Kirk-Othmer Encyclopedia of Chemical Technology.

ANTIPARASITIC AGENTS, ANTHELMINTICS

Human infections caused by worms (helminths) represent one of the most important public health problems in the world. Helminths form three main categories or phyla: Platyhelminths, flatworms; Aschelminthes, roundworms; and Nemathelminthes, thorny-headed worms. Platyhelminths consist of Trematoda and Cestoda. Members of the class Trematoda, or flukes (schistosomes), are slender leaf-shaped organisms that possess attachment organs in the form of cupshaped hooks called suckers. Members of the class Cestoidea, or tapeworms, are flat and ribbonlike. These worms have serially repeated sections behind the neck and an attachment organ called the scolex. The Aschelminthes (class Nematoda) are roundworms, which have a basic cylindrical shape with major variations in proportions, size, and structure. The Nemathelminthes (Acanthocephala), or thorny-headed worms, are widely distributed among animals and generally do not involve a human host.

Over the last several years, substantial progress in the discovery and development of anthelmintic drugs has been made. Effective agents are available for most human gastrointestinal infections (Table 1); however, drugs that are effective in treating the extraintestinal complications of many helminthic infections are still needed.

Frequently, the treatment of helminthic diseases requires adjunct medication. Allergic reactions are commonly seen as a result of tissue invasion by worms or as a consequence of anthelmintic therapy. Antihistamines and corticosteroids may be necessary adjuncts to therapy. Anemia, indigestion, and secondary bacterial infections can also occur and may require concomitant therapy with hematopoietic drugs and appropriate antibiotics.

1. Treatment of Trematode Infections

1.1. Blood Flukes (Schistosomiasis)

Three main species of blood flukes cause schistosomiasis in humans: *Schistosoma haematobium*, *S. mansoni*, and *S. japonicum*. The effectiveness of antischistosomal drugs depends on the reduction or arrest of egg production. Infection only occurs as a result of the penetration of the intact skin by free-swimming cercaria. After they develop to pre-adult forms in the skin and lung, the parasites migrate through host blood vessels to various tissues. Adult worms that are approximately 2 cm in length remain paired within the portal or intestinal vasculature of the host. The female, however, travels as far as possible toward the capillary beds to lay eggs, a portion of which embolize to the liver and induce granuloma formation. During the early stages of the disease, patients may experience fever, gastrointestinal distress, headache, and fatigue. In later stages of the disease, signs of hepatic fibrosis and ascites are seen. The number of worm pairs found in a patient may vary from a few to over 100. In untreated patients, adult worms are now generally assumed to live less than 5–10 years.

Table 1. Anthelmintics: Uses and Properties

Drug	Structure number	CAS Registry Number	Trade name	Physical properties	Solubility	Disease (organism)	Reference
praziquantel	(**1**)	[55268-74-1]	Biltricide solid, Cesol, Livera, Pontel, Prazi, Pyquiton	mp 136–138°C	practically insoluble in water; sparingly in alcohol, chloroform, and ether	flukes (*C. sinensis, F. buski, P. westermani, S. haematobium, S. mansoni, S. japonicum*), tapeworms (*H. nana, T. solium, T. saginata, D. latum*), and larval stage (cysticercosis)	(1, 2)
oxamniquine	(**2**)	[21738-42-1]	Mansil, Vansil	pale yellow crystals	sparingly soluble in water; soluble in acetone, chloroform, and methyl alcohol	flukes (*S. mansoni*)	3
metrifonate	(**3**)	[52-68-6]	Bilarcil	white crystals, mp 83–84°C	1 g in 6.5 mL water, 33 mL chloroform, 5.9 mL ether	blood flukes (*Schistosoma haematobium*)	4
bithionol[a]	(**4**)	[97-18-7]	Bitin	crystals or gray-white powder, mp 188°C	insoluble in water, acetone, and 4% NaOH	lung flukes (*Paragonimu westermani*), sheep liver flukes (*Fasciola hepatica*)	(5, 6)
tetrachloroethylene	(5)	[127-18-4]	Nema worm capsules, Perklone	colorless, nonflammable fluid, ethereal odor, deteriorates in warm climates, bp 121°C	soluble 1:10,000 in water; miscible with ethanol	intestinal fluke (*Fasicolopsis buski*)	7
niclosamide	(**6**)	[50-65-7]	Cestocida, Mansonil, Nasemo, Niclocide, Sulqui, Yomesan	pale yellow crystals, or yellow-white powder, mp 225–230°C	insoluble in water; sparingly soluble in ethanol	tapeworms (*T. saginata, T. solium*, and *D. latum*)	8
quinacrine	(**7**)	[83-89-6]	Atabrine hydrochloride[b]	yellow crystals,[b] mp ca 250°C	1 g in 36 mL water; slightly soluble in ethanol	pork tapeworm (*Taenia solium*)	9
piperazine citrate[c]	(**8**)	[144-29-6]	Antepar, Helmezine, Pinozan, Pinrou, Uvilon	white crystalline powder, mp ca 185°C (dec)	freely soluble in water; insoluble in ethanol	roundworms (*Ascaris lumbricoides*)	10
diethylcarbamazine citrate	(**9**)	[1642-54-2]	Banocide, Filarex, Hetrazan, Notezine	white crystalline powder, mp 141–143°C	soluble in water and hot ethanol; insoluble in acetone	lymphatic filariases (*Wuchereria bancrofti, Loa loa*, and other filaria)	11

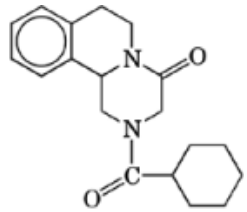
Table 1. ***Continued***

Drug	Structure number	CAS Registry Number	Trade name	Physical properties	Solubility	Disease (organism)	Reference
pyrantel pamoate	(**10**)	[22204-24-6]	Antiminth, Cobantil, Combantin, Helmex, Pyrantin	white or yellow or tan crystalline powder, melts and decomposes, mp ca 250°C	insoluble in water and nearly so in ethanol	pinworms (*Enterobius vermiculus*), roundworms (*Ascaris lumbricoides*), hookworms (*Ancylostoma duodenale, Necator americanus*)	12
mebendazole	(**11**)	[31431-39-7]	Meben, Totamin, Vermox, Vorme	crystals or yellow amorphous powder, mp 289°C	very slightly soluble in water and most organic solvents	whipworms (*Trichuris trichiura*), hookworms (*Ancylostoma duodenale, Nector americanus*), filariasis (*Mansonella perstans*), roundworm (*Ascaris lumbricoides*), Trichinosis (*Trichinella spiralis*)	13
thiabendazole	(**12**)	[148-79-8]	Foldan, Lombrstop, Mintezol, Minzolum, Nomoxiur, Thibenzole, Tiabenda, Triasox, TBZ	white crystals, mp ca 300°C	almost insoluble in water; slightly soluble in ethanol	hookworms (*Trichostrongylus sp.*, cutaneous larva migrans, *Angiostrongylus costaricensis*, and *Strongyloides stercoralis*)	14
ivermectin[a]	(**13**)	[d]	Eqvalan, Ivomec, Mectizan	off-white powder, mp 155–157°C	4 μg/mL water, insoluble in saturated hydrocarbons, very soluble in propylene glycol	filariasis (*Onchocerca volvulus*)	15

[a] Available from the CDC Drug Service.
[b] The dihydrochloride dihydrate [69-05-6].
[c] Formed from 3 mol piperazine (**8**) and 2 mol citric acid.
[d] See Figure 1.

1.1.1. Praziquantel

This drug (**1**), $C_{19}H_{24}N_2O_2$, can be used to treat schistosomiasis caused by any one of the three major species. Praziquantel is an acylated pyrazino–isoquinoline derivative that has replaced the traditional (and more toxic) trivalent antimonial compounds.

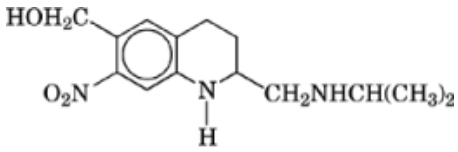


(**1**)

Praziquantel is thought to alter the permeability of the worm's cell membrane to calcium, resulting in tetanic paralysis and the dislodging of schistosomes from their attachment sites. The drug also causes the disintegration of the schistosome tegument, which is followed by host phagocytosis (16). Adverse reactions include dizziness, headache, and gastrointestinal distress. Cure rates of approximately 85% have been achieved with a single treatment regimen. The principal producer of praziquantel in the United States is Miles Pharmaceutical of West Haven, Connecticut. Other manufactures include Bayer A.G. of Leverkusen, Germany and Chinoin of Budapest, Hungary.

1.1.2. Oxamniquine

This tetrahydroquinoline (**2**), $C_{14}H_{21}N_3O_3$, has been proven effective for the treatment of *S. mansoni* infections. It is clinically ineffective against *S. haematobium* and *S. japonicum* infections.

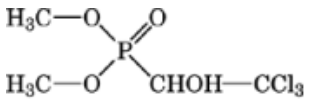


(**2**)

Its precise mode of action is not known, although it does exhibit anticholinergic properties (17). Oxamniquine is generally well tolerated, although dizziness, with or without drowsiness, does occur in at least one-third of the patients taking the drug. Allergic-type reactions, including fever, increased circulating immune complexes, pulmonary infiltrates, and pruritic skin rashes, may also occur. These allergic symptoms may be due to the death of the infecting parasites (18). A single dose is usually sufficient for strains of *S. mansoni* acquired in the Western Hemisphere; those acquired in East Africa may require longer periods of treatment. Oxamniquine is solely manufactured by Pfizer, Inc. in the United States, United Kingdom, and France.

1.1.3. Metrifonate

This organosphosphorus compound (**3**), $C_4H_8Cl_3PO_4$, was first used as an insecticide.



(**3**)

In the body, metrifonate converts to the active metabolite dichlorvos, (2,2-dichlorovinyl dimethyl phosphate), which is responsible for the inhibition of the enzyme acetylcholinesterase in the susceptible worm. This

effect alone is unlikely to explain the antischistosomal properties of metrifonate (19). Clinically, metrifonate is effective only against infection caused by *S. haematobium*. Metrifonate is administered in three doses at 2-wk intervals (17). The drug is well tolerated. Side effects such as mild vertigo, nausea, and cramps are dose-related. This product is not available in the United States. The only manufacturer of metrifonate is Bayer A.G. of Leverkusen, Germany.

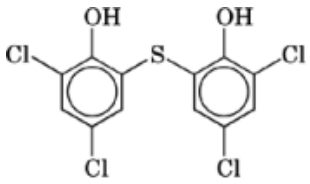
1.2. Lung and Liver Flukes

Paragonimus organisms (lung flukes) are about 1 cm long and normally live encapsulated within lung cysts. They primarily infect lung tissue, but may be found in other viscera or in the brain, producing tumorlike symptoms.

Fasciola organisms (liver flukes) are about 3 cm long. After extensive migration, young flukes invade and mature in the bile ducts of the liver, where heavy infections may result in fibrosis of the bile duct wall. Flukes migrating through the peritoneal cavity may become lodged in other locations, causing intense tissue reactions.

1.2.1. Bithionol

This compound (**4**), $C_{12}H_6Cl_4O_2S$, can be used to treat persons infected with either *Paragonimus* or *Fasciola* organisms. It is a phenolic compound similar in structure to hexachlorophene.



(**4**)

Bithionol and hexachlorophene have been used as anthelmintics in veterinary medicine. In the past, because of its antibacterial activity, bithionol was incorporated into at least 20 medicated skin cleansers manufactured in the United States; however, this agent proved to cause skin irritation, and its use as an antibacterial cleanser was discontinued.

Bithionol interferes with the neuromuscular physiology of helminths, impairs egg formation, and may cause defects in the protective cuticle covering the worm. At the biochemical level, the oxidative phosphorylation of the worm is inhibited.

Bithionol is an iron chelator and therefore may inactivate iron-containing enzyme systems (20). A 10-d oral regimen of bithionol may resolve the pathology ie, abnormalities of lung disease in about three months, but improvement in cerebral paragonimiasis and *Fasciola hepatica* (sheep liver fluke) infections are variable. Adverse effects include abdominal pain, diarrhea, vomiting, rashes, and photosensitivity. The drug is available in the United States through the CDC Drug Service of Atlanta, Georgia. The only manufacturer of bithionol is Tanabe Seiyaku of Osaka, Japan.

Praziquantel (**1**) (previously mentioned for the treatment of schistosomiasis) is also effective against all *paragonimus* species.

1.2.2. Chinese Liver Fluke

The adult worm of the Chinese liver fluke (*Clonorchis sinensis*) can grow to be 2 cm long. Worms infect the biliary tree where they cause local inflammation, diarrhea, and hepatomegaly in the acute infection. Progressive biliary obstruction and cirrhosis can occur in the more advanced disease state. The presence of 20–200 worms

is common, but they may number over 20,000. Infection is the consequence of eating raw fish that contain viable parasites. Untreated worms can live for up to 30 years. Treatment is with praziquantil (**1**).

1.3. Intestinal Fluke

The intestinal fluke, *Fasciolopsis buski*, which can reach a length of 8 cm, lives attached to the wall of the small intestine. Rarely, untreated heavy infections may cause ulceration, toxemia, and death in children. Praziquantel (**1**) or tetrachloroethylene (5) are both effective in the treatment of *Fasciolopsis* infection.

1.3.1. Tetrachloroethylene

This chlorocarbon (5), $Cl_2C{=}CCl_2$, has been used as a solvent in dry cleaning and a metal degreaser as well as an anthelmintic. Tetrachloroethylene, C_2Cl_4, has replaced carbon tetrachloride, CCl_4, which is very hepatotoxic, in the treatment of intestinal flukes. Investigators do not agree on the mechanism of action of tetrachloroethylene or on its basic pharmacology. Some investigators believe that tetrachloroethylene dissolves the cell lipids in the helminthic neuromuscular system and interferes with neuromuscular function. In the treatment of flukes, a single oral dose is given on an empty stomach preceded by a day of low fat diet. A 24-h period of low fat intake is necessary because fat in the gastrointestinal tract increases drug absorption, thereby increasing its toxicity. This drug is primarily used in veterinary medicine (21).

2. Treatment of Cestode Infections

Fish tapeworm (*Diphyllobothrium latum*) grows to a length of 10 m with 4000 proglottides, or segments, each containing reproductive organs. The proglottides tend to remain attached to the intestinal wall and discharge eggs, which are passed into the feces. Besides ingesting host nutrients, this worm avidly sequesters vitamin B_{12} and folic acid. The closer to the stomach that the intestinal fluke is attached, the more vitamin the worm ingests. Depletion of host B_{12} supplies leads to the development of pernicious anemia, with associated neurological symptoms. There is usually only one worm in a patient and it can survive for 10 years.

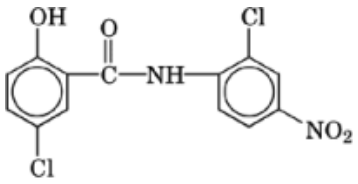
Beef tapeworm (*Taenia saginata*) is found worldwide in people who eat rare beef and is most common in developing countries. Worms are often 5–10 m long with about 1000 proglottides. Usually a patient carries only one worm. Infected persons are frequently asymptomatic, but intestinal disturbances can occur. Detached sections of worm $0.5\ \text{cm} \times 2\ \text{cm}$ may creep out of the end of the digestive tract.

Both the adult and the larval cysticerci (bladderworm) of *Taenia solium* (pork tapeworm) are able to live in humans; the parasite is found sporadically in uncooked pork. In the stomach, the larva is digested out of the pork flesh; it then grows and attaches to the wall of the small intestine. Maturity is reached in 5–12 weeks. The adult is 5 m long, and untreated adult worms may survive for 25 years.

Dwarf tapeworm (*Hymenolepis nana*) is the only human tapeworm that does not utilize an intermediate host. Infection is transmitted directly from person to person. *H. nana* is only 2–4 cm long, it is of universal distribution in mice and humans in temperate zones, where children, especially those in institutions, are most frequently infected. Although an infected person is often symptomless, this tapeworm can cause abdominal discomfort and diarrhea if infection is heavy.

2.1. Niclosamide

This drug (**6**) is a halogenated salicylanilide derivative, $C_{13}H_8Cl_2N_2O_4$.



(6)

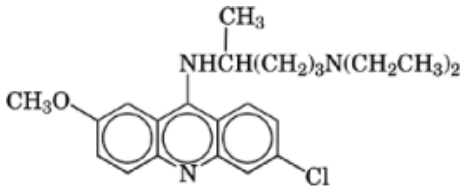
The modes of action for niclosamide are interference with respiration and blockade of glucose uptake. It uncouples oxidative phosphorylation in both mammalian and taenioid mitochondria (22, 23), inhibiting the anaerobic incorporation of inorganic phosphate into adenosine triphosphate (ATP). Tapeworms are very sensitive to niclosamide because they depend on the anaerobic metabolism of carbohydrates as their major source of energy. Niclosamide has selective toxicity for the parasites as compared with the host because little niclosamide is absorbed from the gastrointestinal tract. Adverse effects are uncommon, except for occasional gastrointestinal upset.

Niclosamide causes the tapeworm head to disengage from the intestinal wall of the host and the body wall of the parasite to disintegrate. The first dose of niclosamide disposes of the worms in the intestinal cavity; however, any worms in developing stages in the tissues of the intestinal wall are unharmed. Therefore, dosage must be repeated in 5–7 days to destroy the worms that will finish their development and reenter the intestinal lumen.

Niclosamide given in a single oral dose is effective for the treatment of tapeworm infections. A large percentage of patients are cured, and adjunct therapy is not required when used against beef tapeworm (*T. saginata*), the dwarf tapeworm (*H. nana*), or the fish tapeworm of humans (*D. latum*) and most other human intestinal cestode infections. It is also effective in the treatment of pork tapeworm (*T. solium*), but not against infection with larval *T. solium* (cysticercosis) for which praziquantel (**1**) is preferred. Niclosamide is available in the United States and is manufactured by Miles Pharmaceutical of West Haven, Connecticut. Other manufacturers include Bayer A.G. of Leverkusen, Germany and Bellon Laboratories of Neuilly-sur-Seine, Cedex, France.

2.2. Quinacrine

Quinacrine (**7**), $C_{23}H_{30}ClN_3O$, is an acridine derivative. It is used in the form of the dihydrochloride dihydrate, $C_{23}H_{32}Cl_3N_3O\cdot 2H_2O$, [69-05-6].



(7)

This drug was used prior to the availability of niclosamide and is considered less satisfactory for the treatment of tapeworms than niclosamide (24). It causes more side effects and produces severe nausea. Quinacrine, however, is preferred by some clinicians for the treatment of *Taenia solium* infection because, unlike niclosamide, it expels the worms intact, thus reducing the theoretical risk of cysticercosis (25).

Quinacrine concentrates in the scolex of the parasite and causes the muscles needed for holding onto the intestinal wall to relax. The worms are stained yellow and pass from the body, still alive. Quinacrine can intercalate with DNA and inhibit nucleic acid synthesis. It creates fluorescent bands in deoxyadenylate–deoxythmidylate-rich regions of DNA and has been used as a stain in the study of human genetics.

The drug is readily absorbed from the gastrointestinal tract and may persist in human tissues for two months after administration. Quinacrine is given as a single dose for the treatment of tapeworms; it is manufactured by Winthrop-Breon of New York, New York.

2.3. Paromomycin

Paromomycin [7542-37-2] is a broad-spectrum antibiotic that has been used in the treatment of *H. nana* and *T. saginata*, and amebiasis, and also as an antibacterial agent in cases of diarrhea and dysentery (see Antibiotics, oligosaccharides).

3. Treatment of Nematode Infections

Female roundworms of *Ascaris lumbricoides* are about 30 cm × 0.5 cm. The adults live and feed in the small intestine where they can cause abdominal discomfort or pain. Frequently, light infections are symptomless. The worm develops through four larval stages, with a molt between each successive stage. The eggs of the adult are deposited in the feces. Eggs do not hatch in the soil or enter the body through the cutaneous route. Infective eggs are swallowed and the larvae hatch in the stomach. Hatched larvae actively migrate into the lungs. Larvae continue to develop in the lungs, then migrate through the respiratory passages to the throat and are swallowed. In the stomach they molt and grow to the mature adult form. Untreated adult worms may live for a year and a half.

The pinworm (*Enterobius vermicularis*) is distributed worldwide in temperate zones. In cities, it is frequently a disease of households or institutions. Female worms are about 1 cm long. While growing to maturity, they live in the gut lumen, attaching by their mouths to the intestinal mucosa. Itching in the perianal region occurs when the mature female migrates out the anus to discharge her eggs. Usually an intestinal population is less than 100 worms; however, more than 5000 have been recovered from a single patient. The eggs are resistant to drying and may get into household dust and be inhaled or swallowed by household members, causing light infections with few worms in the adult relatives of infected children.

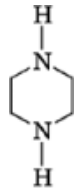
Whipworm (*Trichuris trichiura*) adult females are 5 cm long. These worms thread their entire body into the epithelium of the colon, where they feed on tissue juice and small amounts of blood. Infections of several hundred worms may cause irritation and inflammation of the mucosa, with abdominal pain, diarrhea, and gas. Eggs are discharged and passed into the feces. Infections result from the swallowing of eggs that are obtained directly from contaminated soil. Untreated adult worms live for years.

The two most common hookworms in humans are *Ancylostoma duodenale* and *Necator americanus*. *A. duodenale* adult worms are 8–13 mm in length. The filariform larva found in moist soils may be either ingested or penetrate the skin of its host. It is then carried through the circulatory system to the lungs and migrates up the respiratory tree into the digestive tract. The worms feed on intestinal tissue and blood. Some worms may persist in humans as long as nine years. Infestations cause cutaneous reactions, pulmonary lesions, intestinal ulcerations, and anemia.

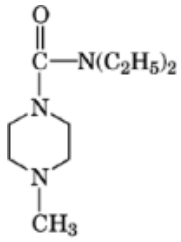
American hookworm (*N. americanus*) adult worms, 7–11 mm in length, may live up to 15 years. The life cycle of the *N. americanus* is similar to *A. duodenale* except that *N. americanus* requires a pulmonary migration with development in the lungs before it can develop to the adult worm in the intestine.

3.1. Piperazine Salts

Piperazine citrate is highly effective against both *A. lumbricoides* (large roundworm) and *E. vermicularis* (pinworm). A large number of substituted piperazine derivatives exhibit anthelmintic activity; however, only diethylcarbamazine (**9**) is used clinically (26).



(**8**)



(**9**)

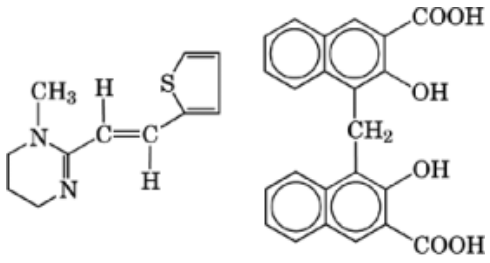
Piperazine is taken orally by nonfasting subjects. For large roundworms, one dose a day on two consecutive days reportedly cures approximately 90% of cases treated (27). This drug can be used for pinworms with a 7-d course of treatment.

Piperazine causes flaccid paralysis of *Ascaris* by blocking the worms' ability to respond to acetylcholine, thus dislodging the worms from their position in the digestive tract. The worms are passed through the digestive tract still alive. The drug is well absorbed from the human intestine, and the reason for its selective toxicity is still uncertain.

Occasional side effects from piperazine include abdominal cramps, nausea, vomiting, and diarrhea. Rarely, patients may experience headache, vertigo, and tremors, or they may feel weak and have difficulty concentrating. Red patches can appear on the skin, sometimes with the flat, elevated, itching welts of urticaria. Piperazine is manufactured by Burroughs Wellcome Company in Research Triangle Park, North Carolina and Wallace Laboratories of Cranbury, New Jersey. Other manufacturers include Laboratories Clin Midy of Paris, France, Regent Laboratories Ltd. of London England, and Lennon Ltd. of Saxonwold, South Africa.

3.2. Pyrantel Pamoate

This drug (**10**), $C_{34}H_{30}N_2O_6S$, cures pinworm infections and is close to 100% effective against *Ascaris* when given in a single dose (28, 29). Pyrantel pamoate is also a principal drug for the treatment of hookworm infections; thus it is useful in patients with mixed worm infections.



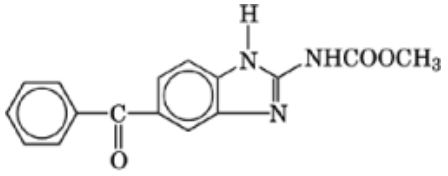
(**10**)

For hookworms, treatment is continued for three days. In roundworms, muscle tissue is stimulated continuously, resulting in spastic paralysis. The drug was introduced in veterinary medicine in 1966 and then applied to clinical medicine three years later.

Since about 85% of the administered dose is passed unchanged in the feces of the patient, selective toxicity of the drug can be attributed primarily to poor absorption. Side effects include abdominal pain, nausea, vomiting, diarrhea, loss of appetite, headaches, and vertigo or drowsiness. Skin rashes can also develop. Pyrantel pamoate is produced by Pfizer, Inc., New York, New York.

3.3. Mebendazole

In therapeutic dosages administered orally for three or four consecutive days, mebendazole (**11**) is highly effective against whipworm (*Trichuris trichiura*). In addition, a single dose usually cures pinworm infections. Mebendazole is also effective against trichinosis (*Trichinella spiralis*), hookworms (*Ancylostoma duodenale* and *Necator americanus*), and *Ascaris*, partially effective against threadworms (*Strongyloides*), and taeniid tapeworms. This benzimidazole derivative, $C_{16}H_{13}N_3O_2$, is a broad-spectrum anthelmintic (30) and is used in veterinary medicine as well as in clinical practice. It belongs to the same series of drugs as thiabendazole, $C_{10}H_7N_3S$ (**12**).



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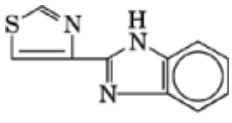
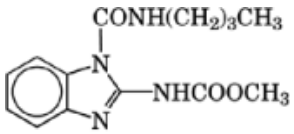


(**12**)

These drugs are closely related to fungicides such as benomyl [17804-35-2] (**13**), $C_{14}H_{18}N_4O_3$.



(13)

Mebendazole interferes with the glucose metabolism of helminths, irreversibly inhibiting glucose uptake. When the glycogen stores in the worms are depleted, ATP supplies fail. The worms are slowly immobilized, die, and are excreted over a period of three days. In developing *Trichuris* eggs, larvae fail to develop normally. Selective toxicity of mebendazole may be due to its antimicrotubule action on nematode intestinal cells with no effect on mammalian cells. Furthermore, relatively little drug is absorbed from the human gastrointestinal tract. Adverse effects in patients include abdominal pain and diarrhea. Mebendazole is manufactured by Janssen Pharmaceutica, Inc., Piscataway, New Jersey. Other manufacturers include Esteve Drug of Barcelona, Spain and Cadila Laboratories of Maninagar, Ahmedabad, India.

4. Treatment of Tissue Roundworm (Nematode) Infections

Many parasitic worms cause systemic infections outside the gastrointestinal tract. These include: *Strongyloides stercoralis* (threadworm), *Trichinella spiralis*, *Dracunculus medinensis*, and the several species of nematodes that cause filariasis (*Mansonella perstans* and *Onchocerca volvulus*).

S. stercoralis mature adult worms are between 2 and 3 mm long. Threadworms have two separate developmental stages. In the first stage, the worm has a complete free-living nonparasitic life cycle, and in the second stage, a filariform larvae penetrates the skin of its host and moves into cutaneous blood vessels. The larvae are then carried to the lungs. In the lungs, the migrating larvae break out of the pulmonary capillaries and migrate through the respiratory passages to the throat where they are swallowed. Once they are inside the intestine, they become imbedded in intestinal wall.

Trichinosis is the condition caused by the adult worm of *T. spiralis* which is between 1 and 2 mm long. The cysts are found in contaminated meat, primarily pork. When ingested, cysts release immature larvae, which invade the intestinal lining and develop into adult worms. Mature worms mate in the submucosa and deposit mobile larvae, which migrate into intestinal lymphatics. They are then disseminated throughout the body and become encapsulated within striated muscle fibers. Adult worms live about one month. Mebendazole (**10**) is highly effective against *T. spiralis* infections. Treatment with mebendazole for trichinosis is for 13 days.

4.1. Thiabendazole

This benzimidazole derivative (**12**) is an effective oral drug used in the treatment of intestinal roundworms and selected tissue parasites. Infections with *S. stercoralis* are commonly treated with thiabendazole for two days. Disseminated strongyloidiasis is treated for at least five days. Satisfactory results have been reported when used for *T. spiralis* infections; however, its effectiveness on encapsulated muscle larvae has not been clinically demonstrated. Extensively used in veterinary medicine, thiabendazole was the first broad-spectrum benzimidazole anthelmintic. It is widely used in the United States. The mechanism of action is not clearly understood, but it has been shown that thiabendazole inhibits the enzyme fumarate reductase, which is found specifically in the mitochondria of helminths (31).

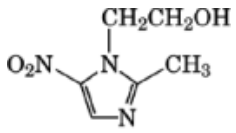
One ppm of thiabendazole prevents *Ascaris* eggs from maturing. In therapeutic topical concentrations, it is used to prevent the development of dog and cat hookworm larvae that have invaded human skin, causing cutaneous larva migrans. In laboratory animals, thiabendazole has antipyretic, analgesic, and antiinflammatory

properties, as well as anthelmintic properties. These properties are probably also exhibited in humans and may account for the symptomatic improvement in persons with early systemic trichinosis.

The adverse effects include digestive disturbances, neurological symptoms, and manifestations of allergic responses. As many as half of the patients taking it are incapacitated by some of these adverse reactions for several hours. Whether these symptoms are caused by hypersensitivity to the drug, the parasite, or by a manifestation of the disease is not known. Overall, effects are dose-related and transient.

4.2. Guinea Worm

Thiabendazole (**12**) and metronidazole (**14**) [443-48-1], $C_6H_9N_3O_3$, the broad-spectrum antiprotozoal agent



(**14**)

are used in the treatment of the guinea worm (*Dracunculus medinensis*) (see also Antiparasitic agents, antiprotozoals). These stringlike worms, about 1 m long but less than 2 mm in diameter, can be seen and felt below the skin surface. The head of the worm is usually exposed in an ulcer on the foot. The far end of the worm is hooked, so that although it is possible to grasp the front end and pull, the worm does not slide out easily and is apt to break, causing infectious, allergic, and toxic consequences as the remainder of the worm under the skin dies and deteriorates. After drug therapy, the worm either exits or it can be pulled easily without danger of breakage. Although metronidazole and thiabendazole have no direct effect on guinea worms, their effectiveness against the guinea worm may be due to their antiinflammatory effects. If left untreated, within a month the worm may come out naturally, withdraw from the opening, and be resorbed or become calcified in the body.

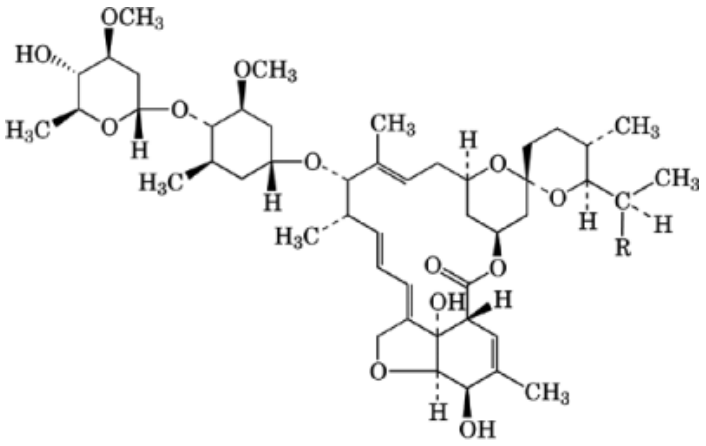
4.3. Filarias

Diethylcarbamazine (**9**) (orally administered) has been successful for decades in the treatment of filariasis, eg, elephantiasis (32). It kills microfilariae in the blood of the filarial worms *Wuchereria bancrofti*, *Brugia malayi*, and *Loa loa*.

Diethylcarbamazine has limited antimicrofilarial activity against *Onchocerca volvulus*. Adults of *W. bancrofti*, the filarial worm causing elephantiasis, coil in the lymph system. Here females can attain a length of 10 cm. Over the years, tissue reactions result in obstruction to lymph return. Lymph nodes, lymph vessels, and the spleen become enlarged. The condition of elephantiasis is a late and unusual complication of filariasis, where the lower extremities of the body become edematous, enlarge, and over a period of time harden with a rough nodular skin.

Untreated adult worms live for 5–10 years. *Loa loa* females are about 6 cm long and migrate constantly through connective tissues. Calabar swelling occurs as a result of local responses to worms. The swelling lasts two or three days and then subsides. If a worm migrates into the anterior chamber of the eye, the patient may be able to see it. Sometimes one eye is swollen shut when a worm is in the vicinity. Untreated worms will live as long as 10 years.

Microfilariae in the tissues of the lung (ie, eosinophilic lung or tropical eosinophilia) produce symptoms of chest pain, cough, and asthma, which are often relieved by the administration of diethylcarbamazine.



(15)

Fig. 1. Ivermectin [70288-86-7] is a mixture containing at least 80% 22,23-dihydroavermectin B_{1a} [70161-11-4], wherein $_{R=}$ C_2H_5, and not more than 20% B_{1b} [70209-81-3], where $_{R=}$ CH_3.

4.3.1. Diethylcarbamazine

This derivative of piperazine (**9**), causes the microfilariae to become susceptible to phagocytosis by the macrophages in the reticuloendothelial system. Its pharmacological effects enhance the body's immunologic response. The mechanism of the filaricidal action on adult *Wuchereria* and *Loa* is unknown. The selective toxicity of diethylcarbamazine is as yet unexplained. It is well absorbed and widely distributed throughout the body and does not accumulate, even after repeated doses. The adverse effects of nausea, fever, headache, and dizziness may occur during diethylcarbamazine therapy. The simultaneous administration of corticosteroids and antihistamines is intended to reduce the occurrence of rash, itching, edema, and other severe allergic reactions to the disintegration of the worms. Diethylcarbamazine is used in veterinary and clinical medicine. It is manufactured by Lederle Laboratories of Pearl River, New York. Other manufacturers include the Wellcome Foundation Ltd. in Cheshire, England, Cidan of Castellon, Spain, and Specia S.A. in Paris, France.

Mansonella perstans adult worms live encysted in various peritoneal tissues (eg, pericardium, pleura, and peritoneum). *M. perstans* microfilariae are not affected by diethylcarbamazine but mebendazole has been successful in treating *M. perstans* filariasis (33).

4.4. Ivermectin

This drug 1 is a semisynthetic derivative of one of the avermectins, which are macrocyclic lactones produced by the actinomycete *Streptomyces avermitilis* (34) (Fig. 1). This antiparasitic agent has a broad spectrum of activity against nematode worms and insects in animals and is widely used in veterinary medicine (see Antiparasitic agents, avermectins). The drug acts on susceptible organisms by potentiating the release of γ-aminobutyric acid [56-12-2](GABA) and binding the GABA at postsynaptic sites on the neuromuscular junction, thus paralyzing the nematode. Ivermectin acts slowly and has a long duration of action. Ivermectin has no effect on adult filariid nematodes, but it has proved to be superior to diethylcarbamazine as a microfilaricidal agent in the treatment of onchocerciasis. Neither drug completely cures the infection. More recent medical studies have also shown that ivermectin has a high activity against various intestinal nematodes (eg, *A. lumbricoides*, *T. trichiura*, and *E. vermicularis*) (35).

Systemic reactions are less severe than with diethylcarbamazine. The most commonly seen reactions are fever, rash, and lymph-node pain or swelling. Suppressive ivermectin therapy consists of a single oral dose

every 6–18 months. The required duration of suppressive therapy is unknown, probably at least three years (36). Ivermectin is available from the CDC Drug Service on request. It is manufactured by Merck Sharp and Dohme in the United States and England.

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