CHEMOTHERAPY OF INTESTINAL PARASITES IN SOUTHEAST ASIA

DANAI BUNNAG and TRANAKCHIT HARINASUTA

Department of Clinical Tropical Medicine and Hospital for Tropical Diseases, Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand.

INTRODUCTION

The common intestinal parasites in the Southeast Asian countries are as follows:

Protozoa:

Giardia lamblia
Entamoeba histolytica

Helminths:

Hookworm
Ascaris lumbricoides
Enterobius vermicularis
Trichuris trichiura
Strongyloides stercolaris
Capillaria philippinensis
Taenia saginata, Taenia solium
Fasciolopsis buski
Opisthorchis viverrini
Other intestinal flukes.

The treatment of these parasitoses are variable.

Giardiasis

Giardiasis is most common in children especially in orphanages and other institutions, and is manifested by recurrent episodes of watery or bulky motions and diarrhoea. An effective drug has been mepacrine, 100 mg three times daily for five days yielded a 100% cure, but the drug is no longer marketed. Nitroimidazole derivatives are also effective; tinidazole, metronidazole and ornidazole in a single dose of 2 gm gave cure rates of 86%, 52% and 96%, respectively (Sabcharoen *et al.*, 1980) while Kavousi (1979) obtained a 100% response using metronidazole 15-25 mg/day for five days. In another study Levi *et al.*, (1977) used metronidazole and tinidazole for 7 days and obtained cure rates of 80% and 97% respectively. The side effects were mild gastrointestinal disturbances.

Amoebiasis

Asymptomatic amoebiasis or cyst passers is commonly encountered, but the prevalences varied widely. The prevalent rate in children in Indonesia were 21% in West Flores and 31% on Alor Island (Partono and Soewata, 1980; Carney *et al.*, 1974), whereas the prevalence on children in a Bangkok Orphanage was 18%, in school children from provincial towns of Chumporn and Nakhon Nayok, Thailand were 0.8% and 0.6% respectively (Chongsuphajaisiddhi *et al.*, 1978).

Dichloroacetamide derivatives are sparingly absorbed from the intestines. These are white or yellowish powders, insoluble in water and tasteless. Four compounds are in use but only diloxamide furoate is effective; 500 mg three times daily for 10 days gave a high cure rate of 96% (Woodruff and Bell, 1960). The mode of action is not known.

Symptomatic intestinal amoebiasis is relatively mild and very few cases of fulminating amoebic dysentery with the passage of intestinal casts are encountered. Dichloroacetamide and nitroimidazole derivatives are commonly used. The former group includes:

Clefamide N-(B-oxyethyl)-N-(p-phenoxy-) 4-nitro)-benzyl) dichloroacetamide (250 mg tab)

Etofamide closely related to clefamide (200 mg tab)

Teclozan dichloroacetyl-ethyl- amino-ethyl-benzene, (100 mg tab)

The nitroimidazole derivatives are completely absorbed from the intestines and kill the trophozoites; the amoebic cyst however resists these compounds at low dose, (Chongsuphajaisiddhi, 1971). Metronidazole has been used since 1959 for *Trichomonas vaginalis* and in 1965-1966 it was prescribed for amoebiasis. Side effects occur in 20-30% and include metallic taste, upper gastrointestinal symptoms. The nervous system is less frequently affected, producing headache, dizziness and numbness of limbs. The dosage used in symptomatic amoebiasis is 600 mg three times daily for 5-10 days.

Tinidazole has similar properties to metronidazole but the blood level at 24 hour after administration was higher (Sawyer *et al.*, 1976). It is excreted unchanged. Disulfiram-like reactions with alcohol are observed as in metronidazole and are characterised by confusion, flushing, headache, drowsiness, nausea, vomiting and hypotension. The optimal dosage is 2 gm daily for 2-3 days which is a shorter course than that of metronidazole.

Ornidazole is similar to tinidazole and metronidazole and the manufacture claims a high plasma concentration in 1-2 hours, no incompatibility with alcohol, little neurotoxicity, no teratogenicity and no carcinogenicity. It has been recommended in symptomatic intestinal amoebiasis at 500 mg twice daily for 5-10 days (Gruneberg *et al.*, 1970; Schweitzer, 1976).

Emetine and dehydroemetine hydrochloride are less frequently used nowadays.

Tetracycline 1 gm daily for 10 days in symptomatic amoebiasis yielded a high cure rate of 97% (Powell *et al.*, 1965).

Prophylactic treatment of intestinal amoebiasis is often practised using dichloroacetamide derivatives, the efficacy of which has not been evaluated.

Amoebic liver abscess is the most common form of extraintestinal amoebiasis. In Thailand we have recorded about 1,000 cases during the past 30 years and has been routinely treated this condition with tissue amoebicides and aspiration of pus. During the last 14 years metronidazole was used with varying dosages and for the last 10 years tinidazole has been used in the Hospital for Tropical Diseases. So far, there has been no relapses or treatment failures.

Metronidazole 400 mg three times daily for 10 day yielded a 100% cure with 6 months follow up (Harinasuta *et al.*, 1975).

Tinidazole 800 mg three times a day for 5 days yielded the same result in 8 patients (Bunnag and Harinasuta, 1973). A single day dose of 2.4 gm and 1.2 gm were studied in 12 and 5 patients respectively, obtaining excellent results (Bunnag and Harinasuta, 1974). Since then a single dose of 1.2 gm has been given to 34 patients, the clinical response and the healing of the abscess cavity have been satisfactory. Occasionally very large abscesses, with a diameter of 15 cm and over are encountered, then 2.4 gm dose for five days was used. A patient with an abscess of 31 cm vertical diameter was sucessfully treated with 2.4 gm daily for five days and 28 aspirations of 5.53 litres of pus.

Occasionally amoebic liver abscess is complicated with *Escherichia coli* infection and a dose or two of aminoglycoside diluted with 20 ml of distilled water is introduced into the cavity after aspiration. The aspirates from subsequent attempts are cultured to monitor the presence of bacteria. Aspiration should be performed daily or on alternate days until the pus is sterile or when there

is no faecal odour. Systemic antibiotics are recommended in severely ill patients.

The cavity of an abscess in the liver can be visualised roentgenologically by injection of radio opaque medium (5 ml of 40% iodised oil) and 50-100 ml of air; P.A and lateral films are then taken. By measurement of the vertical and horizontal and anteroposterior diameters, the size of the cavity is estimated (Harinasuta and Harinasuta, 1966).

The study of the rate of healing was carried out by taking X-rays at intervals (both P-A and lateral films). When the cavity was obliterated, the oil was seen as collection of droplets. If there was recrudescence i.e. the cavity being formed again, the opaque medium would spread and line the bottom of the cavity. A medium size abscess cavity (7.0-8.0 cm in diameter) in our series took about 4-6 weeks to heal (Harinasuta and Bunnag, 1970).

The healing process of amoebic liver abscess was also studied in 125 patients. It was noted that the abscess cavity healed from the central towards the peripheral part of the liver (Harinasuta and Bunnag, 1970).

Surgical drainage should be avoided as secondary infection is very common and leakage of pus into the pleural cavity is often unavoidable; antibiotics are needed in large amount for these patients.

Hookworm infection

Severe hookworm disease is not common however hookworm infection is a common soil-transmitted helminthic infection in Southeast Asia. Various drugs have been used. Ma-klua (*Diospyros mollis*), fruits from an indigenous plant used to dye cloth black has been used in treatment of human hookworm (Sadun and Vajrasthira, 1954). The dose is calculated by age, one fruit for each year of life for a maximum number of 25 fruits (Harinasuta, 1962). The fruits are pounded and the juice collected by straining and 15-30 ml of lime water or coconut milk added. The cure rate was 30-80% (Migasena *et al.*, 1974; Unhanand *et al.*, 1978). About one million people was treated in mass campaign against intestinal parasites in 1977-1979, however optic atrophy was reported in 8 patients who had taken the juice kept over-night (Limpaphayom *et al.*, 1977). This might be due to the oxidative process during storage and some had taken an over dose. The substance could be toxic to the retina and optic nerve.

Pyrantel pamoate, a tetrahydropyrimidine is a crystalline powder, insoluble in water and slightly absorbed. It inhibits neuromuscular transmission producing spastic paralysis of the worms. The drug is given at 10-20 mg/kg/day for two-three consecutive days with cure rate of 63%-83%. The side effects are mild and transient including nausea, vomiting, diarrhoea and abdominal cramps (Bhaibulaya *et al.*, 1975; Migasena *et al.*, 1978).

Mebendazole, a benzimidazole derivative, is a white, yellowish powder, very slightly soluble in water and tasteless. It inhibits the glucose uptake leading to glycogen depletion and death of the worms. When the drug is used at 100 mg twice daily for three days, it yielded a 90% cure rate. The side effects are mild and transient (Bunnag *et al.*, 1976; Migasena *et al.*, 1978).

Flubendazole, is a paraflouro analoque of mebendazole and when given in two doses of 300 mg at 24 hour intervals yielded a 81% cure rate by egg count method, the mean percentage of egg reduction was 96. The side effects weee mild and transient. It has the same efficacy as mebendazole (Bunnag *et al.*, 1980c).

Tetrachloroethylene given at 0.1 ml per kg, the maximum dose of 4-5 ml in gelatine capsule. The drug has to be swallowed whole on an empty stomach and fat free diet to prevent absorption of tetrachloroethylene. The cure rate was 77% (Magasena *et al.*, 1978). This drug should be given with care and should be avoided when *Ascaris* infection is present. It is known to cause *Ascaris lumbricoides* to be erratic. Side effects are usually mild and transient, however transient acute brain syndrome was reported in 4 patients (Jaroonvesma *et al.*, 1972).

Iron supplementation is also required in patients with anaemia.

Ascariasis

Occasionally ascariasis can cause intestinal obstruction but in mild infection the use of pyrantel pamoate, mebendazole or flubendazole in conventional doses is effective (Bunnag *et al.*, 1976, 1980). The drug of choice however is levamisole in a single dose of 150 mg. Tetramisole and levamisole are two additional benzimidazoles which are readily absorbed and act on the neuromuscular system producing paralysis of the worms. Agranulocytosis is known to occur after prolonged use of these drugs, however, the side effects are minimal and rare. Mebendazole is well-known to cause erratic worms. Pyranel pamoate at 10 mg/kg single dose gave a 87% cure rate (Abidin *et al.*, 1978) while with smaller doses of pyrantel pamoate 2.5 mg, 5 mg and 7.5 mg/kg. Hsieh and Chen (1971) reported cure rates of 68%, 80% and 97% respectively.

Piperazine in a standard dose of 165 mg/kg and maximal dose of 4 gm is still commonly used in weekly dose for 2 weeks.

Enterobiasis

Enterobiasis is common among school children and families in slum areas. There is considerable choice of anthelminthics in the treatment of pinworm infection. A single dose of 10 mg/kg body weight of pyrantel pamoate or a single dose of 100 mg of mebendazole are effective. Since it is a family group infection problem, all members of the family should be treated.

Trichiuriasis

Trichuris trichiura infection in Southeast Asia is rather mild except in certain parts of Malaysia where prolapsed rectum is a common presentation. Flubendazole and oxantel pamoate are effective. Oxantel pamoate is trans-1, 4, 5, 6-tetrahydro-2-(3-hydroxstyryl)-1-methyl pyrimidine hydrochloride and has similar action as pyrantel pamoate but acts on *T. trichiura* only. The side effects are mild and transient. The recommended dose is 10-15 mg/kg/day for 2-3 days. A combination of pyrantel pamoate and oxantel pamoate has been recommended as a broad spectrum anthelminthic for *Ascaris lumbricoides*, hookworm, *Enterobius vermicularis* and *Trichuris trichiura* infections (Margono *et al.*, 1980).

Flubendazole is the parafluoro analoque of mebendazole, the parent compound of a large series of benzimidazole derivatives and has proved effective against nematodes especially *T. trichiura* infection (Janssen Pharm.) when given in two doses of 300 mg orally at 24 hour interval gave promising results (Bunnag *et al.*, 1980 c).

Strongyloidiasis

Strongyloides infection is more common in adults than in young children and is prevalent in mental hospitals and crowded prisons. Infection otherwise well tolerated may by internal autoinfection become severe in patients receiving steroid therapy for other diseases. Thiabendazole 50 mg/kg body weight for 2-3 successive days is effective in

the treatment of strongyloidiasis. (Campbell and Cuckler, 1969). Mebendazole is effective at 100 mg bid for 3 days but with a lower cure rate.

Capillariasis

Intestinal capillariasis was found to be endemic in Northern Luzon, Philippines since 1963. Mebendazole, 400 mg daily for 20-30 days yielded a 91-100% cure. Clinical improvement was obtained in nearly all patients (Singson *et al.*, 1975).

In Thailand, Bhaibulaya *et al.*, (1980 pers. c.mm) have treated 12 patients with 400 mebendazole daily for 3-4 weeks with a 100% cure rate. The gastrointestinal symptoms improved in 3-4 days.

Taeniasis

In man *Taenia saginata* infection is more common than *T. solium* infection but in meat at slaughter houses *Cysticercus cellulosae* is more prevalent than *Cysticercus bovis*. *Cysticercus cellulosae* in man including *Cysticercus racemosus* and *Cysticercus cerebralis* is often encountered.

Niclosamide inhibits the oxidative phosphorylation process in the mitochondria which releases the parasites from the intestinal mucosa. It is not absorbed therefore no side effects are produced. A 2 gm dose of niclosamide, chewed and swallowed with liquid, preferably on an empty stomach will produce cure in most patients.

Charoenlarp *et al.*, (1977) carried out the trial of Thai herbal medicine in taeniasis using 5 gm of aqueous extract of *Artocarpus lakoocha* (Puag Haad). Segments of tape worm were expelled from 29 of 32 patients treated and 26 (24 *T. saginata* and 2 *T. solium*) scolices were recovered.

Other tapeworm infections including *Hymenolepsis nana*, *Railietina siriraji* are occasionally encountered. The treatment is the same as for *Taenia saginata* infection but for *H. nana* a longer course of 5-6 days is needed.

Fasciolopsis buski

This species of intestinal fluke is prevalent in the central plain of Thailand. Niclosamide and tetrachloroethylene are quite effective. Niclosamide at 2 gm given daily for 3-5 days produce a high cure rate. Tetrachloroethylene at a single dose 0.1 ml/kg, (maximun 4-5 ml) yielded almost a 100% cure (Suntharasamai *et al.*, 1974).

Other intestinal flukes

Many species of small intestinal flukes including *Prosthodendrium molenkampi* and *Phaneropsolus bonnei*, *Haplorchis taichui* and *H. yokogawai* are common intestinal flukes in Northeast Thailand. Praziquantel at a dosage of 40 mg per kg body weight is effective in expelling these worms.

Opisthorchiasis

Human opisthorchiasis in Thailand is caused by *Opisthorchis viverrini*. It has been estimated that some 6 million people of the Northeast and the North of Thailand harboured this fluke. From 1960 to 1978 various drugs had been studied, the results were unsatisfactory except for cloxyle (Hetol) (Bunnag *et al.*, 1970) but it was later found to be nephrotoxic and neurotoxic in dogs thus the drug was withdrawn from clinical use.

Praziquantel is an isochinolin-pyrazine derivative of a new acylated heterocyclic compound. It is a colourless, crystalline powder, with a bitter taste and slightly soluble in water. It is readily absorbed and reaches maximal plasma level in 2 hour, the half life is 4 hours. The mode of action is not yet fully known but the integument of the fluke balloons at various points and finally ruptures. This effect was

observed using scanning electron microscopy by Mehlhorn *et al.*, (1980), when *Clonorchis sinensis* was incubated with praziquantel at concentrations of 1-1000 μg/ml.

Praziquantel was used in treating 155 patients with *Opisthorchiasis viverrini* at varying dosages viz:

Regimen: I 25 mg/kg body weight tds pc for 2 days.

II 25 mg/kg body weight tds pc for 1 days.

III 25 mg/kg body weight bd pc for 1 day.

IV 25 mg/kg body weight single dose after meal.

V 40 mg/kg body weight single dose after meal.

The patients were carefully studied both clinically and by laboratory testing before treatment and 30 and 60 days after treatment. One hundred per cent cure rates were achieved by regimen I and regimen II, while in regimen III, IV and V cure rates were 89%, 44% and 91% respectively. Egg output ceased within 10 days of starting treatment. Worms were expelled and were recovered in stools. There was no correlation between the egg output per gramme of faeces and the number of flukes recovered in the stools. A total of 2,822 worms were collected from one patient.

Side effects including abdominal pain, vomiting, diarrhoea, lassitude, myalgia, headache, dizziness, tachycardia, insomnia, drowsiness and sweating, were mild and transient, and more frequent with the higher doses. No laboratory evidence of toxicity was observed.

Table 1

Efficacy of praziquantel in opisthorchiasis.

Regimen	Dosage mg/kg body wt	No. of patients treated	Pre-treatment EPG mean (range GM-EPG)	Day 60 No. neg*/ No. exam.	Cure rate%
I	6 × 25	29	10,833 (1932-93,211)	26/26	100
II	3 × 25	29	11,676 (1282-57,322)	23/23	100
III	2 × 25	30	15,504 (679-77,573)	23/26	88.5
IV	1 × 25	12	13,510 (1184-43,468)	4/9	44.4
V	1 × 40	55	12,858 (929-97,380)	40/44	90.9

*By faecal concentration method.
EPG = Eggs per gramme of faeces, GM = Geometric Mean.

REFERENCES

ABIDIN, S.A.N., ISMID, I.S., MARGONO, S.S. and RUKMONO, B., (1978). Treatment trial for minimum effective dose of Combantrin in ascariasis. The Asian Parasite Control Organization, (*APCO*) Japan. *1* : 275.

BHAIBULAYA, M., PUNNAVUTTI, V. and YAMPUT, S., (1975). Mass treatment of hookworm infection with single dose of pyrantel pamoate. *J. Med. Ass. Thailand, 58* : 347.

BUNNAG, D. and HARINASUTA, T., (1973). Clinical trial of tinidazole (Fasigyn) in amoebic liver abscess. *In:* Proc. of Twelfth SEAMEO-TROPMED Seminar: Biology, immunology and treatment of parasitic and bacterial diseases of public health importance in Southeast Asia and Far East. TROPMED, p. 11.

BUNNAG, D. and HARINASUTA, T., (1974). Clinical trial of tinidazole in amoebic liver abscess using low doses. *In:* Proc. Third Inter. Congr. Parasit., Munchen, *3* : 1276.

BUNNAG, D. and HARINASUTA, T., (1980 a). Studies on the chemotherapy of human opisthorchiasis. I. Clinical trial of praziquantel. *Southeast Asian J.Trop. Med. Pub. Hlth., 11* : 528.

BUNNAG, D. and HARINASUTA, T., (1980 b). Praziquantel: A drug of choice for human opisthorchiasis. *In:* Abstracts of Tenth International Congress on Tropical Medicine and Malaria, Manila, Philippines. November 9-15, p. 307.

BUNNAG, D., HARINASUTA, T., HARINASUTA, C., SUNTHARASAMAI, P., VIRAVAN, C. and PETCHKLA, S., (1970). Clinical trial of hetol (1, 4-bis-trichloromethybenzol) in the treatment of opisthorchiasis. *Ann. Trop. Med. Parasit., 46* : 109.

BUNNAG, D., HARINASUTA, T., VASUVAT, C., VISUTHIKOSOL, Y., VIDHYANONT, C. and CHULAJAT, N., (1976). Clinical trial of mebendazole on whipworm and hookworm. *J. Med. Ass. Thailand, 61* : 319.

BUNNAG, D., HARINASUTA, T., VIRAVAN, C., JARUPAKORN, V., CHINDONOND, D. and DESAKORN, V., (1980c). Clinical trial of flubendazole on hookworm, *Trichuris trichiura* and *Ascaris lumbricoides* infections. *Southeast Asian J. Trop. Med. Pub. Hlth., 11* : 363.

BUNNAG, D., HARINASUTA, T., VIRAVAN, C., VANIJANONTA, S. and JAYANAVEJ, A., (1975). Clinical trial of metronidazole low dosage in amoebic liver abscess. *Southeast Asian J. Trop. Med. Pub. Hlth., 6* : 99.

CAMPBELL, W.C. and CUCKLER, A.C., (1968). Thiabendazole in the treatment and control of parasitic infections in man. *Tex. Rep. Biol. Med.*, (Suppl. 2) *27* : 665.

CARNEY, W.P., ATMOSOEDJONO, S., HADI, S. and ARABIAN, J., (1974). Intestinal parasites and malaria in Sukowati Pasaman Regency, West Sumatra. *Bull. Hlth. Studies, Indonesia, 2* : 61.

CHONGSUPHAJAISIDDHI, T., PAIROJBOOT, N., CHUENCHUSIN, S. and HARINASUTA, T., (1971). Treatment of *Entamoeba histolytica* cyst passers with metronidazole. *Southeast Asian J. Trop. Med. Pub. Hlth., 2* : 29.

CHONGSUPHAJAISIDDHI, T., SABCHAROEN, A., ATTANATH, P., PANASOPONKUL, C., and RADOMYOS, P., (1978). Treatment of soil-transmitted nematode infections in children with mebendazole. *Ann. Trop. Med. Parasit., 72* : 59.

GRUNEBERG, E., CLEELAND, R., PRINCE, H.N. and TITSHORTH, E., (1970). L-chloromethyl-5-nitro-1- imidazole-ethanol (Ro 7-0207), a substance exhibiting antiparasitic activity against amebae, trichomonads and pinworms. *Proc. Soc. Exp. Biol. Med., 133* : 490.

HARINASUTA, T., (1962). Handbook of Tropical Medicine, 1st ed.Aksorn Sumbhanta, Bangkok.

HARINASUTA, T. and BUNNAG, D., (1970). Study of healing of amoebic liver abscess by roentgenography. *Southeast Asian J. Trop. Med. Pub. Hlth., 1* : 275.

HARINASUTA., T. and HARINASUTA, C., (1966). The visualization of amoebic liver abscess cavity and its rate of healing. *J. Med. Ass. Thailand, 49* : 96.

HARINASUTA, T., WIRIYAVIT, P., BUNNAG, D. and TEJAVANIJA, S., (1968). Clinical trial of Flagyl in amoebic liver abscess. *Indian Practitioner, 21* : 732.

HSIEH, H.C. and CHEN, E.R., (1971). Treatment of *Ascaris lumbricoides* with small dose of pyrantel pamoate (Combantrin). *Southeast Asian J. Trop. Med. Pub. Hlth., 2* : 362.

JAROONVESMA, N., HARINASUTA, T. and BUNNAG, D., (1972). Transient psychosis from tetrachloroethylene. *In:* Proceedings of The Tenth SEAMEO-TROPMED Seminar; Chemotherapy in Tropical Medicine of Southeast Asia and the Far East, Bangkok, 26-30 October 1971, TROPMED, p. 165.

KAVOUSI, S., (1979). Giardiasis in infancy and childhood: A prospective study of 160 cases with comparison of quinacrine (Atabrine) and metronidazole (Flagyl), *Amer. J. Trop. Med. Hyg., 28* : 19.

LEVI, G.C., DE AVILA, C.A. and NETO, V.A., (1977). Efficacy of various drugs for treatment of giardiasis. *Amer. J. Trop. Med.Hyg., 26* : 564.

LIMPAPHAYOM, P., WANGSPA, S. and LILAPATANA, P., (1977). Optic atrophy from Maklua. *Siriraj Hosp. Gaz., 29* : 454.

MARGONO, S., MAHFUDIN, H., RASIDI, R. and RASAD, R., (1980). Oxantel-pyrantel pamoate for the treatment of soil-transmitted helminths. *Southeast Asian J. Trop. Med. Pub. Hlth., 11* : 384.

MEHLHORN, H., BECKER B., RIM, J.J., ANDREN, P. and THOMAS, M., (1980). *In:* Proc. Tenth International Congress on Tropical Medicine and Malaria Manila, Philippines, November 9-15, 1980, p. 297.

MIGASENA, S., SUNTHARASAMAI, P. and HARINASUTA, T., (1978). Mebendazole, tetrachloroethylene and pyrantel pamoate in the treatment of hookworm infection. *Ann. Trop. Med. Parasit., 72* : 199.

MIGASENA, S., SUNTHARASAMAI, P., INKATANUWAT, S., CHINDANOND, D. and HARINASUTA, T., (1974). Clinical trial of the extract of *Diospyros mollis* fruit in hookworm infected patients. Report of the Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand.

PARTONO, P.F., and SOEWATA, A., (1980). Human intestinal parasites in Karakuak, West Flores, Indonesia and the effect of treatment with mebendazole and pyrantel pamoate. *Southeast Asian J. Trop. Med. Pub. Hlth., 11* : 324.

POWELL, S.J., MCCLEOD, I.N., WILMOT, A.J. and ELSDON-DEW, R., (1965). Future drug trials in acute amoebic dysentery : demethylchlor, tetracycline, methacycline, ampicillin, and chlorhydroxy quinoline. *Trans. Roy. Soc. Trop. Med. Hyg., 59* : 709.

SABCHAROEN, A., CHONGSUPHAJAISIDDHI, T. and ATTANATH, P., (1980). Treatment of giardiasis in children with quinacrine, metronidazole, tinidazole and ornidazole. *Southeast Asian J. Trop. Med. Pub. Hlth., 11* : 280.

SADUN, E.H., and VAJRASTHIRA, S. (1954). The effect of Maklua (*Diospyros mollis)* in the treatment of human hookworm. *J. Parasit., 40* : 49.

SAWYER, P.R., BROGDEN, R.N., PINDER, R.M., SPEIGHT, T.M. and AVERY, G.S., (1976). Tinidazole : A review of its

anti-protozoal activity and therapeutic efficacy. *Drugs, 11* : 423.

SCHWEITZER, H., (1976). Zur Frage de Alkohol toleranz nach gabe eines neuen nitroimidazole derivative. *Blutalkohol. 13* : 75.

SINGSON, C.H., BANZON. T.C. and CROSS, J.H., (1975). Mebendazole in the treatment of intestinal capillariasis. *Amer. J. Trop. Med. Hyg., 24* : 932.

SUNTHARASAMAI, P., BUNNAG, D., TEJAVANIJ, S., HARINASUTA, T., MIGASENA, S., VUTIKES, S. and CHINDANOND, D., (1974). Comparative clinical trials of niclosamide and tetrachlorethylene in the treatment of *Fasciolopsis buski* infection. *Southeast Asian J. Trop. Med. Pub. Hlth., 5*: 556.

UNHANAND., M., SRINOPHAKUN, S., SEEDONROSMI, T., JERADIT, C., NILAPAN, S. and SATHILAYATHAI, A., (1978). Study on the efficacy of an alcoholic extract of Maklua (*Diospysos mollis*) against hookworm, *Ascaris* and *Trichuris* infections. *APCO, Japan, 1* : 289.

WOODRUFF, A.W. and BELL, S., (1960). Clinical trial with entamide furoate and related compounds. *Trans. Roy. Soc. Trop. Med. Hyg., 54* : 389.