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CHEMOTHERAPY OF PARAGONIMIASIS WITH BITHIONOL
II. CLINICAL OBSERVATIONS ON THE TREATMENT OF BITHIONOL

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Introduction

In the previous report I the authors described a very strong activity of Bitionol (Bitin, the Tanabe Seiyaku Co. Ltd.) against the *Paragonimus westermani* and *Paragonimus ohirai* in animals as the first trial with this drug. Later on the authors made a trial with this drug in human paragonimiasis and found that it was far superior to the hitherto used drugs in its activity against this disease.

Although this trial is a very recent one and the number of cases treated with this drug was not large enough, the follow-up data during six months after treatment have indicated that all of the 13 cases treated in this trial have been completely cured.

The publication of a paper at this stage will be justified on the ground that physicians have waited long for the discovery of a potent therapeutic agent active against the lung fluke; the authors will feel happy, if this report stimulates the interest of investigations in this drug and encourage them to repeat the trial.

Materials and Methods

Drug used:

The drug used for this trial, Bithionol, is a compound with such a structure as shown in Fig. 1 in the previous report 1. The properties of Bithionol were also described in the previous paper.

In this trial Bitin, Tanabe Seiyaku Co. Ltd. was used. A great caution was taken to evaluate the magnitude of side-effects due to the drug in this trial. Concerning toxicity and other features of the drugs, readers are also reffered to detailed accounts given in the previous report.

Problems of the therapeutic dose:

Now, for the first time, the authors attempted to determine the therapeutic dose for use in human case, a dose level where the maximum effect and maximum safety are both attained; for this purpose Bitin was given in different doses and the relative incidence of side-effects was evaluated. Thus Bitin was given in a single oral dose of 30, 50 or 150 mg/kg to human subjects in fasting condition and the subjects were examined, before and after the administration, for the urine (protein, glucose, urobilin, urobilinogen, bilirubin, all qualitatively; S. G. and sediments) together with the subjective symptoms. With 30 mg/kg, no side-effect occurred; with 50 mg/kg diarrhea occurred; with 150 mg/kg nausea, abdominal pain and frequent diarrhea appeared, but all those symptoms subsided spontaneously and needed no therapeutic treatment. The urine was normal at all dose-

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levels. From this result and the results used animals in the previous study, the conclusion was reached that it will be safe to give this drug in the daily dose of 50 mg/kg or less and that, in the case of continued administration where the cumulative effect must be considered, the best tentative plan will be to give it in the daily dose of 50 mg/kg in 3 divided "takes" after each meal and every other day for 10～15 times. A trial was then made according to this plan and the observed side-effect was limited to a single incidence of diarrhea. Urine was completely normal. It was thus found that the continued therapy with this drug caused no material side-effect, if the drug was given after each meal and every other day.

Blood concentration :

Since the authors have set the standard daily dose at 50 mg/kg mainly from the consideration of the side-effect, it is necessary to determine whether this dose secures a sufficient tissue-concentration of the drug. For this purpose human subjects were examined, after the oral administration of Bitin, for the serum concentration of the drug at different points of time. This measurement was undertaken at the Laboratory of the Tanabe Seiyaku Co., Ltd. by Dr. Akio Kiyomoto, pharmacologist Kyoko Iwakura and Kiyoko Tanaka ; 3 healthy male subjects were used ; one subject received the 1st and 2nd one-third portion of the 50 mg/kg of Body weight dose of Bitin on the afternoon and evening of the 1st day (after lunch and after supper) and the final one-third portion of the drug immediately after the breakfast on the 2nd day ; after this no Bitin was given (No. 1) ; in the 2nd and 3rd case (no. 2 and 3) Bitin was given, on the top of this after the lunch and supper on the 3rd day and after breakfast on the 4th day. Blood samples were withdrawn at different points of time up to the end of 75 hours ; the results are shown in Fig. 1.

After the initial dose of 50 mg/kg of Bitin the blood concentration was increased abruptly and it reached 121.0 γ/cc－141.6 γ/cc in 27 hours ; during the next 24 hours of pause it was decreased down to 83.13 γ/cc－97.0 γ/cc as measured at the 47th hour. Upon addition of the 2nd dose here, it was increased again and reached 133.3 γ/cc－154.3 γ/cc at the 75th hour. In No. 1 where the 2nd dose was not given the blood concentration was steadily decreased with time. Yet the blood concentration was as high as 68.0 γ/cc－105.3 γ/cc at the 75th hour.

From these observations it is clear that the blood concentration of Bitin is unexpectedly high and that it stays high over a fairly long period

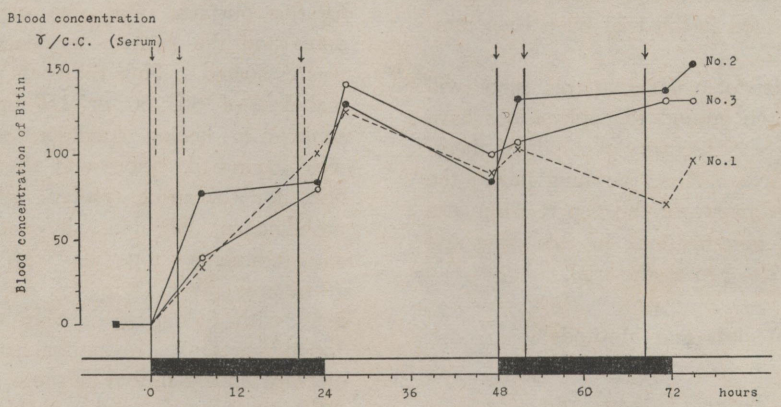

Fig. 1. Blood concentration of Bitin. (In human serum)

Dose administrated : 50 mg/kg
Limits of error : ± 5 γ/c. c.

× : No. 1 case
● : No. 2 〃
○ : No. 3 〃
↓ : Medication

of time. It is quite possible, therefore, that a high blood concentration is maintained with the administration of the drug at intervals of 2 or 3 days.

Methods of therapy and examinations;

Most of the patients with paragonimiasis to be organized in this study and hospitalized for this purpose were sent to us by physiceans for this new trial, because of the invalidity of the treatment with Emetine-hydrochloride combined with sulfonamide. The intradermal test, complement-fixation test, stool examination, sputa examination and Chest-X-Ray were performed on all of the patients before treatment. Only those who showed paragonimus eggs in sputa and stools were hospitalized and treated with Bitin in the daily dose of about 50 mg/kg (1.5~3.0 g) divided into 3 "takes" after meals every other day. According to the number of doses given (definition: one dose means one "daily dose") the entire group was divided into 3 sub-groups, (I) receiving 5 doses (one case) (II) receiving 10 doses (4 cases) and (III) receiving 15 doses (8 cases); follow-up studies were made in each sub-group and the results were compared.

The authors took a great caution to detect the side-effect as early as possible; thus every individual was examined, before and after the completion of the therapy, for the blood and liver function test; on the top of these tests urine specimens were also examined for various functions. The blood tests included erythrocyte counts, leukocyte counts, Hb-index, hemogram and erythrocyte sedimentation rate. The liver function tests included Takata's reaction, Cobalt reaction, Choline esterase activity, Jaundice index, serum protein contents, CCFT and CPR. The urine was examined for protein, glucose, urobilinogen, bilirubin, all qualitatively, and for S. G. and sediments.

The efficacy of the treatment was evaluated

Table 1. Description of 13 cases treated with Bitin

Case No.	Name	Age	Sex	Lapse of time from the onset of disease to the treatment	Past history with respect to treatment	
1*	N. S.	36	M	about 4 years	SM PAS Emetine	10 grams 300 grams 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.	9	M	3 years 4 months	SM PAS	25 grams 800 grams
6	H. K.	24	M	about 10 years	none	
7*	Y. M.	21	F	5 years 1 months	SM PAS Emetine	60 grams 3,000 grams 56 ampoullae
8*	H. K.	17	M	5 years 9 months	SM PAS Emetine	52 grams 2,800 grams 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 Pararosaniline	10 ampoullae 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 lung-t.b. and treted with SM (Streptomycin) and PAS (-para-amino-salycylic acid).
** an ampoule contains 1 cc 4% Emetine hydrochloride.

Table 2. Results of

Group of treatment	Case No.	Name	Age	Sex	No. Items.	Before treatment	Dose (gram) and times 1	2	3	4	5	6	7	8	9	10	11	12
I 5 doses	1.	M. S.	36	Male	1		2.0		2.5		2.5		2.5		2.5			
					2	⊕		−		⊕								
					3	+		+		+		+	−	−	−			
					4				D			D						
II 10 doses	2.	K. C.	16	Female	1		2.0		2.0		2.0		2.0		2.0		2.0	
					2	⊕	−	+	+				−	−		−		−
					3	+	+	+	+	−	−		+	−		−		−
					4						V							
	3.	M. R.	19	Male	1		2.5		2.5		2.5		2.5		2.5		2.5	
					2	⊕				⊕	⊕			⊕				
					3	+		⫴		⫴			+					
					4						D							
	4.	M. K.	11	Male	1		1.5		1.5		2.0		2.0		2.0		2.0	
					2													
					3	+	⫴	⫴	⫴	+	+	−	−	−	−	−	−	−
					4								U		U			
	5.	I. M.	9	Male	1		1.5		1.5		2.0		2.0		2.0		2.0	
					2													
					3	+	+		+		+	−	+			−	−	−
					4				A								D	D
III 15 doses	6.	H. K.	24	Male	1		2.0		2.5		2.5		2.5		2.5		2.5	
					2	⊕	⊕	⊕		+	+		−					
					3	+	+	+		+		−				−		−
					4				D				D	D				
	7.	Y. M.	21	Female	1		2.5		2.5		2.5		2.5		2.5		2.5	
					2	⊕	⊕		+	⊕	⊕	⊕					−	⊕
					2	+	+		+	−	−	+		−			−	−
					4		A											
	8.	H. K.	17	Male	1		1.5		2.0		2.0		2.5		2.5		2.5	
					2	⊕				+	+							
					3	⫴	⫴		⫴			⫴			−		−	
					4													
	9.	T. K.	8	Male	1		1.5		1.5		1.5		1.5		1.5		1.5	
					2													
					3	+	⫴		⫴		⫴				−			−
					4													
	10.	T. T.	35	Male	1		2.0		2.5		2.5		2.5		2.5		2.5	
					2	+	+				⊕				+	+		
					3	+		+		+		+		−			−	−
					4				D				D					
	11.	T. M.	15	Male	1		2.0		2.5		2.5		2.5		2.5		2.5	
					2	+												
					3	+	+	+	+		−	−	−			−	−	
					4													
	12.	S. T.	12	Male	1		1.0		1.5		2.0		2.5		2.5		2.5	
					2	⊕	⊕	⊕			⊕	+	+	−				
					3	+	+	+			+	+			−	−		
					4												N	
	13.	M. S.	28	Male	1		2.0		2.5		2.5		2.5		2.5		2.5	
					2	⊕			+	+								
					3	+	+		+	−					+		−	
					4									U	U			

Remarks: 1: dose of Bitin (grams)
2: eggs in sputa

⊕: Sputa are bloody and positive for paragonimus eggs.
⊖: Sputa are bloody and negative 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 Bitin

(days) of administration of Bitin																	After treatment			
13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	1 month	2 months	3 months	6 months
2.0		2.0		2.0		2.0															
	−	−		−		−	−											−	−	−	−
		A				D	D														
2.5		2.5		2,5		2.5															
	−			−														−	−	−	−
		D				D	A														
2.0		2.0		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		2.5					
				−											−						
	−		−	−	−				−		−		−			−	D	−	−	−	−
												V		A							
2.5		2.5		2.5		2.5		2.5		2 .5		2.5		2.5		2.5					
																−					
			−		−			−		−	−		−			−		−			−
D				D																	
2.5		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		1.5					
			−			−	−			−		−		−		−		−			−
2.5		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		2.5					
		+*				+*															
−			−	−		−	−			−		−			−			−	−	−	−
				D							D	D									
2.5		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		2.5					
−			−		−		−			−			−			−		−	−	−	−
																D					

3 : 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 for paragonimus eggs.

4 : side effects

A : Abdominal pain D : Diarrhea N : Nausea
U : Urticarial eruption V : Vomiting

mainly on the basis of the clearance of the stool and sputa in terms of the eggs. During the period of the treatment the whole bulk of each day's stool was examined for its nature and weight; then 4.0 g and 1.0 g of the stool were taken and examined for E. P. D. (Eggs per day) with the modified Stoll's egg-counting method and centrifugation technique using AMS III method respectively. Concerning sputa the whole daily output was collected and, after examining its nature, it was dissolved with N/10 NaOH and centrifuged to make egg counts from the whole output. After completion of therapy each patient was asked to present about 5 g of stool for inspection for 3 consecutive days every month for six months after complection of treatment, which was examined for eggs with AMS III method. If the stool was negative the fecal examination was repeated 2 more times, to make the test reliable.

Besides the examination for eggs, complement fixation test and X-ray test were also repeated at proper intervals in the follow-up study.

Explanation of 13 cases treated with Bitin:

The 13 patients treated with Bitin consisted of 11 male and 2 female ranging from 8 to 38 years of age, as is shown in Table 1. The lapse of time from the onset of the disease to this treatment varied from 3 months to 10 years; 9 of 13 cases have been treated previously with Emetine combined with sulfonamide or other drugs in vain. In 4 cases the initial condition was mistaken for the pulmonary tuberculosis and they were subjected to the anti-TB chemotherapy with Streptomycin, or PAS, for periods varying from 3 months to 1 year, in the course of which sputa or stool were found to be positive for the Paragonimus eggs, necessitating the reversal of the diagnosis.

The present status of the patients consisted of "frequent bloody sputa" in 8 cases (61.5%), "intermittent bloody sputa" in 4 cases (30.8%). In chest X-ray shadows suggestive of the worm-cysts were positive in 12 cases (92.3%) in the dorsoventral radiogram and tomogram.

Parenthetically, No. 4 was a case with the cerebral involment due to the Paragonimus infection; his limbs on the left were spastic and he was blind on both sides; but no definite shadows were noted on X-ray films of the head or chest.

All 13 cases were positive for intradermal test with V. B. S. antigen, complement fixation test and the eggs of *Paragonimus westermani* in the stool.

Table 3. Variations in E. P. D. in stools and the clearance after the administration of Bitin. (Sedimentation techniques with the A. M.S. III Method and Stoll's egg counting technique)

Days	Cumulative number of the doses	**	Sub-group of the 10-dose-regimen				Sub-group of the 15-dose-regimen							
		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

Results

As shown in Table 2 all cases were cleared for eggs in the sputa or stools, associated with the disappearance of bloody sputa, with 2–5 daily doses of Bitin. Table 3 shows egg counts in the stool in terms of E. P. D. measured with Stoll's egg counting technique and AMS III method. E. P. D. was 23,435 in the maximum case but less than 3,000 in most cases. Egg counts in the sputa were less than 3,000 and less than 500 in most cases. The administration of Bitin caused no increase in the number of degenerated or deformed eggs.

In case No. 11 and 12 a few eggs reappeared in the sputa once again during the course of treatment. However, most of these eggs were deformed and the number of the eggs was small. Since this was follwed by the final and lasting disappearance of eggs, those eggs which reappeared at the time may have originated from the worm-cyst or bronchi where they have lurked.

The follow-up studies were carried out during the period of six months after completion of treatment as shown in Table 2. All of the subjects remained negative for eggs in the stool examinations for six months. There was no case of relapse either in terms of the subjective symptoms. The data of various tests are not yet complete at present. Röntgenologically, there were 12 cases who gave positive signs and the arrangement of the follow-up tests checked up every month are now in progress.

The complement fixation tests were also performed on all of them every other month during the period of follow-up studies. The results of these tests will be made in a forthcoming paper.

The incidence of side-effect is listed in Table 4; 12 out of 13 cases had one or another side-effect, but all side-effects were transient and scarcely needed any symptomatic treatment. The blood, urine and liver functions remained normal throughout the entire period of observation. Table 5 shows the blood counts before and after treatment with Bitin.

Table 4. The side-effects due to Bitin. (13 cases)

Diarrea	9	69.2 %
Abdominal pain	5	38.5 %
Nausea	3	23.1 %
Vomiting	2	15.4 %
Urticarial eruption	2	15.4 %
No side-effect	1	7.7 %

Table 5. Blood counts before and after treatment with Bitin.

Case No.	Name	Age	Sex	Red blood cell ($\times 10^4$)		Eosinophilic cell (%)	
				before	after*	before	after*
1	M. S.	36	M	448	461	6	2
2	K. C.	16	F	515	495	2	3
3	M. R.	19	M	421	430	12	6
4	M. K.	11	M	429	452	6	4
5	I. M.	9	M	474	442	1	1
6	H. K.	24	M	452	476	6	3
7	Y. M.	21	F	413	405	8	3
8	H. K.	17	M	436	448	6	4
9	T. K.	8	M	490	508	1	1
10	T. T.	35	M	440	464	1	0
11	T. M.	15	M	514	560	1	1
12	S. T.	12	M	522	516	7	6
13	M. S.	38	M	434	409	2	3

* 1~3 month after treatment

Discussion

The authors made a trial with Bitin in human cases with paragonimiasis, the first trial for this drug to be used in men ; so it will be worthwhile to comment on some of the observations.

Initially the authors intended to treat the patients in 2 divisions, one division treated with 10 oral doses of Bitin (50 mg/kg a dose, i. e. per day) and the other, with 15 oral doses to examine the acute and long-range effect of the treatment. However, one patient from the division of the 10-dose-treatment did not stay in hospital beyond the 5 th dose and no further administration was possible in this case. Therefore the set-up of the population was changed into a three-division-system.

However, the data for all cases belonging to three sup-groups followed-up for 6 months seemed to suggest that a satisfactory therapeutic effect was achieved with such a daily dose as the authors used in this trial, i. e., 50 mg/kg, (1.5 ~3.0 g. daily dose) if the drug is given more than 5 times every other day.

In view of the fact, described in Report I, that 5 or 6 oral doses of Bitin had only a temporary clearing effect on the eggs in the stool in animals, such as heavily infected dogs, the stool becoming positive again after 2–3 weeks, it can be the case that the therapy is complete or incomplete with 5 oral doses in men. More cases of 5-dose-treatment should be added. However, the authors feel encouraged by the fact that, with this drug, there was no case of relapse within 6 months after therapy, while, with the combined use of Emetine and sulfonamide, Komiya, Yokogawa *et al.* (1952) found that the relapse became obvious most frequently by the end of one month in the case of a mass treatment for 10 consecutive days.

Now, a few remarks concerning the dose of Bitin. In the preliminary experiment, the authors found that, with Bitin given in dose of 50 mg/kg every other day, the blood concentration of the drug could be maintained at the level of 80 γ/cc – 150 γ/cc during the entire period of the therapy, a blood concentration equivalent to 1 : 6,600 to 1 : 12,500 dilution. Since the relative susceptibility of *Paragonimus westermani* to the directly applied drug differs from larvae to grown-up worms with a proportion of 1 : 10 according to an in vitro study of Yokogawa *et al.* (1956) and since the observed LD50 for larvae in the authors' observation was 1 : 1,390,000 dilution in 24 hours, it can be calculated that the LD50 for grown-up worms will be about 1 : 140,000. Comparing this value with values found for the blood concentration (and converted in terms of the corresponding dilution), i. e., 6,600 – 12,500, it is apparent that the observed blood concentration, which tends to be sustained, is 10 – 20 times the LD50 for grown-up worms. On the other hand, it must be acknowledged that the method of the measurement of the blood concentration of Bititn was not yet satisfactory and that the measured value may include both active form and broken-down form of the drug, a situation where the measured value cannot be accepted as the true blood concentration of Bitin as such. At any rate the matter is quite different from the case of Emetine according to Miyagawa (1956) who injected 10 mg/kg of Emetine hydrochloride, the blood concentration was only 10 γ/cc at maximum and as low as 2 γ/cc after 12 hours, indicating a steep fall in the blood concentration. Under these circumstances every effort mast be made to maintain the blood concentration of Emetine hydrochloride at a reasonably high level for a long period of time ; sulfonamides serve for this purpose and they are used as the adjuvant to Emetine. It may well be that the high potency of Bitin depends on its ability to remain in the blood with a high concentration. While studies are in progress concerning the acting mechanism of Bitin on the lung flukes, it may be stated that the most pronounced change found in grown-up worms separated from the lungs of animals treated with 5–6 doses of Bitin, is that of the uterus ; that is to say, the uterus is degenerated and necrotic. Even if the worm is alive, the uterus is already vacant, no eggs being visible ; when degeneration goes to extreme, the uterus itself is no longer visible. This fact is on line with the fact, noted in the case of Bitin quite characteristically, that the therapy was followed by an abrupt and

pronounced decrease of the eggs, not associated with even a temporary increase of the eggs as seen in the case of treatment with the combined method of Emetine and sulfonamide or with chloroquine, a finding suggesting a marked effect on the reproductive organs. While the daily dose was tentatively set at 50 mg/kg in this trial and the administration was repeated 15 or 10 times every other day, future analysis of various points, e. g., duration for which the blood concentration is sustained high or the incidence of the side-effect, will settle the matter about the therapeutic dose, duration of the therapy and method of the administration more properly than now.

With regard to the side-effect, 11 of 13 cases studied have transient and mild side-effects, such as diarrhea, abdominal pain, nausea or vomiting ; 2 cases had urticarial eruption. However, in no case was the blood, urine or the liver function changed. This fact is quite remarkable. While side-effects are strong and a continued therapy presents a difficult problem in the case of Emethine or Chloroquine, Bitin could be given repeatedly for 10 or 15 times. The most frequent side-effect was diarrhea, beginning shortly after the oral administration in most cases and subsiding spontanously after the passage of one to several loose stools ; there was no tenesmus nor bloody stool. Patients with more or less habitual diarrhea seemed to be relieved with the combined administration of alumi-gel (2.0 – 3.0 g) together with Bitin. Parenthetically, in case No. 5, from the group of the 15-dose-regimen, diarrhea continued relatively long. This patient, a case of chronic colitis, has had frequent diarrhea since 10 years or more ago and he was under a symptomatic treatment at the time of the trial. Whether the diarrhea was due to the administration of Bitin or due to the original disease itself can not be decided. It appeared that a diarrhea is apt to occur when the subject eats the fat-rich food. In most cases, the number of vomiting, abdominal pain occurred immediately after the administration of the drug. Nausea or vomiting appeared to be relieved much by lying restifully for 30 minutes to one hour after the drug administration. This was particularly true in nervous subjects. The urticarial eruption started in 10 minutes to 1 hour after the administration of the drug and this occurred under a particular condition, i. e., before defecation or under constipation. This side-effect no longer occurred when a caution was taken to let the subject pass the stool, with a laxative, if necessary, before the administration of the drug. From this fact it appears that the urticarial eruption is a phenomenon related to the decomposition products of Bitin or the blood concentration of the drug rather than anything of a hypersensitivity nature. Parenthetically, the eruption occurred over the limbs, abdomen and face and caused a mild itch and paresthesia. Upon the injection of antihistaminic drugs or defecation by enema disappeared in several hours.

Finally a few words about the egg counts. For the entire bulk of one days' stool the maximum E. P. D. measured by Stoll's egg counting or A. M. S. III method was 23,435 and the value was less than 3,000 in most cases. E. P. D. for the entire bulk of one day's sputa was 2,451 at maximum but less than 500 in most cases. This figure is surprisingly low in comparison with the figures of E. P.D. estimated by M. Yokogawa (1955) and Suguro (1959) in animals, i. e., 10,000 – 30,000 for a single grown-up *Paragonimus kellicotti* and *P. westermani* respectively. According to S. Yokogawa (1916), and M. Yokogawa (1960) most cases of the *Paragonimus westermani* infection in man in Japan harbor only one worm ; it may well be that this was the case for most of the patients discussed here. This may explain in part why the observed therapeutic effect was remarkable ; it remains to be seen whether an equally remarkable efficacy obtains in the more heavily infected population.

With the discovery of Bitin we are now in a position to be able to treat the paragonimiasis infection in men conveniently with an oral drug. With the future refinement of this drug some day we will be able to cure, completely, this disease to the joy of nearly one million patients with this disease ; then a new era is open to the anti-paragonimus campaign in this country. No reliable drug being available, it has not been

very easy to conduct a truly satisfactory survey about the Paragonimus infection and its distribution in different population. It is hoped that the introduction of this potent drug will help smooth-up this sort of survey.

Summary

It was found that Bithionol (Bitin) had a remarkable potency to kill the *Paragonimus westermani in vitro* as well as in animal experiments; the authors applied Bitin, for the first time, to the treatment of the *Paragonimiasis westermani* of 13 human cases. The main observations were as follows:

(1) *In vitro* the observed LD50 for the excysted larvae of *Paragonimus westermani* at the end of 24 hours was 1 : 1,390,000 dilution.

(2) Given in the daily dose of 50 mg/kg (1.5~3.0 g) every other day (in 3 divided "takes"), Bitin was maintained in the blood at the concentration of 80-150 γ/cc.

(3) A total of 13 cases were given Bitin in the daily dose of 50 mg/kg (1.5~3.0 g in 3 divided "takes") and every other day in 3 sub-groups, a sub-group receiving 15 doses (8 cases), a sub-group receiving 10 doses (4 cases), and a sub-group receiving 5 doses (1 case).

The follow-up studies were carried out for 6 months after treatment. It was proved that all cases were cleared.

(4) Bitin gave rise to the side-effects, such as diarrhea, abdominal pain, nausea, vomiting or urticarial eruption which were all mild and transient.

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肺吸虫症の化学療法に関する研究
(II) Bithionol (Bitin) による人体肺吸虫症の臨床治療成績

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Bithionol (Bitin) による動物肺吸虫症の治療成績（第1報）に基ずき本剤の臨床的応用を始めて試みた．先づウェステルマン肺吸虫成虫及び幼虫に対する *in vitro* における殺虫効果と著者等自ら30 mg/kg～150 mg/kg の種々の量の Bitin を内服した場合の本剤の血中濃度や副作用等の点から有効且安全な服用量は 50 mg/kg (1.5～3.0 g) 分3隔日に継続投与が可能であることが明らかにされた．今回入院治療を行つた13例の多くはエメチン治療歴を持ち，自覚的にも他覚的にも症状の顕著な男11名，女2名で内8歳の男児は脳肺吸虫症を合併していた．全症例とも治療前喀痰或いは糞便内に肺吸虫卵を確認し血痰をみとめる者が多かつた．治療は上述の量の Bitin を隔日5回のもの1例，同10回のもの4例，15回のもの8例で治療前より治療終了まで毎日以後毎月1回6カ月間に亘り喀痰及び糞便内の虫卵の消長を AMS III 法及び Stool の変法によつて観察した．猶之等の期間を通じ屢々補体結合反応 (C. F. T.) 検索のため採血し，心，肝，腎機能検査やX線による精査が行われた．何れの症例においても Bitin の 2～5回投与によつて糞便内及び喀痰内肺吸虫卵は全く消失し，血痰も次第に消失し治療後6カ月に至るも虫卵はみとめられなかつた．本剤の副作用には特に留意したが上述の各種機能検査では何等の異状をみとめなかつたが服薬期間中には1例を除き他の12例には下痢9例 (69.2 %) 腹痛5例 (38.5 %)，悪心3例 (23.1 %)，嘔吐2例 (15.4 %) 及び蕁麻疹様発疹2例 (15.4%) をみとめたが之等の症状も早晩何等の治療を要せず消失した．猶本剤による貧血はみとめられず総じて好酸球数の減少 (平均治療前，4.5 %治療後 2.8 %) を示した．

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