Chapter I

RECENT DEVELOPMENTS IN THE TREATMENT OF HOOKWORMS AND CESTODE INFECTIONS
The gastrointestinal tract of man is the most common seat of predilection for several infective diseases apparently because of the abundance of ideal conditions for survival and replication of the parasites. The intestinal helminth infections constitute one of the most widely prevalent disease of man affecting nearly 2500 million people around the world\(^1\). A number of helminths parasitizing the gastrointestinal tract are asymptomatic and rarely cause much trouble to the host while a few bear great public health significance and also hamper the socio-economic development by inhibiting the production of milk, meat, wool and leather in several third world and developing countries of the world. The hookworms and the cestodes are two important helminth parasites which have recently attracted the closer attention of medicinal chemists, parasitologists and clinicians because of their world-wide prevalence, greater pathogenic significance and concomitant detrimental effects on human body functions.

Among the measures available today for treating intestinal helminthiasis, the chemotherapeutic approach seems to be quite rational and deserve detailed work out. During the last two decades several newer classes of compounds
have been synthesized which have provided definite advantage over the classical antihookworm and anticestode drugs. The present review is mainly concerned in providing a precise account of the recent developments in the chemotherapy of hookworm and cestode infections in man and domestic animals. A detailed account of the classical anthelmintics used to treat various forms of intestinal helminthiasis is available.^

1. The Hookworm Infections

The hookworm infections, chiefly prevalent in the rural population of agriculture based regions of the underdeveloped world, is acquired by walking barefoot in damp soil contaminated with infective larvae. The hookworm larvae penetrate the skin and migrate to lungs and finally to intestine where they develop into adult worms and live on the direct blood feed of the host. The disease is distributed widely in the tropical and sub-tropical regions of the world; however it is endemic in India, China, Japan, Central America, Mexico, Panama, West Indies, Venezuela, Peru, Argentina, Paraguay and various parts of Northern and Eastern Africa. It is estimated that more than 700-800 million people around the world are the victims of hookworm disease. In India the infection is common in farmers working in rice, banana, maize and potato fields and affects nearly 205 million people in Assam, Bengal,
Bihar, Orissa, Kerala, Madras, Uttar Pradesh and other parts of the country.

The hookworms are endoparasitic nematodes found attached to the mucosa of the intestinal wall. The common hookworms which infect man are *Ancylostoma duodenale*, *Ancylostoma ceylanicum* and *Necator americanus*. The domestic animals are also infected by various hookworms like *Ancylostoma caninum* (dogs), *Ancylostoma braziliense* (cats), *Bunostomum trigonocephalum* (cattle) and *Giaigeria pachyscelis* (sheep and goats).

The main clinical manifestations of this disease are marked hypochromic microcytic anaemia leading to general weakness, fatigue and lack of physical and mental growth and reduced productivity of the host. In addition, the patient may also experience abdominal pain, constipation, anorexia and giddiness.

1.1 Chemothery of hookworms

1.1.1 Older drugs

The classical drugs which have been used to treat various human and animal hookworm infestations were drawn chiefly from halogenated hydrocarbons (tetrachloroethylene\(^1\) and mentomide \(^1\)\(^2\) etc.) and substituted phenols (2,4,5-trichlorophenol \(^2\)\(^1\)\(^3\), 4-cyano-2-iodo-6-nitrophonol \(^3\)\(^1\)\(^4\) etc.); however their clinical use was limited due to their
low activity and narrow margin of safety and, therefore, have been replaced slowly by more active drugs. Another group of compounds showing a wide range of pharmacological and antiparasitic activity are the quarternary ammonium salts of which bephenium hydroxynaphthoate (4) was developed by Wellcome laboratories as human antihookworm drug. Bephenium hydroxynaphthoate has been recommended at a dose of 5 g (=2.5 g of base) per adult showing 28-90% clearance of *N. americanus* and 80-100% clearance of *A. duodenale* infection. However, the drug is toxic, bitter in taste and produces several side effects. Following the discovery of bephenium, a large number of its structural analogs were synthesized but none surpassed the potency of the parent drug. The most active congeners of bephenium were
thenium (5)\textsuperscript{26}, diphezyl (6)\textsuperscript{27} and styrylpyridinium (7)\textsuperscript{28} but none proved its usefulness in treating clinical hookworm infections and were confined in controlling canine and feline hookworm diseases.

\begin{align*}
\text{R} & = \text{CH}_3 \\
\text{Cl} & = \text{N} \text{H}_2 \text{C} = \text{CH}_2
\end{align*}

A few cyanine dyes have also been used in the treatment of hookworm infestations in man and animals; the most important being dithiazanine (8) which is given to patients having \textit{N. americanus} and \textit{A. duodenale} infections with variable activity\textsuperscript{29,30}.

1.12 \textbf{New candidate anti-hookworm agents}

\textbf{Benzimidazoles}

The first truly modern anthelmintic was thiabendazole (2) discovered in 1961 by Merck\textsuperscript{31}. The drug shows high
Table 1  Details of some potent benzimidazole anthelmintics

<table>
<thead>
<tr>
<th>No. of Drug</th>
<th>Name of Drug (Discover)</th>
<th>Year</th>
<th>Activity in animals</th>
<th>Activity in humans</th>
<th>Dose in mg/kg</th>
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<tr>
<td>9</td>
<td>Thiabendazole (Merck)</td>
<td>1961</td>
<td>Active against A. caninum in dogs and other hookworms in sheep and cattle.</td>
<td>Active against N. americanus and cures creeping eruption caused by A. braziliense.</td>
<td>25-100 for 1-6 days.</td>
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<td>10</td>
<td>Cambendazole (Merck)</td>
<td>1970</td>
<td>Active against A. caninum in dogs and other hookworms in pets.</td>
<td>-</td>
<td>100</td>
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<td>11</td>
<td>Parbendazole (Smith Kline &amp; French)</td>
<td>1967</td>
<td>Eliminates A. caninum from dogs.</td>
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<td>20</td>
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<td>12</td>
<td>Mebendazole (Janssen)</td>
<td>1971</td>
<td>Active against N. brasiliensis, A. ceylanicum and A. caninum in mice, hamsters and dogs.</td>
<td>Removes A. duodenale and N. americanus from man.</td>
<td>100*</td>
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<td>13</td>
<td>Oxibendazole (Janssen)</td>
<td>1973</td>
<td>Active against various nematodes in mice, sheep, cattle &amp; horses.</td>
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<td>14</td>
<td>Fenbendazole</td>
<td>25-50</td>
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<td></td>
<td>(Hoechst)</td>
<td>N. americanus.</td>
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<td>1974</td>
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<td>U. stenocephala</td>
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<td>H. contortus in</td>
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<td>dogs, sheep and</td>
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<td>goats.</td>
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<td>15</td>
<td>Oxfendazole</td>
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<td>and goats.</td>
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<td>Albendazole</td>
<td>50</td>
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<td></td>
<td>(Janssen)</td>
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<td>and B. phlebotomum</td>
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<td>in dogs and cattle.</td>
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<td>17</td>
<td>Flubendazole</td>
<td>10-100</td>
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<td></td>
<td>(Janssen)</td>
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<td>against nematodes</td>
<td>N. americanus and</td>
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<td>and cestodes in</td>
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<td>pigs, dogs and</td>
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<td>sheep.</td>
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<td>18</td>
<td>Cibendazoleazo</td>
<td>Eliminates hookworms 600</td>
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<td></td>
<td>(Janssen)</td>
<td>as active as</td>
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<td>1977</td>
<td>mebendazole.</td>
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<td>rodents.</td>
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*Given at a dose of 100 mg/adult for 3 days.*
activity against human hookworms at a dose of 25-100 mg/kg given in a single or multiple doses. Thiabendazole is one of the most active drugs for treating creeping eruption caused by the larvae of *A. braziliense* in man. At a dose of 50 mg/kg given orally or applied locally, it effectively cures the lesions.

The discovery of thiabendazole stimulated a world-wide research resulting in the evolution of a series of powerful anthelmintics (Table 1). The most potent members of this series are mebendazole (12) and fenbendazole (14). Mebendazole possesses high activity against a number of species of nematode and cestode parasites in different hosts. The drug causes complete clearance of *Nippostrongylus brasiliensis* in mice, *A. ceylanicum* in hamsters and *A. caninum* in dogs and has been recommended as an ideal anthelmintic for small animals. Mebendazole is equally effective in eliminating *N. americanus* and *A. duodenale* infections in adult and child patients at a dose of 100 mg/adult given twice a day for 3 days. The children accordingly receive lower dosages.

Fenbendazole (14) exhibits potent activity against different species of lung worms and intestinal nematodes. It gives high cure rates against *A. caninum* in dogs and *Haemonchus contortus* in sheep and goats at a dose of
50 and 5 mg/kg respectively. When given at a dose of 100 mg/kg it also eliminated *N. americanus* in man.

The other 'benzazole' anthelmintics have also been used successfully to treat hookworms infections in cattle, sheep, goats, poultry and pets with good success. Some of them, like flubendazole (17) and ciclohexadazole (18) have shown promising results in treating human hookworm diseases.

The majority of benzimidazole anthelmintics were earlier shown to exert their activity by inhibiting the fumarate-reductase enzyme activity of the parasites which plays crucial role in worms anaerobic cycle. The inhibition of this step in the metabolism would cut-off the energy supply of the worm leading to its paralysis. Later the activity of various benzimidazole anthelmintics (9-18) has been attributed to their ability to bind with mammalian tubulin and to inhibit the assembly of microtubules.

Mebendazole is known to disrupt cytoplasmic microtubules resulting in degeneration of *Ascaris suum* intestinal cells. More recently it has been shown that mebendazole and fenbendazole bind (inhibition constants $1.9 \times 10^{-8}$ and $6.5 \times 10^{-8}$ respectively) with embryonic tubulin of *A. suum* which has been carried out by inhibition studies with $^3$H.
10

Thus the anthelmintic action of benzimidazole anthelmintics may be due to their differential binding affinities between nematode and mammalian tubulin (the inhibition constant of mebendazole and fenbendazole for bovine brain tubulin is 250-400 times higher than for *A. suum* embryonic tubulin).

**Imidazolines**

In a follow up study of the potentiality of imidazolines in parasite chemotherapy, Janssen Pharmaceutica came out with a new broad spectrum anthelmintic, tetramisole (12)^57. Tetramisole is a racemic mixture of R- and S-, 2,3,5,6-tetrahydro-6-phenylimidaz[2,1-b]thiazole which have been resolved and their absolute conformation established^58. The anthelmintic activity of tetramisole is due to its...
S(-)-isomer called levamisole. Levamisole possesses high activity against different gastrointestinal nematodes of sheep, dogs, swine, fowl, cattle, horses and man. At a dose of 2.5 mg/kg given orally it eliminates various round worms including hookworms in man and shows fewer side effects. Levamisole is a potent inhibitor of fumarate-reductase in various nematodes and shows immunostimulant properties in man and animals. The R(+)-isomer, surprisingly has antidepressant activity.

Pyrimidines

Tetrahydropyrimidines are another class of compounds with potent anthelmintic activity which has been studied extensively at Pfizer laboratories. The most active member of this series is pyrantel. Pyrantel pamoate has been found to give 75-91% cure rates against N. americanus and A. duodenale in man at a dose of 10-100 mg/kg depending upon the nature and intensity of the infections. It is equally effective against various intestinal helminths of sheep, goats, dogs, cattle, horse, swine and fowl.
The structural modifications of pyrantel have led to
the synthesis of a large number of its molecular congeners
of which morantel (21) and oxantel (22) have shown
high promise in curing different nematode infections in
man and animals.

\[
\begin{align*}
20, \ R = H, \text{ Pyrantel} \\
21, \ R = \text{CH}_3, \text{ Morantel}
\end{align*}
\]

Isothiocyanates

Among the several aryl isothiocyanates possessing
high nematodicidal activity, phenyl isothiocyanate (23) and
1,4-phenylenediisothiocyanate (24, bitoscanate, developed
by Hoechst) show high antihookworm activity in man. 23 has
been demonstrated to cure human hookworm infections at a
dose of 300 mg/kg given in three divided doses. Clinical
studies carried out with bitoscanate have shown that the
drug gives 47-96% and 25-96% cure rates against A. duodenale
and N. americanus infections respectively at a dose of
3 x 100 mg for adults and 2 x 100 mg for children given at
12 hr intervals. The side effects of bitoscanate are
nausea, vomiting, headache, abdominal pain and weakness which
are generally mild and transient.

\[
R \quad \text{NCS}
\]

\begin{align*}
23, \ R &= \ H \\
24, \ R &= \text{NCS, Bitoscanate}
\end{align*}

Recently Ciba laboratories have introduced 4-iso-thiocyanato-4' - nitrodiphenylamine (25, amoscanate) for treatment of hookworm and other nematode infections in man. Three doses of this compound at 100, 125 or 250 mg at 8 or 12 hr intervals were found to cause complete removal of \( A.\) duodenale and \( N.\) americanus in man. The oxygen analogs of amoscanate is nitroscanate (26) which eliminates hookworms from cats and dogs.

\[
\begin{align*}
0_2N \quad \text{X} \quad \text{NCS}
\end{align*}
\]

\begin{align*}
25, \ X &= \text{NH, Amoscanate} \\
26, \ X &= \text{O, Nitroscanate}
\end{align*}

1.13 Recent antihookworm agents

Febantel (27) and amidantel (28) are the two new anthelmintic developed by Bayer. Febantel shows high activity against different species of nematodes and cestodes in mice, rats, dogs, sheep and cattle. At a dose of 1-5 mg/kg it eliminated \( A.\) cunicum, Uncinaria stenocephala, Nematospiroides
duibius, H. contortus and B. trigonocephalum from various animals. Amidantel also clears Nippostrongylus muris, N. dubius and A. caninum at a dose of 250 x 3, 250 x 4 and 25 mg/kg respectively.

A series of avermectins (29), produced by Streptomyces avermitilis, have been developed at Merck laboratories which show high order of antiparasitic activity. Avermectin B1a and B2a possess marked activity against A. caninum and A. braziliense in dogs at an oral dose of 0.003-0.005 mg/kg. Later it was demonstrated that compounds of this class are highly effective against various gastrointestinal helminths of sheep and cattle at an oral dose of 0.05-3 mg/kg.
The cestode infections are generally considered as the helminth diseases of minor importance as compared to nematode and trematode infections. This is probably because the cestodes produce lesser pathogenic manifestations and are prevalent in smaller section of the population. The comparative rate of incidence of various helminth diseases would indicate that nearly 2500 million people are infected with intestinal nematodes\(^1\) while 200 million subjects harbour schistosomiasis\(^6,85\). In contrary, about 100 million people are the victims of intestinal cestodes all over the world\(^1,86,87\).

Although the incidence of cestode infections is not as high as other helminth infestations, they have a distinct influence on the human and animal health, and are generally difficult to eradicate. In addition, the risk of acquiring cysticercosis and hydatid disease poses potential danger of producing several serious and grave clinical manifestations for which an ideal remedy is yet to be discovered.

The cestodes, infecting man, possess a world-wide distribution; however, they are chiefly prevalent in the tropical and subtropical regions. The endemic areas of this infection are Iran, Iraq, Israel, Jordan, Lebanon,
Saudi Arabia, Syria, Turkey, Pakistan, India, Tibet, Korea, Japan, U.S.S.R., different parts of Africa, Mexico, Brazil, Peru and Chile. The cestode infections have also been reported from some parts of Europe, Australia and America.

Like hookworms, the cestodes are also endoparasitic, hermaphroditic tape-like helminths living in the alimentary canal of the vertebrates. The main cestodes infecting man are _Taenia saginata_ (beef tapeworm), _T. solium_ (pork tapeworm), _Diphyllobothrium latum_ (fish tapeworm) and _Hymenolepis nana_ (dwarf tapeworm). The important cestodes infecting animals are _Dipylidium caninum_ and _D. mansoni_ (cats and dogs), _Moniezia expansa_ (sheep), _T. pisiformis_ (dogs, foxes), _T. hydatigena_ (dogs), _T. taeniformis_ (cats) and _Raillietina cesticillus_ (fowls).

The life cycle of cestodes normally requires one intermediate host such as cattle, pigs and fishes. Man acquires this infection by eating poorly cooked infected beef, pork or fish; the cysticerci present in the flesh emerge out and attach themselves to intestinal wall where they grow, attain maturity and live for several years with the host. The cestode infections are generally asymptomatic; however the patient may suffer from nausea, diarrhea, hunger pains, weakness, malaise, weight loss and anaemia.
The cysticerci may migrate in any part of the body and cause several complications. The cysts may cause blindness and nervous disorders if migrate in eye and brain respectively.

2.1 Chemotherapy of Cestodiasis

2.1.1 Older drugs

A number of plant products such as *Aspidium oleorosin* (extract of male fern, *Dryopteris mas*)\(^4\), arecoline (30)\(^88\), pumpkin seeds\(^89-91\) have been used since long for treating human cestodiasis. Several tin compounds have been shown to possess high activity against different cestode parasites in man and animals\(^92\). A few derivatives of acridines such as quinaclorine (31)\(^93-95\) and acranil (32)\(^96,97\) were used earlier to cure cestode infections in man. In general these drugs showed several toxic effects in hosts, required intensive medical care of the patients and also did not cause complete elimination of the infection. Due to these shortcomings better chemotherapeutic agents were discovered which slowly replaced older drugs in the clinical treatment of cestodiasis.
2.12 New Anticestode Drugs

Dichlorophene (33)

This is an old antimicrobial, germicidal and fungicidal agent which has been found to eliminate *T. pisiformis* and *D. caninum* from dogs and cats at a dose of 200 mg/kg\(^2\) and *Moniezia* sp. from sheep at a dose of 150 mg/kg\(^1\).\(^1\)

The drug has been extensively used since 1959 to treat *T. saginata* infection in man\(^3\)-\(^5\). The usual recommended adult dose of dichlorophene is 60-100 mg/kg not exceeding 5 g in a day; the children receive accordingly smaller doses. The cure rates were between 50-86%. Dichlorophene is usually safe at therapeutic doses and does not produce any side effects; however some allergic reactions may be noticed\(^6\). At higher doses the drug may produce nausea, vomiting, diarrhea, colic and jaundice and may require special care to patients with heart and liver diseases.

![Chemical structure of Dichlorophene](image)
Bithionol (34)

This was initially used as an antimicrobial and topical antiseptic agent but later found to exhibit activity against a wide range of cestode parasites in men and animals. It caused 70-85% removal of *T. hydatigena*, *T. ovis*, and *M. multiceps* at a dose of 150 mg/kg while all the *D. caninum* worms from dogs were eliminated at a dose of 150-200 mg/kg and no side effects were observed except occasional diarrhea and softening of faeces. The drug showed 100% efficacy against *Moniezia* and *Ancylocephala* species in sheep at a dose of 100 mg/kg.

Bithionol has also been used successfully to treat *T. saginata* and *D. latum* infections in man. A dose of 40-60 mg/kg, given once or in two divided doses, was sufficient to cure patients infected with *T. saginata* or *D. latum*; however scolex was removed only in 37.5-50% of the cases. The common side effects of this drug are nausea, vomiting, anorexia, general fatigue and epigastric pain. High cure rates in human cestodiasis have also been obtained when the patients were given a combination of 0.5-1 g of bithionol with 1-2 g of niclosamide.

![Chemical Structure](image)

34, Bithionol
Halogenated salicylanilides

Niclosamide (Yomesan, 35) is the first member of this class which was introduced in 1960 by Bayer116,117 and since then it became the primary drug to treat different forms of tapeworm infections in man and animals. In the preliminary experiments carried out on animals, it showed high cure rates against *T. hydatigena*, *M. multiceps* and *D. caninum* in dogs at a dose of 50 or 100-300 mg/kg116,119. At lower dosages (110-200 mg/kg) also, given in capsules or in food, it eliminated all *T. visiformis* and *D. caninum* infections from dogs120. Later it was demonstrated that niclosamide can cause complete eradication of *T. hydatigena* in dogs at a dose as low as 32 or 62 mg/kg121. The drug is also highly effective against *D. caninum* (250 mg/kg)119 and *H. taeniaeformis* (750 mg dose or 100-200 mg/kg) in cats122,123.

Sheep infected with *M. expansa* and *M. benedeni* were completely freed of tapeworms when treated with niclosamide at a dose of 75 mg/kg and no toxic effect was observed124-126. It was also highly effective against *Raillietina* in chickens at a dose of 20-25 mg/kg127,128.
Halogenated salicylanilides

Niclosamide (Yomesan, 35) is the first member of this class which was introduced in 1960 by Bayer116,117 and since then it became the primary drug to treat different forms of tapeworm infections in man and animals. In the preliminary experiments carried out on animals, it showed high cure rates against T. hydatigena, M. multiceps and D. caninum in dogs at a dose of 50 or 100-300 mg/kg118,119. At lower dosages (110-200 mg/kg) also, given in capsules or in food, it eliminated all T. pisiformis and D. caninum infections from dogs120. Later it was demonstrated that niclosamide can cause complete eradication of T. hydatigena in dogs at a dose as low as 32 or 62 mg/kg121. The drug is also highly effective against D. caninum (250 mg/kg)119 and H. taeniaeformis (750 mg dose or 100-200 mg/kg) in cats122,123.

Sheep infected with M. expansa and M. benedeni were completely freed of tapeworms when treated with niclosamide at a dose of 75 mg/kg and no toxic effect was observed124-126. It was also highly effective against Raillietina in chickens at a dose of 20-25 mg/kg127,128.
In clinical practice niclosamide has shown excellent results in treating practically all human tapeworm infections\textsuperscript{129-137}. Patients suffering with \textit{D. latum} and \textit{H. nana} infections were given 2-4 chewable tablets (each containing 1 g of niclosamide) after breakfast when all the cases were cured with minor side effects\textsuperscript{138}. It cured Diphyllolobothrium infection in several patients when given 1 g/adult followed by 1 g/adult after two hours and then a saline purge after 3-4 hours\textsuperscript{139}.

Treatment of \textit{H. nana} infection in adult and child patients can be carried out at different dose schedules. When niclosamide was given at a dose of 1 g per adult daily for 6-13 days, the drug gave 74-75\% cure rates against \textit{H. nana}\textsuperscript{140,141}. Better results were obtained against the above infection by giving the patients 60 mg/kg of the drug followed by 15 mg/kg for 6-7 days\textsuperscript{142,143}. Children infected with \textit{H. nana} were given 0.5 g of niclosamide daily for 6 days or a single dose of 100-130 mg/kg of the drug when high cure rates were achieved\textsuperscript{140-144}.

Niclosamide has also been found to possess high activity against \textit{T. solium} and \textit{T. saginata} in man. A dose of 2-3.5 g/adult given in single or divided doses with or without a saline purge, has been found to cure 85-97\% of patients infected with \textit{T. solium} and \textit{T. saginata}\textsuperscript{138,139,142,145-147}.

Niclosamide is practically devoid of any
contra-indication and may be used safely during pregnancy also. The drug possesses low toxicity which is probably due to its poor absorption through the intestinal wall.

Based on the high activity exhibited by niclosamide, Hoechst laboratories introduced 4'-bromo-γ-resorcylanilide (Terenol, 36) as a useful veterinary cestodicidal agent. At a dose of 10-25 mg/kg, terenol eliminated H. diminuta from rats. It was equally effective against Moniezia in cattle and goats at a dose of 0.5 ml of suspension (65 mg of terenol)/kg body weight when 100% clearance of the tapeworms were observed.

Oxyclozanide (37) is a polyhalogenated analog of niclosamide developed by ICI laboratories. The drug removed 13 day old H. diminuta from rats at a dose of 4 mg/kg. It is a well tolerated compound which destroyed the 7 day old H. diminuta in mice at the similar dose given in above experiment.
Merk Sharpe and Dhome developed a diiodo analog of niclosamide, rafoxamide (38) which showed cestodicidal activity in rodents infected with *H. nana* and *H. diminuta*.

![Chemical Structure](image)

During the search of more potent congeners of niclosamide, a large number of substituted salicylanilides have been prepared at this laboratory many of which exhibit cestodicidal activity superior to that of parent drug. Thus, a series of 5-chloro-3'-nitro-4'-substituted salicylanilides were found to possess high anticestode activity; the best compound of the series was 5-chloro-3'-nitro-4'-cyclohexylaminosalicylanilide (39) which eliminated all the worms of *H. nana* in mice at a dose of 30-50 mg/kg. Similarly 2'-chloro-4,4'-dinitro-3'-oxy-5'-nosalicylanilide (40) and 4',5'-dichloro-3'-nitroalicylanilide (41) cleared 100% of *H. nana* infection in mice at a single oral dose of 250 mg/kg.
A series of substituted-3,5-dibromosalicylanilides have been prepared many of which caused 100% eradication of *H. nana* from rats and mice at a dose of 10–250 mg/kg. The best member of this series was 3,5-dibromo-2'-chloro-4'-isothiocyanatosalicylanilide (42) with marked anthelmintic activity and would be discussed later.

**Isothiocyanates**

Bitoscanate (42) is the first member of this class which was developed by Hoechst laboratories in 1960's to treat hookworm and cestode infections in man and animals. At a dose of 6 mg/kg it showed high activity against *T. pisiformis* in dogs. It also eliminated 99.2–100% of the *H. nana* worms from mice when given at a dose of 50–170 mg/kg.
Clinical studies with bitoscanate showed that the drug was effective in eliminating *H. nana* from children (5-9 years old) at a dose of 200 mg/kg given in two divided doses at 12 hours interval. The cure rate was 67%. The older children and adult patients needed 300 mg/kg (in three doses of 100 mg, 12 hours apart) to yield 95% cures against *H. nana* infection.173.

\[ \text{SCN} \text{-} \text{NCS} \]

43

A series of substituted diphenyl sulfides, disulfides, sulfoxides, sulfones, ethers, methanes, ketones and ethylenes carrying an isothiocyanato group in one or both the phenyl rings have been synthesized of which 4,4'-diisothiocyanatodiphenyl sulfone (44) and its corresponding sulfide (45) showed the highest activity.174-177. Compound 44 was highly effective in removing >90% *H. nana* worms from mice and rats at a dose of 10 and 100 mg/kg respectively, its maximum tolerated dose in mice was found to be >2.7 g/kg174,175. Further studies on this compound indicated that it was also effective against *Taenia* species, *D. caninum* and *Raillietina* species at an oral dose of 50-100 mg/kg.176. 4,4'-Diisothiocyanatodiphenyl sulfide (45) exhibited marked activity against *H. nana* in mice and rats at a dose of
Based on the powerful cestodicidal activity of niclosamide and 44, a series of halogenated isothiocyanato- salicylanilides were synthesized possessing potent activity against *H. nana* in rats. The best compound of this class was 3,5-dibromo-2'-chloro-4'-isothiocyanatosalicylanilide (42) which displayed high order of activity against a number of nematodes and cestodes in different hosts. At a dose of 100 mg/kg, it caused 100% elimination of *H. nana* in mice and rats and *H. diminuta* in Mostomys natalensis and also provided 100% cure rates except for *H. nana* in mice where the cure rate was 82%. In this test the drug was found to be better than niclosamide but inferior to praziquantel.

In an expanded study 42 was evaluated against a number of nematode and cestode parasites. It removed 100% of *H. nana* from mice and rats, *Raillietina* species from fowls and *Taenia* species from cats at a dose of 25-70 mg/kg. It was equally effective against *Ankylostoma ceylanicum* in hamsters, *Syphacia obvoluta* in mice, *Ascaridia galli* in fowls,
Toxascaris species, Toxocara species, Anclylostoma tubaeformis and Gnathostoma spinigerum in cats and A. ceylanicum and T. canis in dogs at a dose ranging from 25-50 mg/kg given for 1-3 days. Some of the isothiocyanatonaphthanilides have also been found to possess high order of activity against different cestodes. The most potent member of this class was 46 which resulted in 100% elimination of H. nana in rats at an oral dose of 7.5 mg/kg. It also showed high activity against H. diminuta in rats and Taenia species in dogs. A single oral dose of 5 g/kg of this compound was well tolerated by rats. It was equally safe when given to mice, Mastomys and dogs.

The oxygen analog of amoscanate (47, Nitroscanate, GS-23654) has been found to possess high antitapeworm activity in dogs. At a dose of 1 g/kg or 250 mg/kg x 2, it eliminated all Echinococcus granulosus while a dose of 64 mg/kg of the drug was sufficient to remove T. hydatigena from dogs. In another experiment against E. granulosus in dogs, nitroscanate was given as 25% suspension at a dose of 100, 200 and 400 mg/kg divided in 1-3 doses, when three
doses of 400 mg/kg removed 92.6% of the tapeworms. The lower doses were less active.

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**Substituted Amidines**

In 1965, Wellcome laboratories reported the anthelmintic activity of a series of substituted naphthamidines of which N,N-dibutyl-4-n-hexyloxy-1-naphthamidine (48, Bunamidine) was found to exhibit the most potent taenicidal activity. Since then bunamidine has been used extensively to treat various cestode infections in dogs, cats, sheep and poultry. Although this drug is too toxic for humans, it may be successfully used to prevent man from hydatid disease by eliminating *Echinococcus* reservoirs from cats and dogs.

At a dose of 15-40 mg/kg, bunamidine hydrochloride caused 90-100% clearance of *Dipyldium* from cats and dogs. Treatment of sheep infected with *M. expansa* needed 12.5 mg/kg of the drug for lighter infections while a dose of 25-50 mg/kg of it was required for eliminating heavier infections. Bunamidine was also highly effective in eliminating majority of *T. pisiformis, H. taeniaeformis*
and *M. multiceps* from cats and dogs at a dose of 25-50 mg (base)/kg. The drug showed differential response against *American* and *English* strains of *T. pisiformis*. The efficacy of various salts of bunamidine has been demonstrated against *R. cesticillus*, *R. tetragona* and *R. echinobothrida* in chickens.

Benzimidazoles

Mebendazole (12) was given to 31 patients infected with *T. solium* and *T. saginata* at a dose of 100 mg twice daily for 2 days or at 200 mg twice daily for 4 days when 20, 72.7, and 90% cure rates were obtained. In another clinical trials carried out in Costa Rica, 37 patients with *T. solium* and 4 patients with *T. saginata* infections were treated by mebendazole at a dose of 100-300 mg given twice daily for 2-6 days. This treatment removed long chains of proglottids from several patients 24-48 hours after drug administration and only fewer side effects were noticed.

Mebendazole was equally effective in removing tapeworms from pets. At a dose of 1 g given daily for 14 days, it killed both mature and immature cysticerci of
of *T. pisiformis* in rabbits. It has been used to treat *Uncinaria stenocephala*, *T. pisiformis* and *D. caninum* infections in dogs at a dose of 100 mg given twice for 5 days. The cysts of *T. hydatigera* and *T. ovis* in sheep were killed by mebendazole when given at a dose of 50 mg/kg given for 14 consecutive days.

Fenbendazole (14) has been found effective in eliminating *H. diminuta* from rats and *M. expansa* from sheep and cattle at a dose of 10-25 mg/kg and other tapeworms from domestic animals.

Oxfendazole (15) has been used to treat dogs infected with *Echinococcus granulosus* and *T. hydatigera* and sheep-carrying *Moniezia* at a dose of 4.5-20 mg/kg when the animals were cured considerably.

Albendazole (16) shows high activity in removing *Moniezia* from sheep at a dose of 10 mg/kg and *T. saginata* from calves at a dose of 45-50 mg/kg. It also caused complete eradication of natural infections of *M. expansa* and *M. benedeni* from sheep at a dose of 10-20 mg/kg and was highly effective against *Mesocestoides corti* in dogs.

Squibb laboratories have developed two injectable benzimidazoles, [5-[(cyclopropylmethyl)sulfinyl]-1H-benzimidazol-2-yl]carbamic acid methyl ester (49) and
[5-[(2-methylpropyl)sulfinyl]-1H-benzimidazol-2-yl]carbamic acid methyl ester (50) to treat nematode and cestode infections. A single s.c. injection of 49 given at a dose of 5 mg/kg removed 100% of Moniezia from naturally infected sheep. It was equally effective against Moniezia sp. at an oral dose of 2.5 mg/kg.  

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**Praziquantel**  
A large number of pyrazino-isoquinolines (51) have been synthesized jointly by Merck and Bayer laboratories which show high activity against H. nana in mice at a minimum inhibitory concentrations of 25-50 mg/kg. From this series, 2-cyclohexylcarbonyl-1,2,3,6,7,11b-hexahydro-4H-pyrazino[2,1-a]isoquinolin-4-one (52; EMBAY 8440, Biltricide, Praziquantel) emerged as the most potent anthelmintic. Praziquantel possesses high activity against the blood flukes Schistosoma haematobium, S. japonicum, S. mansoni and S. intercalatum and cestode parasites in man and animals. Recently the physical, chemical and biological properties of praziquantel has been published.  
At a dose of 2.5 mg/kg, praziquantel eliminated all
T. hydatigena from dogs and Hydatigera taeniaeformis from cats\textsuperscript{221}. However, a dose of 1 mg/kg of the drug was sufficient to remove all the worms of T. pisiformis and T. taeniaeformis from dogs and cats respectively\textsuperscript{222}. Hamsters infected with D. latum showed high response when treated with praziquantel using at a dose of 50 mg/kg\textsuperscript{223}.

![Chemical structures](image)

2.2 The Hydatid Disease

The hydatid disease, prevalent wherever man is closely associated with dogs, sheep and cats, is one of the most serious and fatal infection caused by cestodes. The disease is acquired by ingestion of eggs of Echinococcus granulosus and E. multilocularis. The definite hosts for these cestodes are the canine animals such as dogs, wolves, foxes, jackals and cats who harbour the adults worms in their small intestines. The intermediate hosts are man, sheep, cattle, dogs and camels.
The hydatid diseases generally do not show any symptom at the early stage, however various clinical manifestations such as nausea, vague abdominal pain, bulging of the right hypochondium or epigastrium due to hepatic enlargement and recurrent pyrexia associated with coughing paroxysms may occur which depend upon the size, type and site of the cysts. Sometimes the cyst may rupture due to some reasons which may give rise to anaphylactic shock with vasomotor collapse, oedema, urticaria and respiratory discomfort.

2.2.1 Treatment of hydatid infections

Arecoline hydrobromide (30) has been used since long to treat dogs infected with *Echinococcus*. At a dose of 4 mg/kg, arecoline HBr or HCl gives 95-98% efficacy against *E. granulosus* in dogs\(^{224,225}\):

Bithionol (34) and its corresponding sulfoxide have been recommended for treating dogs carrying *E. multilocularis* infection and give high cure rates at 150 and 200 mg/kg respectively\(^{226}\).

Niclosamide (35) shows variable activity against *E. granulosus*\(^{227,228}\), however at a single oral dose of 50 and 100 mg/kg it removed 50% and 98-100% of these tapeworms from dogs\(^{229}\).
Bunamidine (48) is the most extensively used drug against *E. granulosus* in dogs and sheep and is generally employed as its hydrochloride or hydroxynaphthoate. The drug is generally given in two doses at 24 or 48 hours intervals\(^{230-232}\). Bunamidine hydrochloride removed 90-94\% of *E. granulosus* worms from several dogs at a single dose of 50 mg/kg\(^{233,234}\), while at a dose of 25 mg/kg, 50 mg/kg or 25 mg/kg given twice at 48 hour intervals resulted in 98.8, 85.9, and 98.5\% reduction of *E. granulosus* respectively in 12 dogs\(^{235}\). In some countries dogs and sheep with potential exposure of *E. granulosus* infections were treated biweekly (with 100 mg/kg) or monthly (with 25 mg/kg) by bunamidine for a long period resulting in sharp fall in hydatid infections. No toxic symptoms developed even the animals were treated for several years\(^{236,237}\). Bunamidine hydrochloride is also effective against *E. multilocularis* in dogs at a dose of 40 mg/kg\(^{226}\).

Bunamidine hydroxynaphthoate, at a single oral dose of 100 mg/kg cleared 97\% of *E. granulosus* infection from 12 of 15 dogs\(^{238}\).

Mebendazole (12) is another recent drug which has been found to exhibit high activity against *E. granulosus* at a single or multiple dose of 1.25-160 mg/kg causing significant reduction of parasites in different animals\(^{239-241}\).
Mebendazole, given intraperitoneally at 75-150 mg/kg daily for 3 days, was 95-100% effective against *E. multilocularis*.241

Praziquantel (52) is the latest drug introduced to treat hydatid diseases in dogs, cats and sheep with high success. It is 100% effective against *E. granulosus*242,243 and *E. multilocularis*244 at a dose of 5 mg/kg.

3. Conclusion

It is evident from the present survey that a number of broad-spectrum anthelmintics have been developed replacing old traditional drugs which can be used successfully to eradicate various gastrointestinal helminths from both man and domestic animals. However, keeping in view the high rate of incidence of intestinal helminthiasis disease, risk of reinfection and lack of long-effective drugs, the search for newer chemotherapeutic agents still continues. There is ample scope to develop longer-acting drugs effective on immature, mature and cystic forms of the worms. Synthesis of large number of compounds based on empirical and semi-empirical approach and evaluation of their anthelmintic efficacy and detailed SAR of potent drug series would help in enlightening newer avenues.
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