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The challenge of endoparasitism: developments in the control of nematode infections of sheep

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ABSTRACT

Preventive control programmes for nematode infections of sheep, which depend upon strategically timed treatments of anthelmintics, are based on epidemiological knowledge of the time relationships between contamination of pastures and seasonal availability of infective larvae in different climatic regions.

In Australia by the time these programmes were being actively promoted resistance to two of the three families of anthelmintic drugs had already emerged. A high prevalence of resistance is now widespread in Australia and measures for the management of resistance have been incorporated into recommendations of worm control. These include, a reduction in frequency of treatments, elimination of underdosing, assessment of effective drugs, their use at high dose rates in an annual rotation and the integration of treatment with grazing management. Nevertheless, there is concern that preventive control programmes may not be sustainable over the long term.

Increased attention is now directed to alternative means of control, such as vaccination of sheep against nematode infections and breeding sheep with enhanced resistance to infection. The integration of these measures into preventive control programmes and the extent to which they can replace chemotherapy are topics for ongoing study.

Keywords Sheep, nematode infections, control programmes , anthelmintic resistance, sustainable control.

INTRODUCTION

It is only comparatively recently, over the past two or three decades, that sufficient knowledge of parasite biology and a range of appropriate tools has been available for effective control of nematode infections in sheep.

A new era in worm control was heralded by the introduction of thiabendazole in 1962. The high efficacy, broad spectrum of activity, safety and ease of use of this compound contrasted with previous preparations and allowed, for the first time, estimates to be made of the losses directly attributable to endoparasitism. During the next decade or so, information from a series of epidemiological studies became available which provided a broad understanding of the natural history of nematode infections and the rationale for preventive control programmes

However, by the time these programmes had achieved general acceptance in Australia, worms resistant to anthelmintics had emerged and have now become so common that a growing number of producers can no longer rely on this convenient means of worm control. Consequently, the challenge ahead will focus on control programmes which can be sustained over the long term.

An overview of developments in the control of nematode infections provides a perspective on current and future options for producers to limit or eliminate losses in productivity from endoparasitism.

NEMATODE INFECTIONS OF SHEEP - AN OVERVIEW

The genesis of current approaches to control of nematode infections in sheep can be found in the late 40's and 50's when the strategic concept of limiting contamination of pastures was enunciated by Gordon (1948). By that time differences in the geographical distribution of the common nematode species had been recognised and different timing of treatments was recommended for summer and winter rainfall regions, Gordon (1950, 1953, 1958). Some success was achieved with the use of phenothiazine but outbreaks, particularly of haemonchosis continued to occur.

The studies undertaken in the 60's and 70's, which described the availability of infection to sheep in relation to contamination of pastures and worm burdens acquired by weaners and breeding ewes, led to a change in thinking about the time relationships between the key factors in the epidemiology of nematode infections. This work and its implications for control has been extensively reviewed, for regions in Australia, Donald (1974), Anderson *et al.* (1978), Donald and Waller (1982) and for New Zealand, Anon (1975), Brunsdon (1980).

The notion of successive parasite generations at intervals of a month or so was untenable following the demonstration that the time taken for the development of the free-living stages and their translation from faecal deposits to herbage occupied many weeks, Donald (1967) or even months if dry weather supervened, Anderson (1983). Two or at most 3 generations per year are now considered more realistic estimates. Summer rains were found to favour the survival of significant numbers of infective larvae for two to three months and winter rains enabled larvae, derived from eggs deposited in late summer and autumn, to survive until rising temperatures in late spring brought about their demise.

The significance of the post-parturient rise in worm egg output of ewes for worm burdens acquired by lambs was recognised, together with the beneficial effects of moving weaned lambs from highly contaminated lambing paddocks to areas with low residual infections. These "safe" pastures could be prepared in a number of ways but required forward planning. Hay aftermath, stubbles, summer crops or pastures grazed by cattle or adult, non-lactating sheep for the 6 months before the move were considered "safe" pastures, (Barger, 1978; Morley and Donald, 1980; Brunsdon, 1980.

Usually, such studies included groups of different treatment schedules designed to improve productivity from sheep. Barger (1978) collated this data and concluded that losses in productivity attributable to internal parasites amounted to between 14 and 79% for liveweight and between 9 to 30% for wool production in young sheep. Mortality due to uncontrolled parasitism ranged from 10 to 68%. While effects on liveweights of untreated breeding ewes were much less, similar losses in wool production have been observed. One comparison showed that the return on funds invested in the control of parasitism amounted to 538% for weaners and up to 1,200% for breeding ewes, Morris *et al.*, (1977).

PREVENTIVE PROGRAMMES FOR WORM CONTROL IN SHEEP IN AUSTRALIA

The growing body of epidemiological knowledge and access to anthelmintics of high efficacy has enabled the formulation of preventive worm control programmes for sheep in each of three broad regions of climate, namely the summer, uniform and winter rainfall regions.

Summer Rainfall Region

Haemonchus contortus and *Trichostrongylus colubriformis* are the dominant nematode species in this region, in association with *Ostertagia* and *Nematodirus spp*, which are not often encountered as primary pathogens. Numbers of *H. contortus* and *T. colubriformis* larvae on pasture increase early in summer, reach a peak in late summer and early autumn and progressively decrease during winter to their lowest values in late spring. Worm burdens of lambs born in spring follow the same pattern but the effects of *H. contortus* usually become obvious earlier than those due to *T. colubriformis* infection which may not induce clinical disease until the quality of fodder declines in winter.

The critical time for preventive measures to start is in spring while the small overwintering infection is decreasing and before new contamination increases larval numbers on pasture. Treatment of all classes of stock with a broadspectrum anthelmintic early in August and again early in November, when in addition, ewes and lambs are moved to "safe" pasture, is usually adequate to control infections of *T. colubriformis* because acquired immunity is sufficient to protect adult sheep during summer. Lambs are treated with the ewes in November and again at weaning in February when they are moved to "safe" pasture. The last treatment is given in April. Unfortunately, this schedule alone is not sufficient to limit the numbers of *H. contortus* which can increase dramatically when moist warm, weather prevails. The narrow spectrum salicylanilide, closantel, which binds to plasma proteins and provides four to six weeks protection against reinfection by the blood sucking *H. contortus*, has provided a crucial adjunct to this programme Dash (1986). Treatments to adult stock early in August, November and February and to lambs in November and February have been dramatically successful in suppressing infections of *H. contortus*, often to an undetectable level. The timing of these treatments is summarised in Table 1.

TABLE 1 The WORMKILL preventive worm control programme. Recommended times of treatment with closantel (Clos) and broadspectrum (B/spec) anthelmintics to different classes of sheep and times to move sheep to "safe" pasture for summer rainfall regions in Australia.

Month	Adult	sheep	Lambs/Weaners		Move to
	Clos	B/spec	Clos	B/spec	"safe" pasture
August	+	+			
November	+	+	+	+	Ewes & Lambs
February	+		+	+	Lambs
April				+	

This preventive treatment schedule was introduced to Northern NSW as the WORMKILL programme in July 1984. Vigorous promotion, mounted jointly by CSIRO and the NSW Department of Agriculture, involved news releases in local papers, magazines and on radio, brochures mailed to producers, field days and local meetings. Emphasis was placed on personal contact with producers to explain the principles of the programme. Within defined limits, treatment schedules could be modified to take account of individual needs. Most importantly, an "after sales service" was provided by officers of the Department to solve problems during implementation. Regular monitoring on selected farms provided further confidence in the programme. Acceptance by producers was rapid, about 75% of producers adopting the programme within a year and 90% within 2 years of its introduction. A reduction of 53% in the frequency of treatment with broadspectrum anthelmintics was achieved over two years with direct cost savings of close to $A2 million per year, (K.M. Dash, personal communication.)

Uniform Rainfall Region

A more or less uniform distribution of annual rainfall favours development and survival of the free-living stages of all the common nematode genera.

Initial infection of lambs after weaning in early summer has its origin in the high amounts of pasture contamination from ewes during the period of the post-parturient rise in worm egg output. This infection gives rise to high rates of contamination by lambs during summer and early autumn which in turn, leads to disease producing amounts of infection during autumn and winter. Because of rapid reinfection in this environment, anthelmintic treatments are coupled with moves to "safe" pasture. If this can be done, then treatments at weaning in late November/early December and again in late February/early March are all that is required to achieve the benefits of preventive control, see Table 2.

TABLE 2 Times of anthelmintic treatment for sheep under alternative preventive control programmes recommended for New Zealand, adapted from Brunsdon (1980), Vlassoff and Brunsdon (1981).

Month	Adult Sheep	Lambs	Move to "safe" pasture
Integrated Control[a]			
November/ December		+	Lambs
February/ March		+	Weaners
Preventative Drenching[b]			
December	+	+	
January		+	
February		+	
March		+	

Note: Where haemonchosis occurs regularly treatments of closantel can be given in November/December and February/March.

[a] Lambs receive a second drench 3 weeks after each move.

[b] Additional drenching on the basis of faecal egg count.

However, provision of "safe" pasture requires that two grazing sectors be established on the farm, the first being used from August to December and the second from December to March. The first sector is used again between March and August, Brunsdon (1980).

This "treat and move" strategy has been advocated for New Zealand producers since the mid 70's, Anon (1975), Brunsdon (1976, 1980) but a survey conducted at the end of the decade, Brunsdon *et al.*, (1983), showed that the frequency of anthelmintic use in lambs was much higher than recommended, between five and seven treatments each year, implying that adequate amounts of "safe" grazing could not be made available. Treatments at weaning and at monthly intervals in January, February and March appear to have become standard practice in New Zealand after Vlassoff and Brunsdon (1981) demonstrated their efficacy for preventive control. Where broad spectrum treatments are few in number, such as in the central tablelands of NSW, treatments of closantel, in November/December and February/March can be used to good effect in preventing haemonchosis.

Winter Rainfall Region

Ostertagia and *Trichostrongylus spp* predominate the worm burdens of sheep in this region. *H.contortus* does occur along southern coastal areas of Australia which receive sufficient rain in summer months to facilitate transmission of infection and outbreaks of haemonchosis occur in years with wet summers. More typically, in this region, very few larvae of any species are available on herbage residues during the hot, dry weather of summer. Larval numbers increase after the onset of autumn rains most being derived from eggs deposited in late summer and autumn and smaller numbers from depositions made in the previous spring. Peak amounts of infection occur in winter when disease among weaners and breeding ewes becomes apparent. Treatment of all sheep with an effective broadspectrum anthelmintic, when pastures are drying off in late spring and early summer, reduces contamination substantially at a time of little reinfection. A second treatment in February/ March extends the period of minimum contamination into autumn thus reducing the pool of free-living stages. Further treatments to susceptible weaners are recommended for April and July, as measures to further reduce contamination or to reduce the effects of winter infection.

This treatment schedule, see Table 3, constitutes the DRENCHPLAN and analogous programmes which have been actively promoted since 1985. However, promotion has not been as vigorous as that used for WORMKILL, because of limited resources, and consequently adoption rates among producers have been lower.

TABLE 3 The DRENCHPLAN preventive worm control programme. Times of broadspectrum anthelmintic treatment to sheep and times to move sheep to "safe" pastures for winter rainfall regions of Australia.

Month	All adult sheep	Lambs Spring born	Lambs Autumn born	Move to "safe" pasture
November/ December	+	+		Lambs
February	+	+		Weaners
April		+		
July		+	+	Weaners
September			+	

BROADSPECTRUM ANTHELMINTICS FOR SHEEP

Any list of broadspectrum anthelmintics for sheep, such as the indicative one in Table 4, contains features of significance to worm control programmes. The first broadspectrum anthelmintic for ruminants, phenothiazine, was introduced in 1938 and remained in virtual sole use for close on 25 years before the introduction of thiabendazole. Since then the number of compounds has increased rapidly, mainly as a result of modifications to benzimidazole structure which gave increases in potency and in spectrum of activity. The carbamated derivates, now in common use, are effective against all the major gastro-intestinal nematodes, the lungworm *Dictyocaulus filaria* and against *Monezia spp* tapeworms. An additional claim for moderate activity against the adult liver fluke, *Fasciola hepatica*, is also made for albendazole. The latest inclusion in such a list, ivermectin, is the first compound with efficacy against nematodes and external parasites, namely, ticks, mites and Dipteran flies.

However, despite the large number of compounds now available only four distinctive modes of pharmacological action have been discovered since phenothiazine was introduced in 1938. The latter drug is no longer in general use and because resistance to one member confers resistance to other members of the same pharmacological family, in practical terms there are only three broadspectrum anthelmintics for worm control in sheep. Widespread resistance to two of these, the benzimidazole and levamisole groups, means that for many producers ivermectin is the only choice. Conservation of effective anthelmintics therefore forms a vital part of their usage.

NEMATODE RESISTANCE TO ANTHELMINTICS

Resistance to anthelmintics was first noted within a few years of the introduction of each of the major compounds. For almost two decades these reports were considered isolated occurrences, viewed more as a curiosity than as grounds for serious concern, largely because most had arisen as a consequence of frequent treatments associated with experimental procedures and were thus atypical of anthelmintic usage in general. The first survey, Webb *et al.*, (1979), detected resistance to thiabendazole among *H.contortus* populations on 22 of 40 farms on the Northern Tablelands of NSW. Subsequent surveys have confirmed Australia's pre-eminence on the world scene for high prevalences of resistance to both benzimidazole and levamisole compounds, Waller (1985), Webb and Ottaway (1986), Edwards *et al.*, (1986). Despite this and the undeniable experience where resistance has caused failures in control programmes, it is not at all clear whether detection of resistance constitutes a universal problem for all sheep producers. This point was made in the review by Prichard *et al.*, (1980) which has been seminal in focussing attention on the biological and operational factors favouring the development of resistance and potential means for management. Later reviews by Donald (1983), Martin (1987) and Waller (1987) have amplified these aspects in the light of results from recent studies. Given that resistance to anthelmintics is the inevitable outcome of continued use, as part of the evolutionary process, the challenge lies in determining whether the process can be delayed and which strategy prolongs the delay longest? Two aspects which are relevant to the implementation of such strategies are the nature of selection and the detection of resistance on farms.

Selection for Resistance to Anthelmintics

In all the major nematodes of sheep, resistance to benzimidazole compounds is a polygenic trait inherited additively. Resistance alleles appear to be co-dominant and there is a large maternal effect most likely due to the maternal contribution to the oocyte, Martin *et al.*, (1988). In contrast, selection studies on a *T.colubriformis* population with levamisole, show that resistance to this compound is conferred by one or a small group of genes present on the sex-determining chromosome, P.J. Martin personal communication. However, with respect to fitness in the presence of anthelmintics, resistance is incompletely recessive which means that the lethal dose for heterozygotes is the same or similar to that for homozygous susceptible genotypes.

Resistance genes arise by mutation and initially exist only the heterozygous state. In the absence of anthelmintic they remain at a rare frequency, estimated to be about 1 in a million, by the counterbalancing forces of mutation and natural selection. If a new anthelmintic is introduced at a dose rate above the 100% lethal dose (LD100) then clearly the heterozygotes will be removed and there will be no selection for resistance.

Unfortunately, practical use of anthelmintics inevitably means that dose rates less than the LD100 are usually presented to nematode populations thus constituting a strong force for selection of resistant ecotypes. In past decades little care has been taken in the application of recommended dose rates of benzimidazole and levamisole anthelmintics. Together with faulty dosing practices and host idiosyncrasies, such as closure of the rumino-reticular groove, Prichard and Hennessy (1981), it is little wonder that strong selection for resistance has occurred.

Worms that survive treatment contribute to the next generation with consequent accumulation of resistance alleles. Initially this is slow because resistance genes are rare.

However, once the proportion of worms with resistance reaches about 25% a rapid increase to 75% occurs and the anthelmintic ceases to be effective. Subsequent accumulation of resistant alleles slows once again.

The sigmoid nature of this selection curve, applies to all anthelmintics, including mixtures of them, and the rate of progress will vary according to the frequency of resistance alleles. For example, if two entirely new compounds were introduced as a mixture, instead of separately, then the initial frequency for resistance to both compounds would be the product of the frequencies for the separate components, ie a mutation rate of 10^{-12} rather than 10^{-6}. The early selection process would therefore be correspondingly slower than for the separate components and thus mixtures of anthelmintics would be more valuable if used at high dose rates, preferably above LD100, when the number of genes conferring resistance is rare. Unfortunately, this is not the current situation in Australia where a high prevalence of resistance to benzimidazoles and levamisole already exists.

Reversion of Resistance

A reduction in the frequency of resistance alleles depends upon the strength of selection by other adaptive traits or the use of pharmacologically unrelated drugs. At high frequencies of resistance, the counter selective force of other adaptive traits, such as survival of free-living stages, establishment and survival in the host, tend to be weak because during the course of the selection process, recombination within the genome brings together adaptive and resistance traits thus conferring high degrees of general fitness on resistant individuals. The disadvantage for survival in a mutant with a drug resistance allele is soon removed, McKenzie (1985).

Reversion and counter selection have been studied under laboratory and field conditions but always with strains with a high degree of resistance, Donald *et al.*, (1980), Hall *et al.*, (1982), Le Jambre *et al.*, (1982), Waller *et al.*, (1983, 1985). Results from these studies have been variable with some reduction in resistance occurring in some isolates and not in others. In general, it would appear that simply withdrawing treatment does not reduce the degree of resistance but changes can be expected under field conditions, if counter-selection is used. This phenomenon has been attributed to the interplay between the small resistant population surviving treatment and the much larger numbers in the reinfection pool which will generally have a lower degree of resistance. While the effect has been positive on a number of occasions it does not inevitably occur and the rate of change is slow such that, even after several years of using an alternative drug, susceptibility to the drug inducing resistance is not fully restored, Martin *et al.*, (1988), Waller *et al.*, (1988). Furthermore, changing back to the initial compound will again select strongly for resistance.

A more radical solution to the problem of resistance could be to enhance reversion by the deliberate introduction of susceptible genotypes. Sufficient epidemiological information is available to select times when part or total population replacement could be undertaken expediously from an initial seeding on a small area. Once the resistance status of a farm had been changed from resistant to susceptible, procedures for the long term management of resistance to anthelmintics could then be put in place. Encouraging results have been reported for a pilot study with *H.contortus*, Van Wyk and Van Schalkwyk (1990).

Detection of Resistance

Unfortunately, there is currently no direct measure of the number of resistance alleles in a nematode population. Indirect assessment can be made from tests used to detect resistance. The *faecal egg count reduction test*, (FECRT), is the most convenient test for use on farms and has the advantage of comparing all anthelmintics for the purpose of choosing an effective drug.

However, the FECRT is neither sensitive nor accurate. A measure of its sensitivity has been obtained from tests conducted on prepared strains of worms derived from larvae of resistant and susceptible ecotypes mixed in different proportions. Resistance was detected when resistant individuals comprised about 25 - 30% of the population thereby indicating the presence of a high frequency of resistance alleles in the population, Martin *et al.*, (1989).

The accuracy of the FECRT is determined by the variability in worm egg counts from sheep in both control and treated groups. Consequently, each mean percentage reduction has an error associated with it. A convenient means of expressing this variation is to calculate the 95% confidence interval. Results from farms show means with overlapping confidence intervals. Therefore, some arbitrary definition for detecting the presence of resistance is needed.

In prevalence surveys conducted during the 80's, resistance was declared when the mean reduction was less than 90%, Webb *et al.*, (1979), Kemp and Smith (1982), Kettle *et al.*, (1981), Edwards *et al.*, (1986), Webb and Ottaway (1986). This figure is now considered too low so a mean reduction less than 95% is generally accepted as evidence for the presence of resistance. If only the mean is used, then resistance will be declared on half the times when it is not, so it has been suggested that the lower confidence limit be included in the definition, Anon (1989). Therefore, resistance will be declared if the mean reduction is less than 95% and the lower confidence limit is less than 90%. Conversely, an effective anthelmintic will be one giving results higher than these values. Generally, results from tests will be clear but occasionally the mean value will exceed 95% with the lower confidence limit less than 90%. Such a result is usually associated with one moderately high count among a majority of zero values in the treated group. Since the definition is an arbitary one, interpretation of results is necessary. In this case an average reduction above 95% indicates a highly effective anthelmintic which could be used in a preventive control programme. However, continued use of the drug would lead to a rapid increase in resistance.

Resistance on Farms

Where a high prevalence of resistance prevails, all available anthelmintics, and appropriate mixtures of them, should be included in the FECRT to determine which ones are effective. A differentiation of larvae cultured from eggs is needed to determine the species present. A mixture of anthelmintics would be expected to be highly effective when different worm species have resistance to different compounds. Similarly, if one species has resistance to both components of a mixture, when given separately, then the mixture would be effective when the proportion of individuals with multiple resistance is less than 25 to 30% of the population and ineffective at proportions greater than that. Even though the efficacy of a mixture is due to the additive actions of the components, it is difficult to calculate the expected efficacy of the mixture from results obtained from using the single components, because of the poor accuracy of the FECRT. It has been shown that on 50% or more farms with evidence of resistance to both benzimidazole and levamisole, a mixture of the same anthelmintics has proved to be highly effective, Anderson *et al.*, (1988, 1990). In Australia the value of mixtures as effective anthelmintics may well be only temporary but in New Zealand, where the prevalence of resistance is much lower, their use could be a major advantage for the management of resistance. Provided thay are used wisely. This means on farms where resistance to the compnent drugs has not been detected, otherwise thay could exacerbate the problem by selecting for dual resistance.

MANAGEMENT OF RESISTANCE

Active promotion of preventive control programmes was initiated at a time when account had to be taken of a growing number of reports on the detection of resistance to anthelmintics. Consequently, management of resistance now forms part of the recommendations for these programmes.

There are a number of operational procedures which can be undertaken by producers to limit selection for resistance to anthelmintics. Adoption of a preventive control programme will reduce the frequency of treatment. Use of a narrow spectrum drug, such as closantel for *H. contortus* infections, also reduces the number of treatments with broadspectrum products. Visual assessment of sheep by producers almost invariably results in the under estimation of liveweight of sheep by 20 to 40%, Besier and Hopkins (1988). Therefore, sheep need to be weighed and the heaviest weight used to calculate the dose for all sheep in that group. Dosing equipment needs to be checked regularly for accuracy and spillage during administration avoided. These measures reduce or eliminate under-dosing and high dose rates maintain resistance alleles effectively recessive with respect to fitness.

Testing for the presence of resistance provides a choice of effective anthelmintics which should be used in an annual rotation to reduce the intensity of selection for resistance. Annual rotation of drugs with different modes of action is based on the selection and counter selection factors described earlier and thus constitutes a "best bet" strategy owing more to theoretical arguments than to established fact, Prichard *et al.* (1980). To avoid the introduction of resistance onto a farm, a highly effective anthelmintic should be used when sheep are first introduced to the flock.

All of the regional programmes outlined above include the recommendation to move treated stock to "safe" pastures at specified times. When comparisons have been made this strategy has shown greater benefits than set-stocking, in terms of reduced parasite numbers and increased productivity, Donald (1974), Brunsdon (1976), Donald and Waller (1982). However, when anthelmintics with reduced efficacy due to resistance are used, then higher degrees of resistance can be expected on the pasture to which the animals are moved because contamination of them will be from worms surviving the treatment, Le Jambre (1978), Martin (1987).

NEW ANTHELMINTICS AND FORMULATIONS

While the profit motive will continue to foster efforts for the development of new anthelmintics, expectations for a continuous supply of drugs with novel actions must be tempered with reality.

Only four distinct groups of broadspectrum anthelmintics have reached the market place in the past 50 years, (Table 4.)

The selective nature of their toxic effects, in exploiting metabolic or physiological differences between host and parasite, is indicative of the limited possibilities for the discovery of compounds with novel anthelmintic activity. Furthermore, the growing costs, in both time and money, associated with procedures for testing efficacy and safety, provide a disincentive for the development of all but a small number of compounds, Hotson (1985).

Having several anthelmintics with high efficacy greatly assists in the management of resistance. The use of mixtures of anthelmintics should be viewed in this light, Anderson *et al.* (1988, 1990). Simulation studies on pesticide resistance show that the development of resistance is slower when mixtures of two compounds are used than if the separate components were used sequentially or in rotation, Mani (1985), Curtis (1985).

TABLE 4 An indicative list of broadspectrum anthelmintics for sheep, times of commercial application, potency, spectrum of activity and family groups.

Anthelmintic	Commercial application	Dose Rate mg/kg	Spectrum of activity*
$CuSO_4$	1935	7/8	H.c. mainly.
Phenothiazine	1938	600	H.c., T.a., Oes, mainly
Thiabendazole[1]	1962	44	GI nematodes Nem & Im moderate
Tetramizole[2]	1966	15	GI nematodes Lungworm.
Levamisole[2]	1969	6.8	GI nematodes, Lungworm
Fenbendazole[1]	1975	5	Nematodes, lungworms, Monezia spp.
Albendazole[1]	1980	3.8	Nematodes, lungworms Monezia, Fasciola
Ivermectin	1988	0.2	Nematodes, lungworms Ticks, mites Dipteran flies

*H.c = Haemonchus contortus, T.a = Trichostrongylus axei, Oes = Oesophagostomum columbianum, GI = gastrointestinal, Nem = Nematodirus spp., Imm = immature stages.

[1,2] The anthelmintics with the same superscript have similar pharmacological actions.

As mentioned earlier the frequency of worms with resistance to both components of a mixture will be the product of frequencies of resistance alleles to each component. Consequently, the use of mixtures for delaying the development of resistance will have greater impact at lower than at higher frequencies of resistance alleles. Further delay can be anticipated if mixtures are used in rotation with other effective compounds within the frame-work of a preventive control programme.

CONTROLLED RELEASE TECHNOLOGY

The general purpose intraruminal controlled release capsule, Laby (1978), provides a convenient means for the application of small amounts of highly potent anthelmintics over months of time, Anderson (1985). The currently available capsule releases 32.5 mg of albendazole each day for 100 days and is recommended for use in sheep of 35 to 65 Kg. The heaviest animal in this range receives 0.5mg/kg/day which is highly effective against benzimidazole susceptible strains of the major nematode species and causes a sustained reduction of 70 to 80% in the output of worm eggs from sheep infected with benzimidazole resistant strains of *Ostertagia* and *Trichostrongylus spp.* High efficacy against the establishment of newly acquired infection has also been demonstrated, Anderson (1985), Barger (1988).

It has been shown, that a capsule designed to prevent pasture contamination for about 100 days at critical times, produces dramatic effects on the epidemiology of nematode infections. Use of the capsule increases the certainty of success of preventive control programmes because, in contrast to conventional treatments, rapid reinfection cannot occur within the life-time of the capsule despite the occurrence of weather conditions conducive to the transmission of infection. Areas of "safe" pasture can be prepared using capsule treated sheep and these in turn can be integrated into a preventive control programme.

Controlled release technology provides the potential for exploitation of a wide range of agents for the purpose of disrupting the nematode life-cycle with consequent effects on their numbers, Anderson (1985).

ALTERNATIVE APPROACHES TO WORM CONTROL

The high prevalence of resistance to benzimidazole and levamisole anthelmintics and the belief that resistance will negate the gains achieved from chemical control has provided a stimulus to research on alternative approaches to worm control. Vaccination of sheep against nematode infections and breeding sheep resistant to infection are two approaches which have been under investigation for the past two or three decades.

Vaccination of Sheep against Nematode Infections

Natural immunity to nematode infections is acquired with increasing experience of infection but is usually not adequately expressed until sheep attain maturity. This immunity appears to be neither absolute in effect nor is a high degree maintained continuously throughout the life of the sheep. For example, breeding ewes are more susceptible to worm infections during the first half of lactation than at other times and contamination of pastures arising from this infection is a serious hazard to lambs at and after weaning, Brunsdon (1976).

Immunity to gastrointestinal nematodes is a complex matter which involves a number of specific and non-specific components, Dineen (1985). An account of these and the prospects for successful vaccination against nematode infections will be given in a subsequent paper, Douch (1990).

Breeding Sheep Resistant to Nematode Infections

There is ample evidence of differences both between and within breeds of sheep in their capacity to develop resistance to infections of gastrointestinal nematodes, Albers and Gray (1986), Gray *et al.* (1987). Reviews of data from selection experiments dating back to the mid 70's show moderate heritability estimates of about 0.3 for resistance to *H. contortus* and *T. colubriformis* infections. These estimates are comparable to those obtained for production traits. Furthermore, the genetic correlations between resistance characteristics and those of production when sheep were not infected, were not significant indicating that selection for resistance would not adversely affect productivity in sheep, Piper (1987), Piper and Barger (1988). Also selection for resistance to one nematode species appears to be well correlated with resistance to others in different genera.

While Le Jambre *et al.*, (1982) reported that measures such as haematocrit depression can be used as a selection criterion for resistance to *H. contortus*, the mean egg count obtained from lambs at four to five months of age provides the most convenient index for selection. Whether the counts are derived from natural or experimentally induced infections seem immaterial but as Piper and Barger (1988) point out natural infections are preferred because fewer assumptions are made about the physiological basis of resistance to infections. In practice, experimental infections with large single doses of either *H. contortus* or *T. colubriformis* are used because of the convenience of adopting standard protocols. Piper and Barger (1988) also discuss the difficulties of estimating the costs and benefits of selection for resistance which are needed for inclusion in a breeding programme. Costs of testing can be readily estimated but the value of each unit of increased resistance cannot be assessed when amounts of infection change in response to variable weather or to other measures for reducing parasite numbers. Benefits will also depend on the expected rate of progress which in turn depends on heritability and the total variation in the trait. Gray *et al.* (1987) estimated the coefficient of variation at 42% and suggested that at usual selection intensities resistance among Merinos could be increased to that of resistant breeds within two or three generations.

The resistance of selected animals is believed to be due to an enhanced capacity to acquire natural immunity at weaning age, much earlier than the usual time of 7 to 10 months. In degree, such immunity appears comparable to that acquired at maturity and therefore the principal advantage expected is protection of the young animal on first exposure to infection and more importantly a reduction in the contamination of pastures. Such efforts will be highly valued in summer and uniform rainfall regions where lambs are often exposed to high rates of infection at and soon after weaning. However, in winter rainfall regions breeding for resistance may have little advantage for lambs born in spring and weaned in November/December when the availability of infection will soon be low for the next four or five months.

At present there is no indication that resistance derived from a breeding programme differs from that acquired naturally which in itself, varies in intensity according to the reproductive and nutritional status of the host and the fluctuating amounts of infection. It seems likely that when mature age sheep selected for resistance are exposed to uncontrolled amounts of infection they will sustain significant pathological effects with consequent decreases in productivity, much in the same way as sheep with naturally acquired immunity respond to reinfection, (Barger, 1973; Yakoob *et al.*, 1983; Reid and Armour, 1975; Brunsdon *et al.*, 1986.

Nevertheless, induced immunity to nematode infections, be it by vaccination or from selective breeding urgently needs assessment in a grazing context to determine the contribution that these measures can make to present control programmes and the extent to which they can replace chemotherapy.

PROSPECTS FOR THE FUTURE.

Endeavours over the past three decades have enabled the successful development of cost effective preventive programmes for worm control in different climatic regions. Further improvement will be dependent upon new information on aspects for which only a broad understanding is currently available. Included among the topics for future experimentation should be studies on more sensitive tests for detecting resistance to anthelmintics, quantitative studies on the ecology of free-living populations, and an epidemiological evaluation of sheep resistant to infection. Eradication of parasitic nematodes has been considered a pipedream largely because of the high fecundity of parasitic populations and their long survival as free-living stages, Michel (1969) Brunsdon (1980). However, it is useful to reflect that in Australia *Oesphogostomum columbianum* has disappeared from areas where it caused serious disease some three decades ago. Furthermore, *H. contortus* remains undetectable on some farms three years after the use of closantel in the WORMKILL programme ceased (I.A. Barger, personal communication). The challenge ahead is to understand how these events occurred so that similar strategies can be applied to other species. In this context, controlled release technology offers possibilities not previously available.

While these studies are being undertaken concurrent efforts are needed to determine how sustainable are the current recommendations for worm control. Preventive control programmes provide cost-effective means of reducing worm numbers below threshold values which cause losses in productivity. Because weather conditions play a central role in determining worm numbers, a spectrum of sustainable programmes can be envisaged which increase in complexity in environments more favourable for parasite transmission.

At one end of the spectrum, there are probably large tracts of grazing land where one or two strategically timed treatments to sheep each year will prove to be successful over the long term providing proper account is taken of drug resistance. At the other end of the spectrum, where sheep encounter intense and almost continuous infection, options based on breeding sheep for resistance to infection or vaccination against infection could prove more satisfactory in the long term than reliance on frequent treatment with anthelmintics.

In Australia, it is pleasing to see specialist sheep production consultants implementing preventive control programmes, as part of their appraisal and restructuring of farm enterprises. Early success has been dramatic in some cases but overall, sufficient time has not yet elapsed for long term judgements to be made. Unfortunately, this excellent service is provided to less than 10% of producers leaving the majority either ignorant of current information or with access to a diminishing amount of expertise because of policy changes within Departments of Agriculture. A "fee for service" approach will benefit many producers who seek assistance but is not conducive to a higher or faster adoption rate of current information.

An experimental evaluation of a control programme for long term effects hardly seems appropriate "given the diversity of production systems within different environments and the lengthy time scale of such an evaluation." Consequently, some monitoring capability needs to be set in place to measure the success of programmes implemented on farms. Private enterprise could not be expected to embrace such a task and Departments of Agriculture are actively divesting themselves of this responsibility. It would be a pity if the Meat and Wool Producer Boards choose not to support this activity, even at a modest level, given that much of the research funded to date has its application in sustainable programmes for worm control.

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