URINARY BILHARZIASIS : TREATMENT AND CLASSIFICATION OF RESULTS*

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This paper not only concerns the treatment of the individual patient, but also the control of the disease in general.

In the drug treatment of bilharziasis, there is a real necessity for greater control, and for comparison under controlled conditions. At present we have to try to assess the results obtained in different areas, by different investigators, using differing dosage schedules and differing follow-up methods. We believe that the only way we can attempt to gauge the relative efficiency of drugs is to split our subjects into groups, which are as nearly equal as they can be in all respects, with the single exception of the drug used per treatment.

As regards bilharziasis the factors for which groups must be standardized are as follows:

1. *Ethnic group.*
2. *Tribe.*—In fact, tribal group is probably not nearly as important as the relative watershed, or geographical area, from which the subject comes.
3. *Sex.*
4. *Age.*
5. *Time* since onset of disease.
6. *Severity* of infestation.
7. *The presence* of co-existing *S. mansoni* infestation and *S. bovis* infestation.
8. *The 'complicated' case rate.*

In addition to this standardization, the trial of drugs must be adequately controlled and the allocation of drugs to cases should be made on a random basis.

In spite of standardizing on these aspects, we are still left with considerable uncertainty regarding the natural course of the disease. This applies particularly to our situation in the gold-mining industry because we 'import' labour. We draw men from areas which are vastly different in both physical and psychological environment, from those areas in which they are to be employed. We must then postulate some idea of the natural course of the disease under these different circumstances before we can attempt to assess treatment.

NATURE OF EXPERIMENT

As an introduction to the data presented, we must describe the nature of an experiment conducted at the Ernest Oppenheimer Hospital.

1. We decided to test 4 drugs against bilharziases. On being diagnosed, every case was allocated with complete impartiality to 1 of the 4 drugs in strict rotation. This rotation was interrupted twice only, and was caused by the fact that one of the drugs was said to be specifically contraindicated in cases with *Herpes labialis.* Every fifth case was left untreated as a control case.

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The drugs used were 'win. 13820', 'nilodin', 'astiban', and 'triostam'.

2. We used large groups with the idea of obviating any marked differences in age, severity of infestation, time since onset, tribal group, and the presence of complications. Season of the year, if it *has* any effect, was obviated as a cause of difference by virtue of the method of allocation of drugs.

3. We selected drug treatments which were intended to keep the patient in hospital for nearly the same length of time.

4. The pre-treatment investigation was identical for each patient. Every case was diagnosed on microscopic examination of the urine, and every case had a rectal snip. Patients receiving astiban received an intestinal anthelminthic as a routine 2 days before treatment commenced. (The drug used was 'antepar'). As far as is known this drug has no influence on the blood flukes and the reason for its use was that astiban also kills ascaris; it was felt that this might intensify the nausea occasioned by the drug. This fact might possibly have minimized the toxic effects of astiban, but it will not affect the results of treatment in our opinion.

5. The dosage schedule of each drug is set out in Table I.

TABLE I. DOSAGE SCHEDULES

Win. 13820, 45 mg. per kg. per day for 4 days. Oral administration *p.c. b.d.*

Astiban (*Twsb/6*).

Recommended dose: 2·0 G per adult, regardless of weight.

Dose used: A minimum of 40 mg. per kg. *total* dose, divided into equal daily doses, and given over 4 days in 10% solution in sterile water.

By this schedule our patients nearly always received more than the recommended dose. At 55 kg. body weight 2·2 G, and at 70 kg., 2·8 G.

Nilodin (*Lucanthone hydrochloride*).

Dosage schedule: 25 mg. per kg. per day for 4 days.

Oral administration *p.c. t.d.s.*

Total dose over 4 days: 100 mg. per kg. (45·4 mg. per lb.)

Recommended dose: 20 mg. per lb. over 3 days.

Triostam (*Trivalent sodium antimonyl gluconate B.P.*)

Recommended total dose: Per adult—12 - 17 mg. per kg. I.V.I. over 6 days.

Dosage used: (Total dose.) Minimum of 15·0 mg. per kg., given in equal daily doses by I.V.I. over 4 days.

COMMENTS ON DOSAGE SCHEDULES

The 'blanket' form of dosage schedule is obviously bad, and means that there is really no basis for assessing results, unless a randomized block experiment is used or until a drug which is so effective and so non-toxic is produced that killing of all the *worms* in the heaviest patients is ensured without killing any of the *lightest patients*!

By 'blanket' dosage is meant that all adults get the same dose, regardless of weight and based usually on 70 kg. body weight.

Since we did not think the 'blanket' form of dosage to be good enough scientifically, we assumed that the adult dose was based on an average weight of 70 kg., and we worked out the dose of each patient on the basis of body weight—using differences of 5 lb.

In the case of astiban this would have come to 28·5 mg. per kg. total dose, whereas we used 40 mg. per kg., based on the results of recent work.

In the case of triostam the dose worked out was 16 mg. per kg., whereas for convenience we used 15 mg. per kg.

It is important to show here how this may have affected the results. If, in the treatment of Bantu patients in the mining population with an average body weight of 125 lb., the 'blanket' dose of triostam is given, such patients would receive 20 mg. per kg. total dose over 4 days. On the basis of weight for weight, such patients would receive only 15·5 mg. per kg. total dose.

In this trial triostam may have suffered adversely, *by comparison only*, because, whereas the other drugs were administered in *greater* than recommended dosage, triostam was given in 'recommended' dosage. However, the results are valid under the circumstances of the trial.

6. The follow-up was identical for each drug, and every control case, and was carried out as follows:

One month after cessation of treatment a rectal snip and microscopic urine examination were performed. Thereafter microscopic examination of the urine was performed every 2 weeks until the end of the 3rd month. Thereafter the urine examination was performed at monthly intervals until the 9th month, when a rectal snip was again performed.

Table II shows the initial egg count and the egg counts at successive examinations.

The method used was standardized for every patient and every examination. A specimen of urine of not less than 120 ml. was collected at each examination between the hours of 10.00 a.m. and 11.30 a.m. daily. The specimen was then allowed to stand in a conical urinalysis glass for not less than 15 minutes. Thereafter the supernatant urine was decanted, and the last 15 ml. was collected and centrifuged. (3,000 r.p.m. for 3 minutes.) The supernatant fluid was decanted from the centrifuge tube and then the entire deposit was examined and the ova counted.

In summary the egg counts were the counts of the entire bladder contents at the time of collection of the specimens.

There are 383 re-examinations of the control cases shown here. On 93 occasions there was no gross change in the egg output when compared to the initial egg count. On 89 occasions there were more ova than on the initial count, while there were *less* ova on 185 re-examinations. On 12 occasions no ova were found at all (3 of these being in 1 case who had a very minor infestation—Case 222.) On 4 occasions only dead ova were found. This information is summarized in the list below:

Comparison between initial and follow-up egg counts on control cases

No change	93
More ova	89
Less ova	185
No ova	12
Dead ova only	4
Total	383

If the counts subsequent to the initial count were twice as great they were recorded as 'more'; if half as great they were recorded as 'less'; if within these limits as 'no change'.

Now this may mean that there *is* an actual diminution in egg output in these cases. On the other hand we know that there can be fantastic variation (from between 0 - 80,000 ova per day) in egg output in any one case. It is fairly well established now that there is a peak of output of ova during the day—but we really know nothing of the long-term periodicity in egg output. Although these figures seem to prove the diminution, we must bear in mind the fact that the control group showed a much higher mean count of viable eggs on the initial examination than did the other groups.

The mean counts were:

Win. 13820	80	Grand mean: 143·4
Astiban	84·1	
Nilodin	153·6	
Triostam	182·5	
Control	195·0	

(One exceptional count of over 5,000 ova was excluded from the calculation of the mean for the astiban group because it would have changed the mean from 84·1 to 224·1).

If we consider the mean of the follow-up examination *only*, this appears to have regressed towards the grand mean of the 5 initial counts (143·4). The mean of the follow-up examinations on the control cases was 126·6.

There is, at any rate, no evidence that any case was spontaneously cured, regardless of what interpretation one wished to put on the table!

Case 222, obviously with a very minor worm load, has been negative at the last 2 examinations, and negative for 3 out of the 6 examinations recorded.

Case 177 showed gross variation, as shown in Table II. He showed only 2 viable ova on initial examination. Subsequently he has been shown to pass over 500 ova at one re-examination.

With reference to the *mean counts*, it does appear that, in spite of our random allocation of cases, the groups treated

TABLE II. SUCCESSIVE EGG COUNTS—CONTROL CASES

Serial no.	Initial count	1 Month		2 Months		3 Months	4 Months	5 Months	6 Months	7 Months	8 Months	9 Months
		First	Second	Third	Fourth	Fifth	Sixth	Seventh	Eighth	Ninth	Tenth	Eleventh
167	500	100	1,000	100	500	200	700	100	800	1,000	24	>300
177	2	100	N	500	500	52	100	100	100	200	200	89
187	34	50	18	5	12	25	73	10	34	14	5	32
192	16	88	38	30	29	N	23	14	57	66	47	18
197	100	34	100	100	65	20	56	29	55	150	11	—
202	1,000	500	500	100	1,000	40	100	300	500	200	500	>100
207	100	2,000	500	200	300	100	400	200	100	100	200	>150
212	44	90	71	12	35	60	50	22	20	N	9	>100
217	86	62	77	42	56	15	37	36	20	62	14	2
222	1	1	2	12	3	1	N	21	N	N	N	8
227	500	200	100	100	D	—	—	—	—	—	—	—
232	39	15	6	2	NVSH	NVSH	36	1	54	8	8	20
237	200	100	200	700	80	78	72	100	23	81	100	—
242	100	34	59	34	25	14	18	27	16	MNNV	31	>200
247	500	100	5,000	100	100	3,000	60	500	200	100	300	20
252	400	200	2,000	100	100	71	100	100	200	200	200	>100
257	500	300	74	100	100	500	200	100	100	100	100	30
262	38	200	45	100	100	100	200	100	D	—	—	—
267	100	26	100	36	100	100	200	43	42	86	15	25
272	9	7	17	5	45	37	26	26	1	2	4	5
277	19	N	14	4	40	45	68	6	6	8	12	10
282	55	55	50	100	100	75	100	100	100	100	40	25
287	3	8	2	20	1	13	14	5	N	8	2	5
292	1,000	100	500	200	62	100	200	100	36	20	200	>200
297	400	100	40	93	200	300	100	63	64	100	50	2
302	45	11	34	300	58	66	39	11	54	36	50	4
307	600	100	72	100	100	200	18	100	66	24	100	>100
312	100	100	100	300	200	300	100	100	46	200	50	>100
317	21	100	100	100	300	100	150	14	25	100	30	50
322	30	15	14	7	N	2	N	24	NVSH	20	2	NVSH
327	64	12	21	25	7	9	18	2	1	6	6	>100
332	14	15	8	55	92	200	1	28	42	100	100	N
337	100	59	21	60	46	100	35	74	58	200	15	50
342	100	100	100	200	30	46	30	86	200	25	80	10
347	100	100	100	200	100	100	100	100	80	60	44	>100
352	1,000	100	93	100	100	100	62	100	200	80	150	90

Dash = No examination performed. D = Deserted Company service. NVSH = Only *non*-viable ova found. MNNV = Morphologically normal ova, but flame-cells not pulsating. N = No ova found. (Counts below 100 indicate viable ova only. Counts above 100 indicate all ova—however, the vast majority of *these* counts show 90-99% viable ova.)

were not equal in respect of worm load. These means of initial egg count based on one examination only are probably misleading because of the gross fluctuation that can occur. The worm loads were checked by another method.

We examined the groups from the point of view of 'high' and 'low' worm load. Any case passing 200 or more ova on initial examination was probably 'heavily' infested, and if less than 200, 'lightly' infested.

The groups were seen to be divided more or less equally as can be seen from Table III, which is a contingency Table.

TABLE III. GROUPS DIVIDED MORE OR LESS EQUALLY

	Win. 13820	Astiban	Nilodin	Triostam	Control	Totals
200-9,999	6	9	10	10	8	43
1- 199	30	28	26	25	28	137
Totals	36	37	36	35	36	180

Ax^2—test on this table shows that there is very little difference in the groups on this criterion. $P<\cdot8, >\cdot7$.

In summary, we think that Table II shows that, untreated, the disease carries on unchanged by the different environment and a full diet and full employment. It also demonstrates the effectiveness of the method of examination used.

RESULTS OF TREATMENT

The results of treatment at 3, 6, and 9 months are given in Table IV.

Criterion of 'Cure': That no viable ova shall be found at any follow-up examination. (First follow-up exactly 28 days after conclusion of treatment.)

An analysis of the results at 3 months shows that there is overall heterogeneity, which means that tests for significance between any *2* members of the 4 drugs would be valid ($P<\cdot001$ on dispersion test.) In point of fact a test for significance between win. 13820 (64·9%) and astiban (73·7%) was negative. A test between win 13820 and nilodin (83·3%) was significant at the 5% level. However, it is obvious that the overall heterogeneity between the 4

TABLE IV. GROUP I. NON-TRANSMITTERS

Cases that have not passed a single viable ovum at any one re-examination, but which may have passed unfertilized ova.

Length of follow-up	*3 Months*		*6 Months*		*9 Months*	
Win. 13820	64·9%	24/37	59·4%	22/37	52·8%	19/36
Astiban	73·7%	28/38	68·4%	26/38	64·9%	24/37
Nilodin	83·3%	30/36	83·3%	30/36	71·4%	25/35
Triostam	32·4%	12/37	27·2%	10/37	21·6%	8/37

M = months.

drugs is largely due to the difference between triostam and the other 3 drugs. A dispersion test on these 3 drugs was *not* significant, and hence one is not entitled to compare any *2* drugs within this group.[1] (One would need a 10% difference between cure rates, over *50* cases, before

10% constituted a significant difference, provided there was also overall heterogeneity).

This is very important. In a large number of articles all sorts of conclusions regarding efficacy are drawn from less than 10% differences over small numbers of cases, quite apart from other uncontrolled features.

These results are interesting enough in themselves, but we intend to consider only one point, and that is the suitability of these drugs for mass treatment of the disease from the point of view of their ability to control *transmission* of the disease.

We think it is time that we grouped the results of treatment into 3 categories, namely:

Group I. No Transmission

A. Absolute cures.

B. Cases passing only unfertilized ova.

Group II. Doubtful Transmitters

A. 'Technical' failure of treatment. These are cases which may still pass 1 viable ovum at any 1 re-examination.

B. Cases with a marked reduction in worm load. I consider cases passing up to 10 viable ova at any 1 re-examination to be in this group.

Group III. Transmitters

A. Asymptomatic Failures. These cases have a marked reduction in worm load, but pass more than 10 viable ova at any 1 re-examination.

B. Symptomatic Failures. These are cases passing more than 30 viable ova at any 1 re-examination, or cases with recurrence of severe haematuria and dysuria, owing to the continued presence of many live worms. Obviously the complications of the disease have to be borne in mind before labelling a case a symptomatic failure. One must find live ova to start with, and investigate fully, and perhaps re-treat with a more effective drug.

Many people will not agree with the criteria we have adopted, admittedly arbitrarily. One major point is that some *initial* egg counts did not exceed 5. On the other hand, in the control group we can see that cases passing only 5 ova on admission were subsequently observed to pass many more than 5 or even 30, and in some cases over 1,000, whereas we specify that they must not pass more than 5 ova at *any 1* re-examination.

In any event, using this classification we can re-assess our results of treatment according to Table V.

TABLE V. GROUPS I AND II COMBINED—DOUBTFUL TRANSMITTERS

Based on Criterion A—not more than 10 viable ova at any one re-examination.

Length of follow-up	*3 Months*		*6 Months*		*9 Months*	
Win. 13820	78·4%	29/37	78·4%	29/37	77·7%	28/36
Astiban	92·1%	35/38	92·1%	35/38	91·9%	34/37
Nilodin	91·6%	33/36	91·6%	33/36	91·4%	32/35
Triostam	45·9%	17/37	45·9%	17/37	45·9%	17/37

M = months.

Table V is based on a criterion of not more than 10 viable ova at any 1 re-examination. It is apparent that on this criterion the first 3 drugs could be considered as suitable for mass treatment. However, as regards mass treatment, 2 of these drugs, astiban and nilodin, have considerable toxic effects, the first also has to be administered parenterally.

TABLE VI. GROUPS I AND II COMBINED—DOUBTFUL TRANSMITTERS

Based on Criterion B—not more than 5 viable ova at any one re-examination.

Length of follow-up	*3 Months*		*6 Months*		*9 Months*	
Win. 13820	67·5%	25/37	67·5%	25/37	66·6%	24/36
Astiban	81·5%	31/38	81·5%	31/38	81·0%	30/37
Nilodin	91·6%	33/36	91·6%	33/36	91·4%	32/35
Triostam	45·9%	17/37	45·9%	17/37	40·5%	15/37

M = months.

Table VI is based on a criterion of 'non-transmissability', of 5 viable ova at any 1 re-examination. In this Table only 2 drugs could be considered as suitable for mass treatment.

Provided that the optimum dosage schedule of the third drug—win. 13820—can be found, it may well prove suitable for mass treatment because of its relatively low toxicity.

We wish only to draw attention to the concept—we would be very unhappy at accepting the first criterion given above. We think we would be very much safer with the second one—but there will be considerable disagreement on this point. The question of re-treatment has been left open.

Nilodin, in the dosage used, showed acute toxic effects in 86% of cases—vomiting occurring in 76%.

Astiban showed toxic effects in 60% of cases—vomiting occurring in 34%.

Win. 13820 caused acute toxic effects in 38% of cases, but vomiting occurred in only 22%.

Triostam in the dose used was practically completely non-toxic, and perhaps confirms that the dose of triostam was inadequate.

CONCLUSION

In conclusion this experiment has taught us the following points:

1. The necessity for strict control of trials is borne out by the results. Even taking large numbers of cases in strict rotation may *not* lead to satisfactory standardization of cases as regards worm load. In other words, we may not have treated groups equal in all respects. Future trials should be conducted on the randomized block experiment basis.

2. Drug dosage should be calculated on body weight, but a certain amount of experience is needed in deciding the correct dose, especially where a manufacturer recommends a 'blanket' form of dose schedule.

3. That it will be useful, not only to assess whether a case is a failure, but also the 'type of failure'.

4. That *untreated*, the progress of the disease is not altered by the good diet, housing and general health improvement brought about by the industrial environment of the mines.

5. That unless one has magnificent facilities, such as those made available to us by the Anglo-American Corporation of South Africa, one cannot even think of a trial of this nature.

SUMMARY

The necessity for controlled therapeutic trials in attempting to assess anti-schistosomal drugs is discussed. The variables thought to have a bearing on results of treatment are mentioned.

A controlled experiment is described in which 4 drugs

were tried against each other in *Schistosoma haematobium* infestations. In addition, a control group of patients with the disease were left untreated and were followed-up in an exactly similar way to the other cases.

An apparent diminution in egg output in the control cases with progression of time is discussed. The fact that no case undergoes spontaneous cure is shown.

The results of treatment with the 4 drugs are discussed and a proposal is made that treatment should be assessed not only from the point of view of 'cure', but also whether transmission of the disease would be controlled. The suitability of the drugs for mass treatment is briefly discussed.

If there is any basis to the theory that a light infestation protects against subsequent infestation, then it will be doubly useful to assess treatment on the basis mentioned.

Finally the lessons learned in conducting therapeutic trials of these drugs are mentioned.

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