

## EPIDEMIOLOGY AND THERAPY OF HELMINTHIASIS

### A Study of the Re-infection Period in School Children treated with Thiabendazole and Tetramizole

Geraldo CHAIA<sup>(1)</sup> and Aloisio Sales da CUNHA<sup>(2)</sup>

#### SUMMARY

The present investigation has supplied the first official data regarding the assessment of drug therapy in school children helminthiasis in Brazil. Under the schedule of treatment used, the highest percentages of cure obtained with thiabendazole were the following: *Strongyloides stercoralis* 92.3%, *Enterobius vermicularis* 90.0% and *Ascaris lumbricoides* 51.5%. As regards tetramizole, a rate of 100% could be obtained in the therapy of *Ascaris lumbricoides*. However, 5 months after treatment, the percentage of school children already re-infected was rather high, leading the investigators to realize that many are indeed the handicaps to be overcome in order to succeed in the control of helminthiasis. Such problem is still aggravated, as has been demonstrated, by the fact of the specific drugs used not having any therapeutic action on the prepatent forms of infection with *Ascaris lumbricoides* and *Strongyloides stercoralis*. The Authors believe the control of helminthiasis to be closely correlated with the development of the country in question.

#### INTRODUCTION

As no official data regarding the assessment of mass treatment in school children helminthiasis were so far available in our country and as we had in hand a drug like thiabendazole, which displayed therapeutic action on some helminths, we decided to perform an investigation on the aforementioned line and carry on the experiment by following up those children in their re-infection period, thus continuing the observation under the same socio-economical conditions.

#### MATERIAL AND METHODS

##### I — Experiment on humans

Three hundred and thirty school children (from 7-13 years of age), all of them living at Vila São Vicente, Belo Horizonte, were selected for this study and divided into

Groups I (250 individuals), II (20) and III (the remaining 60 children).

*Group I* — Only 191 of the 250 children in this group (Table I) were treated with thiabendazole, the remaining 59 being taken as controls (Table III) and, therefore, receiving no treatment.

Many of these 191 children under treatment were found to be infected with other helminths, such as (Table I): *Ascaris lumbricoides* (133 children), *Ancylostomidae* (59), *Trichuris trichiura* (126) and *Strongyloides stercoralis* (62).

*Treatment* — The children were submitted to two courses of treatment with thiabendazole, the second one being performed 6 months after the completion of the first. All the 191 children were included in the first treatment whereas, in the second one, only

Work sponsored by WHO (Grant HQS/168/150)

- (1) Fellow of "Conselho Nacional de Pesquisas" and "Centro de Pesquisas René Rachou". Caixa Postal 1743 — Belo Horizonte, Brazil
- (2) Associated Professor of the Chair of "Clínica Terapêutica" of the "Faculdade de Medicina Federal da Universidade de Minas Gerais, Belo Horizonte, Brazil"

169 of them. The therapeutic schedule was the same in both cases: two series of thiabendazole with an 8-day interval between them, each series consisting of a single daily dose of 500 mg administered after lunch, for 3 consecutive days.

*Selection of the school children and helminthiasis control* — The children were selected and their helminthiasis controlled through coprological examinations performed after HOFFMAN, PONS & JANER'S<sup>9</sup> qualitative method of spontaneous sedimentation of eggs and STOLL'S<sup>14</sup> quantitative method for the counting of eggs. Those examinations were performed before treatment and, later on, after treatment, once a month.

*Group II* — The 20 children in this group, all of them infected with *Enterobius vermicularis*, were subdivided into two groups of 10 individuals each, the first group being treated with thiabendazole at the dosage mentioned above and the second one, with a single dose of pirvinium pamoate (10 mg/kg). Ten days after treatment, assessment of therapy was made by using JACOB'S<sup>10</sup> Scotchtape technique modified and described later on by BEAVER<sup>1</sup>, which had also been employed for the selection of the children.

*Group III* — The 60 children in this group, all of them infected with *A. lumbricoides*, were also subdivided into two groups: the first one, comprising 40 children to be treated with a single dose (6 mg/kg) of tetramizole after lunch and the second group including 20 children to be kept as controls and who, therefore, were not to be submitted to drug therapy. Selection and control of the children were performed by the same methods mentioned in Group I.

## II — Experiment on animals

Twenty-seven mice selected for this study were infected, per os, with about 2,000 eggs of *Ascaris lumbricoides*. Two days after infection, 24 of those mice were divided into three groups of 8 specimens in order to be orally treated with a single dose of:

- tetramizole (10 mg/kg) — group I
- piperazine (10 mg/kg) — group II
- thiabendazole (50 mg/kg) — group III

The remaining 3 mice of the original group were set apart as controls, not being, then, submitted to any treatment. Eight days after infection the mice in the 3 groups were sacrificed, their lungs being dissected into tiny fragments and placed between slide and coverslip for microscopical examination.

*Procurement of eggs* — A female *Ascaris lumbricoides*, recently expelled, was dissected with the help of a stiletto and its uterus taken out and placed into a PÉTRI dish containing H<sub>2</sub>SO<sub>4</sub>N/10 solution. It was, then, sliced into tiny fragments that were pressed with a pair of pincers so that the eggs might come out into the dish, which, afterwards, was placed into an incubator at 28°C.

Twenty days later the eggs, already at the infecting stage (Figs. 3, 1), were counted and given to the mice per os. The counting was performed by placing several 0.10 ml-suspension samples between slide and coverslip, the number of eggs per ml being evaluated afterwards.

## RESULTS

*Group I* — As concerns this group, *Ascaris lumbricoides* and *Strongyloides stercoralis* proved to be the most sensitive to the drug therapy, the percentages of cure regarding *A. lumbricoides* (Table I) being, respectively, 51.5% and 51.1% after the first and the second course of treatment, whereas, regarding *S. stercoralis*, the percentages were 89.6% and 92.3%.

It was observed a marked decrease in the number of *A. lumbricoides* eggs both after the first (96.0%) and the second treatment (82.7%). Further data can be found on Table I.

*Group II* — Concerning the children infected with *Enterobius vermicularis* and treated either with thiabendazole or piperazine, the results obtained were similar in both cases, the percentage of cure being 90%.

*Group III* — As can be seen from Table IV, although the percentage of cure in the group treated was 100.0%, 5 months after treatment the mean number of eggs per gram of feces was observed to be 5,000, the positivity rate being then about 45.0%.

TABLE I

Results obtained with a two-course treatment with thiabendazole in school children naturally infected with helminthiasis. Each treatment comprised 2 series of drug administration (a single daily dose of 500 mg for 3 consecutive days) with a week interval between them

Helminths	Treatment	no. of children treated and controlled	Children cured		Eggs per gram of feces		
			no.	%	Treatment		% of decrease in the number of eggs
					Before	After	
<i>A. lumbricoides</i>	1 <sup>st</sup>	128	66	51.5	9,866	397	96.0
	2 <sup>nd</sup> *	86	44	51.1	6,830	1,183	82.7
<i>Ancylostomidae</i>	1 <sup>st</sup>	57	25	43.8	569	150	73.5
	2 <sup>nd</sup>	32	11	34.3	730	668	8.5
<i>T. trichiura</i>	1 <sup>st</sup>	90	32	35.5	751	277	63.2
	2 <sup>nd</sup>	102	23	23.6	618	327	47.1
<i>S. stercoralis</i>	1 <sup>st</sup>	58	52	89.6	—	—	—
	2 <sup>nd</sup>	13	12	92.3	—	—	—

\* performed 6 months after the first treatment

### Experiment on animals

Thiabendazole, piperazine and tetramizole proved to be quite ineffective against the larval forms found in the pre-patent period of *A. lumbricoides* infection. Table V shows that the positivity rates concerning mice treated with the aforementioned drugs were quite high — 87.5% and 100%. Further data are also to be found on that Table.

### DISCUSSION

Since 1962 has thiabendazole therapeutic action against human helminthiasis been studied. VILELA et al.<sup>15</sup> and, afterwards, FRANZ<sup>8</sup>, CROCE et al.<sup>5</sup>, CHAIA & CUNHA<sup>3</sup>,

FERRAZ et al.<sup>7</sup> and ESCOBAR<sup>6</sup>, have confirmed its efficacy in strongyloidosis. Its action against oxyuriasis and ascariasis has also been demonstrated by several investigators, among whom we can see ESCOBAR<sup>6</sup>, VILELA et al.<sup>15</sup>, FERRAZ et al.<sup>7</sup>, BOTERO<sup>2</sup> and MOST et al.<sup>12</sup>. Moreover, CHAIA & CUNHA<sup>4</sup> found out that thiabendazole, when administered in the doses used in this experiment, does not afford significant side-effects.

The fact of having in hand a drug like thiabendazole, which proved to display therapeutic action against some helminths, led us to undertake mass treatment of children infected with helminths so as to study, under the very same socio-economical conditions, the period during which those children got re-in-

T A B L E I I  
Assessment of therapy with thiabendazole chewing tablets on school children (7 to 13 years) living at Vila São Vicente. Each treatment comprised 2 series of drug administration (a single dose of 500 mg for 3 consecutive days) and 8-day interval between them

Monthly Examinations	H E L M I N T H S													
	A. lumbricooides				Ancylostomidae				T. trichiura				S. stercoralis	
	no. of patients	Positive Cases		no. of patients	Positive Cases		no. of patients	Positive Cases		no. of patients	Positive Cases		no. of patients	Positive Cases
	no.	%	Mean number of eggs per g of feces		no.	%	Mean number of eggs per g of feces		no.	%	Mean number of eggs per g of feces		no.	%
T	191	133	100.0	9,866	59	100.0	569	126	126	100.0	751	62	62	100.0
1 <sup>st</sup>	186	62	48.4	397	32	56.1	150	122	90	73.7	277	58	6	10.3
2 <sup>nd</sup>	184	57	45.9	777	26	52.0	256	117	95	81.1	376	53	5	9.4
3 <sup>rd</sup>	180	63	51.2	1,513	28	47.4	135	122	94	77.0	504	60	7	11.6
4 <sup>th</sup> *	—	—	—	—	—	—	—	—	—	—	—	—	—	—
5 <sup>th</sup>	165	61	59.2	3,700	28	57.1	342	106	93	87.7	518	52	12	23.0
6 <sup>th</sup>	154	70	71.4	5,785	29	59.1	697	98	83	85.7	593	49	8	16.3
T	169	98	100.0	6,830	36	100.0	730	109	109	100.0	618	15	15	100.0
1 <sup>st</sup>	151	42	48.8	1,183	21	65.6	668	102	79	77.4	327	13	1	7.6
2 <sup>nd</sup>	144	52	65.0	2,768	21	80.7	557	96	78	81.2	380	8	2	25.0
3 <sup>rd</sup> *	—	—	—	—	—	—	—	—	—	—	—	—	—	—
4 <sup>th</sup>	143	76	92.6	6,847	22	78.5	471	108	101	93.5	782	9	2	22.2

T = Treatment

\* School holidays: no examinations performed

fectured and thus be able to assess the effects of mass treatment in such environment.

Taking, for example, *S. stercoralis* and *A. lumbricoides*, the former for having been the helminth most widely affected by drug therapy and the latter for being the commonest helminthiasis found in our country, we could observe that, a few months after treatment, the school children under study were already highly infected with such helminths (Table II).

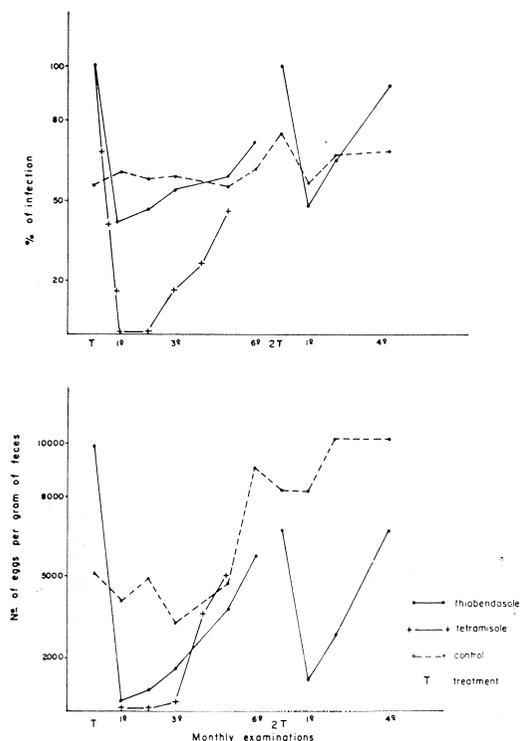


Fig. 1 — Percentage of re-infection by *Ascaris lumbricoides* as estimated by the number of eggs monthly detected in the feces of 133 school children after treatments with thiabendazole and of 40 school children treated with a single tetramizole dose (6 mg/kg)

As regards *S. stercoralis*, it was seen that, 5 months after treatment, the percentage of infection in the group treated (23.0% — Table II) was already practically similar to that of the school children taken as controls (Table III).

Likewise, in the case of *A. lumbricoides*, it was also observed that, although the decrease in the number of eggs per gram of feces had reached 96.0% (Table I), 6 months after completion of treatment the number of eggs in the feces was already 5,785 (Table II).

Even using a drug of specific therapeutic action such as tetramizole, with 100.0% of cures observed (Table IV), we could find out that, 5 months after treatment, the percentage of re-infection had already reached 45.0%. Feces examination of the children treated with a second course of thiabendazole (Table II) also demonstrated them to be re-infected again (Figs. 1 and 2).

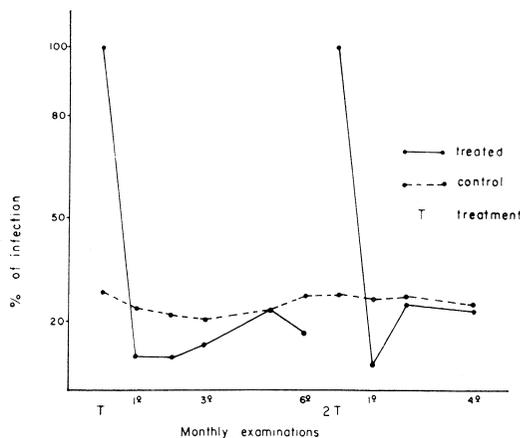


Fig. 2 — Percentage of re-infection as estimated by the presence of *Strongyloides stercoralis* detected in monthly stool examination of 62 school children after treatments with thiabendazole

Unfortunately, it was not possible to follow up the cases of re-infection with *E. vermicularis* since the children treated refused to be monthly submitted to the Scotch tape method for checking up the presence of such helminths.

Many are, then, the handicaps to be overcome in order to succeed in the control of helminthiasis. It was demonstrated, at one of WHO's<sup>16</sup> meetings for the exchange of views about ascariasis control that, to check the progress of such helminthiasis, it would be necessary the availability of drugs effective against both the pre-patent and patent forms

TABLE III  
Results from monthly coprological tests of school children (7-12 years of age) living at Vila São Vicente and selected for the Control Group

Monthly Examinations	no. of School Children	HELMINTHS											
		<i>A. lumbricooides</i>			<i>Ancylostomidae</i>			<i>T. trichiura</i>			<i>S. stercoralis</i>		
		no.	%	Mean number of eggs per g of feces	no.	%	Mean number of eggs per g of feces	no.	%	Mean number of eggs per g of feces	no.	%	Mean number of eggs per g of feces
1st	59	33	55.9	5,131	13	22.0	160	40	67.7	428	17	28.8	—
2nd	55	33	60.0	4,036	12	21.8	86	38	69.0	355	13	23.6	—
3rd	58	33	56.8	4,955	11	18.9	124	39	67.2	389	12	20.6	—
4th	58	34	58.6	3,351	14	24.1	117	39	67.2	258	10	17.2	—
5th*	—	—	—	—	—	—	—	—	—	—	—	—	—
6th	56	31	55.3	4,881	14	25.0	103	33	58.9	354	13	23.2	—
7th	51	31	60.7	9,176	10	19.6	226	37	72.5	556	14	27.4	—
8th	45	34	75.5	8,431	9	20.0	107	30	66.6	415	13	28.8	—
9th	53	30	56.6	8,392	12	22.6	143	39	73.5	615	14	26.4	—
10th	48	32	66.6	11,567	10	20.8	116	27	56.2	429	13	27.0	—
11th	—	—	—	—	—	—	—	—	—	—	—	—	—
12th	49	32	65.3	10,978	10	20.4	109	26	53.0	397	12	24.4	—

\* School holidays: no tests were performed.

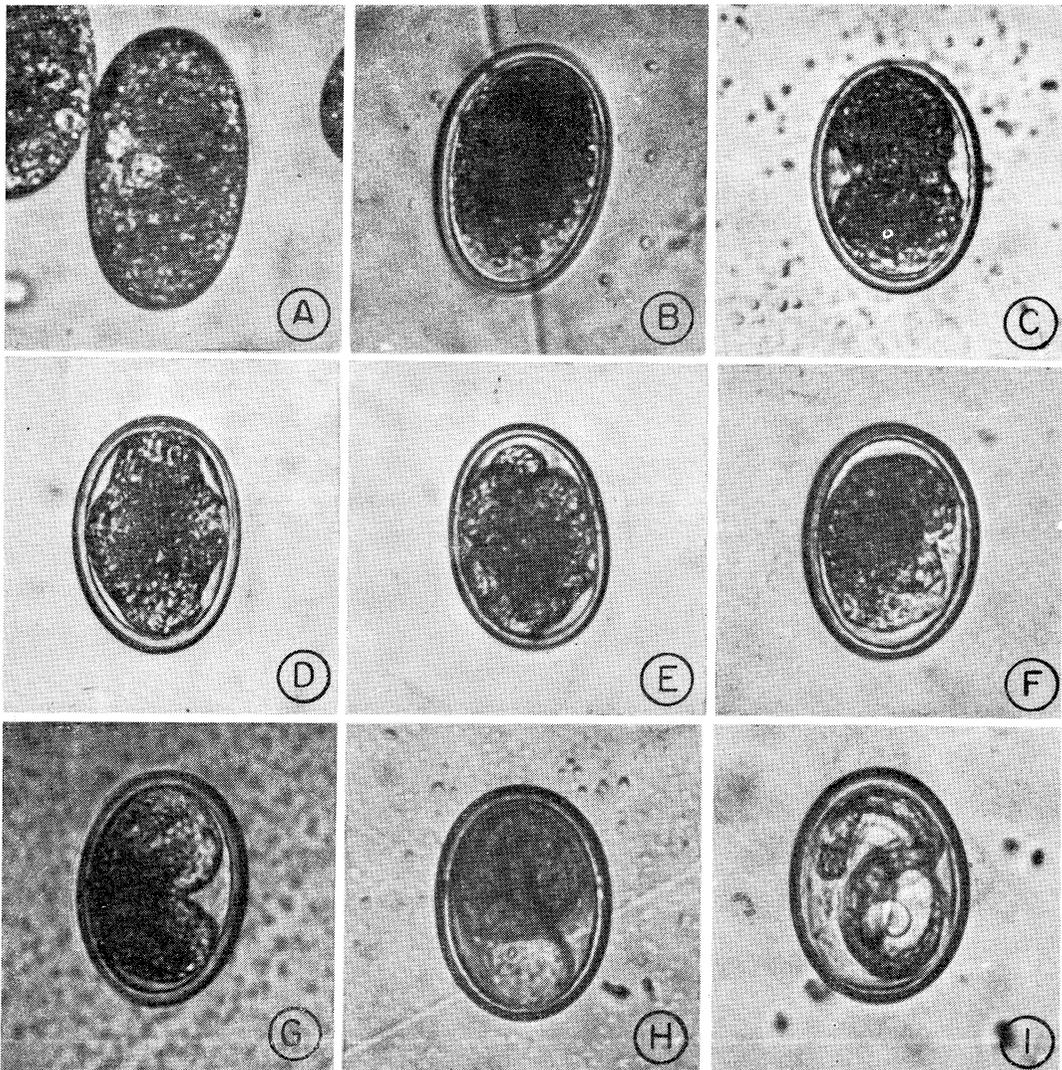


Fig. 3 — Development of *Ascaris lumbricoides* eggs kept in N/10 sulfuric acid at 28°C. A — Immature eggs. B — I — Development of the eggs to infectant phase. 345 X

of the disease. PIKE<sup>13</sup> pointed out that piperazine citrate, administered to mice 24 hours after their ingestion of *A. lumbricoides* eggs, had shown no action against the helminth's larval forms. The present paper (Table V) also shows that none of the drugs used (tetramizole, thiabendazole and piperazine) has proved effective against *A. lumbricoides* larval forms. CHAIA & CUNHA<sup>3</sup> have also demonstrated that thiabendazole displayed no action against the pre-patent forms of *Strongyloides ratti*.

We believe that, under the present circumstances, no means of controlling the helminthiasis is so far achievable in our environment. We also think that, only in highly-developed countries, can such helminthiasis be kept under control. Although greatest attention must be paid to the problem of helminthiasis in under-developed countries, where their prevalence is alarmingly high, it must be pointed out that no answer to this problem can now be found. Furthermore, if LITTLE'S<sup>11</sup> preliminary investigations

CHAIA, G. & CUNHA, A. S. da — Epidemiology and therapy of helminthiasis. A study of the re-infection period in school children treated with Thiabendazole and Tetramizole. *Rev. Inst. Med. trop. São Paulo* 12:152-160, 1970.

TABLE IV

Assessment of therapy in Ascariasis of school children treated with a single tetramizole dose (6 mg/kg). Vila São Vicente, Belo Horizonte, Brazil

Monthly Examinations	Group of patients	no. of patients	no. of tests performed	Positive Tests		
				no.	%	Mean number of eggs per g of feces
T	A	40	40	40	100.0	10,225
	B	20	20	20	100.0	11,355
1 <sup>st</sup>	A	35	35	0	0.0	0
	B	20	20	20	100.0	14,048
2 <sup>nd</sup>	A	35	35	0	0.0	0
	B	19	19	19	100.0	19,132
3 <sup>rd</sup>	A	35	35	6	17.0	387
	B	18	18	13	72.0	20,777
4 <sup>th</sup>	A	26	26	7	26.0	3,657
	B	15	15	13	86.0	34,400
5 <sup>th</sup>	A	33	33	15	45.0	5,000
	B	13	13	8	61.0	29,975

A = treated  
B = control  
T = treatment

TABLE V

Mice inoculated, per os, with eggs of *Ascaris lumbricoides* and treated, 2 days after inoculation, with tetramizole (10 mg/kg), piperazine (10 mg/kg) and thiabendazole (50 mg/kg)

Group *	MICE ON EXPERIMENT			Mice examined **		
	no. of mice	no. of eggs inoculated per animal	Drug single dose	no.	Positive tests for larvae	
					no.	%
I	8	2,000	10	8	7	87.5
II	8	2,000	100	8	8	100.0
III	8	2,000	50	8	8	100.0

\* Treated with: I — tetramizole; II — piperazine; III — thiabendazole

\*\* 8 days after inoculation the animals' lungs were examined for checking the presence of *A. lumbricoides* larval forms

— The control mice (3) were found to be positive

about the pig's *Ascaris* being able to infect man be proved, true, the problem will be still harder to be faced. We are then strongly convinced that the control of helminthiasis is closely correlated with the development of the country.

#### RESUMO

#### *Epidemiologia e terapêutica das helmintíases. Estudo do período de reinfeção de escolares tratados com o tiabendazol e tetramisole*

Este trabalho vem oferecer aos órgãos do Ministério da Saúde, pela primeira vez em nosso País, dados oficiais de uma avaliação terapêutica em escolares infetados pelas helmintíases. Com o esquema terapêutico empregado, os maiores índices de cura obtidos com o tiabendazol foram os seguintes: *Strongyloides stercoralis* 92,3%, *Enterobius vermicularis* 90,0% e *Ascaris lumbricoides* 51,5%. O percentual de cura de *Ascaris lumbricoides* em escolares tratados com o tetramisole foi de 100,0%. Entretanto, 5 meses após o tratamento o percentual de reinfeção dos escolares pelas helmintíases já era bem elevado. Os Autores concluem que inúmeras são as dificuldades para se obter algum êxito no controle das helmintíases. Este problema ainda se agrava, porque como ficou demonstrado, as drogas empregadas não têm ação terapêutica sobre as formas pré-patentes das infecções pelos *Ascaris lumbricoides* e *Strongyloides stercoralis*. Infelizmente, os Autores acreditam que o controle das helmintíases está intimamente relacionado com o desenvolvimento dos Países.

#### REFERENCES

1. BEAVER, P. C. — Methods of Pinworm Diagnosis. *Amer. J. Trop. Med.* 29:577-587, 1952.
2. BOTERO, D. — Report on clinical investigations with thiabendazole (MK — 360). *Tribuna Médica* 3:1-8, 1964.
3. CHAIA, O. & CUNHA, A. S. — Atividade terapêutica do tiabendazol na estrogiloidose humana. Considerações sobre a endo e a autoinfecção. *Rev. Inst. Med. trop. São Paulo* 5:261-264, 1963.
4. CHAIA, G. & CUNHA, A. S. — Novo esquema terapêutico com o tiabendazol na estrogiloidose humana. *Rev. Inst. Med. trop. São Paulo* 8:173-176, 1966.
5. CROCE, J.; CAMPOS, R.; NETO, U. A.; PIRES, C. D.; CASTRO, A. C. M.; LAURENTI, R. & ALBUQUERQUE, F. J. M. — Tratamento da estrogiloidose pelo tiabendazol. *Rev. Inst. Med. trop. São Paulo* 5:194-197, 1963.
6. ESCOBAR, J. J. — Thiabendazole a new wide spectrum anthelmintic. *Antioquia Medica* 14:3-20, 1964.
7. FERRAZ, W. G.; CABEÇA, M.; SARRA, C. & GUIMARÃES, R. X. — Tratamento da estrogiloidose e da ascariase com thiabendazol. *Hospital* (Rio) 64:109-116, 1963.
8. FRANZ, K. H. — Clinical trials with thiabendazole against human strongyloidiasis. *Amer. J. Trop. Med.* 12:211-214, 1963.
9. HOFFMANN, W. A.; PONS, J. A. & JANER, J. L. — Sedimentation concentration method in *Schistosomiasis mansoni*. *Puerto Rico J. Pub. Health & Trop. Med.* 9:283-298, 1934.
10. JACOBS, A. H. — Enterobiasis in children: Incidence, Symptomatology, Diagnosis, with a simplified Scotch cellulose Tape Technique. *J. Pediatrics* 21:497-503, 1942.
11. LITTLE, M. D. — Comparison of Human and Pig *Ascaris*. Abstracts & Reviews, *Eight International Congresses on Tropical Medicine and Malaria* p. 181, 1968.
12. MOST, H.; YOELI, M.; CAMPBELL, W. C. & CUCKLER, A. C. — The treatment of *Strongyloides* and *Enterobius* infections with thiabendazole. *Amer. J. Trop. Med. & Hyg.* 14:379-382, 1965.
13. PIKE, E. H. — The effect of piperazine citrate on hatching and migrating larvae of *Ascaris lumbricoides* (Research notes). *J. Parasit.* 45:46, 1959.
14. STOLL, N. R. — Investigation on the control of hookworm disease. XV — An effective method for counting hookworm eggs in feces, *Amer. J. Hyg.* 3:59-70, 1923.
15. VILELA, M. P.; RODRIGUES, D. L.; CAPEL, I. J.; BRANDÃO, A. J.; MARTIRANI, I. & ZUCATO, M. — O emprêgo do tiabendazol no tratamento da estrogiloidose e de outras parasitoses humanas. *Hospital* (Rio) 62:691-710, 1962.
16. W.H.O. — Control of Ascariasis — Report of a WHO Expert Committee. *W.H.O. Techn. Rep. Ser.* no. 379, 1967.

Recebido para publicação em 26/9/1969.