

Studies on endemic hookworm : 2. Comparison of the efficacy of anthelmintics in Taiwan and Liberia

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Along with development of vaccination and improvement of sanitation, searches for safe, effective and cheap anti-hookworm drugs have remained an important part of research on endemic hookworm.

Following experimental work by Perroncito (1879-1880) and clinical trials by Bozzolo & Pagliani (1880) in Italy, thymol, a phenolic compound obtained from the aromatic oils of *Thymus vulgaris*, was found to be useful against hookworm. It was, however, unpleasant to take and rather toxic. As indicated in the Bibliography of Hookworm Disease published by the Rockefeller Foundation in 1922 and the Bibliography of Hookworm Disease (Ancylostomiasis) published by the World Health Organization in 1965, the therapeutic efficacy of more than 50 drugs against hookworm had been tested by 1962. Among them were oil of chenopodium (Vervoot, 1913), carbon tetrachloride (Hall, 1921 ab), tetrachlorethylene (Hall & Shillinger, 1925), β -naphthol (Caius & Mhasker, 1921) and hexylresorcinol (Maplestone & Mukerji, 1932). Komyia (1958) reported that β -naphthol and carbon tetrachloride are more toxic than thymol, oil of chenopodium, tetrachlorethylene, hexylresorcinol, 1-bromo-2-naphthol and O-R 30. In Japan, 1-bromo-2-naphthol was introduced against hookworm by Miura *et al.* (1953) and O-R 30 [combination of

Octylchlororesorcinol (70 parts) and Octylresorcinol (30 parts)] by Yamasaki *et al.* (1954).

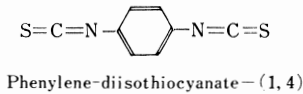
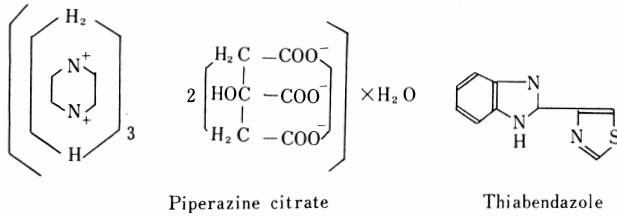
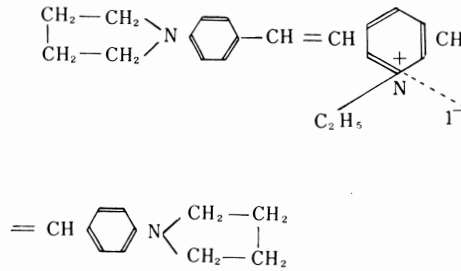
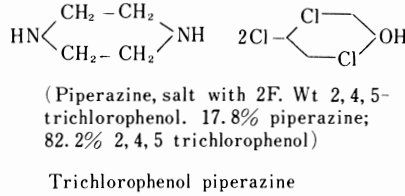
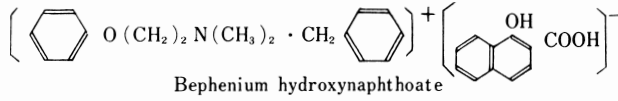
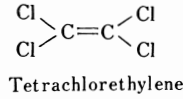
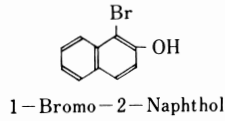
Since 1959, in Taiwan, the author and his co-workers have evaluated the anthelmintic activity of 1-bromo-2-naphthol (Hsieh *et al.*, 1960 a; Hsieh & Chen, 1965), piperazine compounds (Brown *et al.*, 1959; Hsieh *et al.*, 1961 c, 1965), tetrachlorethylene (Hsieh *et al.*, 1960 a; Brown *et al.*, 1959; Hsieh *et al.*, 1961 c; Hsieh & Chen, 1965), bephenium hydroxynaphthoate (Hsieh, 1959; Hsieh *et al.*, 1960 b, 1961 bc; Hsieh & Chen, 1965), stilbazium iodide (Hsieh *et al.*, 1963 a), trichlorophenol piperazine (Hsieh *et al.*, 1963 b), thiabendazole (Hsieh, 1963) and phenylenediisothiocyanate (Hsieh *et al.*, 1970), dithiazanine iodide (Brown *et al.*, 1959), ascaridol (Brown *et al.*, 1959), and pyrvinium pamoate (Hsieh *et al.*, 1963 b), combination of santonin and kainic acid (Hsieh *et al.*, 1961 c), and hetol (Lee *et al.*, 1969).

This paper compares the therapeutic efficacy of the first 8 anthelmintics in the author's series which were confirmed to be effective drugs against hookworm; with special reference to unpublished data of evaluation on thiabendazole in Taiwan, and on bephenium hydroxynaphthoate, tetrachlorethylene, their combination, piperazine citrate, and phenylenediisothiocyanate in Liberia, West Africa. The structural formula of these anthelmintics is as follows:

Materials and Methods

The anthelmintics and their dosage regi-

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mens tested by the author and his co-workers in the earlier evaluations were described in the published papers (Hsieh, 1959; Brown *et al.*, 1959; Hsieh *et al.*, 1960 ab, 1961 bc, 1963 abc).

Thiabendazole used for the investigation

in Taiwan in 1963 was supplied by the Merck Sharp and Dohme Research Laboratories in New York. For the investigation in Liberia in 1969, bephenium hydroxynaphthoate (manufactured by Burroughs Wellcome & Co., London), tetrachlorethylene (manufactured by

Speke, Liverpool), piperazine citrate (manufactured by Halewood Chemical, LTD., Staines, Middlesex, England) were purchased from drug stores in Liberia. Phenylene-diisothiocyanate was produced and supplied by Farbwerke Hoechst AG., Frankfurt, Federal Republic of Germany.

A. The dosage regimens for the unpublished evaluation were as follows:

1. *Thiabendazole* (oral suspension)
Fifty mg/kg weight once or 25 mg/kg twice a day for 2 or 3 days.
2. *Phenylene-diisothiocyanate* (50 mg in each capsule)

For adults: 3 doses of 100 mg (or approximately 6 mg/kg weight divided in 3 doses) at 12 hour interval.

For children: 2 doses of 100 mg (or approximately 6 mg/kg weight divided in 2 doses) at 12 hour interval.

3. *Bephenium hydroxynaphthoate* (2.5 gm base in the form of granules)
A single dose of 1.25 gm or 2.5 gm base, given with or without combination of tetrachlorethylene.
4. *Tetrachlorethylene* (0.2 ml in capsule)
A single dose of approximately 0.07-0.11 ml/kg weight, but not more than 5 ml, given with bephenium hydroxynaphthoate.
5. *Piperazine citrate* (0.5 gm tablet)
A single dose of approximately 63-199 mg/kg weight.

B. Administration of the drug for the unpublished evaluation was as follows:

Each dose of phenylene-diisothiocyanate to be given after substantial meals at 12 hour anthelmintics, except for thiabendazole, to be administered about 3 hours after supper in Liberia. The single dose or the first dose of thiabendazole was given about 3 hours after supper and the second dose before breakfast. No purgative was given before or after therapy. No iron medication was intended. The side effects due to these anthelmintics complained of by patients were recorded.

C. People treated:

All people in the study groups were the native inhabitant living in the highly endemic area of *N. americanus* and *A. duodenale* in Taiwan or Liberia. The Liberian group was examined monthly by the author before medication, and never received any anthelmintics during the observation period.

D. The methods for evaluation:

For most of the investigations on anthelmintics made by the author, the Stoll's dilution egg counting method (Stoll, 1962) was employed to determine the egg reduction. Either the modified test-tube filter-paper cultivation (MTFC) method (Hsieh, 1970) or simple test-tube culture (Hsieh, 1963) were employed for all investigations to determine the hookworm species. The "cure" rates were determined by the negative finding of the Stoll and MTFC methods. The post-treatment stool examination was made 4 weeks after therapy.

It should be noted that the MTFC method (Hsieh, 1970) was primarily aimed at the collection of the infective larvae from both the filterpaper and the water in the test-tube culture for specific identification of *A. duodenale* and *N. americanus* as the filariform larvae of *N. americanus* have a greater tendency to stay on the filter-paper in the MTFC culture than those of *A. duodenale*.

The author employed the MTFC method along with the Stoll dilution egg counting method for estimation of the relative burden of *A. duodenale* and *N. americanus* in an individual or group of people in Liberia where the two hookworms were endemic. Combined application of the two methods was found to possess special value for comparing the therapeutic efficacy of an antyelmintic relatively against *A. duodenale* or *N. americanus*.

Results

Results of the latest evaluation made in Liberia in July 1969 are first shown in Table 1, and the summary was further compared with those in Taiwan in Tables 2-6.

The therapeutic efficacy of phenylene-

Table 1 Comparison of the therapeutic efficacy of 4 anthelmintics against *N. americanus* (Na) and *A. duodenale* (Ad) among Liberians

Regimen	No. of cases treated	Results					
		Na		Ad		All species	
		CR	ERR	CR	ERR	CR	ERR
Phenylene-diisothiocyanate approximately 6 mg/kg weight divided in 3 doses at 12 hour interval	14*	29	79	0	26	21	77
Phenylene-diisothiocyanate approximately 6 mg/kg weight divided in 2 doses at 12 hour interval	16	44	90	36	95	19	92
Bephenium 1.25 or 2.5 gm once	21	0	65	81	99	0	81
Bephenium 2.5 gm and Tetrachlorethylene (0.07-0.11 ml/kg) once	18	22	93	78	98	12	96
Piperazine citrate (63-100 mg/kg) once	8	0	84	25	81	0	82

CR: "cure" rate (%) ERR: Egg reduction rate (%)

* Four of 14 cases are concurrently infected with *A. duodenale*

diisothiocyanate with 3 doses of 100 mg (approximately 2 mg/kg weight) given for Liberian adults at 12 hour intervals was observed in 14 cases of *N. americanus* infections and 4 cases of *A. duodenale* in association with *N. americanus* infections. As shown in Table 1, the 300 mg of phenylene-diisothiocyanate (approximately 2 mg/kg weight) reduced the egg-count by 77%. Despite their light infection, none of the 4 cases of *A. duodenale* infections was "cured". However, the "cure" rate was 29% for *N. americanus* and 21% for all hookworm infections. When 200 mg of this drug were given in 2 doses (approximately 3 mg/kg weight) for 16 Liberian children at 12 hour interval, as shown in Table 1, the egg reduction rate was improved to 92%. The "cure" rate was improved to 44% for *N. americanus*, 36% for *A. duodenale* and 19% for all hookworm infections. The above two groups equally received approximately 6 mg/kg of phenylene-diisothiocyanate as the total dose. However, the egg reduction and "cure" rates in the second group which received the approximately 3 mg/kg (single dose) were apparently higher than those in the first group which

received the approximately 2 mg/kg (single dose).

A single dose of bephenium hydroxynaphthoate (1.25-2.50 gm base) was given to 21 Liberians with both *N. americanus* and *A. duodenale*. As shown in Table 1, the egg reduction rate was 81% for the group; 99% for *A. duodenale* and 65% for *N. americanus*. Eighty-one % of *A. duodenale* infections but none of *N. americanus* infections were "cured". Therefore, on the whole, none of the 21 Liberians infected with the two species was "cured" with a single dose of bephenium hydroxynaphthoate.

When a combined dose of tetrachlorethylene and bephenium hydroxynaphthoate was given to 18 Liberians infected with both *N. americanus* and *A. duodenale*, as shown in Table 1, the egg reduction rate was raised to 96% for the group; 93% for *N. americanus* and 98% for *A. duodenale*. And the "cure" rate was also raised to 17% for the group; 22% for *N. americanus* and 78% for *A. duodenale*.

A single dose of piperazine citrate (approximately 63-100 mg/kg weight) was given to 7 cases with *N. americanus* and *A. duo-*

denale, and to 1 case with *A. duodenale*. As shown in Table 1, even the single dose of piperazine citrate caused an egg reduction as high as 82%, although none of the 8 cases became negative. The egg reduction rate for the two hookworm species showed no significance, but 25% of *A. duodenale* was "cured". Further investigations should be made to confirm the efficacy of piperazine derivatives against hookworm.

Discussion

The therapeutic efficacy and the side effects of 8 anthelmintics evaluated by the author and his co-workers during the last decade may be compared and discussed as below:

As shown in Tables 2-6, when given with one or two doses a day without purgation, 1-bromo-2-naphthol (Wormin), tetrachlorethylene, bephenium hydroxynaphthoate (Alcopar), and phenylene-diisothiocyanate (Jonit) were found to be more effective than the rest. The patients in Taiwan best tolerated 1-bromo-2-naphthol and complained of considerable side effects due to other drugs.

As shown in Tables 2-3, bephenium hydroxynaphthoate was effective against both *A. duodenale* and *N. americanus* but it showed a special efficacy against the former species.

In Taiwan a single dose of bephenium hydroxynaphthoate (2.5 gm base for adults and children), usually caused a 90% or more egg reduction and a 50% or more "cure" rate. The "cure" rate among the lightly-infected groups (below 2,000 EPG) was apparently greater than that of the heavily-infected group. For treatment of schoolchildren infected with both *A. duodenale* and *N. americanus*, one or two reduced doses of bephenium hydroxynaphthoate (1.25 gm base) proved to be as effective as those with the 2.5 gm dosage. The reduced dose could produce 86 to 99% reduction of the egg-count but the "cure" rate varied from 27 to 96%. The variation might be chiefly due to difference in the ratio of *N. americanus* to *A. duodenale* in the worm burden.

Bephenium hydroxynaphthoate has a bitter taste, yet it is acceptable to both children and adults. Daily doses of 2.5 gm (base) for 5 to 7 days caused dizziness, nausea, vomiting, abdominal discomfort, diarrhea and headache in children. These side effects were of sufficient severity and frequency to limit the use of the therapeutic regime in mass therapy. When the dosage was reduced to 1.0 to 1.5 gm of the compound twice daily for 2 days or 2.5 gm twice daily for 1 day, the side effects were greatly reduced and consisted of

Table 2 The therapeutic efficacy of Bephenium hydroxynaphthoate (BH), for schoolchildren and adults, published by Hsieh *et al.* from 1960 to 1970 in Taiwan and Liberia

Authors (year)	Dosage (base)	Cases studied	"Cure" rate (%)	Egg reduction rate (%)	Method of evaluation
Hsieh <i>et al.</i> (1960)	BH, 2.5 gm once daily for 7 days	6	Ad>Na [#] : 83	100	MTFC & Stoll
Hsieh <i>et al.</i> (1961)	BH, 2.5 gm once	48	Ad: 58	93	"
"	"	69	Ad>Na: 28	91	"
"	"	69	Ad: 78	—	MTFC
"	"	69	Na: 19	—	"
Hsieh <i>et al.</i> (1970)*	BH, 1.25 to 2.5 gm once	21	Ad>Na: 0 Ad: 81 Na: 0	81	MTFC & Stoll

* Table 1 in this paper

[#] Ad>Na: more Ad than Na

Table 3 The therapeutic efficacy of Bephenium hydroxynaphthoate (BH), for schoolchildren, published by Hsieh *et al.* from 1960 to 1970, in Taiwan

Authors (year)	Dosage (base)	Cases studied	"Cure" rate (%)	Egg reduction rate (%)	Method of evaluation
Hsieh <i>et al.</i> (1960)	BH, 2.5 gm once daily for 5 days	2	Ad>Na: 100 [#]	100	MTFC & Stoll
"	BH, 1-1.5 gm twice daily for 2 days	17	Ad>Na: 64	100	"
"	BH, 2.5 gm twice daily	23	Ad>Na: 74	99	"
Hsieh <i>et al.</i> (1961)	BH, 1.25 gm once	54	Ad: 89	97	"
"	BH, 1.25 gm twice	47	Ad>Na: 96	99	"
"	BH, 1.25 gm once	33	Ad>Na: 70	86	"
"	BH, 1.25 gm twice	33	Ad>Na: 79	96	"
"	BH, 1.25 gm once	33	Ad>Na: 27 Ad: 85 Na: 27	89	"
"	BH, 1.25 gm twice	33	Ad>Na: 58 Ad: 97 Na: 58	95	"
Hsieh <i>et al.</i> (1965)	BH, 1.25 gm once	296	Ad>Na: 80	93	"

[#] Ad>Na: more Ad than Na

only occasional vomiting and headache, diarrhea and abdominal discomfort. All side effects quickly subsided when the drug was discontinued. Yokogawa *et al.* (1962) reported that side effects due to bephenium hydroxynaphthoate occurred in 34.9% of 149 schoolchildren treated in Japan but they are also transient.

As shown in Table 4, tetrachlorethylene was also effective against the two hookworm species among Chinese and Liberians, but it was more active against *N. americanus*. A single dose of this drug (0.1 mg/kg weight) caused a 67% reduction in the egg-count and a 33% "cure" rate among schoolchildren in Taiwan. The Taiwan result gave a lower removal rate of *N. americanus* with tetrachlorethylene viewed in the light of the report of Carr *et al.* (1954), who removed 92% of *N. americanus* from a large group of adults with a single dose of the same drug. Fan *et al.* (1956) reported their result of hookworm treatment that astin (active principle of oleum chenopodium) gave a

"cure" rate of 81% with 72% of side effects and tetrachlorethylene 91% with 71% of side effects. The anthelmintic efficacy was evaluated by concentration method. The incidence of side effects due to tetrachlorethylene observed by Hsieh in this paper was higher than that reported by Fan *et al.* (1956). Approximately 80% of the people receiving tetrachlorethylene showed one or more of the following side effects: dizziness, nausea, vomiting, headache, drunkenness, and abdominal pain. About one per 100 persons treated showed apprehensive emotional reactions.

When bephenium hydroxynaphthoate were combined for the treatment of *A. duodenale* in association with *N. americanus*, the removal rate was greater than that with a single dose of each drug. The side effects due to the combined dose was also greater than those with the separate dose. However, the side effects were tolerated.

As shown in Table 5, 1-bromo-2-naphthol which was developed and mostly used in Japan was observed to be another useful anti-

Table 4 The therapeutic efficacy of Tetrachlorethylene (TCE) and its combination with Bephenium hydroxynaphthoate (BH), published by Hsieh *et al.* from 1960 to 1970, in Taiwan and Liberia

Authors (year)	Dosage (base)	Cases studied	"Cure" rate (%)	Egg reduction rate (%)	Method of evaluation
Hsieh <i>et al.</i> (1961)	TCE 2 ml & BH, 2.5 gm once for adults	9	Ad>Na: 22 Ad: 89 Na: 22	98	MTFC & Stoll
"	TCE 5 ml & BH, 2.5 gm once for adults	6	Ad>Na: 67 Ad: 67 Na: 100	100	"
"	TCE 0.1 ml/kg & BH, 1.25gm once for children	18	Ad>Na: 94 Ad: 94 Na: 100	99	"
Hsieh <i>et al.</i> (1960)	TCE 0.2 ml/year of age up to 3ml as the maximum dose	190	Ad & Na: 16	—	MTFC
"	"	51	Ad & Na: 16	55	MTFC & Stoll
Hsieh <i>et al.</i> (1961)	TCE 0.1 ml/kg for children	33	Ad & Na: 33 Ad: 39 Na: 70	67	"
Hsieh (1970)*	TCE 0.07-0.11 ml/kg & BH, 2.5 gm once	18	Ad<Na: 17 Ad: 78 Na: 22	96	"

* Table 1 in this paper (study in Liberia)

‡ Ad>Na: more Ad than Na

hookworm drug. The comparative anthelmintic effects of 1-bromo-2-naphthol against *A. duodenale* and *N. americanus* were made by Matsuzaki (1957), Yamazaki (1955), Yoshida *et al.* (1960), Hsieh *et al.* (1960 a, 1965). Matsuzaki (1957) and Hsieh *et al.* (1960 a, 1965) reported that this drug is more effective against *N. americanus* than *A. duodenale* although Yoshida *et al.* (1960) reported that this drug is almost equally effective against both species of hookworm in man. The evidence obtained by Hsieh *et al.* (1960 a, 1965) as to the efficacy of 1-bromo-2-naphthol against *A. duodenale* and *N. americanus* is in full agreement with earlier data reported by Yamazaki (1955). It might be safely mentioned that 1-bromo-2-naphthol is effective against both species of hookworm but more effective against *N. americanus*. Komyia & Kobayashi (1963) recommended that a single dose of 6 gm of this compound (9 gm of "Wormin" granules) is the best in mass treatment of *N. americanus*. The results of a

clinical trial (4 gm base of "Wormin" granules as the adult dose twice at 10 hour interval) made by Hsieh *et al.* (1960 a, 1965) in Taiwan indicated that this drug reduced from 75 to 86% of the egg-count, and "cured" from 39 to 58% of the patients infected with *A. duodenale* and *N. americanus*.

Hsieh *et al.* (1965) later treated 143 children with 2 or 3 gm base of 1-bromo-2-naphthol once a day for 2 consecutive days. The initial treatment reduced 92% of the eggcount and "cured" 58% of hookworm infections, who were predominantly infected with *A. duodenale*. This regimen was repeated every other month for about one year and the egg reduction rate was maintained at a low level, although the "cure" rate varied from 75 to 90%. Children tolerated well repeated doses of 1-bromo-2-naphthol. Approximately 25% of the people who received 1-bromo-2-naphthol showed one or some of the following tolerable side effects: abdominal pain, nausea, dizziness and headache.

Table 5 The therapeutic efficacy of 1-Bromo-2-Naphthol (1-B-2-N), Trichlorophenol piperazine (TP), Stilbazium iodide (SI) and Piperazine citrate (PC), published by Hsieh *et al.* from 1960 to 1970, in Taiwan and Liberia

Authors (year)	Dosage (base)	Cases studied	"Cure" rate (%)	Egg reduction rate (%)	Method of evaluation
Hsieh <i>et al.</i> (1960)	1-B-2-N; 4 gm (base) twice at 10 hour interval for adults, reduced doses for children	241	Ad>Na: 39	—	MTFC
"	"	132	Ad>Na: 57	75	MTFC & Stoll
Hsieh <i>et al.</i> (1965)	"	114	Ad>Na: 58	86	"
"	1-B-2-N; 2 or 3 gm (base) once a day for 2 days in children	324	Ad>Na: 46	85	"
"	"	143	Ad>Na: 58	92	"
Hsieh <i>et al.</i> (1963)	TP, 70 mg/kg once	25	Ad>Na: 20 Ad: 24 Na: 80	96	"
"	TP, 50 mg/kg once	12	Ad>Na: 33 Ad: 50 Na: 58	81	"
"	SI, 300 mg twice a day for 3 days in children	7	Ad: 0	62	"
Hsieh (1970)*	PC, 63-10 mg/kg once	8	Ad & Na: 0 Ad: 25 Na: 0	82	"

* Table 1 in this paper (study in Liberia)

As shown in Table 6, phenylene-diisothiocyanate was confirmed to be effective for hookworm in Taiwan and Liberia. Recently Hsieh *et al.* (1970) used phenylene-diisothiocyanate for treatment of 30 adults in Taiwan. All of them were infected with *A. duodenale* and 17 of them were concurrently with *N. americanus*. Three doses of 100mg phenylene-diisothiocyanate (approximately 2 mg/kg weight) at 12 hour intervals were able to reduced 98% of the egg-count, and "cured" 47% of *A. duodenale* and 100% of *N. americanus*, although the degree of *N. americanus* in this group was lighter than that of *A. duodenale*. In respect to the "cure" rate and the egg reduction rate for phenylene-diisothiocyanate (Jonit), the figures obtained by the author were below the average obtained by the majority of investigators using the Stoll method alone, but with similar frequency of

follow up examinations as reported in the Abstracts of Symposium on Jonit (1968). Comparing the Taiwan and Liberian data, it was confirmed that phenylene-diisothiocyanate has an effective anthelmintic activity against both *A. duodenale* and *N. americanus*. However, the therapeutic activity appeared to be more effective against *N. americanus*. In Liberia, the egg reduction rate of this anthelmintic was high at the dose of approximately 3 mg/kg weight twice at 12 hour interval against the two hookworm species in man. However, this 2-dose regimen has been reported to be somewhat less effective in other investigations than the three times every 12 hour regimen (Hoechst' Symposium on Jonit, 1968). The high frequency of side effects due to this drug among Chinese might prevent it from repeated mass treatments of hookworm in Taiwan. However, in the

Table 6 The therapeutic efficacy of Phenylene-diisothiocyanate (PD) and Thiabendazole observed among Chinese and Liberians by Hsieh or Hsieh *et al.* from 1960 to 1970.

Authors (year)	Dosage (base)	Cases studied	"Cure" rate (%)	Egg reduction rate (%)	Method of evaluation
Hsieh <i>et al.</i> (1970)	PD 100mg thrice at 12 hour interval for adults	30	Ad>Na : 47 Ad : 47 Na : 100	98	MTFC & Stoll
Hsieh (1970)*	"	14	Ad>Na : 21 Ad : 0 Na : 29	77	"
Hsieh (1970)*	PD 100mg twice at 12 hour interval for school-children	16	Ad>Na : 19 Ad : 36 Na : 44	92	"
Hsieh (1970)#	PD 50 mg twice at 12 hour interval for school-children	6	Ad>Na : 0 Ad : 0 Na : 0	63	"
Hsieh (1970)#	PD 50 mg once for schoolchildren	5	Ad>Na : 0 Ad : 0 Na : 20	68	"
Hsieh (1963)##	Thiabendazole 50 mg once for adults	23	Ad : 39	62	"
"	"	41	Ad>Na : 2	33	"
"	Thiabendazole 25 mg twice a day for 2 days for adults	7	Ad>Na : 71	97	"
"	Thiabendazole 25 mg twice a day for 3 days for adults	10	Ad>Na : 100	100	"

* Table 1 in this paper (study in Liberia)

Unpublished data from Liberia

Unpublished data from Taiwan

countries like Liberia, where people used to believe manifestation of side effects due to drugs as an indication of effective medicines, this anthelmintic might be useful. The commonest side effects due to 3 doses of 100 mg for 30 adults in Taiwan were anorexia, diarrhea, abdominal fullness, nausea, malaise and vomiting etc. They were however well tolerated. The commonest side effects complained of by Liberians were diarrhea and vertigo, and their severity and frequency were apparently milder than those complained of by the Chinese.

As shown in Table 5 trichlorophenol piperazine (Hsieh *et al.*, 1963 c) was more effective

against *N. americanus* than against *A. duodenale*. A single dose of 50 or 70 mg/kg weight yielded 81 or 96 % reduction of the egg-count respectively. However, the severe side effects due to the drug made it very unpopular. The commonest side effects were dizziness, abdominal pain and vomiting.

Stilbazium iodide was found by Swartzwelder *et al.* (1962) that a significant anthelmintic against *E. vermicularis*, *A. lumbricoides*, *T. trichiura* and *S. stercoralis*. Hsieh *et al.* (1963 a) confirmed the anthelmintic activity of this drug against *E. vermicularis*, *A. lumbricoides* and *T. trichiura*, and also reported excellent results against *F. buski* and moderate

efficacy against *A. duodenale* (62% of the egg reduction). Huang and Brown (1964) further confirmed the moderate efficacy of this drug against *A. duodenale* and *N. americanus*. They evaluated the efficacy by the smearing, flotation and Stoll dilution egg count methods. Vomiting and abdominal discomfort were common among those who received 300 mg base twice daily on 3 consecutive days, but no other side effects were complained of by the patients.

As shown in Table 5, a single dose of piperazine citrate (63–100 mg/kg), which is also useful for the mass treatment of *A. lumbricoides*, produced 82% reduction of the egg-count for hookworm and the "cure" rate for *N. americanus* and *A. duodenale* was 0 or 25% respectively.

Thiabendazole, as shown in Table 6, was confirmed to be an effective drug for hookworm. When 25 mg/kg of this drug was given twice a day for 2 or 3 days against mixed infections of *N. americanus* and *A. duodenale*, the result showed 97 or 100% of the egg reduction and 71 or 100% "cure". Franz (1963) reported the therapeutic efficacy of thiabendazole against *S. stercoralis*. This anthelmintic might be a choice of drug for the patients infected with both *S. stercoralis* and hookworm. A single dose regimen of 50 mg/kg produced only moderate anti-hookworm activity in 2 groups of adults. Although transient side reactions of dizziness and nausea following administration of the drug were not serious, the incidence of these reactions was high. Huang & Brown (1963) reported that thiabendazole in the dosages of 2 gm, approximately 40 mg/kg, as a single dose for 1 day in adult patients has a moderate anthelmintic activity against both *A. duodenale* and *N. americanus* as judged by egg-count reduction.

For the treatment of the mixed infection of *N. americanus* with *A. duodenale*, a single dose of tetrachlorethylene in combination with bephenium hydroxynaphthoate could improve the egg reduction and "cure" rates especially against *N. americanus*. However, in the Liberian groups two doses of phenylene-

diisothiocyanate (approximately 3 mg/kg weight) caused a 92% egg reduction and a 19% "cure" rate, which was close to that due to the combination of tetrachlorethylene with bephenium hydroxynaphthoate.

When the therapeutic efficacy of bephenium hydroxynaphthoate, tetrachlorethylene, their combination, and phenylene-diisothiocyanate against hookworm were compared among the groups in Taiwan and Liberia with similar methods for evaluation, the Taiwan groups generally showed better results than the Liberian groups. On the other hand, the Chinese complained of more side effects due to anthelmintics than the Liberians.

Two general approaches to the control of hookworm infections are known. One method consists in prevention of new or additional infection, the other in treatment of existing infections. The first approach resolves itself largely into the improvement of sanitary conditions with consequent elimination of soil pollution until effective vaccination can be developed, while the second approach necessitates the use of anthelmintics. The first approach is universally recognized as the one of choice, and the only method which can be depended upon to bring permanent relief. But simple as it seems in theory, it is no easy matter to induce hundreds of millions of people to change habits which are ingrained by countless of use. Consequently sanitary reforms are slow, requiring labor, patience and time. The treatment method, on the other hand, can bring immediate relief to the individuals involved, but to have any prolonged effect it must be applied to the majority of a group all at once in the form of a mass treatment, and must be repeated at intervals. The benefits of mass treatments can be better demonstrated on estates, plantations, and isolated islands of regions.

For the mass treatment of hookworm in the endemic area, simple medication is always advisable. For this reason, the use of one dose of tetrachlorethylene, and bephenium hydroxynaphthoate, or 2 doses of 1-bromo-2-naphthol, and phenylene-diisothiocyanate mi-

ght be recommended until cheaper and less toxic drugs could be developed. The egg reduction rate of these anthelmintics was found to be considerably high against both *A. duodenale* and *N. americanus*, although their "cure" rate against each species was different and the frequency of side effects complained of by the patients were not uncommon.

Emphasis is made that administration of one or two doses of these selected anthelmintics at a reasonable interval has demonstrated to be useful for bringing the worm burden from moderate or high level to a low level with lessened clinical significance. This approach seems to be sufficient as the majority of hookworm cases in most of the endemic villages in Taiwan and Liberia appeared to be lightly infected and without clinical significance. The frequency of medication and the worm burden without clinical significance in each country, however, should be determined by the nutritional condition, and the socioeconomic status, and the endemic species as *A. duodenale* is generally accepted to be more pathogenic than *N. americanus*.

Peña Chavarria *et al.* (1969) reported that cure rates of infections, with a single oral dose (12 mg/kg weight) of dichlorvos, were 85.7% for hookworm, 87.8% of *T. trichiura*, and 77.8% for *A. lumbricoides*; egg-count reductions in the cases not completely cured were 97.3, 98.5, and 83.7%, respectively. Cervoni *et al.* (1969) also reported that the trichuricidal action, broad-spectrum anthelmintic activity, and good tolerance upon single dosage (6 or 12 mg/kg weight) of dichlorvos. The relative efficacy of this drug against *A. duodenale* and *N. americanus* has not been evaluated but if the broad-spectrum anthelmintic activity of this new drug could be confirmed, it might have a place for the mass treatments of hookworm and associated helminths.

Summary

1. The anti-hookworm activity of phenylene-diisothiocyanate (Jonit), was recently

compared with those of bephenium hydroxynaphthoate (Alcopar), tetrachlorethylene, combination of bephenium hydroxynaphthoate and tetrachlorethylene, and piperazine citrate in Liberia, West Africa. The result was further compared with results of 8 anthelmintics evaluated by the author and his co-workers in Taiwan during the last decade.

2. Among the 8 anthelmintics against endemic hookworm, one dose of tetrachlorethylene (0.1 ml/kg weight) or bephenium hydroxynaphthoate (1.25 gm base for children and 2.5 gm base for adults) or 2 doses of 1-bromo-2-naphthol (4 gm base for adults and reduced dose for children at 10 hour interval) or 2 doses of phenylene-diisothiocyanate (3 mg/kg weight at 12 hour interval) produced a considerably higher reduction of the egg-count in spite of their different "cure" rate against *A. duodenale* and *N. americanus*. Bephenium hydroxynaphthoate was more effective against *A. duodenale*, but the other drugs were more effective against *N. americanus*.

3. The "cure" rate of phenylene-diisothiocyanate, bephenium hydroxynaphthoate and tetrachlorethylene among Chinese were found to be higher than that among Liberians. On the other hand, more side effects due to these anthelmintics were complained of by Chinese than Liberians.

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地方病性鉤虫に関する研究：

2. 台湾およびリベリヤにおける駆虫剤の比較研究*〔特別掲載〕

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“治癒率”が高く副作用少く且つ経済的な駆虫剤を求める研究は地方病性鉤虫の防遏に関する諸研究の中でも依然として重要な一項である。著者は約10年間台湾と熱帯アフリカのリベリヤ共和国において鉤虫に対して種々の駆虫剤を比較研究する機会に恵れた，“治癒”の判定には始めは原田・森濾紙培養法後には著者の考案した試験管濾紙培養法 MTEC とストール氏虫卵計算法を併用した。EPGの減少率はストール氏法を採用した。

本文では最初にリベリヤにおける実験成績を報告した後台湾成績と比較考察した。実験に供した鉤虫駆虫剤は次の8種である。

1. phenylene-diisothiocyanate (1, 4)
2. bephenium hydroxynaphthoate
3. tetrachlorethylene
4. 1-bromo-2-naphthol
5. piperazine citrate
6. stilbazium iodide

7. trichlorophenol piperazine

8. thiabendazole

これらのうちの1から4までの4種駆虫剤は両種の鉤虫に対する“治癒率”は同一ではないがリベリヤと台湾両地において1回乃至2回の投与法で80%又はそれ以上のEPG減少率が得られたので大幅のEPG減少をねらう集団治療作業には有用である。ジビニ鉤虫優先分布の台湾では駆虫効果の点からは bephenium hydroxynaphthoate が好ましいが、1-bromo-2-naphthol をのぞけば他の駆虫剤も同様であるが、bephenium hydroxynaphthoate に対して副作用を訴へるものが多かつた。リベリヤの如きアメリカ鉤虫優先地では tetrachlorethylene が高い駆虫効果と薬価の低い点から好ましい。phenylene-diisothiocyanate 或いは 1-bromo-2-naphthol もよいが、鉤虫と糞線虫の混合感染がしばしばみられるリベリヤの場合は thiabendazole が良い。リベリヤでの少数例についての実験では意外にも piperazine citrate が高い鉤虫の EPG 減少率を上げた、一般的にいつてリベリヤ黒人は中国人より諸種の駆虫剤に対して副作用を訴へるものが少ないことが注目された。

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