mais une importante réduction de ce nombre du 14^e au 21^e jour après le traitement, époque à laquelle fut observée une disparition complète d'œufs viables de l'urine.

Sur une période d'observation de 3 à 6 mois, il n'y eut aucun échec, quoique tous les cas continuèrent à éliminer une très faible quantité d'œufs morts. L'expérience montre, par un contrôle parasitologique continu chez les malades vivants en zone endémique et traités à l'antimoine, que seule une faible proportion de ces malades éliminant des œufs morts présentera une récurrence dans les premiers 6 mois. La trouvaille d'œufs morts après le traitement a peu d'importance pour juger du potentiel d'activité d'un traitement antibilharzien urinaire.

Des essais plus étendus, à l'hôpital et dans le champ, sont indiqués pour juger de la vraie valeur du CIBA 32644-Ba dans le traitement de la bilharziose urinaire, tant comme agent thérapeutique pour supprimer ou contrôler la parasitose chez l'individu et chez les communautés infestées. Il est également nécessaire d'étudier plus avant les modifications ECG observées.

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