REVIEW ARTICLE

THE APPLICATION OF SOME ANTHELMINTICS IN VETERINARY PRACTICE

By R. B. Griffiths, B.V.Sc., M.R.C.V.S.

From the Department of Entomology and Parasitology, Liverpool School of Tropical Medicine, and the Faculty of Veterinary Science, University of Liverpool

Helminthological Considerations

A comparison of the comprehensive account of the use of anthelmintics in veterinary practice by Chopra and Chandler[1] with the recent review of present-day treatments of parasitic infections by Foster,[2] illustrates that the past 25 years have witnessed some remarkable advances in the chemotherapy of the diseases of animals caused by helminths. Progress has been made in several directions which include not only the development of new anthelmintic drugs, but also advances in their application in the light of advancing knowledge of the epizootiology of some of the more important parasitic diseases.

Anthelmintics in veterinary practice are used in two important ways; namely, as adjuncts to the control of parasitic disease, and as curative agents when prophylaxis has not been practised or when it has failed. At the outset, however, it must be realised that anthelmintics do not represent the complete answer to the control of helminths of stock. They have their limitations, and though a few drugs are effective against the immature stages of some worms, most fail in this respect especially against larval stages which migrate within the body. Such a limitation is serious in the many cases where immature forms are more important pathogens than the sexually mature adults. Moreover, few anthelmintics are 100 per cent. efficient even against adult helminths. For many reasons, therefore, it will be clear that the aim in control should be to prevent infection by a combination of several methods. In the case of the important strongyloid nematode infections, emphasis must be placed on measures to reduce the chances of acquisition by the grazing host of the infective stages of the parasite through improvements in animal husbandry and grassland management. We must recognise, however, that with these parasites, the host rather than the pasture is the reservoir of infection and anthelmintics have a very important part to play in control, since their rational use represents an attack on the contamination phase of the life-cycle[3]. As prophylactic agents, therefore, the principle of anthelmintic usage comprises the elimination of significant burdens of harmful parasites and the prevention of their further accumulation to clinical or even sub-clinical levels. One method by which this may be achieved consists in the periodical dosing of animals constantly exposed to infection. In this way gross contamination of the grazing by helminth eggs and larvæ, which under present-day conditions of intensive stocking might otherwise lead to epizootics of severe disease, is avoided and susceptible young stock are thereby protected.

It is appropriate to refer at this stage to an entirely new method for the control of many of the important strongyloid nematodes of stock which has been developed within the last 10 years or so consequent upon the introduction of phenothiazine. Early in the development of the use of the drug, Shorb and Habermann[4] showed that although small sub-therapeutic doses of the drug in sheep had no immediate lethal effect on adult susceptible worms, they caused marked suppression of egg-laying by the female helminths and the few eggs that were produced were rendered non-viable. Taylor and Sanderson[5] also recorded inhibition of development of trichostrongylid eggs excreted by goats receiving small doses of phenothiazine. These observations opened a new field for prophylaxis because it became clear that if low-level administration could be made a continuous routine, without toxic effects, a very marked reduction in pasture contamination could be effected, and young susceptible animals grazing along with older stock could be given a considerable degree of protection. This method of administration has now been developed as a practical procedure for certain species of hosts. For example, where sheep have a sufficiently high salt requirement the administration of phenothiazine and salt mixtures, fed continuously, is widely practised in some countries in the control of certain strongyloid nematode infections. This principle of prophylaxis has also been developed for horses, in which the daily administration of small doses of phenothiazine causes a reduction to very low levels in the egg output of strongylid worms. This phenomenon, together with the failure of excreted eggs to develop into infective larvæ, has resulted in such a degree of protection for foals running with mares that it is now practically possible to rear these young animals nearly or completely worm-free as far as the strongylid worms are concerned.

So far, our discussion on anthelmintic usage in prophylaxis has been concerned with the strongyloid nematode infections of grazing animals, but it will be appreciated that in the remaining many and varied helminthiases the principles involved in control will vary considerably, and no hard and fast rules can be laid down since the epizootiological factors involved are not constant for all the parasites concerned. Limitation of space does not permit a detailed account of these manifold considerations, but one further example might be taken in order to outline some general principles. In selecting *Fasciola hepatica*, a very important parasite in ruminants, our purpose is to stress that reliance on anthelmintics alone can be regarded as no more than a contributory factor in the fundamental problem of control of fascioliasis. The helminth concerned is mollusc-transmitted and clearly the aim must be to prevent infection, preferably by eliminating the vector. But as long as snails abound, routine anthelmintic treatment will continue to provide a very valuable means of reducng the losses from chronic fascioliasis and, by eliminating the parasites from infected animals, such a routine will reduce pasture contamination with the eggs of the parasite. It must be recognised, however, that anthelmintics against *F. hepatica* have their limitations. In some areas the drugs prove too toxic for general use. Moreover, in epizootic years, when the snail populations increase markedly there is the possibility of severe losses from

acute fascioliasis caused by the mass migration of immature flukes through the liver substance. The known therapeutic agents are generally considered to be of little value against these immature forms. It will be clear that an attack upon the snail intermediate hosts, wherever possible, is a primary necessity in effecting a reduction in the incidence of fascioliasis. Effective molluscicidal development and application must accompany advances in chemotherapy.

The Administration of Anthelmintics

It is not possible within the scope of this review to discuss the administration of anthelmintics in detail, because the numerous species of animals involved have their own special requirements for particular drugs. The ruminants, however, do merit special attention in this respect since research during the past 20 years on the œsophageal groove reflex has constituted one of the important advances in anthelmintic development, particularly in sheep. It is well known that some anthelmintics, for example, carbon tetrachloride, phenothiazine, hexachlorethane and lead arsenate are effective no matter whether they are swallowed into the rumen or into the abomasum, but others, which include tetrachlorethylene, copper sulphate, soluble arsenical compounds and nicotine sulphate, are ineffective if swallowed into the rumen, and must be swallowed directly into the abomasum; an effect which can only be achieved by closure of the œsophageal groove. It follows, therefore, that closure of the groove by stimulating substances administered before, or in some cases together with, the anthelmintic agent increases the activity of the latter against worms in the abomasum and small intestine.

A considerable amount of research has been carried out in sheep. It is now well known that the oral administration of an aqueous solution of copper sulphate and certain other copper salts will stimulate closure of the groove in a high percentage of these animals, but it is important to recognise that this does not occur in all cases, and some instances of failure of anthelmintics known to be effective when swallowed directly into the abomasum are attributable to this fact[6].

Roberts[7] has discussed the position in cattle. Here there is a pressing need to test critically anthelmintics other than phenothiazine which, though effective against some helminths of cattle such as *Hæmonchus contortus*, *Œsophagostomum radiatum* and to some extent *Ostertagia ostertagi* and *Trichostrongylus axei*, leaves much to be desired in the treatment of certain other nematodes, such as *Cooperia* spp. and *Bunostomum phlebotomum*. But tests with anthelmintics, other than phenothiazine, in cattle have been impeded by a lack of knowledge concerning the stimuli causing closure of the groove in these animals. Copper sulphate, in contrast to its efficacy in sheep, has little effect on the bovine œsophageal groove. As long ago as 1930, however, Wester[8] showed that closure of the groove could be induced by the administration of various sodium salts including sodium bicarbonate. Riek[9] recently confirmed this observation and found that 60 ml. of a 10 per cent. aqueous solution of sodium bicarbonate was effective in closing the groove of

93 per cent. of 110 animals used. These developments should now enable critical tests to be made on those anthelmintics which are effective only when swallowed into the abomasum.

Anthelmintic Substances

The review which follows concerns some of the more important anthelmintics in current use in veterinary practice. In order to limit the extent of the article, particular reference will be made to the more recently introduced drugs. Reference to many of the older preparations must needs be omitted and, therefore, certain well-tried anthelmintics whose properties are well known are not discussed. These include copper sulphate, copper sulphate-sodium arsenite and copper sulphate-arsenic pentoxide mixtures used in the treatment of ovine hæmonchosis; copper sulphate-nicotine sulphate mixtures which are effective against *H. contortus* and, to a lesser extent, against *Ostertagia* and *Trichostrongylus* spp. and possibly against *Nematodirus* spp. and *Moniezia* infections in sheep; and sodium arsenite enemata against *Œ. columbianum*, the ovine nodular worm. Gordon[3 10] has given a concise account of the use of these anthelmintics in the control of sheep diseases. Copper sulphate and copper sulphate-nicotine mixtures are also used to a limited extent against trichostongylids in cattle, but further critical work is necessary to determine their efficacy in this host.

No detailed reference will be made to tetrachlorethylene, a drug which, if preceded by copper sulphate in order to close the œsophageal groove, is of value against *H. contortus*, *B. trigonocephalum*, and fairly effective against *Ostertagia* spp. and *Trichostrongylus* spp. in sheep. The efficacy of this drug against related helminth species in cattle requires further investigation. Tetrachlorethylene finds a wide use in the treatment of dogs and cats suffering from ascarid and hookworm infections against which it is highly efficient. Carbon tetrachloride, which is a highly effective agent against *Fasciola hepatica* in sheep, and also of value against *Ascaridia* in fowls, *Amidostomum* in geese and, to some extent, in the treatment of equine strongylidosis, has also been omitted.

Certain useful agents against ascarids, such as oil of chenopodium and carbon disulphide, are so well known that detailed discussion is unnecessary. Oil of chenopodium is still widely used against ascarids in pigs and, to a lesser extent, against roundworms in dogs, but for the latter hosts more satisfactory drugs are now available. Carbon disulphide, though possessing several disadvantages, remains the drug of choice for the control of ascariasis in horses and for the treatment of gastric myiasis caused by *Gastrophilus* larvæ.

Some reference will be made to diethylcarbamazine as an anthelmintic against ascarids in dogs and cats, but the filaricidal properties of this drug are not discussed in detail. Certain other agents used in canine filariasis including antimonials and arsenamide are beyond the scope of this article. Useful recent reviews on the use of these drugs in the treatment of *Dirofilaria immitis* infection of dogs have been prepared by Otto and Maren[11] and Otto[12].

As regards the treatment of cestode infections many of the older anthelmintics are now obsolete and they have been omitted. For example, extract of male fern is rarely used nowadays for dogs, its place being taken by more effective agents.. In the pages which follow, reference will be made to some of these newer preparations, but the arecoline-acetarsol compounds are not discussed because their high efficiency is well known and widely recognised.

PHENOTHIAZINE

Undoubtedly the most important development in anthelmintics has been the introduction of phenothiazine. This drug, first used in 1934[13] as an insecticide, was recognised in 1938 to have marked anthelmintic properties[14], and since then it has been investigated extensively and employed widely in the treatment and control of infections of animals with several species of nematodes. The literature on phenothiazine has become so extensive that it is beyond the scope of the present article to attempt to cover the whole of it. But several important reviews of the uses and properties of phenothiazine have appeared within the last 12 years[15,16], the most recent being that of Harwood[17].

Pharmacology and Toxicology. The fate of the drug in the vertebrate body has attracted considerable attention for several reasons. It is well known that phenothiazine is relatively costly to use, the dosage required is bulky and the preparation is therefore somewhat inconvenient to administer. With a view to reducing the cost and the bulk of the drug necessary to achieve success, attempts have been made to determine whether phenothiazine itself or some derivative of phenothiazine is necessary for anthelmintic activity, but the evidence still points to the former as the active agent. Another reason for research into the pharmacology of this drug is related to one of the earliest recognised effects of phenothiazine in the animal body, namely the red discolouration which appears when the urine and milk of treated animals are exposed to air. It is now well known that colourless leuco compounds (oxidation products of absorbed phenothiazine) are excreted in the urine, becoming converted into red dyes on exposure to the atmosphere. When phenothiazine is spilled on the coat or fleece of animals during administration a similar effect occurs, because phenothiazine undergoes oxidation readily, even outside the animal body, especially when moist. These constitute minor disadvantages of the drug. Research on oxidation products has been further stimulated by the recognition of a photosensitised keratitis which appears in some animals, especially in young cattle, when exposed to sunlight following treatment. This phenomenon can now be explained and reference will be made to it later. In general, phenothiazine is a well-tolerated drug, but toxic effects are occasionally seen, especially in horses and cattle, and this has led to considerable investigations on toxicology, but despite much research there are still many gaps in our knowledge.

The fate of the drug has been studied in several species of animals. Although the details of its metabolism show a variation between species,

it appears that when phenothiazine is administered by mouth some of it is absorbed as such from the alimentary tract (though in ruminants some of it may also be absorbed as oxidised derivatives), and the rest is eliminated with the fæces. The amount of phenothiazine which remains unabsorbed is a very important factor as regards anthelmintic activity. Davey and Innes[15] consider that there is little evidence that a derivative of phenothiazine is the anthelmintic. They believe that phenothiazine itself is the essential substance, and suggest that particles of the drug are taken in through the mouth of the nematode, so that for the dose to be effective a certain concentration of particles of phenothiazine has to be attained in the alimentary content. In support of this they express the view that the pronounced anthelmintic activity of the drug against helminths in the abomasum and large intestine of ruminants, as compared with the lower efficiency against worms in the small intestine, is related to the speed of passage of the drug through the alimentary tract. In connection with the uptake of the drug by the parasite they state that phenothiazine will not penetrate the cuticle, but Lazarus and Rogers[18,19] have investigated the mode of action of phenothiazine as an anthelmintic by using the drug labelled with Sulphur-35. They have shown that phenothiazine can enter the nematode through the cuticle and suggest that this may be the important route of entry. Using *Ascaridia galli*, the large roundworm of the fowl, they demonstrated that the uptake of phenothiazine by the worm was more rapid and much greater than that by the adjacent mucosa of the host's gut, a result which appears to indicate differential selection of the drug by the parasite. As regards the active agent, Harpur *et al.*[20] believe that the anthelmintic activity of the drug is attributable to the unabsorbed, but not necessarily unaltered fraction of the drug, and Esserman[21] concluded that phenothiazine and not its oxidation derivatives is the anthelmintic.

In sheep, Swales and Collier[22] found that roughly equal parts of the drug are excreted in the fæces and lost in the urine, about 40 per cent. being excreted through the kidneys. But the proportion of phenothiazine absorbed from the alimentary tract in relation to the quantity excreted in the fæces varies widely in individuals and in different animal species. It has been suggested that the rate of absorption of phenothiazine is influenced by the particle size of the drug. Collier *et al.*[23] showed that the micronised form is absorbed more readily than the ordinary commercial phenothiazine. On the other hand, Harpur *et al.*[20] found that increasing the particle size does not necessarily cause any decrease in the amount of phenothiazine which is absorbed. It should be pointed out that it is not yet clear what particle size will give most anthelmintic efficiency. It has been suggested that increasing the particle size may decrease the efficacy of the drug, but Guthrie and Harwood[24] found no difference in efficacy between micronised and coarsely ground phenothiazine against *Heterakis* and *Ascaridia* in chickens. It has also been shown that recent increases in particle size in commercial phenothiazine has not reduced the anthelmintic efficiency of the drug against *T. axei* in sheep[25].

Within recent years most work on the metabolism of phenothiazine after absorption has been carried out in ruminants, and although the position is still somewhat confused the recent work of Harpur *et al.*[20,26] has helped to clarify the situation. According to these investigations, the fate of phenothiazine in sheep is as follows. It was found that the drug is absorbed as such and is normally not oxidised to phenothiazone in the rumen of sheep, a finding in contrast to that of Swales and Collier[22] and Collier *et al.*[23], who came to the conclusion that phenothiazine undergoes rapid oxidation in the rumen to phenothiazone which allows increased solubility, ready absorption and rapid appearance of oxidation derivatives in the blood and urine of the treated animal. On the other hand, Clare[27] found phenothiazine sulphoxide in the rumen of sheep and cattle, but Harpur *et al.*[26] commenting on this finding, state that it seems possible that the extent of oxidation in the rumen is variable, and suggest that phenothiazine in the rumen content may undergo oxidation if it comes in contact with air in the presence of alkaline saliva during rumination. They believed that this would explain the occurrence of phenothiazine sulphoxide in the rumen.

After absorption much of the phenothiazine undergoes oxidation within the body, the derivatives being excreted mainly in the urine and bile, and to some extent in the milk of lactating animals. Clare and his colleagues[27,28], working in New Zealand, have been particularly interested in the oxidation products of phenothiazine within the body of cattle, especially since photosensitised keratitis is apt to occur under certain conditions particularly in young cattle[29]. Their results, summarised by Whitten[30], show that in cattle and sheep phenothiazine sulphoxide, which they regard as a common oxidation product of phenothiazine in the alimentary tract, is absorbed and carried by the portal blood to the liver, where it is normally converted into leucophenothiazone; this derivative is then excreted in the bile and urine. In young calves, the liver may fail to convert all of the sulphoxide; excess passes into the systemic circulation and some reaches the aqueous humour of the eye. Phenothiazine sulphoxide is the only known derivative of phenothiazine which is excreted in the lachrymal fluid and constitutes the photosensitising agent. Keratitis may occur if the animal is exposed to direct sunlight 12 to 36 hours after dosing. Wavelengths of 320 to 360 mμ are the active ones. By keeping the animals indoors and protected from sunlight on the day following treatment this hazard can be avoided. In sheep, the conversion of absorbed phenothiazine sulphoxide is more efficient, and as the sulphoxide does not normally appear in the systemic circulation, keratitis is not usually seen after treatment except possibly following the use of very large doses, but Gordon and Green[31] have reported photosensitisation in lambs in Tasmania after 15 g. doses; their cases showed skin lesions on the muzzle and ears as well as keratitis in some animals. Enzie and Whitmore[32] have described photosensitised keratitis in goats after normal therapeutic doses, and photosensitisation of the skin and cornea have been reported on several occasions in pigs. Clare[33] has given a succinct account of these phenomena.

As has been indicated, considerable attention has been given to the oxidation derivatives which appear in the urine, and Harwood[17] has given a summary of the present status of knowledge. In addition to phenothiazine itself, the products which appear in the urine vary in composition and relative proportion in different animal species, but as already indicated the colourless leuco compounds, leucophenothiazone and leucothionol, free or conjugated, are excreted. On exposure to the air these form the fast red dyes, phenothiazone and thionol. Coloured derivatives of phenothiazine also occur in the milk of lactating animals after treatment. Although they have not been investigated very extensively, they do not appear to be harmful when ingested along with milk; however, they render the milk æsthetically undesirable for man, and in view of the variation in susceptibility of man to phenothiazine, such milk should not be used for human consumption[34]. It may be used for stock feeding, however, as long as colouration persists. In addition to excretion in the urine and milk, oxidation products of phenothiazine are also excreted in the bile and derivatives have been identified in several animal species.

As regards the possible harmful effects of phenothiazine on the treated animal we have already stated that the drug is generally well-tolerated, but in some species there are toxic hazards and sometimes there is individual susceptibility even within an animal species. Davey and Innes[15], in their review, have considered toxicity at length because, as they remark, it is this factor which determines whether the substance can be regarded as a good anthelmintic. Harwood[17] cites many references to reports of toxicity in mammals. Having regard to the widespread use of phenothiazine in veterinary medicine, however, toxic effects, apart from photosensitised keratitis, have been observed on comparatively few occasions. Nevertheless, the occasional occurrence of poisoning, especially in horses and cattle, cannot be disregarded and care must be exercised in the treatment of debilitated and anæmic animals. Edwards[16] has suggested that it would be prudent also to refrain from administering phenothiazine to very young animals.

It is pertinent to consider the reactions of the various animals to the toxic effects of phenothiazine. Since the introduction of the drug large numbers of horses have been treated and, as long as the dose is kept low, toxic effects are not often seen. Nevertheless, intoxication in the form of marked hæmolytic anæmia has been reported several times, usually after large doses, but even standard therapeutic doses have on occasion produced toxic effects.

The cause of hæmolytic anæmia has not been fully explained but Harwood[17] believes that the lysolecithin theory of Collier and Allen[35] merits further study. These workers have shown that phenothiazine and some of its oxidation derivatives have no direct action on red cells, but *in vitro* they accelerate the lysis of horse erythrocytes by lysolecithin, a normal constituent of horse blood.

Cases of marked hæmolytic anæmia have also been recorded from some individual human beings, cattle and dogs following phenothiazine therapy. As phenothiazine is considered now to be too toxic for use in man and

there are no indications for its application in the treatment of dogs, we need only consider cattle. The toxicity of the drug for cattle is well recognised, but it is generally considered that provided a dosage rate of 0·2 g./lb. of body weight up to a maximum of 60 to 80 g. is not exceeded, toxic systemic effects should be minimal. This observation does not apply to the rather frequent occurrence in some countries, such as Australia and New Zealand, of photosensitised keratitis in calves to which reference has already been made.

Contrary to the position in cattle, sheep are highly resistant to intoxication by phenothiazine. Though Behrens[36] has recorded a reduction in the erythrocyte count and a decrease in hæmoglobin following the administration of phenothiazine, it is generally agreed that hæmolytic anæmia is not observed in sheep following treatment. The only important reservation with regard to sheep concerns its use in late pregnancy. As there are a few records of abortion in ewes following treatment administered during the last month of gestation, it is usually considered advisable that treatment of such animals should be avoided during that period. Goats appear to be nearly as resistant as sheep.

The use of phenothiazine in pigs has not revealed hæmolytic anæmia following treatment but young pigs do sometimes exhibit toxic effects in the form of ataxia and paralysis, although this is usually temporary. Edwards[16] considers that the drug has acquired an undeserved reputation for toxicity in pigs, probably because early experimental treatments were often made with excessive doses. He points out that very large numbers of pigs, infected with the nodular worm, *Œ. dentatum*, have been treated in America with few instances of poisoning.

Birds tolerate phenothiazine very well indeed, and there are few references to toxic effects, but it is interesting to note that Clapham[37] records reduced growth rates in pheasants kept continuously on mash containing 4 per cent. of phenothiazine, and keratitis occurred if the birds were exposed to sunlight.

Anthelmintic uses of phenothiazine: Harwood[17], whose excellent review has been of material help in preparing this section, describes the effectiveness of phenothiazine by taking the helminth parasites in systematic order. This method will be followed here.

There is no reliable evidence that phenothiazine is of any value against helminth parasites belonging to the phylum platyhelminthes. Its usefulness lies in its activity against certain nematodes. It is not effective against *Strongyloides* nor is it effective against helminths belonging to the order Trichinelloidea, and there is not much evidence for activity in spiruroid or filarioid nematode infections.

The chief value of the drug lies in its efficacy against certain worms belonging to the order Ascaroidea and many nematodes in the order Strongyloidea.

Its efficiency against worms in the order Ascaroidea shows considerable variation. It is highly effective in eliminating *Heterakis gallinæ*, the cæcal worm, from chickens and turkeys. And since *H. gallinæ* is of great importance in the epizootiology of histomoniasis ("blackhead") of

turkeys, fowl and other birds, the protozoan parasite being transmitted in large measure from bird to bird through the eggs of the nematode, the use of phenothiazine as a measure of prophylaxis of blackhead by eliminating *Heterakis* has been advocated[15]. Reports are conflicting as to the value of this measure even though successful reduction of *Heterakis* can be achieved by frequently repeated treatment. Wehr and Olivier[38] showed that prolonged feeding of phenothiazine to birds did not control histomoniasis. Their work indicated that phenothiazine given to turkeys in a concentration of up to 2 per cent. in the mash, for 4 to 6 weeks, did not prevent the *Heterakis* infection, although it did result in the subsequent expulsion of the worms before or soon after they reached maturity. But this effect would be too late to afford protection against histomoniasis.

Against *A. galli*, the large roundworm of fowls, the action of phenothiazine is much less marked, but Harwood and Guthrie[39] have shown that in combination with nicotine-bentonite, a synergistic effect was produced which resulted in the removal of a very high percentage of *Ascaridia*. Similar results were obtained by Jaquette and Wehr[40], and Harwood and Stunz[41] found phenothiazine and nicotine-bentonite effective against *Ascaridia* and *Heterakis* in turkeys. Against oxyurids the drug is variable in action. Although it is effective against some of the oxyurids of rodents and against *Enterobius vermicularis* of man, it is not of much value in *Oxyuris equi* infection of horses. Phenothiazine has a limited value as far as the important roundworms in the family Ascaridæ are concerned, but this does not merit discussion since more effective anthelmintics are available for these infections.

The chief value of phenothiazine in veterinary practice lies in its efficacy against many of the strongyloid nematodes. In horses and other equidæ, phenothiazine has a marked anthelmintic value against worms belonging to the family Strongylidæ, helminths responsible for serious losses especially in young horses. Within this family the drug is very efficient in doses of 30 g. for adult horses, against *Trichonema* spp. and other small strongyles. Gibson[42] has shown that it is especially effective against the adult worms, but its efficacy against immature worms does not appear to be so high. He considers, however, that its efficiency against the large strongyles (*Strongylus* spp.) is low. In the early days of work on phenothiazine the drug was thought to have a marked anthelmintic value against these large strongyles, but Gibson's work and the studies of Poynter[43] appear to indicate that the conclusions of earlier workers were sometimes too optimistic; it seems that a very large dose may be highly efficient but there is a danger of toxicity. Nevertheless, standard therapeutic doses of phenothiazine have some anthelmintic value against the adult worms belonging to this genus and, at present, phenothiazine probably represents the drug of choice, although it has been suggested that glycarsamide may have a high therapeutic value,[44] but further investigation is necessary.

The use of periodical full therapeutic doses of phenothiazine given 2 or 3 times a year remains the current method of control of strongyle worms of horses in many countries. It is generally recognised as being imperfect,

however, largely because it does not eliminate infection entirely, and in the intervals between treatments, eggs are produced by those helminths which have escaped anthelmintic action; infective larvæ are produced on the pasture, and when susceptible horses ingest these the developing forms of some species undergo their usual body migration where they may cause serious lesions. Successful control should aim at preventing damage by larvæ. This can only be achieved by grazing clean pastures, but until recently it has been difficult to apply this concept in practice. During the past few years much attention has been given to prophylaxis by means of continuous low level phenothiazine administration, the principle being to reduce pasture contamination by depression of egg production by the worms in the host and inhibition of larval development of any excreted eggs. Foster and Habermann[45] gave 5 g. of phenothiazine weekly in the feed of horses and noted a reduction in the egg-production of strongyle worms. Todd[46] in America has summarised his work in the further development of this method which involves the daily administration of small doses. He describes its practical applications and recommends the administration of 2 g. doses of phenothiazine daily for the first 21 days of each month. There are several reports in the literature which confirm the results of this method, but in adopting this regimen fears have arisen that long-continued dosage might have adverse effect on the horse through a possible cumulative action of the drug. This has not been substantiated[47]. Another doubt arose concerning the possible development of phenothiazine-resistant strains of helminths through continued sub-therapeutic dosage, but there is no evidence that this occurs. A warning has been sounded, however, by Gibson[48] that the production of near worm-free foals, such as this method allows, may not be entirely desirable since such an animal if exposed to heavy infection, when older, may suffer severely from strongylidosis, as a result of its having been deprived of an earlier opportunity to acquire a degree of infection which would stimulate resistance. This hypothesis depends, of course, upon the assumption that resistance against helminths is dependent not only upon age but also upon previous infection.

It is often questioned if prolonged low level administration will eliminate the worms themselves from existing infections in horses. Todd[46] believes that they are gradually eliminated over a period of time, but Drudge *et al.*[49], following upon a long-term study, came to the conclusion that the method was relatively ineffective in removing strongyles from the intestinal tract; moreover, it was relatively ineffective in preventing the development of worms from ingested infective larvæ. The important effect of low level administration lies in the sterilising action on the female worm, the inhibition of development of excreted eggs, and the consequent reduction in pasture contamination.

Phenothiazine has a marked action on certain other helminths in the family Strongylidæ. It is highly effective against the œsophagostomes in all animal hosts, regardless of species, and it has proved a most valuable anthelmintic in the treatment of nodular worm, *Œ. columbianum*, in sheep, a serious condition and the cause of severe losses in some countries. Its

value against the large-mouthed bowel worm, *Chabertia ovina*, is not clear and reports are conflicting. The drug is of no value in the treatment of *Stephanurus dentatus* infection, the kidney worm of pigs, but Threlkeld and Johnson[50] have suggested the possibility of using phenothiazine to control *Stephanurus* by scattering the drug on infected fæces to prevent the development of the larvæ. Against *Syngamus* in birds, therapeutic treatment with phenothiazine given orally to rid the birds of adult worms has not been successful, but Clapham[37] has obtained successful prophylaxis in pheasants by feeding 4 per cent. of phenothiazine in mash continuously which ensures destruction of the infective larvæ before they migrate from the alimentary canal.

The hookworms (family Ancylostomidæ) are not, in general, successfully controlled by phenothiazine with the exception of *B. trigonocephalum* in sheep, in which a high percentage of the worms can be removed by appropriate dosage. Results in the treatment of hookworm of cattle, *B. phlebotomum*, are disappointing. Recent work by Riek[51] indicates that phenothiazine given to calves at dose rates of 0·1 to 0·3 g./lb. of body weight failed to show any marked efficiency against this species. Some slight efficiency was recorded with 0·2 g./lb. of body weight, but it is of interest that an increase to 0·3 g./lb. of body weight was not more efficient against this worm. A possible use for phenothiazine in controlling *Bunostomum* in cattle has been suggested by the work of Mayhew[52] who has shown that, although the daily administration of small doses of 1·5 g. of phenothiazine in the grain ration did not affect egg production, it prevented the development of infective larvæ in the fæces; in this way some degree of control may be expected but more data are necessary.

In addition to its value in strongylidosis of equines and œsophagostomiasis in ruminants, phenothiazine represents the drug of choice for the treatment and control of many of the trichostrongylid infections in ruminants.

We will consider firstly the value of full therapeutic doses. In sheep, phenothiazine has a very high value as an anthelmintic but, with the exception of *H. contortus*, is effective largely against adult worms. *H. contortus* is very susceptible, and doses from 6 to 10 g. give nearly 100 per cent. efficiency[53]. The drug is effective against both the mature and the immature worms, which represents a marked superiority over other agents. Against *Ostertagia* the drug is not so efficient but doses of 20 g. have been recorded as eliminating 90 per cent. of the worms. Further work is necessary, however, to determine the anthelmintic efficacy of phenothiazine against this genus. *T. axei*, the smallest of the trichostrongylid worms in the abomasum of ruminants, is more resistant than *Hæmonchus*, but Gibson[54] has shown that doses of 20 g. will give 96 per cent. efficiency against the worms, and 40 g. doses give 100 per cent. efficiency. The drug has a variable efficiency against trichostrongylids in the small intestine. It is practically inefficient against *Nematodirus* spp. but efficiency can be obtained against *Trichostrongylus* spp. and *Cooperia* spp. provided that full doses of up to 40 g. are given to adult sheep[54]. It has been suggested that the failure of phenothiazine in some outbreaks of trichostrongylosis

is possibly due to development of phenothiazine resistance by the worms, but this has not been substantiated. Sinclair[56] was unable to produce it experimentally in *T. colubriformis* infections in sheep. He emphasises that the customary dose of 20 g. is too low. Gibson[54] has suggested that the true explanation of so-called resistance lies in failure to administer sufficiently large doses.

In goats phenothiazine has proved to be a useful anthelmintic, but Harwood[17] has pointed out that, because these animals seem to be favourable hosts for the intestinal species of *Trichostrongylus*, large therapeutic doses up to 37·5 g. should be used.

In cattle phenothiazine is useful against certain trichostrongylids, but its efficacy against some species in the bovine host, as compared with other ruminants, is of a comparatively low order. Riek[51] has provided a concise review of the literature on the value of the drug against nematodes in cattle. He finds that a dosage rate of 0·1 g./lb. of body weight is effective against *H. contortus* (and *Œ. radiatum*) but a dosage rate of 0·2 g./lb. of body weight is necessary for the removal of *Trichostrongylus* spp. The higher dose, however, has little effect against *Ostertagia* and is only slightly efficient against *Cooperia* spp. Cauthen[57] has also reviewed the literature with special reference to the use of phenothiazine against *O. ostertagi* and *T. axei*. Experimental work recorded by this author shows that doses of approximately 0·2 g. give about 75 per cent. efficiency against *O. ostertagi* and nearly 100 per cent. against *T. axei*. Most workers agree that the maximum dose which can be given reasonably safely consists of 0·2 g./lb. of body weight up to a maximum of 60 to 80 g. but even at this level, occasional toxic effects are noted in animals in poor condition. At this dosage rate, however, taking into consideration all the susceptible nematodes of cattle, it appears that a satisfactory degree of efficiency can be obtained against *H. contortus*, *T. axei* and *Œ. radiatum*, but its efficacy is low against *B. phlebotomum* and *Cooperia* spp. Further investigation is required to determine the value of phenothiazine in *Ostertagia* infections.

We have already referred to the development of phenothiazine and salt therapy for ruminants, and it is appropriate at this point to refer to this new concept in more detail.

Following on the demonstration of the value of small doses of phenothiazine in inhibiting larval development of certain strongyloid nematodes in the fæces of treated animals, Habermann and Shorb[58] developed the principle of low level continuous administration for sheep. They found that the daily ingestion of 0·5 g. per animal was necessary. The details of administration as recommended by various authors differ slightly, but most workers seem to be agreed that, early in spring, the animals should be treated with full therapeutic doses of the drug followed by the use of phenothiazine and salt mixtures at concentrations of 1:9 to 1:14 which are kept before the sheep at all times and protected from the weather. Continuous intake is necessary in order to ensure dependable prophylaxis. Successful results arise in part from the effect of phenothiazine in causing some reduction of egg output of worms present in the bowel (though with

some species this effect may be inconstant) but chiefly from the suppression of development of those eggs which are excreted in the fæces. If any evidence of failure appears full therapy must be instituted, and in any case a full treatment should be given in the early winter.

It has been suggested that third stage larvæ of trichostrongylid worms which are ingested during this method of prophylaxis fail to develop further within the host. But authorities differ and many believe that low level treatment does not necessarily prevent the establishment of infective larvæ within the host. Gibson[59] showed that when a daily dose of 1 g. of phenothiazine was given to lambs within a few minutes of a dose of infective *T. axei* larvæ, the treatment appeared to have some effect in reducing the number of larvæ which developed to maturity. When, however, there was an interval of several hours between the phenothiazine and the larvæ, the treatment had no effect on the establishment of the larvæ in the host. It did not prevent the development of parasitic gastritis in sheep continuously exposed to infection, when several hours elapsed between phenothiazine and larval administration. Gibson[59] suggests that the good results reported from the field must be due essentially to a reduction in the pasture larval count by phenothiazine inhibition of egg development in the fæces. Foster[60] has emphasised that the treatment must be started on the first day on which the sheep are turned onto spring pastures, at the beginning of the grazing season.

The actual worm burden of adult sheep does not appear to be much affected by low level administration, but opinions differ according to whether the method does actually reduce the burden of an infection which was in existence when the regime was started. Gibson[59] found that there was no significant reduction, but it is interesting to note that Page[61], working with lambs with pure infections of *H. contortus*, found that 0·5 g. of phenothiazine administered daily had a marked anthelmintic effect on lambs with heavy infection. It seems that there may be some species differences in this effect.

In Britain, Harbour *et al.*[62] and Pollard *et al.*[63] have reported the value of phenothiazine and salt mixtures in reducing pasture contamination, but the application of this method as a routine has not been adopted because the additional salt requirements of sheep in this country are too low to ensure the adequate ingestion of sufficient quantities of phenothiazine by this device. In America the method is widely used in the control of nodular worm and trichostrongylid infections. Foster[64] has given an account of an 11-year experiment in helminth control in a flock of sheep using this measure, and his results show that although helminths are not eradicated, they are adequately controlled and no clinical outbreaks occurred in his experimental animals except when the drug was withdrawn for a period of about 5 months. He found no evidence that phenothiazine-resistant strains developed.

Low-level administration of the drug has not yet been adopted as a routine procedure in cattle practice. Experimental evidence suggests promising results but its practical application needs further investigation. Much will depend on the status of the animals concerned in relation to

salt and mineral requirement before free-choice methods can be utilised. Foster[65] has reviewed recent experimental work with cattle.

HEXACHLORETHANE

This drug was investigated as long ago as 1925 when Hall and Cramm[66] tested it, without success, for anthelmintic activity against hookworms in dogs. It was first used in the treatment of fascioliasis in cattle in Germany by Thienel[67], and De Blieck and Baudet[68] and Hilz and Scheuble[69] also reported favourably on its efficacy. Its fasciolicidal properties were not widely recognised, however, until Olsen[70] carried out preliminary trials with the drug against *F. hepatica* in cattle in America. The results of more extensive trials by Olsen[71,72] established hexachlorethane as a relatively safe drug with a high degree of efficiency for the treatment of *F. hepatica* in cattle. This constitutes an important advance for it is well known that hitherto the treatment of fascioliasis in cattle had been very unsatisfactory. It is also recommended against *F. gigantica*[73].

Hexachlorethane is also used in fascioliasis of sheep[74], but its anthelmintic activity does not appear to be superior to that of carbon tetrachloride in this host unless the dose is increased from 15 g. to 30 g. for an adult sheep[75]. Southcott[76], however, found that the increased anthelmintic activity from the large dose was more than offset by the enhanced toxicity danger. In connection with the relative efficiency of these two drugs it is interesting to note that Chance and Mansour[77] who made a kymographic study of the action of certain drugs on the liver fluke, found that carbon tetrachloride and hexachlorethane at low concentrations acted as stimulants, but at high concentrations they were lethal to the worms, and hexachlorethane was believed to have a more pronounced effect than the other drugs tested. Hexachlorethane is also of value for the treatment of fascioliasis in goats[78].

In the ruminant the drug is absorbed from the bowel, passes by the portal blood to the liver, and is excreted in the bile where it exerts its effects on mature or nearly mature flukes. Kaplan and Sakellarious[79] claimed, however, that the drug is effective against immature flukes, but most workers believe that the drug is effective only against mature or nearly mature flukes in the bile ducts and immature migrating flukes are unaffected. But even against adult *F. hepatica*, there is a reservation about the efficacy of the drug. It is now well recognised that where marked cirrhosis exists, hexachlorethane may not be effective against flukes lying in grossly thickened bile ducts[78,80], excretion of the drug being inadequate through the damaged tissues so that some worms escape the anthelmintic effect. In general, though the toxicity of hexachlorethane appears to be low (Olsen[74], Lapage *et al.*[81] and Stauffer *et al.*[80] found hexachlorethane to be well tolerated) nevertheless, toxic manifestations do occur occasionally in ruminants, especially in those on a high protein diet. Intoxication is evidenced by incoordination of gait, drowziness and lack of appetite which generally passes off, but some deaths have been recorded. Southcott[76] reported toxicity in sheep after treatment with doses of 15 to 30 g.; some animals recovered after the parenteral

administration of calcium borogluconate, but there were some deaths amongst animals receiving 30 g. doses. It is interesting that his experimental sheep tolerated carbon tetrachloride without ill-effect. It would seem, therefore, that caution should be exercised before the mass treatment of animals is undertaken since herd idiosyncracies may exist. Care must also be taken when debilitated animals, particularly those with severe liver damage, are treated.

Hexachlorethane has also been investigated for activity against other helminths. Kaplan and Sakellarious[79] claimed that the drug was effective against *Dicrocoelium dendriticum* in sheep, but this does not appear to have been confirmed. Olsen[82] showed that hexachlorethane was effective against adult rumen flukes in cattle and sheep, but Gordon (unpublished) points out that the evaluation of hexachlorethane against immature *Paramphistomum* spp. in the duodenum of cattle is a pressing need, because this stage of the parasite is probably of much greater importance than the adult rumen-inhabiting worms.

Olsen[83] reviewed the literature on the use of hexachlorethane against the nematode parasites of cattle. The drug is useful in the treatment of *H. contortus* infection and, to a lesser extent, against *T. axei*, but it appears to be ineffective against *Ostertagia* spp. and *B. phlebotomum*. Roberts *et al.*[84] found the drug to be of little value in cattle against species of nematodes other than *H. contortus*. On the other hand, Daubney[85] removed nearly 100 per cent. of hookworms from a sheep with hexachlorethane. Olsen and Wade[86] investigated its efficacy against certain nematodes in sheep and goats, and found the drug to be highly effective against *H. contortus* but its efficiency was variable against *Ostertagia* spp. It was ineffective against intestinal trichostrongyles, nodular worms and whipworms. Kingsbury[87], however, has reported that the drug is of some value in the treatment of *Nematodirus* infections in lambs.

Sodium Fluoride

The introduction of sodium fluoride for the treatment of *Ascaris lumbricoides* infection of pigs[88] has simplied the anthelmintic treatment of these animals. It is highly effective, removing over 90 per cent. of ascarids and surpasses oil of chenopodium in efficiency[89]. The drug removes both mature and immature worms. It is also fairly effective against some of the stomach-worms of pigs, for example, *Ascarops* and *Physocephalus*; some reports also indicate therapeutic activity against *Hyostrongylus*[90].

Most authorities agree that the drug should be administered in dry ground feed, either as 1 per cent. of the amount of feed which the pig will consume in 1 day, or the dosage may be computed according to body weight at a dosage rate of 0·1 to 0·15 g. of sodium fluoride/lb. of body weight, this quantity being mixed with the amount of feed normally consumed by the pig in 1 day.

The recommendations as regards dosage usually apply to the commercial grade of sodium fluoride which is 73 per cent. pure[91]. Luke and Gordon[92] have drawn attention to possible dangers in using preparations

with a higher sodium fluoride content such as the technical grade which has a purity of about 98 per cent., and they suggest that some deaths which have occurred after treatment may have resulted from using the purer product at the standard dosage rate.

To ensure safety, the aim should be to allow the pigs to ingest small quantities of the medicated feed over the whole day, and by mixing the drug with dry feed, which is thereby rendered somewhat unpalatable, excessive ingestion is avoided. If, however, sodium fluoride is given to pigs under a wet feeding system, the toxic hazard of the drug is increased because wet medicated feed is more rapidly consumed. It is, therefore, important that the drug should be used only for pigs kept on a dry feeding system. With slight overdosage, pigs generally vomit and the danger of excessive intake is thereby lessened, but with gross overdosage a rapidly fatal hæmorrhagic gastro-enteritis follows. When sodium fluoride is used properly the drug is safe for pigs. It has a distinct advantage over other anthelmintics for these animals because it can be given in medicated feed as a mass treatment. The medicated feed should be supplied to pigs in batches of even size, and it is usual to recommend that not more than eight pigs be included in each group, but to avoid excessive consumption by any 1 or 2 pigs in a particular group it is advisable to limit the number to a maximum of 4.

When Habermann *et al.*[88] tested sodium fluoride against helminths in pigs they also investigated the use of the drug in certain other hosts, and evidence of activity against *Parascaris equorum* in horses was obtained. Critical tests with the drug in horses, made by Todd *et al.*[93] showed that a dose of 2·5 g./100 lb. of body weight, administered in aqueous solution, gave a very high degree of efficiency against mature and immature ascarids, over 99 per cent. of the worms being expelled from the small intestine. The drug was fairly well tolerated and although moderate to severe diarrhœa occurred in some of the animals within 48 hours after treatment, no deaths occurred and recovery soon followed treatment. The authors considered that the efficacy of the drug more than offset the temporary gastro-intestinal disturbance. Indeed, the moderate diarrhœa usually encountered was regarded as salutary in the prevention of possible absorption of toxic materials from disintegrating helminths. The drug surpasses carbon disulphide, the present drug of choice in horses, both in efficiency, since it is effective against immature worms in the gut as well as against sexually mature worms, and in the ease of administration because it can be given without preliminary starvation. It cannot be recommended for therapeutic purposes, however, until further investigations have been made concerning the occasional severe diarrhœa and hæmolytic changes in the blood which sometimes follow its use.

Toluene

This drug was previously tested in dogs by Hall and Wigdor[94] in a limited study. Later Enzie[95] examined the anthelmintic action of toluene together with certain halogen substitution products in the dog. He found that although toluene itself constituted a very effective agent

against ascarids and hookworms, the introduction of halogens usually resulted in a reduction of efficiency especially against hookworms. Enzie and Colglazier[96] recorded the results of more extensive trials and showed that toluene at a dosage rate of 0·1 ml./lb. of body weight after 18 to 24 hours fast was well-tolerated and highly effective against ascarids and hookworm in dogs. The drug proved to be equally effective against these worms in cats. Comparative studies showed that it compared very favourably in efficacy and safety with *n*-butyl chloride. Toluene, being easier to administer, may replace *n*-butyl chloride as an anthelmintic for dogs and cats. The drug is sometimes given together with the cestode anthelmintic, dichlorophen, in the form of a proprietary preparation[97,98].

Several studies have been carried out on the use of toluene against ascarids and *Gastrophilus* larvæ in horses[99,100,101]. Critical tests have shown that the drug is well-tolerated and a high degree of efficacy has been obtained against ascarids, but the results are not uniformly good against bot-fly larvæ. *G. intestinalis* appears to be eliminated more readily than some other species and successful results have been recorded by Graham and Alford[102].

Toluene as an anthelmintic for horses is still in the experimental stage and further work is necessary before it can be recommended for use in routine therapy. It would appear, however, that the drug promises to be a more suitable agent against ascarids than carbon disulphide, the present drug of choice, since it can be administered more readily and fasting of the animal, an important consideration in young stock, is not essential. Moreover, severe gastritis which sometimes occurs under carbon disulphide is not a feature of toluene therapy.

n-BUTYL CHLORIDE

This substance which is widely used in canine practice, especially in America, was examined critically together with other chlorinated alkyl hydrocarbons by Wright and Schaffer[103] who found it to be a very effective ascaricide, removing 98·7 per cent. of ascarids. The drug was 84·3 per cent. effective against hookworms, but its efficacy against whipworms averagered only 18·2 per cent. It was ineffective against tapeworms. The drug was well tolerated. Harwood *et al.*[104] confirmed the high efficiency of the drug against ascarids and hookworm, and reported an efficiency of about 52 per cent. against *Trichuris vulpis*, the whipworm of dogs.

A limited amount of investigation concerning its value in horses has been recorded. Harwood *et al.*[105] tested the drug on 3 horses and found that a dose of 0·1 ml./lb. of body weight removed up to 100 per cent. of small strongyles (cylicostomes), and between 74 and 100 per cent. of large strongyles. Trum[106] found that this dose effectively removed small strongyles and *Oxyuris equi* from one animal.

DIETHYLCARBAMAZINE

This piperazine compound has been extensively tested in the treatment if *Dirofilaria immitis* infection in the dog, in which it is highly effective against microfilariæ, but indifferently active against adult worms.[11]

It is highly effective, however, against ascarids of dogs and cats. Hewitt *et al.*[107] tested the drug against these infections in dogs, and found that single oral doses of 50 mg./kg. were nearly 100 per cent. effective; 2 oral doses of 25 mg./kg. within a 24 hour period removing 100 per cent. of the worms. It was also effective when administered intraperitoneally. The drug was ineffective against hookworms, whipworms and tapeworms. Fasting before treatment and purgation after treatment were unnecessary and the drug was well-tolerated, although vomiting occurred in some animals. Harned *et al.*[108] have shown that dogs will tolerate doses many times those necessary for the removal of ascarids. Kanegis[109] used the anthelmintic for the treatment of cats and kittens in oral doses of 25 mg./lb. of body weight, and confirmed its high efficiency against ascarids. Other reports of successful trials in dogs and cats have been recorded[110].

It has been used, apparently successfully, against *Spirocerca lupi* in the dog[111], and in one case of canine strongyloidiasis[112].

Barium Antimonyl Tartrate

Beach and Stewart[113] described the preparation of this compound. It was first used therapeutically by Wehr *et al.*[114] who showed that, when inhaled as a dust, it was 98 per cent. effective against *S. trachea*, gapeworm infection in chickens. Later, Wehr and Olivier[115] described its use for pheasants and showed that it was as effective in these birds as in chickens. Moynihan and Musfeldt[116] confirmed these results. The drug is effective also against *Syngamus* infection in turkeys.

Arecoline Hydrobromide

Hall and Shillinger[117] and Ross[118] described experiments on the efficiency of arecoline against cestode infection in the alimentary tract of the dog. Batham[119] conducted a more extensive study and provided some interesting information concerning the action of arecoline hydrobromide against tapeworms in the dog. His work showed that the drug given orally was highly effective against *Echinococcus granulosus* and against the larger tænioid cestodes. When the drug was given by subcutaneous injection only a purgative action resulted but when the drug was administered orally both an anthelminitic action and purgation followed. From *in vitro* work with some of the larger tænioid cestodes, he concluded that the drug exerts its anthelmintic action by causing the muscles of the tapeworm to undergo prolonged relaxation so that the hold on the intestine is lost and the detached worms are then expelled by the purgative action of the drug. The high efficiency of arecoline hydrobromide against *E. granulosus* makes the drug a valuable anthelmintic in countries where anti-hydatid measures are vigorously pursued, but it should be appreciated that it may fail to eliminate the cestodes in a small proportion of cases.

Dichlorophen

This compound has been introduced for the treatment of *Tænia* and *Dipylidium* infections in dogs[120]. Its action upon these tapeworms is of particular interest because it causes disintegration of the worm

in situ within the bowel, and the proglottids are usually excreted in an unrecognisable form. The drug is generally well-tolerated by dogs, although vomiting sometimes follows its use. Reports as to its efficiency as a tæniacide are conflicting. Some authors have commented very favourably on its value[120,121], but the experience of others indicates that dichlorophen does not compare in efficiency with arecoline hydrobromide or the arecoline-acetarsol compounds. Dichlorophen appears to be of low efficiency against *E. granulosus*[122]; it therefore does not fulfil the requirements of a routine cestode anthelmintic for hydatid control in dogs.

Harries[123] obtained satisfactory results in the treatment of *Moniezia expansa*. infection in sheep with dichlorophen, but Enzie *et al.*[124] observed that the drug is not as reliable as other available agents for the removal of this tapeworm. Olsen[125] investigated the use of dichlorophen against *Thysanosoma actinioides* infection of the liver of lambs. Variable results were obtained, however, and there was no evidence that treatment was justified because the degree of efficiency of the drug was too low to make its use economical. Allen and Jackson[126] also noted little appreciable effect.

Lead Arsenate

This drug was first reported as a cestode anthelmintic by Harwood and Guthrie[127] who used it successfully to remove tapeworms from chickens, but found that it was too toxic for general use. McCulloch and McCoy[128] showed it to be effective for the treatment of *Moniezia* infection of sheep, and Radeleff[129] reported on its use in lambs, kids and calves, in all of which it proved to be a generally satisfactory agent. Calves sometimes showed evidence of colic, but this was relieved by the administration of castor oil one hour after dosing with the anthelmintic. Habermann and Carlson[130] and Ward and Scales[131] have confirmed the value of the drug against *M. expansa.*

As the tapeworm is generally considered to be virtually harmless to the host, some authorities doubt the necessity for the treatment of this infection in ruminants but Foster and Habermann[132] consider that its removal causes a decided improvement in the health of infected animals. In discussing the merits of the drug, they believe that the drug can be used safely, but they emphasise that our knowledge of the toxicity is incomplete and caution must be exercised especially in pregnant animals. Allen and Jongeling[133] recorded mild enteritis, loss of appetite and one death following treatment. Morgan *et al.*[134] found a dose of 1 g. to be 100 per cent. efficient against *M. expansa* in sheep, while 0·5 g. reduced its efficiency to 62 per cent. They consider that the optimum dose and the possibility of cumulative toxic effects merit further investigation. Lead arsenate is compatible with phenothiazine and the two drugs can be administered together[135]. Despite a high degree of efficiency against *Moniezia*, Habermann and Carlson[130] have shown that lead arsenate is ineffective against the fringed tapeworm of ruminants, *T. actinioides*, which lives in the bile ducts.

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