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CHEMOTHERAPY OF PARAGONIMIASIS WITH BITHIONOL
III. THE FOLLOW-UP STUDIES FOR ONE YEAR AFTER TREATMENT WITH BITHIONOL

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Introduction

Since paragonimiasis has clinically a very close resembrance with pulmonary tuberculosis and such serious cases as cerebral paragonimiasis are not at all rare, much attentions were paid to this disease lately in Japan. However, as the treatment of paragonimiasis, only the combined treatment of Emetine-Sulfonamids (S. Yokogawa *et al.*, 1939, 1940) has been taken until recently, the results are not quite satisfactory either in efficacy or in side-effects, and still more effective drug has been expected.

Recently, the authors (1960) proved that Bithionol was very effective for paragonimiasis: in the first report (M. Yokogawa *et al.*, 1961) showed experimental chemotherapy on the animals infected with *Paragoninus*, in the second report (M. Yokogawa *et al.*, 1961) showed the first trial of Bithionol (Bitin, Tanabe Seiyaku Co. Ltd.) for the treatment of 13 cases of human paragonimiasis and the successfull results of this trial.

By this time, the authors have completed the follow-up observations for one year after the treatment and all the cases were proved to be completely cleared. On this report, the authors present the results of those observations.

Objects

As the objects of this experimental therapy, 13 cases of paragonimiasis (male 11, female 2 ranging from 8 to 38 years of age) were selected (Table 1). All these 13 cases live or have lived in those prevalent districts of this disease, Kochi and Ehime Prefectures, and they have all eaten cooked *Eriocheir japonicus*. The supposed lapse of time from the onset of the disease to this treatment varied from 3 months to 10 years. As mentioned before, because of its very close resembrance in clinical symptoms to the pulmonary tuberculosis, there has often been wrong diagnosis by confusion: in 4 cases among those 13 cases whom the authors treated, the initial diagnosis were mistaken for pulmonary tuberculosis and they were subjected to the chemotherapy with SM, PAS, I. N. A. H.: and 9 cases were subjected to the therapy of paragonimiasis with the combined method of Emetine-Sulfonamids. As subjective symptoms, bloody sputa were seen in 8 cases, and as objective ones, abnormal shadows in chest X-Ray were found in all cases. Parenthitically, No. 9 had cerebral paragonimiasis complicated pulmonal paragonimiasis with spastic paralysis on left arm and leg, blind (both eyes) and dysphasia.

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Table 1. Description of 13 cases treated with Bithionol

Case No.	Name	Age	Sex	Lapse of time from the onset of disease to the treatment	Past history with respect to treatment
1*	M. S.	36	M	about 4 years	SM 10 grams PAS 300 grams Emetine 20 ampoullae**
2	K. C.	16	F	2 years 3 months	Emetine 16 ampoullae
3	M. R.	19	M	about 5 years	Emetine 5 ampoullae
4	M. K.	11	M	about 4 years	none
5*	I. M.	11	M	3 years 4 months	SM 25 grams PAS 800 grams
6	H. K.	24	M	about 10 years	none
7*	Y. M.	21	F	5 years 1 month	SM 60 grams PAS 3,000 grams I. N. A. H. 30 grams Emetine 56 ampoullae
8*	H. K.	17	M	5 years 9 months	SM 52 grams PAS 2,000 grams I. N. A. H. 22 grams Emetine 10 ampoullae
9	T. K.	8	M	2 years 10 months	Emetine 6 ampoullae
10	T. T.	35	M	about 2 years	Emetine 40 ampoullae
11	T. M.	15	M	about 2 years	Emetine 10 ampoullae Pararosaniline 22 grams
12	S. T.	12	M	about 2 years	not clear
13	M. S.	38	M	3 months	Emetine 28 ampoullae

* diagnosed wrongly as pulmonary tuberculosis and treated with SM (Streptomycine), PAS (para-amino-salycylic acid) and I. N. A. H. (iso-nicotinic acid hydrazide)
** an ampoule contains 1 cc of 4% Emetine hydrochloride

These 13 cases were all hospitalized and treated with Bithionol.

Method of Therapy

As for the determining of the dose, the consideration of the side-effects and the blood concentration of Bithionol, the authors described in detail in the previous report 2 and therefore omitted in this paper. The daily dose was 2.0 g–2.5 g for adults and 1.5 g–2.0 g for children (40 mg/kg–50 mg/kg). They were given the above daily dose divided into 3 "takes" immediately after meals every other day. And according to the number of doses given (definition: one dose means one "daily dose"), all the cases were divided into 3 groups (I) receiving 5 doses (No. 1) (II) receiving 10 doses (No. 2–No. 5) and (III) receiving 15 doses (No. 6–No. 13); the efficacy of the treatment was examined in each divided group.

Method of Examination

In order to evaluate the efficacy of the treatment and to examine the side-effects, the following tests were given:

1) Stool examination

For 2 or 3 days before the treatment and every day during the period of the treatment, E. P. D. was calculated by centrifugation technique using AMS III method, and after completion of therapy, stools for 3 concecutive days every month were examined for eggs with the same method.

2) Sputa examination

The whole daily output of sputa was collected and after examining whether it was bloody or not, it was fully dissolved with 2% NaOH (3 to 5 times much as sputa) and centrifugated

to make egg counts.

3) Clinical examination

The authors examined various effects of Bithionol on the internal organs and to detect the side-effects as early as possible, the urine, blood, liver function test and the electrocardiogram were applied successively, with constant caution on the patients' subjective symptoms.

4) Complement fixation test

The complement fixation test was conducted with the sera taken periodically before, immediately after, 1 month, 3 months, 6 months and 12 months after completion of the treatment with the technique of the 50 percent end point titration of complement using V. B. S. antigen (×5,000).

5) X-ray examination

Abnormal shadows in Chest X-ray films (plate and tomography) before the treatment were classified into 4 types as infiltrative shadow, ring shadow, nodular shadow and strand shadow according to their shapes and natures, and their changes were observed continually.

6) Investigation of health conditions after the treatment

The health conditions for a year after the treatment with Bithionol were observed continually and were examined whether there were such sequelae as chronic toxicosis due to the successive medications of Bithionol.

Results

1) The results of stool examination

The *Paragonimus* eggs in stools of all cases quickly disappeared after the medications from 2 to 5 doses of Bithionol and no relapses were found in any cases from the results of followup examinations for 9–12 months after completion of the treatment and no significant differences were seen among those groups receiving 5 doses, 10 doses and 15 doses. Besides, the maximum number of eggs per day (E. P. D.) calculated by centrifugation technique using AMS III method was 23,435 as shown in Table 2 and 3.

2) The results of sputa examination

Before the treatment, in those 10 cases, several times of sputa were observed daily and the maximum number of eggs per day in the whole sputa was 2,431. The eggs in sputa of these 10 cases were disappeared after the medication from 2 to 5 daily doses of Bithionol. But in those 2 cases, No. 11 and No. 12, a few deformed eggs reappeared transiently in the sputa during the course of the treatment. However, no relapses were found from the results of the follow-up investigations during the period from 9 months to 12 months after the completion of the treatment as shomn in Table 2.

3) The results of the clinical examinations

(i) The results of urine examination

On all these 13 cases, no abnormal findings were observed in the urine examinations before the treatment, during the treatment and immediatly after the treatment as shown in Table 4.

(ii) The results of blood examination

No quantitative changes were observed among the erythrocyte counts, leukocyte counts and Hemoglobin, as shown in Table 5 and no qualitative or quantitative changes in leukocyte such as the appearance of immature cells, shift to the left or decrease of lymphocyte. Besides, no remarkable eosinophilia were found among those 13 cases before the treatment and one case which have recognized eosinophilia before the treatment was put into normal within one month after completion of the treatment as shown in Table 6.

(iii) The results of liver function tests

The following examinations were conducted as the liver function tests; Takata's reaction, serum cobalt reaction, serum cholinesterase activity, Meulengracht index, serum protein contents, cephalincholesterol test and c-reaction protein. And no abnormal findings were found from the results of these examinations as shown in Table 7.

(iv) The results of the electrocardigram

In those 6 cases of the 15-dose-regimen, the electrocardigram test was conducted immediately after the completion of the treatment, and no abnormal findings were found.

(v) Sbjective symptoms

Sputa and bloody sputa: Befor the treatment, sputa were found in 10 cases out of 13

Table 2. Results of

Group.	Case No.	Name	Age	Sex	No. Items	Before treatment	Dose (gram) and times (days) 1	2	3	4	5	6	7	8	9	10	11	12	13	14
													(days)							
I.	1	M. S.	36	M	a.		2.0		2.5		2.5		2.5		2.5					
					b.	(+)		−		(+)										
					c.	+		+		+		+	−	−	−					
					d.				D			D								
II.	2	K. C.	16	F	a.		2.0		2.0		2.0		2.0		2.0		2.0		2.0	
					b.	(+)	−	+	+				−	−		−		−		
					c.	+	+	+	+	−	−		+	−		−		−		−
					d.						V									
	3	M. R.	19	M	a.		2.5		2.5		2.5		2.5		2.5		2.5		2.5	
					b.	(+)				(+)	(+)			(+)						
					c.	+		ǂ		ǂ			+							−
					d.						D									
	4	M. K.	11	M	a.		1.5		1.5		2.0		2.0		2.0		2.0		2.0	
					b.															
					c.	+	ǂ	ǂ	ǂ	+	+	−	−	−	−	−	−	−	−	−
					d.								U		U					
	5	I. M.	9	M	a.		1.5		1.5		2.0		2.0		2.0		2.0		2.0	
					b.															
					c.	+	+		+		+	−	+			−	−	−	−	−
					d.				A								D	D		
III.	6	H. K.	24	M	a.		2.0		2.5		2.5		2.5		2.5		2.5		2.5	
					b.	(+)	(+)	(+)		+	+		−							
					c.	+	+	+		+		−								
					d.				D				D	D						
	7	Y. M.	21	F	a.		2.5		2.5		2.5		2.5		2.5		2.5		2.5	
					b.	(+)	(+)		+	(+)	(+)	(+)					−	(+)		
					c.	+	+		+	−	−	+		−			−	−		
					d.		A												D	
	8	H. K.	17	M	a.		1.5		2.0		2.0		2.9		2.5		2.5		2.5	
					b.	(+)				+	+									
					c.	ǂ	ǂ		ǂ			ǂ			−		−		−	
					d.															
	9	T. K.	8	M	a.		1.5		1.5		1.5		1.5		1.5		1.5		1.5	
					b.															
					c.	+	ǂ		ǂ		ǂ				−			−		
					d.															
	10	T. T.	35	M	a.		2.0		2.5		2.5		2.5		2.5		2.5		2.5	
					b.	+	+				(+)				+	+			−	
					c.	+		+		+		+		−		−	−	−	
					d.				D				D							
	11	T. M.	15	M	a.		2.0		2.5		2.5		2.5		2.5		2.5		2.5	
					b.	+														
					c.	+	+	+	+		−	−	−			−	−		−	
					d.															
	12	S. T.	12	M	a.		1.0		1.0		2.0		2.5		2.5		2.5		2.5	
					b.	(+)	(+)	(+)			(+)	+	+	−							+*
					c.	+	+	+			+	+			−	−			−	
					d.												N			
	13	M. S.	28	M	a.		2.0		2.5		2.5		2.5		2.5		2.5		2.5	
					b.	(+)			+	+										
					c.	+	+		+	−					+		−		−	
					d.									U	U					

Group I. Group of the 5 doses regimen Group II. Group of the 10 doses regimen
Group III. Group of the 15 doses regimen
Remarks : a. : dose of Bithional (grams)
b. : eggs in sputa
(+) : Sputa are bloody and positive for *Paragonimus* eggs
+ : Sputa are not bloody and positive for *Paragonimus* eggs
− : Sputa are not bloody and negative for *Paragonimus* eggs
+*: Sputa are not bloody and positive for deformed *Paragonimus* eggs

treatment with Bithionol

of administration of Bithionol															After treatment					
15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	1	2	3	6	9	12
							(days)											(months)			
																–	–	–	–	–	–
2.0		2.0		2.0																	
–		–		–	–											–	–	–	–	–	–
A				D	D																
2.5		2.5		2.5																	
		–														–	–	–	–	–	–
D				D	A																
2.0		2.0		2.0																	
–	–	–	–	–	–											–	–	–	–	–	–
2.0		2.0		2.0																	
		–		–												–	–	–	–	–	–
2.5		2.5		2.5		2.5		2.5		2.5		2.5		2.5							
		–											–								
	–	–	–				–		–		–			–		–	–	–	–	–	–
										V		A		D							
2.5		2.5		2.5		2.5		2.5		2.5		2.5		2.5							
	–		–			–		–	–		–			–		–			–	–	–
		D																			
2.5		2.5		2.5		2.5		2.5		2.5		2.5		2.5							
–	–			–		–		–	–		–		–	–		–	–	–	–	–	–
				N																	
1.5		1.5		1.5		1.5		1.5		1.5		1.5		1.5							
	–			–	–			–		–		–		–		–			–	–	–
2.5		2.5		2.5		2.5		2.5		2.5		2.5		2.5							
–		–		–		–	–		–				–			–	–	–	–	–	–
D	D					D	D		D												
2.5		2.5		2.5		2.5		2.5		2.5		2.5		2.5							
+*				+*																	
	–	–		–	–			–		–			–			–	–	–	–	–	
		D							D	D											
2.5		2.5		2.5		2.5		2.5		2.5		2.5		2.5							
–			–	–		–		–		–	–	–		–		–	–	–	–	–	
N																					
2.5		2.5		2.5		2.5		2.5		2.5		2.5		2.5							
	–		–		–			–			–			–		–	–	–	–	–	–
														D							

c. : eggs in stool
+ : E. P. D. less than 3,000
++ : E. P. D. between 3,000 and 10,000
+++ : E. P. D. above 10,000
– : Negative of *Paragonimus* eggs

d. : side effects
A : Abdominal pain D : Diarrhea N : Nausea U : Urticarial eruption V : Vomiting

Table 3. Variations in E. P. D. in stools and the clearance after the administration of Bithionol (Centrifugation technique with the A. M. S. III Method)

Days	Cumulative number of the doses	*	**				***							
		No. 1	No. 2	No. 3	No. 4	No. 5	No. 6	No. 7	No. 8	No. 9	No. 10	No. 11	No. 12	No. 13
Before	0	122	572			456								
1	1		1,410		4,788	248	258	135	6,860	3,150		350	3,215	1,210
2		656	222	23,435	3,780		738				2,178	84	2,548	
3	2		80		4,224	978		1,625	18,330	7,503		261		1,885
4		1,110	0	8.400	2,494		116	0			1,525			0
5	3		0		792	258		0		6,525		0	639	
6		232			0	0	0	312	4,260		129	0	98	
7	4	0	115	550	0	312						0		
8		0	0		0			0			0			
9	5	0			0				0	0			0	392
10			0		0	0	0					0	0	

*: Sub-group of the 5-dose-regimen **: Sub-group of the 10-dose-regimen
***: Sub-group of the 15-dose-regimen

Table 4. Results of urine examinations

Case No.	1	2	3	4	5	6	7	8	9	10	11	12	13
Before treatment													
Glucose	—	—	—	—	—	—	—	—	—	—	—	—	—
Protein	—	—	—	—	—	—	—	—	—	—	—	—	—
Urobilin	—	—	—	—	—	—	—	—	—	—	—	—	—
Urobilinogen	N	N	S	N	N	N	N	S	N	N	N	N	N
Bilirubin	—	—	—	—	—	—	—	—	—	—	—	—	—
Urine sediment	(not remarkable)												
During treatment													
Glucose	—	—	—	—	—	—	—	—	—	—	—	—	—
Protein	—	—	—	—	—	—	—	—	—	—	—	—	—
Urobilin	—	—	—	—	—	—	—	—	—	—	—	—	—
Urobilinogen	S	N	N	N	S	N	N	N	N	N	N	S	N
Bilirubin	—	—	—	—	—	—	—	—	—	—	—	—	—
Urine sediment	(not remarkable)												
After treatment													
Glucose	—	—	—	—	—	—	—	—	—	—	—	—	—
Protein	—	—	—	—	—	—	—	—	—	—	—	—	—
Urobilin	—	—	—	—	—	—	—	—	—	—	—	—	—
Urobilinogen	N	N	N	N	N	N	N	N	N	S	N	N	N
Bilirubin	—	—	—	—	—	—	—	—	—	—	—	—	—
Urine sediment	(not remarkable)												

Remarks: N: normal S: increased slightly

Table 5. Variations of erythrocyte counts and hemoglobin before and after treatment

Case No.	Name	Age	Sex	Erythrocyte counts (×10,000)		Hemoglobin (%)	
				Before	After	Before	After
1	M. S.	36	M	448	461	90	90
2	K. C.	16	F	515	495	100	100
3	M. R.	19	M	421	430	90	90
4	M. K.	11	M	429	452	80	85
5	I. M.	9	M	474	442	92	90
6	H. K.	24	M	452	476	95	97
7	Y. M.	21	F	413	405	85	90
8	H. K.	17	M	436	448	89	93
9	T. K.	8	M	490	508	95	95
10	T. T.	35	M	440	464	95	95
11	T. M.	15	M	514	560	100	100
12	S. T.	12	M	522	516	94	95
13	M. S.	38	M	434	409	100	96

Table 6. Variations of leucocyte count and differential count before and after treatment.

Case No.	Name	Age	Sex		Leucocyte count	Bas.	Eos.	Differential count Neut. 1	2	3	4	5	Lym.	Mon.
1	M. S.	36	M	before	7,400	0	6	3	12	21	18	2	34	4
				after	7,700	0	2	4	19	29	15	4	28	2
2	K. C.	16	F	before	7,600	0	2	1	23	28	10	4	16	6
				after	7,000	0	3	2	24	32	6	8	21	4
3	M. R.	19	M	betore	7,400	0	12	2	11	19	11	5	38	2
				after	6,900	0	6	4	13	24	9	8	33	3
4	M. K.	11	M	before	8,000	0	6	2	12	32	6	3	31	8
				after	8,000	0	6	2	16	36	9	2	26	5
5	I. M.	9	M	before	6,800	0	1	2	24	29	10	3	27	4
				after	7,300	0	1	4	18	33	5	1	30	8
6	H. K.	24	M	before	7,000	0	6	1	12	18	8	6	41	8
				after	6,400	0	3	2	8	16	7	8	50	6
7	Y. M.	21	F	before	6,900	0	8	2	18	33	5	1	29	4
				after	7,000	0	3	0	16	40	4	3	25	9
8	H. K.	17	M	before	7,000	0	6	4	13	37	6	2	29	3
				after	6,800	0	4	1	8	33	12	4	34	4
9	T. K.	8	M	before	7,000	0	1	3	17	41	14	2	19	3
				after	7,000	0	1	2	20	36	10	4	26	1
10	T. T.	35	M	before	7,300	0	1	2	18	21	7	2	43	6
				after	7,100	0	0	1	17	29	2	3	40	9
11	T. M.	15	M	before	7,000	0	1	2	19	39	5	4	25	5
				after	6,800	0	1	3	24	28	7	3	31	3
12	S. T.	12	M	before	5,600	0	7	1	13	34	8	4	25	8
				after	6,300	0	6	3	21	26	4	6	27	7
13	M. S.	38	M	before	7,100	0	2	2	18	29	8	5	30	6
				after	6,400	0	3	0	16	30	14	3	25	9

Table 7. Results of liver functions

Case No.	1	2	3	4	5	6	7	8	9	10	11	12	13
(Before treatment)													
Takata's reaction	—	—	—	—	—	—	—	—	—	—	—	—	—
Serum cobalt reaction	R5(2)	R4(2)	R5(1)	R3(2)	R4(2)	R4(2)	R4(2)	R5(2)	R3(2)	R4(1)	R3(2)	R4(2)	R4(2)
Serum cholinesterase activity (%)	70–80	80–90	80–90	70–80	80–90	70–80	70–80	80–90	70–80	80–90	80–90	70–80	80–90
Meurengracnt index	3	4	5	3	4	4	3	3	4	5	4	4	4
Serum protein (g%)	8.3	8.9	7.6	6.8	7.6	8.0	6.5	7.8	8.6	9.4	8.0	7.8	7.6
Cephalin-cholesterol test	—	—	—	—	—	—	—	—	—	—	—	—	—
c-reaction protein	—	—	—	—	—	—	—	—	—	—	—	—	—
(After treatment)													
Takata's reaction		—		—	—	—					—		—
Serum cobalt reaction		R4(2)		R4(2)	R3(2)	R4(1)					R3(1)		R4(1)
Serum cholinesterase activity (%)		80–90		80–90	70–80	80–90					80–90		80–90
Meurengracht index		4		4	4	4					3		4
Serum protein (g%)		8.4		7.2	8.0	8.2					8.2		8.0
Cephalin-cholesterol test		—		—	—	—					—		—
c-reaction protein		—		—	—	—					—		—

cases except 3 cases of children from one to several times per day and in 8 cases out of these 10 cases were seen bloody sputa. Bloody sputa were generally seen at the time of getting up early in the morning. However, bloody sputa and the amount of sputa were gradually decreased after the medication from 1 to 6 daily doses of Bithionol and finally disappeared and neither bloody sputum nor sputum has been found since the completion of the treatment until now.

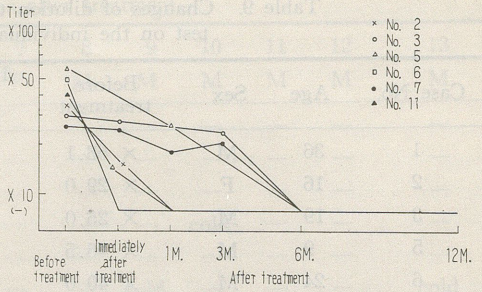
Side-effects: During the period of the administration of Bithionol, 12 cases out of 13 cases showed such symptoms in digestive organs as diarrhea, loose stools, abdominal pain, nausea or vomiting and 2 cases had urticarial eruption. However, all these side-effects were transient and mild, so scarcely needed either symptomatic treatment or stopping the administration of Bithionol except the 2 cases of urticarial eruptions. Besides in the case No. 9, the spastic paralysis on the left limb, blindness, dysphasia were not improved even after the administration of the drug. Again, from the results of 2 female cases, menstruation was normal both during and after the treatment and no effect caused by the administration of this drug could be noted (Table 8).

4) The results of complement fixation test

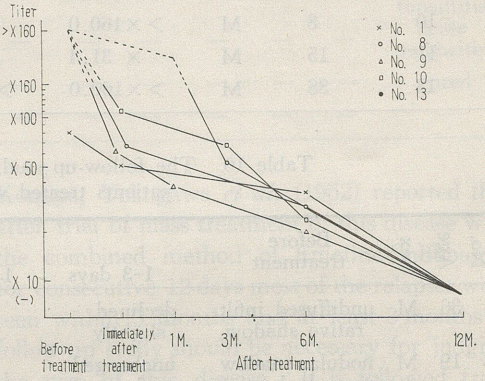
In 11 cases which could be observed continually, it was proved that some cases showed negative reaction in complement fixation test immediately after the treatment, others showed the decrease of antibody titer gradually after the treatment and finally became negative: in one case immediately after the treatment, in 2 cases 2 months after, in 3 cases 6 months after, in the rest 5 cases, 12 months after the treatment. No particular relations were found between the time of becoming negative in complement fixation test and age, sex, or the number of eggs (E. P. D.) of patients, but in the authors' cases the following relation was noted between the lapse of months before the reaction turned negative and the antibody titers before treatment. That is, those 6 cases which became negative within 6 months after the treatment were all less than ×50 in antibody titers before the treatment, while 4 cases out of 5 cases which turned negative in the 12 months after

Table 8. Changes of subjective symptoms

Case No.	Bloody sputa	Abdominal pain	Diarrhea and tendency of loose passage	Nausea	Vomiting	Urticarial eruption	Abnormal menstration	Paralysis of extremity	Disturbance of uision	Disphasia
Before treatment										
1	+									
2	+									
3	+									
4										
5										
6	+									
7	+									
8	+									
9								+	+	+
10			+							
11										
12	+									
13	+									
During treatment										
1			+							
2		+	+		+					
3		+	+							
4						+				
5		+								
6		+	+		+					
7		+	+							
8			+	+						
9								+	+	+
10			+							
11			+							
12				+						
13			+			+				
After treatment										
1										
2										
3										
4										
5										
6										
7										
8										
9								+	+	+
10			+							
11										
12										
13										



(A) 6 cases which became negative within 6 months after treatment



(B) 5 cases which became negative in 12 months after treatment

Fig. 1. Changes of dilution titer of antiserum in complement fixation test on the individuals before and after treatment

the treatment showed more than ×160 in antibody titers as shown in Table 9 and Fig. 1. Thus the relation between the antibody titers before the treatment and the time of turning negative can be seen to some extent, but this still needs further investigation.

5) The results of X-ray examination

The result of Chest X-ray examinations taken periodically after treatment are shown in Table 10. 5 cases were as early to show curative tendency as immediately after the completion of the treatment. Besides, in other cases, most of those abnormal X-ray shadows disappeared between the period from 3 to 6 months after the treatment. In cases where more or less abnormal shadows were noted, those shadows completely disappeared after a year and all the cases were proved to be cured up from X-Ray views.

6) Health condition

Except the case (No. 13) which was complicated with an acute nephritis caused by an acute tonsillitis in the 9th month after the administration of Bithionol, in other 12 cases the authors could not found any remarkable contraction of a disease at all as shown in

Table 9. Changes of dilution titer of antiserum in complement fixation test on the individuals before and after treatment

Case No.	Age	Sex	Before treatment	Immediately after treatment	After treatment 1 M.	3 M.	6 M.	13 M.
1	36	M	× 68.1	× 40.5			×27.5	—
2	16	F	× 29.0	× 12.0	—	—	—	
3	19	M	× 25.0	× 23.1		×20.4	—	—
5	9	M	× 46.5		×21.5		—	—
6	24	M	× 40.0	—	—		—	—
7	21	F	× 22.4	× 20.0	×15.1	×18.6	—	—
8	17	M	>×160.0	× 53.0			×24.2	—
9	8	M	>×160.0	× 53.0	×32.3		×18.8	—
10	8	M	>×160.0	× 86.5		×55.1	×18.2	—
11	15	M	× 31.4	× 12.1	—		—	
13	38	M	>×160.0	>×160.0		×44.6		—

Table 10. The follow-up studies on the chest X-ray findings of the patients treated with Bithionol for 1 year

Case No.	Age	Sex	Before treatment	After treatment 1-3 days	1 month	3 months	6 months	12 months	Efficacy
1	36	M	undiffused infiltrative shadow	declined slightly				disappeared	(healed)
3	19	M	nodular snadow ring shadow diffused infiltrative shadow	unchanged unchanged unchanged		redused unchanged declined	redused disappeared disappeared	disappeared	(healed)
4	11	M	nodular shodow ring shodow diffused infiltrative shadow	unchanged unchanged declined slightly			strand shadow redused disappeared		(healed)
5	9	M	diffused infiltrative shadow	unchanged	disappeared				(healed)
6	24	M	ring shadow undiffused infiltrative shadow	redused declined		disappeared disappeared			(healed)
7	21	F	nodular shadow diffused infiltrative shadow	unchanged disappeared		disappeared			(healed)
8	17	M	nodular shadow undiffused infiltrative shadow	unchanged unchanged			disappeared disappeared		(healed)
9	8	M	strand shadow	unchanged	unchanged			unchanged	(healed)
10	35	M	nodular shadow ring shadow diffused infiltrative shadow	strand shadow strand shadow disappeared		disappeared disappeared			(healed)
11	15	M	undiffused infiltrative shadow	unchanged	unchanged	declined			(healed)
13	38	M	slight bronchiactatic shadow increase of peribronchial marking	unchanged unchanged	declined slightly disappeared			disappeared	(healed)

Table 11. Health conditions after treatment

Months \ Case No. / Sex	1 M	2 F	3 M	4 M	5 M	6 M	7 F	8 M	9 M	10 M	11 M	12 M	13 M
1	—	—	—	—	—	—	—	—	—	—	—	—	—
2	—	—	—	—	—	—	—	—	—	—	—	—	—
3	—	—	—	—	—	—	—	—	—	—	—	—	—
4	—	cold	—	—	cold	—	—	—	—	cold	—	—	—
5	cold	—	cold	—	—	—	—	—	—	—	—	—	—
6	—	cold	—	cold	—	—	—	—	cold	—	—	—	cold
7	—	—	—	—	—	—	—	—	—	—	—	—	—
8	—	—	—	—	—	—	—	—	—	—	—	—	—
9	—	—	—	—	—	—	—	—	—	—	—	—	acute tonsillitis
10	—	—	—	—	—	—	—	—	—	—	—	—	acute nephritis
11	—	—	—	—	—	—	—	—	—	—	—	—	cured
12	—	—	—	—	—	—	—	—	—	—	—	—	—

Table 11. Besides in 2 female cases, no abnormal menstruation was noted.

Discussion

Bithionol is a tasteless, odorless and white crystalline powder and it was originally used as a skin sterilizer added in soap or cosmetics, but Sawada (1957) found that this agent had an excellent anti-helminthic effect on the chicken tape worm (*Raillietina kashiwarensis*), and later Ueno *et al.* (1959) noticed its same efficacy on the liver fluke of cattles, *Fasciola hepatica*, and at present this drug is very widely used in general as an anti-helminthic drug for animal use.

Since the authors introduced this drug as therapeutics of paragonimiasis can be expected as having a remarkable killing potency, the efficacy has been confirmed by many investigators in Japan. The results summed up by Miyazaki (1961) on 61 cases including the authors' 13 cases read as follows : sputa and eggs in stool disappeared in 1 to 8 times of administration of Bithionol. And it is reported that no case out of all 61 cases has seen recurrence after treatment ; 13 cases (the authors' cases) in 12 months after the completion of the treatment ; 15 cases, from 3 to 5 months ; 27 cases from 1 to 3 months ; 6 cases within a month. Komiya, Yokogawa *et al.* (1952) reported that after trial of mass treatment of this disease with the combined method of Emetine-Sulfonamid for consecutive 12 days most of the relapses were seen within 3 months and at least 3 months of follow-up study should be necessary for judging the cure of this disease. It is followed from this fact that out of the above mentioned 61 cases, 28 cases may be assumed their complete cure since no recurrence was found after their treatment. However, this drug is different from emetine hydrochloride in its function and therefore on the period of follow-up observation in the case of treatment with this drug needs further investigation. But in 13 cases in the authors' present study, there were noted no recurrence in the follow-up studies for one year, which is likely to indicate the complete cure of paragonimiasis by this drug. Besides, in the present cases, no difference in the efficacy of the treatment was noted at all among 5-dose-regimen, 10-dose-regimen and 15-dose-regimen ; but judging from the disappearance of the eggs and blood concentration, the authors think the most proper administration to be giving 10 doses every other day. It is again thought to be necessary that the authors examine about the reduction of dose or the duration of the treatment.

As the side-effects caused by the administra-

tion of Bithionol, the authors observed in 12 out of 13 cases (except one case which did not show any side effect at all), diarrhea and tendency of loose stool for 9 cases (69.2%), abdominal pain for 5 cases (38.5%), nausea for 3 cases (23.1%), vomiting for 2 cases (15.4%), urticarial eruption for 2 cases (15.4%); but they were all transient and mild, and no case was stopped administration of Bithionol for those sideeffects. In Miyasaki's report, the mentiond 34 cases (excluding the authors' cases), showed diarrhea and tendency of loose stool 13 cases (38.2%), urticarial eruption 6 cases (17.6%), nausea 4 cases (11.7%) and other symptoms as abdominal pain, loss of appetite, headache, and again these are all transient and mild, and no case was stopped its administration of Bithionol. Besides, the results of the examinations of urine, blood, liver function, electrocardigram done by the authors consecutively till just after the completion of the treatment and the examination of a contraction of a disease for a year after the treatment, are likily to prove there is no danger of chronic toxity caused by the administration of this drug.

Yokogawa (1956, 1961) has often stated the close relation between the complement fixation test in paragonimiasis and the survival of worms. That is, the intradermal test can't be the standard of assuring the cure of this disease because, once infected with this disease the test keeps positive reaction for such a long period as 10 to 20 years even after the cure of the disease; while the complement fixation test, showing the immediate change by cure, etc., can serve for assuring the cure. Yokogawa (1956) applied this to the patient whose worm cyst in the lung was removed surgically, by conducting the complemect fixation test before and after the operation, and proved that the antibody titers in complement fixation test gradually decreased and turned negative after 4 months. Takano (1960) conducted the complement fixation test consecutively for 20 cases who were treated with the combined method of Emetine-Sulfonamids; and found the results as follows. That is, 4 cases turned negative within 3 months out of 7 cases which were assumed complete cure and the other 3 cases also turned negative within 6 months, while 5 cases which were not noted any effect of Emetine at all even during the treatment showed no tendency of decrease of antibody titer in complement fixation test. Kushi *et al.* (1960), too, noted quite similar tendency. Besides in all of the authors' cases, the antibody titers in complement fixation test began to decrease immediately after the treatment; 1 case turned negative just after the treatment, 2 cases after 2 months, 3 cases after 6 months, and the other 5 cases all turned negative after one year. Besides in the authors' cases, the difference in the antibody titers before treatment can be seen clearly between 6 cases which turned negative within 6 months and 5 cases turned negative in later than 6 months: the formers were under ×160. And it seemed that generally the lower the antibody titers before the treatment, the earlier they turned negative. This fact may have some relation with the vitality of the worms before the treatment, but it still somehow needs further investigation. However, it can be said that the complement fixation test give a potent proof not only on the diagnosis but on assuring the cure of paragonimiasis.

Abnormal shadows noted in the chest X-ray examination before the treatment showed the tendency of disappearance, and reduction immediately after the treatment, and all except strand shadow disappeared after 12 months; but the period of change varied by kinds of the shadows. The tendency comes first in the case of diffused infiltrative shadows, of this kind all disappeared during 1 to 3 months; next in the case of ring shadows, while in the case of nodular shadows and undiffused infiltrative shadows, it took far longer period before the disappearance. It is very interesting that, as mentioned above, in X-ray shadows of paragonimiasis when the efficacy of treatment was observed, most in 3 months, later in 6, others in a year saw the cure and it seems that it gives an important proof on assuring the cure of paragonimiasis with the above mentioned complement fixation test.

Summary

The authors applied Bithionol to 13 paragonimsasis patients for the first time, and got the following results from one year's follow-up study.

1) Given in the daily dose of 2.0–2.5 g (adult) and 1.5–2.5 g (child) every other day for 5, 10, and 15 times, all the cases were cleared and no relapses were observed.

2) The side-effects of some transient symptoms in digestive organs and some eruptions but no other abominable side-effects could be noted. Besides no such symptoms as chronic toxicosis as the side-effect of this drug could be observed through the follow-up studies.

3) Complement fixation test and the chest X-ray examination give potent proof not only on the diagnosis of paragonimiasis but on assuring the cure of pargonimiasis.

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肺吸虫症の化学療法に関する研究

(3) Bithionol による臨床治療後1カ年の遠隔成績

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著者らは Bithionol (Bitin) を用いてはじめて13例の人体肺吸虫症患者の治療を試み6カ月までの遠隔治療成績は先きに報告したが(第II報), 今回は1年間の遠隔治療成績を報告する.

Bithionol は1日量を成人 2.0～2.5 g, 小児 1.5～2.0g (40～50 mg/kg)とし分3, 隔日に5回内服 (1例), 10回内服(4例)及び15回内服(8例)の3群について治療期間中に毎日, それ以後は1年間に亘つて毎月連続3日間の糞便及び喀痰について虫卵検査を行つた. また治療前及び治療後に肝機能, 尿, 血液, 心電図の諸検査を行なうと共に1カ年間に亘つて継時的に補体結合反応による抗体価の推移ならびに胸部レ線写真による異常陰影の変動をも観察した.

その結果いずれの群でも数回の Bithionol の投与によつて本種虫卵及び血痰は消失し, 治療後1カ年間の観察結果からも再発は1例もみられず全例に治癒が認められた. 本剤の副作用としては内服期間中に下痢軟便傾向, 腹痛, 悪心, 嘔吐及び蕁麻疹様発疹を認めたが, これらの症状はいずれも軽度のものであり内服完了と共に消失し, また肝機能, 尿, 血液, 心電図の諸検査の結果ならびに治療後1カ年間における疾病罹患状況の調査からも急性あるいは慢性中毒症状の如き危険な副作用は全く認められなかつた. なお経時的に実施した補体結合反応ならびに胸部レ線検査において, いずれも治療直後から1年以内に補体結合反応では抗体価の陰転が, また胸部レ線写真では異常陰影の消失, 瘢痕化等の治癒所見がそれぞれ認められた. これらの観察結果は本症の治癒の判定に有力な根拠を与えるものであると考えられた.