New Aspects In The Treatment of Helminths

Gerald J. Crawley, B.S., D.V.M., M.S.*

WITH THE advent of several new anthelmintic discoveries in the past few years the treatment of the various helminths of domestic animals has taken on new aspects. The problem of parasites and parasite control is not new. Yet, with the ever increasing stress placed on our animals for faster and more economical gains and for greater milk production, the parasitic problem takes on greater significance. It is hoped that a brief discussion of the various anthelmintics and the overall parasite problem will enable the practitioners to handle this problem more effectively.

Animal parasites are a universal hazard to livestock production, although individual species are limited in distribution and intensity by several factors including climate, topography, the presence or absence of intermediate hosts, by the kinds of animals in which they develop, and others.

In general, parasites are insidious, *i.e.* very few cases of clinical parasitism are actually seen, and it is because of this that they are especially dangerous. The problem often goes unrecognized and uncontrolled.

Parasitism is essentially a herd or flock condition, rather than one of individual animals, although it is the rare individual showing clinical symptoms which usually receives the attention of owners and veterinarians alike. Measures to control parasites are effective therefore only if applied to a whole herd or flock as though it were but a single animal.

The basic principles of disease prevention are of extreme importance in an overall program to control parasites. Generally speaking, parasite control is the judicious use of feasible, profitable measures to minimize the losses and the hazards of parasitism. A good share of this program revolves around management practices. However, these practices often will not do the job alone or more often it becomes impractical because of fixed conditions on the farm to follow programs which might be effective. This is where the judicious use of the various anthelmintic chemicals under the direction of the veterinarian can and should play a major role. These agents must not be used promiscuously as has happened in the realm of the antibiotics, but rather as a planned program—both therapeutically and prophylactically.

The term "parasite control" connotes something quite beyond "keeping parasites in check" or "maintaining the status quo". It is not true that a few parasites are not harmful or "may even be helpful", with the possible exception of those parasites which cause an immune reaction such as coccidia. By modern standards eradication is the only rational goal, however remote that prospect or possibility may be. Probably a more practical approach on a beginning program would be "that any practice which will lower the parasite load that does not cost more than the loss that the parasite is causing is justified and reasonable". When this is accomplished, we can seriously think about eradication. At the present, eradication of most parasitic infections is unfeasible in practice, if not impossible, yet there are instances where this possibility is well on its way to reality, or has been accmoplished, (dourine of horses, Texas cattle fever, screwworms in some areas), but these instances are indeed few. Nevertheless, measures are available to control and prevent large animal losses which face livestock men each year because of

* Dr. Crawley is Instructor of Pharmacology at Iowa State University.

parasitism. These measures are based largely on sanitation and medication. Our first problem is one of education of the farmer as to the extent of the parasite problem, our second is the education of the veterinarian as to the chemicals available and their proper use in light of the management practices in any particular series of circumstances. No one program can fit the needs of all clients in an area.

Much work has been accomplished on the first problem, *i.e.* education. Through the efforts of parasitologists, veterinarians, and commercial companies, the story of parasites has been carried to many of the livestock people. However, there are still many who need further education in this field, especially in the area relating to the internal parasites of cattle. The local veterinarian can do more to educate his clientele than any other one force.

The development of control measures requires a full knowledge of immunity, sources of infection, and means of transmission, life cycles including any intermediate or incidental hosts, parasite-host relationships, epizootiology, geographical distribution, and factors which augment or decrease host resistance.

Probably the best overall approach is the so-called "life-cycle approach". This involves a concerted attack on all fronts but with special efforts against that point in the life cycle in which the parasite is most vulnerable. This may be at the time the parasite is in the host, or within an intermediate host or more preferably when it is "free-living" outside the host. Nearly every species has such a "free-living" stage and it would be well to attack the parasite at this time before it can cause any harm to its host and at a place where we need not be so concerned about the toxic effects of a chemical upon the host. However, because of lack of knowledge of many of the complete life cycles, and for many other reasons, mainly managerial and economical in nature, it is often impossible to attack parasites from this approach. Since we are most aware of the parasite and its relation to its host, it is at this point that we often make our attack.

Antiparasitic, more specifically in this discussion anthelmintic, chemicals are powerful aids in this attack. They must not be confused as being synonymous with control or substitutes for it; they are merely aids in the overall program. Some efficient measures of parasite control do not depend upon the use of these agents at all or only incidentally (artificial insemination for control of *Trichomonas fetus*, concrete sanitation systems for swine ascarid control, individual portable pens for control of coccidia in calves, etc.) Neither have many parasites been controlled by the use of these agents alone. However, chemotherapeutic and other chemical measures for destroying parasites do have an important place in parasite control programs. In the same degree that the concept of control embraces all measures aimed at the weakest link in the life cycles of the parasite, the concept of antiparasitic chemicals includes all agents that accomplish, or help accomplish interruption of this cycle. This discussion will be limited to those anthelmintic agents which act upon the parasite during the time of the cycle when it is within the host.

Chemicals are our oldest weapons for combating the parasitic infections. Many of the chemicals which are being used today were not known two decades ago or even ten years ago. Others which have been used extensively in the past are now being replaced by safer and/or more effective chemicals.

Methods, too, have been revolutionized. The effects of new approaches and viewpoints are fully as significant as new drugs and chemicals. Today, because of a better understanding of the nature and gravity of parasitism, the strictly curative use of anthelmintics, as well as many other medicinals, is becoming less common. Emphasis has been placed on prevention rather than cure. This approach has not been without problems. Some of which are the increased possibilities of resistant strains of organisms and of sensitivities arising within individual animals. These have been noted in several areas, especially with the antibiotics. Part of this is inherent with the approach taken while a larger share is due to the unintelligent and promiscuous use of drugs and chemicals by lay and professional personnel as well.

But, it is through experience that much of our learning has arisen, so let us hope that we can profit by these mistakes. All too often, profit becomes the motivating factor in the manufacture, promotion, and sale of a product. Profit is important if we are to continue to make progress through research, but our prime concern should be with the overall best use of any product in its utilization as a prophylactic or therapeutic substance, and not with mass sales to an uninformed, but not unintelligent public.

It can generally be said that most livestock men are aware that swine, horses and sheep may become heavily parasitized. Whether they do anything about it is another question. Many are not aware that cattle also can be parasitized, and it is often difficult to convince them since it is not so readily apparent when helminths are passed in this species as it is when swine ascarids are passed. Many of those who realize animals may be parasitized do not become alarmed until they have a clinical case, although the subclinical parasitic infection may be doing considerable harm. It is up to the local veterinarian to inform these people of the significance of the parasite and of the toll they are extracting annually from the farmer.

About 25 species of roundworms can live in the digestive tract of cattle—ten of which are of considerable economic importance. Over twenty-four species of nematodes occur in the digestive tract of sheep and goats. At least a dozen different nematodes may be found in the gastrointestinal tract of swine, and there are over twice that many found in horses, to say nothing of the bot problem.

Since this is not intended to be a systematic review of the literature pertaining to this subject, but rather a review of older products and an introduction to newer chemicals for anthelmintics, references will only be cited in which the reader may find additional information. This is not intended to represent a comprehensive coverage of the specific chemicals.

Horses

Of the several chemicals which have been used in horses, carbon tetrachloride and tetrachloroethylene should be discarded and considered obsolete because of their toxicity. Phenothiazine, piperazine, toluene and carbon disulfide may still be used for specific conditions alone or in combination. Phenothiazine is effective against strongyles, especially the smaller varieties and is slightly effective against the stomach worm, *Trichostrongylus axei.* It can be used therapeutically and is also recommended as a low level preventative in feed or salt at the rate of two grams per day for 21 consecutive days of each month. There has been some controversy concerning its toxicity because erythrocytes may be destroyed. If used at recommended levels this should not be a problem. Piperazine is highly effective against ascarids of all species and is exceedingly safe. In addition, it is highly effective against the mature horse pinworm, *Oxyuris equi.* It also has some effect against the smaller species of strongyles. Toluene is effective against ascarids and to some extent bots. However, upon repeated usage it may cause a central nervous system depression. Carbon disulfide has been the drug of choice for bots, it is also highly effective against the horse stomach worm, *Habronema.* However, it is toxic and must be administered with care. The best method of administering this compound is via stomach tube. The newer anthelmintics which are currently available may replace these treatments to a large extent. Thiabendazole* has only recently been marketed. It has been shown to be very effective against strongyles. In addition, it is very safe. Finally, the organic phosphate compounds, which have been such effective insecticides, have been shown to have some activity against helminths. Some of these compounds have been more effective than others. One which has seemed to work well in horses and which covers a broader spectrum than any drug heretofore known for horses is Neguvon† (also called Dipterex, Dichlorphon, Dylox, and Bayer L13/59). It is reported as be-

*** Merch, Sharp and Dohme, Rahway, New Jersey—marketed under the trade name of Equizole.**

† Chemagro, Kansas City, Missouri—marketed under trade name of Dyrex by Fort Dodge Laboratories, Fort Dodge, Iowa.

ing active when administered per os against ascarids, strongyles (both large and small), pinworms and bots. It, of course, has the possibility of causing toxicity symptoms as do all the organic phosphates, which are those of cholinesterase inhibition. However, if administered as directed there is a good margin of safety. It might be well to point out that the use of succinyl choline following the use of organic phosphates is specifically contraindicated.

Cattle and Sheep

The drug of choice for treating helminths of ruminants has been phenothiazine. This drug has shown a broad spectrum action being highly effective against Haemonchus, Bunostomum, and Oesophagostomum and somewhat less effective against Trichostrongylus, Ostertagia and therapeutically as a drench or bolus. It Nematodirus. This drug has been used is contraindicated in weak and anemic animals. It may also cause photosensitization. It is very well suited to low level continuous feeding because of its very good stability properties. It has been used in salt and at a 1:9 mixture with variable results. However, much of this was apparently due to its unpalatability which has been largely overcome by commercial preparations.*

In addition, there are several mineral products available which are purported to be highly palatable. The question arises as to whether consumption is great enough to meet the requirements of two grams per day of phenothiazine and whether the cost of the product for amount of drug obtained is warranted. This is where the judgment of the veterinarian can very often be of considerable help to cattle and sheep men. In addition, particle size has been found to be very important —the finer sized particles are more effective and of course more costly, and this is where much discrepancy has arisen in the literature regarding its effectiveness. This is also where questions arise in the minds of farmers when finding such great cost differences among products for what appears to be the same chemical.

It was also reported that low level feeding of phenothiazine in cattle was effective in controlling the lungworm, *Dictyocaulus viviparus*. Recently experimental work indicates that it may be effective in a community program of hornfly control through its action upon the larvae in the manure. It is currently being marketed for this purpose.

It should be pointed out that this chemical usually causes a very red urine and may cause a discoloration of the milk of lactating animals as well as staining the wool and haircoats. The milk is safe for consumption by calves or other animals, but has no beneficial affects.

Piperazine can be used in cattle with no untoward effects. However, it is only effective against the ascarid and this seems to be a problem in cattle only in isolated areas. It has been reported to be quite beneficial in sheep against nodular worms; however, it is not used routinely in this species because of the broader spectrum of other anthelmintics.

The only other drug which has had any widespread popularity as an anthelmintic in cattle has been Kamala. This drug has very poor efficacy, if any, and because of this there is no justification for its use.

Phenothiazine may be replaced to some extent with the advent of Thiabendazole.* This chemical has a high degree of activity against a broad spectrum of gastrointestinal parasites and a very wide margin of safety. Efficacy studies in sheep indicate fourteen species of the following genera are responsive: Trichostrongylus, Haemonchus, Ostertagia, Cooperia, Nematodirus, Bunostomum, Strongyloides, Chabertia, Capillaria, Oesophagostomum and Trichuris. The same or closely related parasites in cattle and goats also respond to this anthelmintic. This chemical may be administered via drench or bolus. The latter has proven to give the best results in experimental trials.

Dipterex (Neguvon) has also shown a

* Saltrazine—Hardy Salt Company, St. Louis, Missouri.

* Thiabendazole—Merck, Sharp and Dohme, Rahway, New Jersey.

TABLE I

TRADENAME	SYNONYM	COMPANY	ANIMAL	INDICATION
Equizole	Thiabendazole	Merck, Sharp & Dohme	Horse	Strongyles (large and small)
Thibenzole	Thiabendazole		Ruminants	Trichostrogyles Haemonchus Ostertagia Cooperia Trichuris Strongyloides
Dyrex	Neguvon Dipterex Dylox Dichlorphon Bayer L13/59	Ft. Dodge (Chemagro)	Horse	Ascarids Bots Strongyles (large and small) *Oxyuris equi*
	Neguvon	Chemagro	Ruminants	Haemonchus Oesophagostomum Trichostrongyles Trichuris
	Phenothiazine		Horse	Strongyles (small) *Trichostrongylus axei* Haemonchus
			Ruminants	Bunostomum Oesophagostomum Trichostrongylus Ostertagia Nematodirus
	Piperazine		Horse	Ascarids *Oxyuris equi*
			Swine	Ascarids Oesophagostomum
			Cattle	Ascarids
	Carbon disulfide		Horse	Bots Habronema
	Hexachlorethane-bentonite		Ruminants	Flukes *Haemonchus contortus*
Ruelene		Dow Chemical Co.	Sheep	*Oestrus ovis* larva Haemonchus Ostertagia Trichostrongylus
	Cadmium Salts		Swine	Ascarids
	Fluoride Sodium		Swine	Ascarids Stomach Worms
Promintic	Methyridine	Imperial Chemical Industries, Ltd.	Ruminants	Ostertagia Trichostrongylus Cooperia Nematodirus Trichuris
Hygromix	Hygromycin	Eli Lilly Co.	Swine	Ascarids Strongyloides Trichuris Lungworms
			Sheep	Fringed tapeworm

high degree of efficacy in sheep and cattle for the following species: Trichuris, Trichostrongylus, Haemonchus, Oesophagostomum, and to a lesser extent Nematodirus. This compound is considerably more toxic to cattle and sheep than thiabendazole as demonstrated by its narrow therapeutic ratio. This is so-called systemic insecticide in additon to its anthelmintic properties. It may be administered intramuscularly or orally.

It would appear that a program combining either thiabendazole or dipterex at various intervals with the continual low level feeding of phenothiazine could result in an excellent control program in cattle and sheep.

Another organic phosphate which is known primarily for its effects as a systemic insecticide is Ruelene.* In experimental trials it has proven to be very effective against the *Oestrus ovis* larvae (all stages) in sheep. It may be administered as a drench, bolus or in the feed. It is quite safe, and it has some effect in lowering the number of Haemonchus, Ostertagia, and Trichostrongylus.

Copper sulfate at one time enjoyed widespread popularity as an anthelmintic in sheep. This compound has been replaced by the much more efficient chemicals mentioned above and its use cannot be justified today, except for its action in closing the esophageal groove in this species.

Hexachlorethane—bentonite suspension is the drug of choice for liver fluke infection of sheep and cattle. It is only effective against the adult fluke. It has also been highly effective against the large stomach worm of sheep, *Haemonchus contortus*. It is ineffective against other parasites except rumen flukes. It, like all the hydrocarbons, may cause destruction of cells of the liver. Animals should be in relatively good condition when using this chemical. Fasting is specifically contraindicated.

Swine

The treatment of swine ascarids with chemicals was one of the earliest examples of parasite control in domestic animals which had widespread usage. Probably more chemicals have been used for this purpose than for any other helminth problem. Many of the older methods would still be effective today, but the newer methods are generally less toxic and more effective. Only those which are still used today will be discussed.

Two chemicals which still may be used but are for all practical purposes obsolete are oil of chenopodium and santonin. Both of these drugs are highly irritating, not only to the parasite, but also to the digestive tract. In addition, they may be absorbed to a great enough degree to cause central nervous system symptoms of depression or excitement.

Another drug which is highly effective for removing ascarids is cadmium. This drug is also being replaced by newer anthelmintics. Several salts of cadmium are available. All of them have the same drawback, *i.e.*, cadmium is deposited in the tissues. It must not be used more than once in the life time of the pig and it must be more than thirty days before they are slaughtered. In addition to these disadvantages, it is administered over a period of days, it causes a mild to severe gastroenteritis, and it may cause severe anemia. Its toxic effects cannot be reversed by any antidote.

Hygromycin* is an antibiotic which has been shown to have a broad spectrum prophylactic action on helminths of swine. It is the only antibiotic which has been shown to be of economical value in the control of parasites in mammals. This compound is only for prophylactic purposes. Its use must be started early and continued up to a certain point in the life of the pig, preferably until they reach 100 to 110 pounds. It is effective against ascarids, Strongyloides, lungworms and Trichuris. Its main action is probably in sterilization of the female. It will kill some of the parasites too, but does not qualify as a drug for treatment purposes. It is administered in the feed. It has one serious drawback, in that it may cause

* Dow Chemical Company, Midland, Michigan.

* Hygromix—Eli Lilly and Company, Indianapolis, Indiana.

deafness. This is of little significance in feeder pigs, but can be very serious in gilts and sows.

The two drugs which are probably most preferred today are sodium fluoride and piperazine. Both of these chemicals are effective mainly against the ascarid.

Sodium fluoride is inexpensive. It is administered in the feed at a 1 per cent concentration for a 24 hour period; the swine must not have access to any other feed. It must be administered only in dry feed and should be reduced to about one-third of what the drove would normally consume because it is quite unpalatable.

Its main disadvantages, then, are its extreme toxicity if too much is consumed; the fact that it must be administered in dry feed; and the problems involved with its administration.

Piperazine is considerably more expensive than sodium fluoride, but still well within reason. It is extremely non-toxic and nearly 100 per cent effective against ascarids, both immature and mature which are in the intestines. It is also fairly effective against nodular worms in swine. In addition, it is water soluble and as such can be administered in water as well as feed.

Its main disadvantages are its unpalatability and the fact that a complete therapeutic dose must be administered within a short time if it is to be effective. Therefore, the feed or water should be removed 12 to 18 hours prior to administration. This is probably the anthelmintic of choice for swine today.

Other New Anthelmintics Which May Soon Be Marketed

A few other chemicals have had some preliminary trials and have looked promising as anthelmintics. The majority of them are the systemic insecticides. Among the ones showing most promise are Trolene* (Dow-ET-57) in cattle and sheep; Dimethoate† for use against the Gastrophilus spp.; and Co-ral (Coumaphos)‡ having some activity against gastrointestinal parasites of cattle and sheep. Another group of compounds which are quaternary ammonium derivatives has shown anthelmintic activity in small and large animals. The most promising one of these for use in cattle is bephenium hydroxynaphthoate (Franten)*. However, there have been some problems with toxicity.

A new compound recently introduced in England which has shown outstanding activity against a broad spectrum of gastrointestinal parasites of sheep and cattle is Methyridine (Promintic)†. This chemical be administered orally or subcutaneously and has shown a remarkable margin of safety although it may cause local irritation at the site of injection.

It must be pointed out that no program of parasite control can ignore the basic principles of disease prevention. The preceding table is a summary of the chemicals discussed.

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