FURTHER OBSERVATIONS ON BILHARZIASIS IN THE NORTHERN TRANSVAAL

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Since publishing our earlier observations[1] further attempts were made to solve the problem of mass treatment of bilharzia sufferers, and the principles of prevention mentioned in that article were followed up. Social control of bilharzia through health education of the Bantu and other people included instruction on the elements of the epidemiology of bilharzia. By means of lectures, films and demonstrations, they were informed of the part they can and should play in preventing the occurrence and spread of the disease in their own territories.

Honey and Gelfand[2] rightly noted that bilharzia is still regarded as a benign disease, an opinion which, so far, is difficult to change or contradict. The result is that people continue to use infected water unconcernedly, and the responsible authorities fail to institute adequate measures against the spread of the disease. Officials of the State Health Department have given 5-day courses of lectures, illustrated by films, and practical demonstrations to some 9 groups, each of 50 chiefs and headmen, over the last 2 years.[3,4]

Apart from these efforts to rouse the conscience of the adult Bantu population, the Department of Bantu Education cooperates in health education, with special reference to bilharzia in school children, through the medium of school inspectors, school principals and teachers. What the children hear at school makes them more receptive to belief in, and application of, the principles of environmental hygiene and sanitation, especially in rural areas.

A large number of school children also receive further instruction and advice on bilharzia prevention when the health staff visits schools to test the incidence of helminthiasis. A large number of district nurses are employed in the various districts where they also give lectures on health in general and on bilharzia and tuberculosis in particular. Farmers' unions receive directions from time to time about the safeguarding of their employees against the 2 prevalent diseases — bilharzia and tuberculosis.

In all this health propaganda, stress continues to be laid on the methods of purifying and safeguarding water supplies in rural areas, and on methods of environmental hygiene and the need for better sanitation. Considerably more money, time, and effort will, however, have to be spent than has been done so far on rousing the conscience of the Bantu sufficiently to recognize the problems involved in bilharzia control and prevention in their territories. Traditional attitudes will have to be altered and many misconceptions about bilharzia removed by more effective health education.

Vector Control

This has so far been considered the duty of the Government, so that individual owners of estates have done little to limit snail breeding on their property. Because the Government undertook large-scale control of malaria and practically eradicated the disease in the Northern Transvaal, the community assumed that the Government would move on to the control of any other widespread disease like bilharzia. There has thus far, however, been no legislation referring specifically to bilharzia or to the allocation of responsibility for vector snail control.

The 2 main vectors of bilharzia, namely, *Bulinus (physopsis) africanus* and *Biomphalaria pfeifferi*, are widespread over the Northern Transvaal, but, peculiarly enough, intestinal bilharzia (*S. mansoni*) is limited to the Eastern lowveld. This is probably because of the lack of free migration of mansoni carriers from east to west — the western area is not very suitable for intensive cultivation, as is the east, and labour is not attracted to that area. Small areas in the west are, however, showing signs of agricultural development, and small foci of *S.mansoni* infestation have appeared there. This has been traced to labourers recruited in the east and settling on farms in the west. This is bound to be the forerunner of further foci of spread of *S. mansoni* in view of developments there.

Chemical Control

This has so far been the only method of snail destruction undertaken on a large scale. Copper sulphate was the molluscicide of choice, although there was only a small range of suitable chemical products available. The conference arranged in April 1960 by the World Health Organization at Lourenço Marques appeared to hold the opinion that the most promising single method of bilharzia control would be the use of an efficient molluscicide. A new product that appears to show much promise is Bayer 4780, a powder that is described by Foster *et al.*[5] as relatively nontoxic to warm-blooded animals. It is an efficient destroyer of snails and their egg clutches in a variety of aquatic conditions. There should therefore be great activity in the coming season regarding snail destruction, and the older molluscicides like copper sulphate and sodium pentachlorophenate will probably be limited to use in those conditions in which they are found to act most efficiently.

In small areas, covering altogether probably not more than 1,500 square miles in the Northern Transvaal, copper sulphate has been used effectively to keep the local human population free of re-infection during chemotherapeutic trials. Although it is realized that the use of copper sulphate is not the answer to the molluscicide problem, Table I shows how the rate of infection might be reduced by its continuous use, to the exclusion of other control measures.

The table shows a reduction in *S. haematobium*, because its vector snail appears to be more susceptible to, and more easily destroyed by, copper sulphate. The reduction is apparent, although the methods of testing stools of patients is considered to have been more accurate in 1959 than in 1955. This accuracy therefore accentuates the fact that copper sulphate caused a reduction in the disease in the children under 5 years of age, while those over 5 years retained their infection and were discovered later by the more recent and accurate testing method.

TABLE I. INCIDENCE OF BILHARZIA IN CHILDREN TESTED IN 1955 AND AGAIN IN 1959: ZEBEDIELA

Nature of infection	*Year*	*Percentage positive under 5 years old*	*Percentage positive 5 years old and over*
		%	%
S. haematobium	1955	42·2	89·6
	1959	12·6	72·4
S. mansoni	1955	38·1	76·4
	1959	11·1	91·7

The effect of the diligent application of copper sulphate in the Mohlaba experimental bilharziasis-control project in the Letaba area is also shown by our findings in 1957 and 1959, as illustrated in Table I A.

TABLE I A. BILHARZIASIS INCIDENCE IN THE NORTHERN TRANSVAAL. ROUTINE SURVEYS IN 1957 AND 1959 IN THE MOHLABA EXPERIMENTAL BILHARZIASIS-CONTROL PROJECT: LETABA DISTRICT

	S. haematobium			*S. mansoni*		
	No. tested	*No. positive*	*% positive*	*No. tested*	*No. positive*	*% positive*
Before molluscicidal measures, May 1957	1,042	516	49·5	1,029	934	90·7
After molluscicidal measures, April 1959	2,390	530	22·1	2,390	1,215	50·8

Physical Control of Snails

This control by engineering and similar measures is a subject to which Marill,[6] Jackson,[7] McMullen and Harry[8] and others have drawn attention. The snail can be limited or destroyed effectively by such measures in irrigation and other water-control schemes. It is here where the interests of the water- and soil-conservation experts, the engineer, and the bilharziologist may diverge.

The conservationist advocates the creation of water 'sponges', which ensure an adequate water supply for plant and animal life in the future. The engineer endeavours to put this idea into practice, while the bilharziologist has the task of eliminating the snail vectors by urging that the water and irrigation schemes, in which the vectors are a danger to public health, be so designed or modified as to limit or control surface water bodies. It is because of these clashing interests that all Government departments should be required to cooperate very closely in order to give all aspects of the bilharzia problem the attention they merit.

Biological control of the vector is also receiving some attention. Although it was decided not to import into South Africa for experimental purposes the predator snail *Ceratodes (marissa) cornuarites*, as described by Ferguson and Palmer,[9] work on other local predators on the snail is going ahead. This subject is receiving some attention because of the resistance problem among insect and other vectors of disease. Furthermore, the extensive use of insecticides shows signs of interfering with the useful work of insects, such as pollination of plants of economic importance. Molluscicides might therefore also be found to interfere with crops irrigated with these chemicals, and it is therefore necessary to have as wide a range of control methods as possible, to be applied under the particular circumstances for which they are most suitable and least likely to do harm. In biological control the agent is more difficult to control after application, and may itself become a pest; for this reason chemical control is much preferred. Finally, the biological agent is often itself subject to attack by other predators according to the laws of the biological balance in nature, a fact which makes this method of control a weapon of uncertain value.

TABLE II. BILHARZIASIS: PREVALENCE IN AGE GROUPS IN NORTHERN TRANSVAAL ROUTINE SURVEYS

		0 - 1 yrs.		2 - 4 yrs.		5 - 9 yrs.		10 - 14 yrs.		15 - 19 yrs.		20 - 39 yrs.		40 yrs. +		Total M	Total F	Grand total
		M	F	M	F	M	F	M	F	M	F	M	F	M	F			
A.	Urines tested for *S. haematobium*	225	197	445	346	7,443	5,012	9,485	6,624	3,304	1,984	1,023	1,239	775	726	22,700	16,128	38,828
	No. positive	35	15	63	61	2,838	2,095	4,360	2,673	1,286	601	212	289	71	176	8,865	5,910	14,775
	Percentage	15·6	7·6	14·2	17·6	38·1	41·8	46·0	39·0	30·3	20·7	23·3	23·3	9·2	24·2	39·0	36·6	38·2
B.	Stools tested for *S. mansoni*	206	188	52	88	5,251	4,118	7,232	4,692	2,209	1,120	303	374	157	365	15,410	10,945	26,355
	No. positive	27	15	5	22	1,049	707	2,209	1,436	253	343	36	123	34	119	3,613	2,765	6,377
	Percentage	13·1	8·0	9·6	25	20	17·2	30·5	30·6	11·5	30·6	11·9	32·9	21·6	32·6	23·4	25·3	24·2

Note: incidence of bilharzia is higher in males than in females in lower age groups and lower in males than in females in higher age groups (over 20 years especially). M = male; F = female.

TABLE III see p 814

TABLE IV. RESULT OF BILHARZIASIS TEST AFTER TWSb

Scholar No.		Weight (kg.)	16.6.59 Total dosage	4.8.59		20.8.59		3.9.59		11.9.59	30.11.59		22.1.60		26.1.60		28.1.60	19.2.60			22.2.60		8.3.60		12.4.60		2.6.60		Reaction	
				Sh	Sm	Sh	Sm	Sh	Sm	RB	Sh	Sm	Sh	Sm	Sh	Sm	Hormone	Sh	RB	Sm	Sh	Sm	Sh	Sm	Sh	Sm	Sh	Sm	1	2
A	1	43	1·0 G.	—	—	—	—	—	—	Y	—	—	L				H	—		+	—	—	—	+	+	—	+	+	—	
	2	32	1·0 G.	—	—	X	—	—	—	Y		A	—	—	—	—	H	—		+	—	—	—	+	+	—	+	+	—	
	3	36	1·0 G.	—	—	X	—	X		Y	—	—	A			A	A		A		—	—	Y	—	—	—	+	+	—	
	4	25	1·0 G.	—	—	X	—	X	—	Y	—	—		—	—	—	H			Y	+	—	+	—	+	—	+	—	—	
	5	61	1·0 G.	—	—		X	X	X	Y		—	—	—	—	—	H	—		+	+	—	+	—	+	—	—	—	PF	
	6	43	1·0 G.	—	—		—	X	X	Y	—	—	—	—	—	—					+		+	+	+	+	+	+	—	
	7	38	1·0 G.	X	X	X	X	X	X	Y	X	—	Y	—		A							+	+	+	+	+	+	—	
	8	29	1·0 G.	—	—	—	—	—	—	Y	—	—	—	—		A							—	+	—	+	—	—	—	
B	1	35	1·0 G.	—	—		A		X	Y	—	+	—	Y	—	—	H		Y		—	+	—	+	—	—	+	+	N	
	2	33	1·0 G.	—	X		A		X	Y	—	—	—	—	—	—	H		Y			A	+	+	+	—	+	+	—	
	3	32	1·0 G.	X	X		X	X	—	Y	—	—	Y	—	—	—							+	+	+	+	+	+	—	
	4	30	1·0 G.	—	—	—	X	—	—	Y	—	—	—	—	—	—							—	+	—	+	+	+	—	
	5	44	1·5 G.	—	—		—	X	—	Y	—	—	—	—	—	—	H		Y		—	—	Y	—	—	—	+	—	PV	
	6	37	1·5 G.	X	—	X	—	—	X	Y	—	—		L															—	
	7	32	1·0 G.	—	—	X	—	—	X	Y	—	—	—	—		A							+	—	+	+	+	—	N	V
	8	34	1·0 G.	X	X		X	—	X	Y	X	—	—	—	—	—							+	+	+	+	+	+		V
C	1	60	10 ml. NaCl		A		X	X	—	Y	—	—	L															—	
	2	51		X	—	X	—	X	—	Y	—	+	—	—	—	—	H	—		Y	+	—	+	—	+	+	+	+	—	
	3	30		—	—	—	—	X	—	Y	—	—	—	—	—	—	H	—		Y	—	—	—	—	+	—	—	+	—	
	4	30		X	—	—	X	—	—	Y	—	—	—	Y	—	—	H	—		+	+	+	Z	+	—	+	+	—	—	
	5	28		X	—	X	—	X	—	Y	X	—	—	—	+	—		—		—		·	+	—	+	—	+	—	—	
	6	36		—	—		—	—	X	Y	—	—	—	—	—	—	H	—		+	—	+	—	—	—	+	+	—	—	
	7	35			A	X	X	X	X	Y		A	—	+		A		—		—					+	+	+	—	—	
	8	35		—	—	X	—	X	—	Y	—	—	—	—	—	—		—		—			—	—	—	—	L		—	
	9	26		—	—	—	—	—	—		X	—	+	—	+	—	L												—	

X = inert ova, Y = dead ova, Z = blood, A = absent, RB = rectal biopsy, H = hormone (10 mg. stilboestrol), L = left school, N = nausea, V = vomiting 2 - 3 hours after meal, P = pain in chest, F = flushing, Sh = *S. haematobium*, Sm = *S. mansoni*, + = live ova, — = no ova.

BILHARZIA CONTROL

Control by destruction of the schistosome parasite in infected persons is not generally considered an acceptable or efficient method with the drugs at present available for the purpose. Table II shows the prevalence of the disease as discovered in surveys in a limited number of areas. It indicates that there is at present great need for a more effective schistosomicide to treat the large number of sufferers already discovered. This table indicates the overall prevalence and does not reveal the same disparity between males and females which was found by Maldonado and Oliver-Gonzáles,[10] while it shows a similar reduction in prevalence, although we used copper sulphate to reach that result.

It is apparent that the disease, especially mansoni bilharziasis, can still spread to the North Western Transvaal and, unless molluscicidal measures are soon extended successfully, more people will be infected than become parasite-free. The demand for an efficient schistosomicide will therefore continue indefinitely unless manufacturers produce a suitable drug soon. The results of many field trials of the present products are not very encouraging and the search for the ideal schistosomicide continues. In this communication we therefore report on our experiences in the search for the ideal drug for use in bilharziasis. No large-scale campaign against bilharziasis has been embarked on because of the lack of an efficient drug which could, without side- or after-effects, destroy the schistosomes after 1 or 2 oral doses or perhaps 2 intramuscular injections.

Side effects in drug treatment are stressed, because in the Transvaal bilharziasis is not as serious a disease as it is in other parts of Africa, and in order to encourage sufferers to come for treatment this should be pleasant and acceptable. The Transvaal being on the southern fringe of the extension of the vector snail distribution, the infections are presumably not as heavy as farther north and east. Another reason why an efficient schistosomicide is urgently needed is the fact that carriers will continue to spread the disease for many years. Even if an efficient molluscicide is discovered now it will take many years before the vector snails are under control. Unless the parasite and the vector snails are kept at a low level simultaneously, eradication will continue to be a problem.

Lucanthone hydrochloride has been tried extensively without proving completely efficacious, but the improvement in treatment by combining 'nilodin' with belladonna extract by Burroughs Wellcome and Co. has reduced its side-effects sufficiently to warrant another trial of this drug at a later stage (see Table V). It must be remembered that school children do not regard bilharziasis seriously and, where they serve as experimental subjects and drug treatment is carried out during their normal school sessions on outpatient lines, the rate of absenteeism rises rapidly. In this respect our experience differs from that of Kloetzel[11] in Brazil, who considers that intolerance of drugs would not interfere with the acceptance thereof in mass treatments. The examination of urines and stools and the administration of drugs interfere with school routine and are not very popular with teachers, although they always co-operate to the fullest extent in the hope that the ideal drug will be discovered. Tests have therefore to be limited to essentials as far as possible, but the danger of error in single tests is realized, and this is shown in Table III.

TABLE III. BILHARZIASIS TESTS, SHILUVANE SCHOOL, LETABA DISTRICT IN THE NORTHERN TRANSVAAL

Tested before September 1959: all negative (216 children).

Tested 6 months later:

Age groups (in years)	Sex	Urines		Stools	
		No. tested	No. positive (*S. haematobium*)	No. tested	No. positive (*S. mansoni*)
5 - 9	M	2	—	2	—
	F	2	1	2	1
10 - 14	M	70	8	70	3
	F	71	11	71	5
15 +	M	64	2	64	6
	F	7	—	7	—
Total		216	22	216	15
Percentage			10·1		6·9

Here 216 children were found at the first test to be negative, but when tested again 5 months later there were variations of 10·1% for *S. haematobium* and 6·9% for *S. mansoni*. It is considered that the chances of re-infection in the area were very small, and the result may indicate the lightness of infestations or the possibility of periodicity in egg-laying by the worms so that their eggs are not discovered in one test. This is discussed again later. The itinerancy of the Bantu population may also lead to infection when they travel long distances to visit friends and relatives who live in uncontrolled bilharziasis areas.

First Series of Observations

These observations concern the use of a new drug TWSb (antimony dimercapto-succinate) which became available for testing through the kind offices of Dr. Ernst A. H. Friedheim.[12] Twenty-four sturdy male Bantu school children between the ages of 10 and 14 years were selected. After repeated testing of their urines and stools for the presence of both *S. haematobium* and *S. mansoni* ova they were admitted in mid-June 1959 to the Douglas Smit Hospital at Shiluvane for treatment with TWSb. They lived in an area where the snail vectors had been under control by copper sulphate for at least 2 years and the possibility of re-infestation after treatment could be excluded. They were divided into 3 groups of 8 children. Each group was kept in hospital for 48 hours and the results of treatment are shown in Table IV.*

Group A received TWSb1 on 2 successive days, group B received 'astaban' (TWSb6) at the same time at dosages shown in the table, and group C received what was considered a harmless physiological solution of normal saline, 5 ml. intravenously on 2 successive days. TWSb was dissolved in pyrogen-free distilled water and in all children the solution was injected intravenously. Soon after the children left hospital the schools closed for the July vacation. There was no opportunity for re-infestation, since the snail vectors had been eradicated in the area and it was winter time, when the infection rate is low in any case. Tests for cure started in August, soon after the schools re-opened. Although Table IV records only monthly test results of our standard sodium sulphate-ether concentration method, other tests were carried out, especially miracidial hatching tests at monthly intervals, and a snail-infection test. Rectal biopsies were done on all the available children on 11 September 1959 and 19 February 1960, as shown in the Table.

It was disturbing to discover the total disappearance of schistosome ova in the control group C, when even the rectal biopsies in September showed only dead ova. On 30 November 1959 the first positive case was discovered by stool examination in child C2. The others in the control group had therefore remained negative for at least 5 months. In the meantime the TWSb groups had also remained negative.

The negative findings in group C, however, call for an explanation. This is based on the observation that the number of schistosome ova increases markedly in pregnant women; it seems that the pregnant state stimulates the schistosomes to greater feats of egg-laying. In our trial it was thought that an injection of stilboestrol or oestrogen may induce any schistosomes remaining in the test subjects to resume egg-laying. It was decided to select a few negative children from the treated and control groups for administration of 10 mg. stilboestrol dipropionate to ascertain whether this would stimulate the worms as anticipated. The hormone was administered on 28 January 1960 after previous testing for the presence of ova in urines and stools. Soon after this the hormone group showed positive results in groups A and C and only later in group B. This appears to bear out Friedheim's opinion that astaban is more effective than TWSb1, since the worms in group B were not able to respond to the hormone by laying eggs as rapidly as those in groups A and C. The first positive finding in group B was in the middle of February 1960, some 8 months after administration of astaban. It may be noticed that child B5 received 1·5 G. astaban and

TABLE V. GENERAL TABLE SHOWING THE RESULTS OF ADMINISTERING VARIOUS DRUGS IN BILHARZIASIS SUFFERERS. BILHARZIASIS THERAPY TRIALS, SHILUVANE SCHOOLS, LETABA DISTRICT*

	TWSb 1 (intravenous) (1·5 G.)			*TWSb 1 (intramuscular) (1·5 G.)*			*Astaban (intravenous) (1·5 G.)*			*Astaban (intramuscular) (1·5 G.)*			*Miracil (oral) (40 mg. per kg.)*			*Nilodin (oral) (40 mg. per kg.)*			*Control (Vit. B. Co.) (1 - 2 tablets)*		
	No. tested	*No. pos. Sh.*	*No. pos. Sm.*	*No. tested*	*No. pos. Sh.*	*No. pos. Sm.*	*No. tested*	*No. pos. Sh.*	*No. pos. Sm.*	*No. tested*	*No. pos. Sh.*	*No. pos. Sm.*	*No. tested*	*No. pos. Sh.*	*No. pos. Sm.*	*No. tested*	*No. pos. Sh.*	*No. pos. Sm.*	*No. tested*	*No. pos. Sh.*	*No. pos. Sm.*
Before treatment, 12.9.59 ..	32	27	32	19	98	74	98	56	30	22	30	19	97	77	97	55	124	93	124	69	114	88	114	65	120	92	120	70
Percent positive		87·5%		59·3%		75·5%		57·1%		73·3%		63·3%		79·3%		56·6%		75%		55·1%		77·1%		57%		77·5%		58·3%
First test, 5.12.59	30	0	30	4	95	14	95	6	28	1	28	4	87	11	87	5	118	26	118	12	107	19	107	14	112	45	112	21
Percent positive		0%		13·3%		14·7%		6·3%		3·5%		13·2%		12·6%		5·7%		22%		10·1%		17·7%		13%		38%		17·8%
Second test, 13.1.60	26	1	26	3	93	19	93	5	23	1	23	1	76	2	76	6	113	20	113	13	106	23	106	14	107	34	107	16
Percent positive		3·8%		11·5%		20·4%		5·4%		4·3%		4·3%		2·6%		7·8%		17%		11·5%		21·7%		13·2%		31·7%		14·9%
Third test, 15.2.60	26	0	26	1	81	15	81	6	22	1	22	2	75	4	75	7	108	25	108	9	104	23	104	9	104	35	104	16
Percent positive		0%		3·8%		18·5%		7·4%		4·5%		9%		5·3%		9·3%		23·1%		8·2%		22·1%		8·6%		33·6%		15·1%
Fourth test, 12.4.60	25	3	25	3	74	21	74	10	20	3	20	1	72	7	72	11	105	39	105	22	101	29	101	22	104	46	104	22
Percent positive		12%		12%		28·5%		13·5%		15%		5%		9·7%		15·2%		37·1%		20·9%		28·1%		21·7%		44·4%		21·1%
Fifth test, 7.6.60	23	3	23	3	67	21	67	15	21	3	21	1	71	10	71	16	99	38	99	14	93	35	93	24	102	55	102	22
Percent positive		13%		13%		31·3%		22·3%		14·3%		4·9%		14%		22·5%		38·2%		14·1%		37·6%		25·8%		53·9%		21·5%

Sh = *Schistosoma haematobium*, Sm = *Schistosoma mansoni*.
*For statistical analysis of table V see tables A — G (pp 817 — 819.)

TABLE VI. BILHARZIASIS OBSERVATIONS: OVA COUNTS*, ZEBEDIELA, 1960

Test material	*Before treatment*									*After treatment*								
	Bilharzia infected children			*S. haematobium*			*S. mansoni*			*Bilharzia infected (120 fields)*			*S. haematobium (60 fields)*			*S. mansoni (60 fields)*		
Col. 1	*No. children tested 2*	*Total ova 3*	*Average no. per child 4*	*No. children tested 5*	*Total ova 6*	*Average no. per child 7*	*No. children tested 8*	*Total ova 9*	*Average no. per child 10*	*No. children tested 11*	*Total ova 12*	*Average no. per child 13*	*No. children tested 14*	*Total ova 15*	*Average no. per child 16*	*No. children tested 17*	*Total ova 18*	*Average no. per child 19*
Sodium chloride sol. (5 ml. i/v)	93	2,678	28·8	65	1,354	21	82	1,324	16	85	1,898	22·3	61	982	16	77	916	12
Stilboestrol (10 mg. i/m)	92	2,415	26·3	75	1,109	19	85	1,206	14	85	2,051	24·1	50	1,039	21	79	1,012	13
TAB (0·5 ml. s/c)	96	1,689	17·6	57	787	14	85	902	11	91	1,430	15·7	60	796	13	91	671	7·4
Adrenaline (10 minims i/m)	96	1,389	14·6	50	663	13	82	735	9	89	1,330	15	51	677	13	76	563	7·4
Triostam (5 ml. i/v)	89	2,050	23	56	1,114	21	77	936	12	75	609	8·1	36	244	7	66	365	6
Control (small glucose sweet)	97	2,121	21·9	50	1,188	23·8	86	933	11	84	1,572	18·7	45	732	16	75	840	11·2

* 20 fields were counted in each one of 3 tests before and after administering the test material.

remained negative till 2 June 1960. He complained of pain over his chest on injection and vomited on the second day, indicating a near toxic dose. There were slightly more side reactions in group B than in group A. The TWSb was dissolved in distilled water, but we note that Alves[13] used sterile saline, which may affect the result in view of our findings in group C.

The conclusion to be drawn from this trial is the need to investigate: (*i*) the effect of normal saline or NaCl further, and (*ii*) the effect of astaban either in large groups, or (*iii*) in different dosage schedules. It also raises the questions: (*i*) whether hormones can be used in the test for cure or persistence of live schistosomes; (*ii*) whether the schistosomes migrate to the liver for protection after treatment; and (*iii*) whether they lay their eggs in the liver, causing greater damage to it than if they remained in the peripheral venous plexuses. In this respect the work of Robinson[14] may have important practical significance and indicate that the drugs and, in this case, saline have either driven the worms from the egg-laying sites or caused the males to separate from the females and reduced egg production. It appears quite certain that no drug trial should be followed up for less than 12 months, and preferably 18 months, if examination of the stools and urine and other examinations remain negative. The testing of these school children continued until they had all become positive. It should be remembered that the natural mortality among the schistosomes might render the stools negative in the odd case.

It will be observed that subjects A1, B6, C1 and C9 left school before the end of our trial and could not be followed up as required. It can further be concluded that the rate of re-infection was extremely low, even if compared with figures given in Table III. This matter is again dealt with later. It is therefore plain that in such trials subjects should be selected who can complete the treatment, without risk of their disappearance resulting in incomplete records. Preliminary observations on miracidia hatching from ova from these subjects appear to indicate that they could not infest vector snails, but these snails are still under observation for the shedding of cercaria to prove non-infestation. Snails were each exposed to more than 100 miracidia, and since they are assumed not to be able to withstand an invasion of more than about 5 - 15 miracidia, their survival for so long is taken as proof that the miracidia were incapable of invading the snails or continuing their life cycle.

Second Series of Observations

These observations were made after astaban had apparently proved successful in the first series described above. TWSb was tested in larger groups, but in view of the inexplicable results with normal saline as a control material in series I, miracil, nilodin and vitamin-B-compound tablets were used in series II. The results of these tests are shown in Table V; the injections and tablets were administered on 12 September 1959. The results of the follow-up are shown till June 1960, and for each group tested a separate statistical table is given which determines the value of the test material and the method of administration more accurately (Tables A - G).

The children were all Bantu school children between the ages of 7 and 16 years, who were treated on an outpatient basis, i.e. they received the injection or the tablets during school hours and continued with their lessons. This had the advantage that they remained under observation for the possible occurrence of side-effects. Not much importance can be attached to the presence of side effects, however, because they are often the result of suggestibility, proved by the fact that some of the children who received harmless products like glucose also felt giddy or nauseated, or even vomited.

Like the results in our first series, the results here are so variable that it is difficult to come to a firm conclusion. This means that the ideal schistosomicide has not yet been discovered.

Although the observations in this trial continue, it may be noted here that TWSb1 may be ignored, because the manufacturers apparently ceased production in view of the heavy cost involved and the doubtful stability and efficiency of the drug in treatment. As regards astaban, the effect of intramuscular injection is important, because this would be the mode of administration of the drug in mass therapy. Astaban given intravenously would be efficacious in hospital and private practice, where intravenous administration is easy and follow-up may be arranged. The intramuscular injection of astaban reduced the incidence of both *S. haematobium* and *S. mansoni* very markedly, and in this respect still follows the pattern of its action in series I. It remains to be seen how rapidly the children become positive.

It is regrettable that the number of children under observation falls off so rapidly, but this has been unavoidable so far.

It is remarkable that children who took vitamin-B-compound tablets also became negative to a significant extent. This phenomenon has been observed before, and was attributed to hormone influences, which, like the additional secretion of adrenaline in fear, may induce the schistosomes to migrate to the liver for protection, or may lead to the disruption of their conjugal state.

This assumption has apparently now received some support from Merskey *et al.*[15] who quoted Macfarlane and Biggs[16] as mentioning that 'acute anxiety and injection of adrenaline increases fibrinolytic activity in the blood'. Merskey argued that 'the influence of emotion on the hormone content of the blood can explain some anomalies in his observations. Although this conclusion may appear to be without scientific basis as yet, it may merit further investigation'.

Third Series of Observations

Further observations were therefore started to test the theory that schistosomes are very sensitive to biochemical or physiological changes (particularly hormones) in the blood stream, to which environment they appear, normally, to be almost perfectly adapted. For the purpose of our observations it appeared necessary to count the number of ova in the urine and in the stools, before and after administering the drug, to ascertain the difference in numbers of ova found, and hence the influence of the drug or agent on egg-laying by the schistosomes. The only available reference to the effects of a hormone is by Robinson,[17] who investigated the effect of testosterone on the development of *S. mansoni*. Apart from testing a hormone like stilboestrol, adrenaline was also included, and it seemed convenient to test sodium chloride, antityphoid vaccine (TAB), and 'triostam' against a control. Some 563 children suffering from bilharziasis were divided into 6 groups, as shown in Table VI. The stools and urine of each child were tested on 3 separate occasions before administering the test material and again 3 times afterwards. At each test the testing procedures were kept as uniform as possible.

At each test 20 fields under low power were counted after finding the first ovum. The urine and stools of each child were examined fortnightly to find the number of ova of both *S. haematobium* and *S. mansoni*. Columns 2 - 10 in Table VI refer to results before administering the drugs, while columns 11 - 19 give results after administering the test materials. Columns 2 - 4 in Table VI show the number of children, the total of ova found in tests in 60 fields, and the average number of ova per child, respectively. Columns 5 - 7 show the number of children infested with *S. haematobium*, the total number of ova and the average number of ova per child. The next 3 columns show the same results for *S. mansoni*. Columns 11 - 19 show the figures after the administration of the test material, firstly for bilharziasis-infected children and then for each worm species separately. A careful study of the figures in this table would indicate a slight reduction in the total number and in the average number of ova in the sodium chloride group (columns 4 and 13) while, as expected, there is a marked reduction in the total and average number of ova in the group receiving triostam. Unfortunately there is a noticeable decrease in the control group, and it has been most difficult to find a harmless, inactive control material. It must now be accepted that (*i*) the emotional state, and consequently the physiological or biochemical composition or hormone content of the blood stream, could be altered by thought processes, and (*ii*) in the egg-laying activity or egg-counts of the schistosome-infected patient we have a sensitive indicator reflecting these biochemical alterations.

In order, however, to ascertain whether further information could be gleaned from the figures, the children were arranged

TABLE VII. SHOWING THE RANGE OF SCHISTOSOME OVA PRODUCED BY BILHARZIASIS SUFFERERS. TWENTY FIELDS WERE COUNTED IN EACH OF 3 TESTS BEFORE AND AFTER ADMINISTRATION OF EACH DRUG

		1 - 5 ova		*6 - 10 ova*		*11 - 15 ova*		*16 - 20 ova*		*21 - 30 ova*		*31 - 40 ova*		*41 - 50 ova*		*51 - 60 ova*		*61 - 80 ova*		*81 - 100 ova*		*101 and over ova*		*Total no. children*
		Sh	*Sm*	*Sh*	*Sm*	*Sh*	*Sm*	*Sh*	*Sm*	*Sh*	*Sm*	*Sh*	*Sm*	*Sh*	*Sm*	*Sh*	*Sm*	*Sh*	*Sm*	*Sh*	*Sm*	*Sh*	*Sm*	
1. NaCl	before	16	32	4	22	10	7	13	7	10	6	2	—	2	1	2	2	2	—	—	3	2	2	145
	after	19	26	11	22	2	12	7	7	6	4	7	1	8	5	1	—	2	—	—	—	—	—	144
2. Stilboestrol	before	16	25	16	23	7	15	4	7	3	9	2	2	2	2	2	1	2	—	1	—	—	1	140
	after	21	28	10	12	3	1	3	1	10	8	3	2	1	3	1	2	1	4	2	—	1	—	138
3. TAB	before		24	12	29	9	14	6	2	4	9	5	1	1	—	2	—	—	1	—	—	—	1	129
	after	20	34	13	22	12	8	4	3	4	10	3	1	1	1	2	—	—	1	1	—	1	1	142
4. Adrenaline	before	14	31	11	14	11	14	9	11	7	10	1	—	1	1	—	—	1	—	—	—	—	—	136
	after	21	33	13	13	9	19	3	3	3	6	3	6	2	—	1	2	1	—	—	—	—	—	132
5. Triostam	before	14	26	12	21	5	14	3	5	8	10	1	1	1	2	1	—	3	—	2	—	1	—	132
	after	24	31	8	24	6	13	4	2	5	3	1	—	1	1	—	—	—	—	—	—	—	—	123
6. Control	before	11	21	12	21	2	14	9	7	7	5	2	11	3	—	—	—	11	—	1	—	—	1	138
	after	13	25	8	19	6	15	5	10	5	3	3	1	1	—	3	—	1	1	3	1	—	—	123

TABLE A. STATISTICAL TABLE SHOWING THE VALUE OF INTRAVENOUS INJECTIONS OF TWSb1 (ANTIMONY DIMERCAPTO-SUCCINATE) (SEE TABLE V)

	Persons who had all 6 tests			*Persons who had tests 0, 1, 2, 3, 4*			*Persons who had tests 0, 1, 2, 3*			*Persons who had tests 0, 1, 2*			*Persons who had tests 0, 1*			*Persons who had test 0 only*			*Total examined*	*Sh*	*Sm*	*Percentage positive*	
	Total	*Sh*	*Sm*	*Total*	*Sh*	*Sm*	*Total*	*Sh*	*Sm*	*Total*	*Sh*	*Sm*	*Total*	*Sh*	*Sm*	*Total*	*Sh*	*Sm*		*Pos.*	*Pos.*	*Sh*	*Sm*
Before treatment, 12.9.59 (test 0)	23	17	13	2	2	0	1	1	1	2	2	0	5	4	4	0	0	0	33	26	18	78·7	54·5
Test 1, 5.12.59	23	0	4	2	0	0	1	0	0	2	0	0	5	0	1				33	0	5	0	15·1
Test 2, 13.1.60	23	1	2	2	0	1	1	0	0	2	0	0							28	1	3	3·5	10·7
Test 3, 15.2.60	23	0	1	2	0	0	1	0	0										26	0	1	0	3·8
Test 4, 12.4.60	23	2	3	2	1	0													25	3	3	12·0	12·0
Test 5, 7.6.60	23	3	2																23	3	2	13·0	8·7

S. haematobium

Positive before treatment	17
Positive after 9 months	3
Percentage positive	17·6%
Percentage cured	82·4%

S. mansoni

Positive before treatment	13
Positive after 9 months	2
Percentage positive	15·3%
Percentage cured	84·7%

TABLE B. STATISTICAL TABLE SHOWING THE VALUE OF INTRAMUSCULAR INJECTIONS OF TWSb1 (ANTIMONY DIMERCAPTO-SUCCINATE) (SEE TABLE V)

	Persons who had all 6 tests			*Persons who had tests 0, 1, 2, 3, 4*			*Persons who had tests 0, 1, 2, 3*			*Persons who had tests 0, 1, 2*			*Persons who had tests 0, 1*			*Persons who had test 0 only*			*Total examined*	*Sh*	*Sm*	*Percentage positive*	
	Total	*Sh*	*Sm*	*Total*	*Sh*	*Sm*	*Total*	*Sh*	*Sm*	*Total*	*Sh*	*Sm*	*Total*	*Sh*	*Sm*	*Total*	*Sh*	*Sm*		*Pos.*	*Pos.*	*Sh.*	*Sm*
Before treatment, 12.9.59 (test 0)	66	49	36	10	9	7	4	4	3	12	8	8	2	2	1	3	2	1	97	74	20	76·2	20·6
Test 1, 5.12.59	66	9	4	10	3	2	4	1	0	12	1	0	2	0	0				94	14	6	14·7	6·3
Test 2, 13.1.60	66	15	2	10	3	0	4	2	1	12	0	1							92	20	4	21·7	4·3
Test 3, 15.2.60	66	10	8	10	3	0	4	1	1										80	14	9	17·5	11·1
Test 4, 12.4.60	66	18	10	10	5	0													76	23	10	30·2	13·1
Test 5, 7.6.60	66	20	15																66	20	15	30·3	22·7

S. haematobium

Positive before treatment	49
Positive after 9 months	20
Percentage positive	40·8%
Percentage cured	59·2%

S. mansoni

Positive before treatment	36
Positive after 9 months	15
Percentage positive	41·6%
Percentage cured	58·4%

TABLE C. STATISTICAL ANALYSIS OF RESULTS OF INTRAVENOUS INJECTIONS OF ASTABAN (SEE TABLE V)

	Persons who had all 6 tests			*Persons who had tests 0, 1, 2, 3, 4*			*Persons who had tests 0, 1, 2, 3*			*Persons who had tests 0, 1, 2*			*Persons who had tests 0, 1*			*Persons who had test 0 only*			*Total examined*	*Sh*	*Sm*	*Percentage positive*	
	Total	*Sh*	*Sm*	*Total*	*Sh*	*Sm*	*Total*	*Sh*	*Sm*	*Total*	*Sh*	*Sm*	*Total*	*Sh*	*Sm*	*Total*	*Sh*	*Sm*		*Pos.*	*Pos.*	*Sh*	*Sm*
Before treatment, 12.9.59 (test 0)	20	13	12	1	1	0	1	1	0	1	1	1	5	4	4	2	2	2	30	22	19	73·3	63·3
Test 1, 5.12.59	20	1	3	1	0	0	1	0	0	1	0	0	5	0	1				28	1	4	3·5	14·2
Test 2, 13.1.60	20	1	1	1	0	0	1	0	0	1	0	0							23	1	1	4·3	4·3
Test 3, 15.2.60	20	1	2	1	0	0	1	0	0										22	1	2	4·5	9·0
Test 4, 12.4.60	20	3	1	1	0	0													21	3	1	14·2	4·7
Test 5, 7.6.60	20	3	1																20	3	1	15·0	5·0

S. haematobium

Positive before treatment	13
Positive after 9 months	3
Percentage positive	23·0%
Percentage cured	77·0%

S. mansoni

Positive before treatment	12
Positive after 9 months	1
Percentage positive	8·3%
Percentage cured	91·7%

TABLE D. STATISTICAL ANALYSIS OF RESULTS OF INTRAMUSCULAR INJECTIONS OF ASTABAN (SEE TABLE V)

	Persons who had all 6 tests			*Persons who had tests 0, 1, 2, 3, 4*			*Persons who had tests 0, 1, 2, 3*			*Persons who had tests 0, 1, 2*			*Persons who had tests 0, 1*			*Persons who had test 0 only*			*Total examined*	*Sh*	*Sm*	*Percentage positive*	
	Total	*Sh*	*Sm*	*Total*	*Sh*	*Sm*	*Total*	*Sh*	*Sm*	*Total*	*Sh*	*Sm*	*Total*	*Sh*	*Sm*	*Total*	*Sh*	*Sm*		*Pos.*	*Pos.*	*Sh*	*Sm*
Before treatment, 12.9.59 (test 0)	65	51	33	8	6	6	3	3	1	1	0	1	10	9	5	6	5	4	93	74	50	79·5	53·7
Test 1, 5.12.59	65	9	5	8	1	0	3	0	0	1	0	0	10	1	0				87	11	5	12·6	5·7
Test 2, 13.1.60	65	2	5	8	0	1	3	0	0	1	0	0							77	2	6	2·7	7·7
Test 3, 15.2.60	65	3	5	8	0	1	3	1	0										76	4	6	5·2	7·8
Test 4, 12.4.60	65	7	10	8	0	1													73	7	11	9·5	15·0
Test 5, 7.6.60	65	10	15																65	10	15	15·3	2·3

S. haematobium

Positive before treatment	51
Positive after 9 months	10
Percentage positive	19·6%
Percentage cured	80·4%

S. mansoni

Positive before treatment	33
Positive after 9 months	15
Percentage positive	45·4%
Percentage cured	54·6%

TABLE E. STATISTICAL ANALYSIS OF THE RESULTS OF ADMINISTERING MIRACIL ORALLY (SEE TABLE V)

	Persons who had all 6 tests			*Persons who had tests 0, 1, 2, 3, 4*			*Persons who had tests 0, 1, 2, 3*			*Persons who had tests 0, 1, 2*			*Persons who had tests 0, 1*			*Persons who had test 0 only*			*Total examined*	*Sh*	*Sm*	*Percentage positive*	
	Total	*Sh*	*Sm*	*Total*	*Sh*	*Sm*	*Total*	*Sh*	*Sm*	*Total*	*Sh*	*Sm*	*Total*	*Sh*	*Sm*	*Total*	*Sh*	*Sm*		*Pos.*	*Pos.*	*Sh*	*Sm*
Before treatment 12.9.59 (test 0)	95	70	51	14	13	5	3	3	2	2	1	2	6	5	3	4	3	4	124	95	67	76·6	54·0
Test 1, 5.12.59	95	20	11	14	4	0	3	0	1	2	0	1	6	2	0				120	27	12	22·5	10·0
Test 2, 13.1.60	95	17	5	14	5	4	3	1	3	2	0	0							114	23	12	20·1	10·5
Test 3, 15.2.60	95	20	8	14	4	1	3	1	0										112	25	9	22·3	8·0
Test 4, 12.4.60	95	34	19	14	5	2													109	39	21	35·8	19·1
Test 5, 7.6.60	95	37	14																95	37	14	38·9	14·7

S. haematobium

Positive before treatment	70
Positive after 9 months	37
Percentage positive	52·8%
Percentage cured	47·2%

S. mansoni

Positive before treatment	51
Positive after 9 months	14
Percentage positive	27·4%
Percentage cured	72·6%

TABLE F. STATISTICAL ANALYSIS OF THE RESULTS OF ADMINISTERING NILODIN WITH 'MARZINE' ORALLY (SEE TABLE V)

	Persons who had all 6 tests			Persons who had tests 0, 1, 2, 3, 4			Persons who had tests 0, 1, 2, 3			Persons who had tests 0, 1, 2			Persons who had tests 0, 1			Persons who had test 0 only			Total examined	Sh	Sm	Percentage positive	
	Total	Sh	Sm	Total	Sh	Sm	Total	Sh	Sm	Total	Sh	Sm	Total	Sh	Sm	Total	Sh	Sm		Pos.	Pos.	Sh	Sm
Before treatment, 12.9.59 (test 0) ..	92	69	53	12	12	7	3	3	1	1	1	0	2	2	0	4	1	3	114	88	64	77·1	56·1
Test 1, 5.12.59 ..	92	15	12	12	2	2	3	1	0	1	0	0	2	0	0				110	18	14	16·3	12·7
Test 2, 13.1.60 ..	92	18	12	12	2	1	3	2	0	1	0	0							108	22	13	20·3	12·0
Test 3, 15.2.60 ..	92	18	8	12	2	1	3	2	0										107	23	9	21·4	8·4
Test 4, 12.4.60 ..	92	27	19	12	3	2													104	30	21	31·7	20·1
Test 5, 7.6.60 ..	92	34	24																92	34	24	36·9	25·0

S. haematobium

Positive before treatment	..	..	69
Positive after 9 months	..	..	34
Percentage positive	..	..	49·2%
Percentage cured ..	..	..	50·8%

S. mansoni

Positive before treatment	..	..	53
Positive after 9 months	..	..	24
Percentage positive	..	..	45·2%
Percentage cured ..	..	..	54·8%

TABLE G. STATISTICAL ANALYSIS OF THE RESULTS OF ADMINISTERING VITAMIN-B-COMPOUND TABLETS (CONTROL) ORALLY (SEE TABLE V)

	Persons who had all 6 tests			Persons who had tests 0, 1, 2, 3, 4			Persons who had tests 0, 1, 2, 3			Persons who had tests 0, 1, 2			Persons who had tests 0, 1			Persons who had test 0 only			Total examined	Sh	Sm	Percentage positive	
	Total	Sh	Sm	Total	Sh	Sm	Total	Sh	Sm	Total	Sh	Sm	Total	Sh	Sm	Total	Sh	Sm		Pos.	Pos.	Sh	Sm
Before treatment, 12.9.59 (test 0) ..	101	75	59	7	7	3	3	3	2	1	0	1	8	6	4	0	0	0	120	91	69	75·8	57·5
Test 1, 5.12.59 ..	101	40	17	7	3	2	3	2	2	1	0	0	8	1	1				120	46	22	38·3	18·3
Test 2, 13.1.60 ..	101	32	15	7	1	1	3	2	1	1	0	0							112	35	17	31·2	15·1
Test 3, 15.2.60 ..	101	33	13	7	1	1	3	2	2										111	36	16	32·4	14·4
Test 4, 12.4.60 ..	101	41	20	7	3	1													108	45	21	41·6	19·3
Test 5, 7.6.60 ..	101	55	22																101	55	22	54·4	21·7

S. haematobium

Positive before treatment	..	..	75
Positive after 9 months ..	..	..	55
Percentage positive	..	..	73·3%
Percentage cured ..	..	..	26·7%

S. mansoni

Positive before treatment	..	..	59
Positive after 9 months ..	..	..	22
Percentage positive	..	..	37·2%
Percentage cured ..	..	..	62·8%

in groups according to the number of ova found in their urine and faeces before and after administration of the various test materials, as shown in Table VII.

Here a 'shift to the left' or decrease can be noticed in the number of ova in the excreta of children in the sodium chloride, the triostam and the control groups, i.e. an increase in the number of children who had fewer ova in their urine and stools after treatment. In the stilboestrol group there is a slight shift to the right, as if there is a significant increase in the average number of ova per child. It may be mentioned that subsequent observations appear to indicate in this group that the increase in ova in the stilboestrol group should not be expected for some weeks after administering the hormone. This conclusion of a shift to the side of either decreased or increased ova per child is further confirmed by adding the number of ova for children in all the columns from 51 ova and more. The apparent increased egg-laying in TAB is in accordance with experience which indicates that more eggs appear in the urine and stools of children taking exercise, with an increase in rate of blood flow such as occurs in feverish conditions like that subsequent to TAB injections.

CONCLUSION

Discussion of these observations revolves round the effect of intravenous injections of common salt on the extrusion of the schistosome ova. Physiological saline is considered a normal constituent of the human body and its blood stream, and presumably of the schistosome parasite. Ten ml. of normal saline increases the total sodium chloride content of the blood stream by only about 90 mg. It would be interesting to follow-up larger groups of children after various dosage schedules to determine the schistosomicidal efficiency of common salt. Meanwhile it is proposed to administer 1·5 G. of TWSb at intervals of 3 or 4 weeks to decide on its schistosomicidal effect. Test for cure will have to continue for at least 12 - 18 months under conditions where re-infection is totally excluded. The appearance of molluscicides, like Bayer 4780 and others, will now facilitate snail elimination and ensure that drug trials can be carried out free of complications from the possibility of re-infection. Great care in the use of a hormone like stilboestrol should be exercised in tests of cure in view of its other effects on the human system, and the subjects should be carefully selected and observed subsequent to administration of the hormone. Its use should be limited as far as possible, but further observations on the behaviour of schistosomes in girls, in relation to menstruation, and in married women, with regard to pregnancy, would be interesting and useful.

SUMMARY

The need for health education in the control of bilharziasis is again stressed. The necessity for the chemical, physical and biological control of snail vectors is discussed. Greater cooperation between the departments concerned with water and soil conservation, with the design and construction of irrigation and water impounding schemes, and with public health, is urged.

Tables are given illustrating the results of a small and a large trial with TWSb (sodium antimony dimercaptosuccinate) and the further investigation of the effect of hormones and normal saline on the results of urine and stool tests. This involved a large number of schistosome egg counts as an indicator of variations in the laying activity of the parasites. The results leave the impression

of the extreme sensitivity of the schistosome to physiological changes in the blood stream. A simple and effective remedy for bilharziasis remains to be discovered. Sodium chloride and sodium antimony dimercapto-succinate (TWSb) both appear to affect the bilharzial parasite, but a final decision on the efficacy of TWSb can only follow after further extensive trials of the drug. The results given here are intended to stimulate the interest of other workers in this field.

We wish to thank the Secretary for Health for permission to publish these observations, and the Senior and Junior Health Inspectors, Technical Officers and field assistants in the Northern Transvaal for their assistance in the various aspects of the work on bilharziasis. We also thank the Bantu Commissioners, Bantu Authorities, chiefs and headmen, for their cooperation and assistance, and the Director of Bantu Education, the Inspector of Schools, and especially the teachers who have so willingly helped with the organization, administration and records of the various trials. We remain indebted to the hospital staffs and others who have been and continue to be so helpful with this considerable amount of work. We thank Dr. E. Friedheim and Messrs. Roche Products Ltd. and their representative, Dr. W. Leigh, for providing supplies of TWSb for the tests, as well as Mr. L. Dey of Burroughs Wellcome Ltd. who gave us advice and assistance.

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