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veterinary parasitology

Veterinary Parasitology 139 (2006) 1–14

www.elsevier.com/locate/vetpar

Review

From discovery to development: Current industry perspectives for the development of novel methods of helminth control in livestock☆

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Received 11 November 2005; received in revised form 23 February 2006; accepted 27 February 2006

Abstract

Despite the extraordinary success in the development of anthelmintics in the latter part of the last century, helminth parasites of domestic ruminants continue to pose the greatest infectious disease problem in grazing livestock systems worldwide. Newly emerged threats to continuing successful livestock production, particularly with small ruminants, are the failure of this chemotherapeutic arsenal due to the widespread development of anthelmintic resistance at a time when the likelihood of new products becoming commercially available seems more remote. Changing public attitudes with regards to animal welfare, food preferences and safety will also significantly impact on the ways in which livestock are managed and their parasites are controlled. Superimposed on this are changes in livestock demographics internationally, in response to evolving trade policies and demands for livestock products. In addition, is the apparently ever-diminishing numbers of veterinary parasitology researchers in both the public and private sectors.

Industries, whether being the livestock industries, the public research industries, or the pharmaceutical industries that provide animal health products, must adapt to these changes. In the context of helminth control in ruminant livestock, the mind-set of 'suppression' needs to be replaced by 'management' of parasites to maintain long-term profitable livestock production. Existing effective chemical groups need to be carefully husbanded and non-chemotherapeutic methods of parasite control need to be further researched and adopted, if and when, they become commercially available. This will require veterinary parasitology researchers from both the public and private sectors to work in close co-operation to ensure 'sustainability' – not only of the livestock industries that they service – but also for their very own activities and enterprises.

Keywords: Helminths; Livestock; Control; Perspectives; Industry; Research; Development

☆ Review presented at the Novartis Symposium held during the 20th World Association for the Advancement of Parasitology (WAAVP) Conference, Christchurch, New Zealand.

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0304-4017/$ – see front matter
doi:10.1016/j.vetpar.2006.02.036

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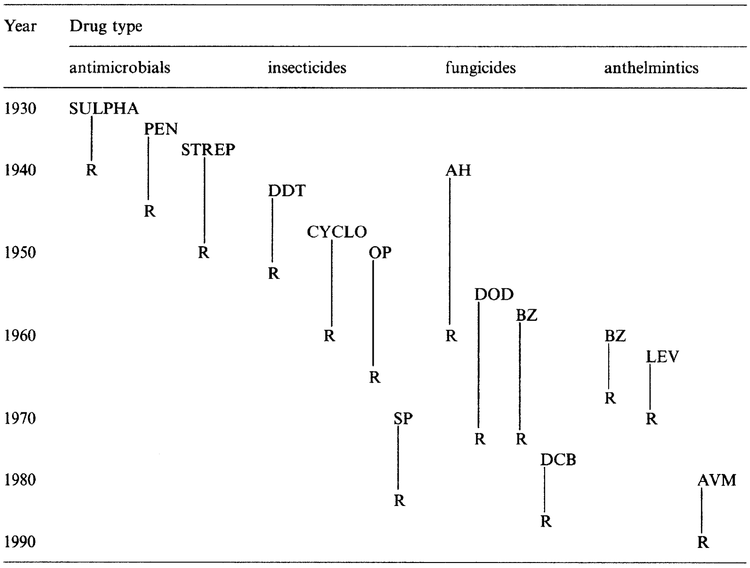
1. Introduction

There is no question of the importance of helminth infection in production livestock, whether for the industrial countries, or the developing countries, of the world. For example, recent surveys conducted in three of the largest sheep producing countries, namely Australia, South Africa and Uruguay, ranked nematode parasites as the most important of all the infectious diseases in sheep, with annual losses estimated to be US$ 222m (McLeod, 1995), US$ 45m (I.G. Horak, personal communication) and US$ 42m (Nari et al., 1997), respectively. A recent exhaustive review (Perry et al., 2002), commissioned by the major international donors to projects in the developing world, which estimated the effects of livestock disease on the poor owners of livestock, concluded that *sic* "on a global basis, gastro-intestinal parasitism emerges with the highest index as an animal health constraint to the poor". Clearly the problem is there, and the industry is responsive.

However, I believe it is necessary at the outset to qualify what is meant by the term 'industry'. In this setting, naturally one thinks immediately of the pharmaceutical industry which is traditionally linked with the business of developing and marketing parasiticides, but in another forum it could well mean the producer organizations representing the production livestock industries. The priorities and the means to achieve parasite control for the livestock industries that the latter bodies represent are much broader and are not necessarily chemically focussed.

Regarding parasites of livestock, superficially the missions of the livestock industry and the pharmaceutical industry may well appear to be dichotomous, with threats to the livestock industry in parasite control, likely to be considered as opportunities by the pharmaceutical industry. However, in this changing world nothing remains static, and this is particularly so with matters relating to livestock production, profitability, parasites and public perceptions. Although I come from a background of having little 'inside' experience on priority setting by livestock producer bodies – and even less with regards to the pharmaceutical industry – I do have the benefit of being 'around for a long time' working in the production livestock/nematode parasite research milieu. During my career as a veterinary parasitologist I have witnessed substantial changes in the positioning and re-alignment of attitudes of the pharmaceutical industry, livestock producer bodies, publicly funded research institutions and the consumers in response to economic and political imperatives of contemporary issues impacting on the management of production



Antimicrobials: SULPHA, sulphonamides; PEN, penicillin; STREP, streptomycin.

Insecticides: DDT, Dicophane; CYCLO, Cyclodienes; OP, organophosphates; SP, synthetic pyrethroids.

Fungicides: AH, aromatic hydrocarbons; DOD, Dodine; BZ, benzimidazoles; DCB, dicarboxamides.

Anthelmintics: BZ, benzimidazoles; LEV, levamisole; AVM, avermectins

Fig. 1. Year of commercial release of broad-spectrum drugs and the first appearance of resistance in target organisms (from Waller, 1994).

livestock throughout the world, and by implication on helminth control practices.

The last century will go down as the 'chemotherapeutic era', heralded by the commercial release of a vast range of wonder drugs used to control diseases of man, his crops and his livestock. Some examples of such drugs in chronological sequence of their appearance onto the marketplace are shown in Fig. 1. Although anthelmintics were 'the last horse out of the box' so to speak, there has been an ever increasing potency and spectrum of activity of new classes of drugs and at the same time ever decreasing dose rates—from 600 mg/kg for phenothiazine to 0.2 mg/kg for the macrocyclic lactones (McKellar and Jackson, 2004; see Fig. 2). Without wishing to be flippant, it does tend to foster an expectation that the next class anthelmintics will require efficacies exceeding 100%, at less than zero dose rate, to be commercially viable?

Therefore by virtue of their remarkable efficiacy, broad spectrum activity, ease and safety of use, and relative cheapness, these modern wonder drugs fostered the notion that disease scourges could be kept permanently in check, if not eradicated, by their frequent use.

The 1960–1980s were the halcyon days for livestock producers and for those pharmaceutical

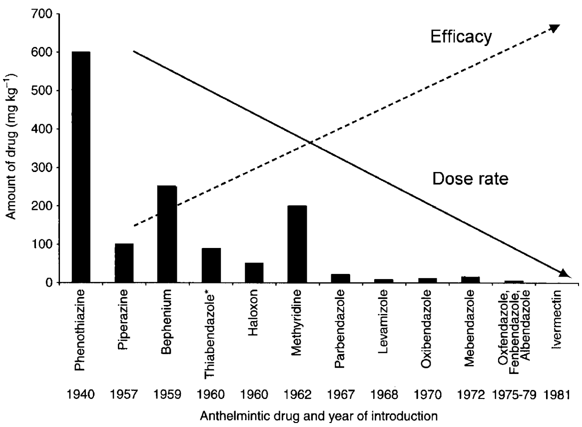


Fig. 2. The evolution of broad spectrum anthelmintics (adapted from McKellar and Jackson, 2004).

companies who were fortunate to have marketable broad spectrum anthelmintic products during this time. For example, the forerunner to the true anthelmintic ‘wonder’ drugs was thiabendazole and large-scale field research studies in Australia by the discoverers, Merck Sharp and Dohme, demonstrated the economic benefits of suppressive (monthly) drenching of sheep (see Fig. 3A). Not to be outdone, the next anthelmintic ‘big gun’ to appear on the marketplace was the imidothiazole, levamisole and ICI, the distributors of this drug to the sheep industry in Australia, recommended that at times farmers considered they had a problem with barbers pole worm (*Haemonchus contortus*), then they could save a lot of money by half-dosing, because Nilverm® (levamisole 7.5 mg/kg) was so highly effective against this parasite (see Fig. 3B). Suppressive, and often half-dosing with these new drugs, became very much in vogue for the treatment of parasites of sheep during the 1960–1980s, at least in Australia.

So these were great days, not only for the veterinary pharmaceutical industry, where seemingly the only

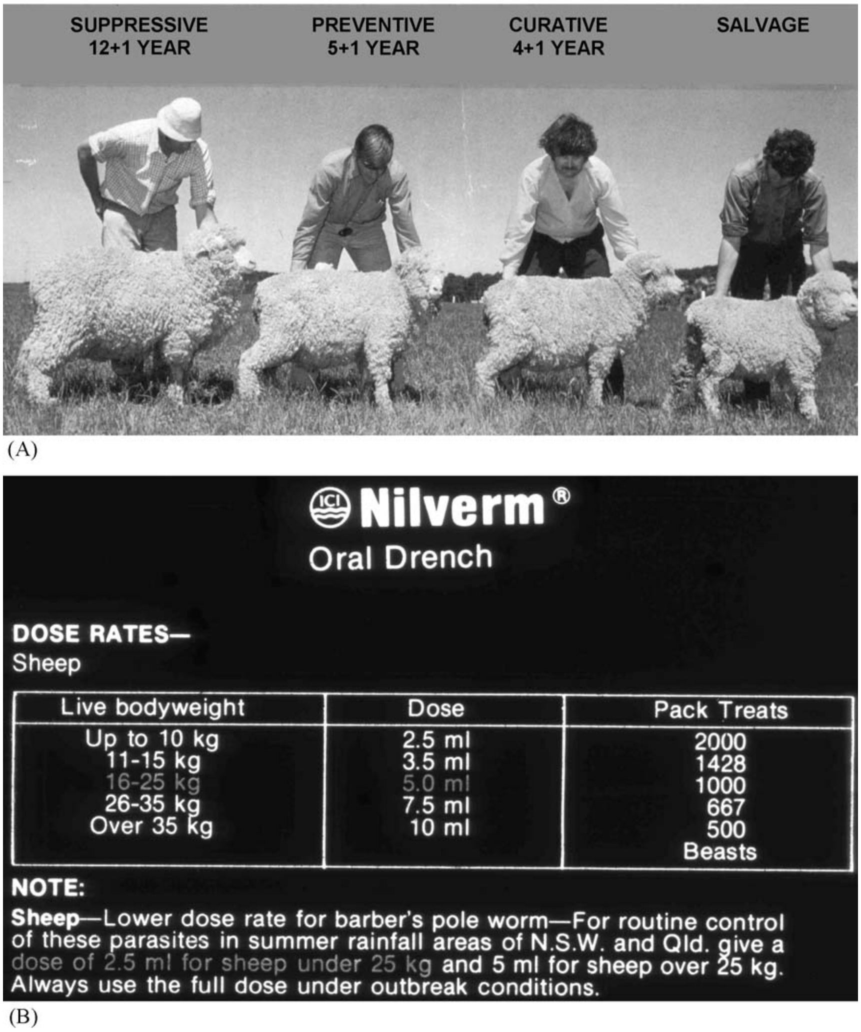


Fig. 3. Pharmaceutical company promotion and recommendations for the treatment of sheep with the anthelmintic ‘wonder’ drugs in Australia during the 1960–1980s. (A) Comparison of different frequencies of Thibenzole® (thiabendazole 44 mg/kg: Merck, Sharpe & Dohme) treatment given to weaner Merino sheep. Visual assessment to promote the concept of ‘suppressive’ (monthly) anthelmintic treatment. (B) Half dosing recommendation with Nilverm® (levamisole 7.5 mg/kg: ICI Australia) to control *Haemonchus contortus*.

problem that they had was supplying enough drench to farmers clamouring for these products, but also for the sheep industry, which in Australia was approximately twice the size of current estimates. However, one would have expected that matters would not have been so rosy for non-drug-related veterinary parasitology research. Because at that time, a generally held notion was that control of worms in livestock could be achieved by the simple expedient of one or several treatments with the new anthelmintic wonder drugs – problem solved – and by implication no need for further research on parasites.

However, quite to the contrary, the 1960–1980s were precisely the time when veterinary parasitology flourished and many research institutions throughout the world reached their zenith during these decades. This apparent paradox could be attributed to the fact that the world economy was generally buoyant and governments of countries in the developed world with significant livestock industries, provided substantial core funding which underpinned activities at their research institutes. The need to write funding proposals to support the activities of veterinary parasitology researchers was virtually unheard of during these days and as a consequence, research often was of an altruistic, serendipitous nature. However, it certainly was the 'golden era' for both basic and applied veterinary parasitology research, resulting in the development of a vast information bank in a wide range of disciplines, such as: host/parasite immunology, physiology, pathology, epidemiology, ecology, etc.

At the same time, the pharmaceutical industry was pretty much doing their own thing, focused of course on the research and development (R&D) of new chemical actives. Some of the large multinational companies developed enormous R&D facilities (state of the art laboratories, field stations, etc.), scattered throughout the world, but concentrating on countries with large grazing livestock industries. Although much of their work was shrouded in secrecy (and still is of course for obvious commercial reasons), there was no shortage of elaborate and expensive new product launches – with the WAAVP conferences being a favoured forum – when scientists from the private and public sectors 'rubbed shoulders', and the chosen few from the public sector were very pleased indeed to be spoilt with drug company largesse which was legendary during this time. However, events were to change.

Attitudes started to harden against ruminant livestock and by association veterinary parasitology research. These were based on perceptions that ruminant livestock caused adverse environmental effects, such as on land degradation, green-house gas emissions and competition for food supply in a hungry world which could best be served by increasing plant rather than animal protein for human nutrition. Added to this was the sustained pressure from competition with synthetic fibre and cotton producers, which led to the virtual collapse of the wool industry towards the end of the last century. Also the very success of the pharmaceutical companies in producing modern anthelmintic wonder drugs, solved the problem of worm parasites in livestock—at least in the minds of many who controlled the financial destiny of veterinary parasitology research.

As a consequence of these negative influences, there was a severe and sustained reduction in veterinary parasitological research and extension to the grazing livestock industries. The mid 1990s onwards has witnessed the virtual dismantling of some of the bastions of applied veterinary parasitology research throughout the world. Of course this was not uniform, with some institutions being relatively unaffected and a very few actually expanding, but some have effectively disappeared leaving regions or countries virtually bereft of veterinary parasitology expertise. Unfortunately this has come at a time when I believe they are most needed.

2. Contemporary issues impacting on industries in relation to parasite control

2.1. Anthelmintic resistance

Firstly was the development of anthelmintic resistance in all the major nematode parasite species of small ruminants. The reality now is that no country in the world where sheep and goats are raised would not consider anthelmintic resistance as a very serious, if not the most important, problem that their producers now have to face (Kaplan, 2004). There is depressing sense of *déjà vu* when one considers that resistance has occurred in all target organisms in chronological sequence to their release (see Fig. 1), so we should certainly have been forewarned of its inevitable appearance with anthelmintics.

One unfortunate fact with the modern anthelmintics was that their very success – with remarkable properties of efficacy, spectrum of activity, safety, ease of use and cheapness – was largely responsible for their downfall. Unfortunately these sophisticated compounds were generally not used in a sophisticated manner, being often overused, misused, or applied incorrectly.

Many technical and research personnel with drug companies were faced with a dilemma. Recognizing that the way to preserve the lifelong effectiveness of their new anthelmintic product meant that it had to be used sparingly and often combined with other means of control. However, they were faced with the economic realities that the company must sell as much product as possible to not only recoup R&D costs, but to make profits so as to keep their shareholders happy before patent protection lapsed. Altruism does not always coexist happily with short-term financial imperatives of the marketplace.

2.2. Costs of anthelmintic research and development

Secondly and more or less concomitantly with the increasing pace in the development of anthelmintic resistance in the sheep and goat industries in the warmer regions of the world, was the exponentially increasing costs associated with R&D for new chemical activities that the pharmaceutical industry had to confront. These increasing costs were largely brought about by the ever increasing rigour imposed by drug registration authorities which progressively adopted a 'zero risk' mentality. Near-miraculous effect on specified target pests had to be demonstrated, whilst at the same time being totally benign to other organisms (both vertebrate and invertebrate), for any new drug in each country where the new product was to be comercially released. Costs of R&D seem difficult to quantify, depending on whether this embraces ongoing fully funded effort, or just the development costs specific for getting a molecule to market. However, either way they are huge. Witty (1999), quotes this figure to be between US$ 50–100m, whereas McKellar (1994), estimates this to be US$ 230m. Wherever the costs lie, they are a quantum leap from the US$ 30m in the two decades or so, since ivermectin entered the market place (Hotson, 1985). It would be interesting indeed to be informed of the current costs, but it seems as though the process is very costly and lengthy (>10 years), in a situation where the global animal health market for sheep is approximately 5% of total animal health sales (Wood Mackenzie, 2005). Although patenting for new actives is still going on apace, with more than 60 patent applications for novel anthelmintics being lodged in 2003 alone, the salutory fact is that there has not been a new anthelmintic class for ruminants appearing on the marketplace since 1981 (McKellar and Jackson, 2004).

2.3. Dynamics of the pharmaceutical industry

Thirdly and again an event associated with the pharmaceutical industry, is the economic and structural changes which also have been going on apace in the last couple of decades. Consolidations among traditional animal health companies over the last 15 years have drastically reduced the number of companies devoted to veterinary drug discovery (see Fig. 4). This in turn has marked a declining trend in global investment in R&D in traditional animal health products (Geary et al., 2004). Coupled with this is the fact that anthelmintic product portfolios held by these multinational 'super' companies are aging. As patent protection lapses, this opens up the market to generic competition. On face value, this would appear to be beneficial to the consumers (livestock producers) as increasing competition is inevitably accompanied by price reductions, but at the same time it increases the risk of substandard product entering the marketplace and reduces the income that can support pharmaceutical R&D.

2.4. Public perceptions

Fourthly are the pressures that have come to bear on both the livestock and pharmaceutical industries by public concerns about two quite different issues—animal welfare on one hand, and drug residues in livestock products and the environment on the other.

2.4.1. Animal welfare

Leaving aside the impact of animal rights, particularly the more extreme elements, on the activities for both the private and public sectors involved in veterinary parasitology R&D, are the emotive issues associated with animal welfare that has become increasingly important for the intensive (housed)

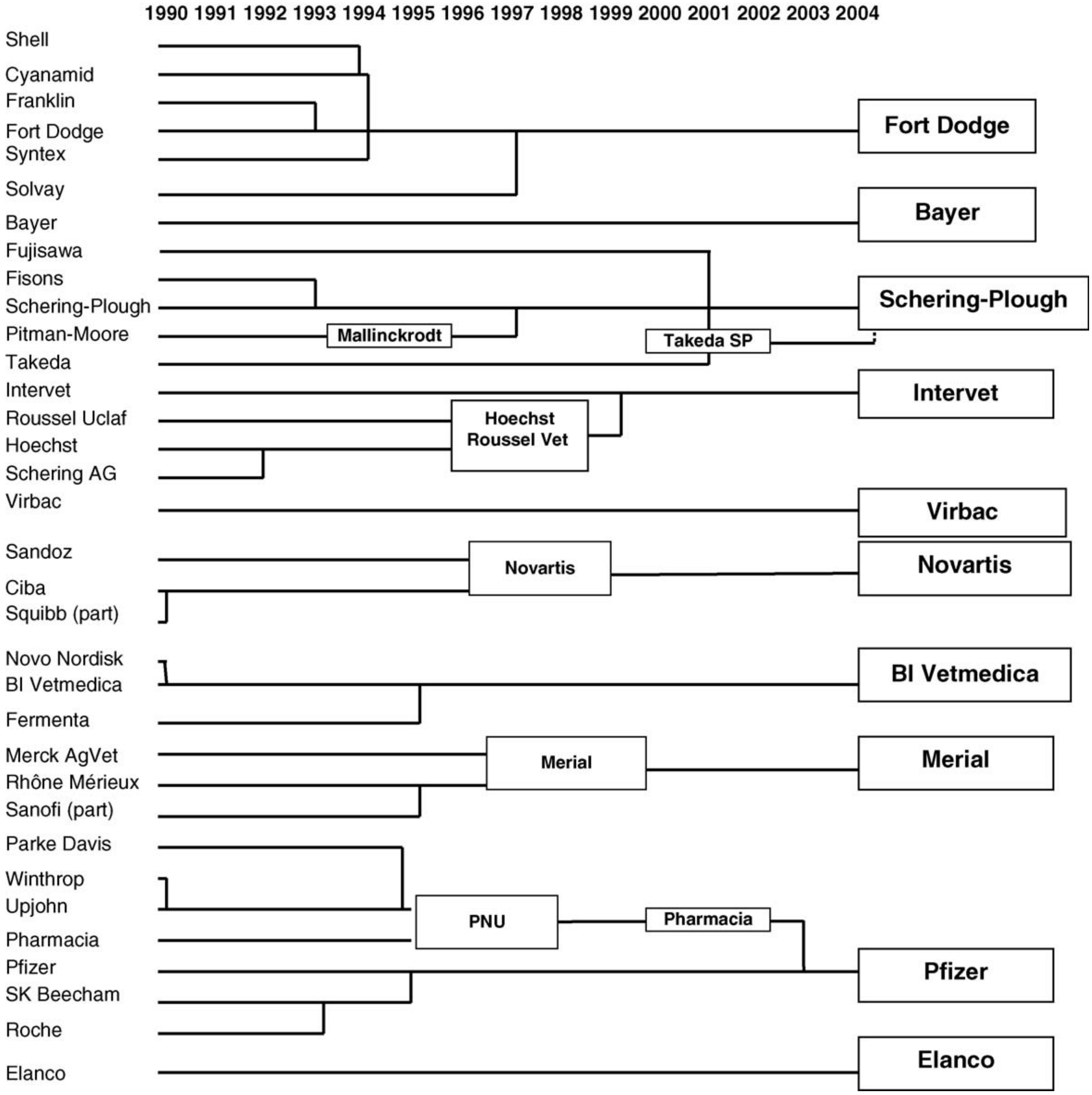


Fig. 4. Evolution of the animal pharmaceutical industry 1990–2004 (reproduced with permission of R. Nicholas and T.G. Geary).

livestock industries of Europe. Housing of ruminant livestock, particularly from spring through to autumn, is becoming increasingly more difficult to justify in this part of the world. The public now demand that cattle, sheep and goats are allowed access to grazing during the pasture growing season in Europe. In addition, ruminants now graze for increasingly longer periods on pasture in Europe for economic reasons (i.e. reduce the costs of housing and hand feeding) and also due to the apparent change in weather conditions where recently winters tend to be shorter and milder and the spring – autumn period, warmer and wetter. This extended time grazing increases the exposure of animals to pasture-borne parasitic infections for owners of livestock who are not experienced, or educated, in these problems and this matter certainly does not enter into the public consciousness as part of the animal welfare debate.

Coupled with this is the rapid trend towards organic farming, especially in Europe driven, as I see it, mainly by government subsidies paid to producers, rather than a public clamouring for organically produced animal products. European Union subsidies introduced in 1987 has resulted in an overall estimate of 2.5% of farms being organic in 1999, with the Nordic countries, Italy and Austria in the order of 5–9% (see; http://www.organic-europe.net/europe_eu/statistics.asp). The 'aura of purity' linked to organic farming often by beguiling advertising, can certainly have its down side. This is because it seems to me that unfortunately many farmers consider that to go organic simply means to stop drenching (along with other chemical inputs to their enterprise), without any serious consideration as to how their animals on pasture should be managed to control parasites. In recent years, I have witnessed, and also been informed by my European veterinary/parasitologist colleagues, of an alarming increase in the number of 'textbook' cases of clinical parasitism in sheep flocks in Europe raised organically by owners ignorant of how sheep become infected with parasites and the consequences on animal health and productivity. I firmly believe that there is a need to define new standards for treatments in the organic or the 'green' sector, where presently there is a blanket ban on the prophylactic use of all drugs.

2.4.2. Drug residues

Now turning to the precieved public concerns of drug residues in food (meat and milk) and the environment. With regards to contamination of food for human consumption, I believe that anthelmintic residues fall off the scale towards insignificance when put into context with ecto-parasiticides and particularly chemical contaminants used for horticultural, or industrial purposes. This is particularly so when one considers how generally infrequently anthelmintics are used and almost always concentrated on a minor proportion (generally young animals) of the herd or flock. Furthermore, many veterinary anthelmintics are also licensed for use in humans, hence their safety profile is well known and the risks posed by minute residues in animal products is infinitessimally small.

With regards to the ecotoxicity issue of anthelmintics. There is no doubt that in certain circumstances anthelmintics have the potential for localised, short-term, negative environmental effects on coprophilic organisms (particularly dung beetles), but I consider that these circumstances are relatively rare and thus of little consequence. Furthermore, I believe that a lot of the emotion, sometimes bordering on hysteria conjuring up the 'Silent Spring' scenario regarding anthelmintics and the environment, can be attributed to the selective use of information, or misinformation, by those with a vested interest. Here I include the hyerbole used by some researchers wishing to present a 'non-chemical case' for projects they wish to conduct on parasite control in livestock, in the best light to potential funding bodies. Demonstrating the presence of anthelmintic drug in the environment using exquisitely sensitive analytical apparatus is one thing, but demonstrating significant perturbations to the biomass that are anything more than ephemeral, is another. Not wishing to be an apologist to the drug industry on this matter, it seems to me that it does not matter how much pro-active research is done to prove that anthelmintic residues are environmentally bio-benign for the vast majority of scenarios, it only takes one individual – often unencumbered with solid evidence – to publically state that this is not the case for them to be believed and the drug company(s) forced to react, or if they do not, be automatically branded as villians. The consequences of broad acre application of herbicides, fungicides and insecticides, including fertilizer, need to enter into any balanced debate with regards to the impact of man-induced chemical application to the environment.

So these are the current issues and their impact on parasite control in production livestock as I see them. I would now like to present my view of the challenges that researchers, technologists and extensionists in academia and industry (both private and government) now face in bringing to the market innovative solutions for nematode parasite control for the production livestock industries. Novel methods of control are needed. These will include novel actives, as well as novel approaches or applications, both chemical and non-chemical.

3. Current practices and future challenges to industry with regards to parasite control

3.1. New anthelmintics

Anthelmintics still, and will for the foreseeable future, comprise the largest sector of the animal pharmaceutical industry by volume and value and for which the cattle market accounts for the greatest sales (Geary et al., 2004; McKellar and Jackson, 2004). The cattle anthelmintic market is well served by the available drugs, although concerns are now being expressed with regards to the emergence of macrocyclic lactone resistance in cattle parasites, particularly in the intensive beef operations found in New Zealand and Latin America, where suppressive anthelmintic treatment is currently being practised (a less than surprising result). So despite the needs of countries, which have substantial sheep industries, notably Australia, South Africa, Brazil and New Zealand, and by implication substantial anthelmintic resistance problems, the development agenda for new anthelmintic products will largely be driven by the cattle and the companion animal market.

However, no matter how you look at it, really the veterinary market is only minor when compared with the human drug arena. Block-buster drugs in human medicine achieve sales >US$ 1 billion/year, whereas few veterinary drugs exceed sales of US$ 100 million/year (Geary et al., 2004). So with the R&D costs and risks exploding, it is not surprising that that many companies conclude that it is financially unrewarding to invest in veterinary anthelmintic research.

3.2. *'Responsible use' of anthelmintics*

Using anthelmintic products in a responsible way maybe too late for many sheep and goat farmers throughout the world, because of resistance. By definition, a responsible way usually means less often and to achieve this may well mean government intervention. This has happened in Scandinavia where anthelmintics for use in production animals are sold only on prescription from veterinarians who firstly must make a diagnosis of parasitism. This practice relies on a more therapeutic than prophylactic approach and often takes no account of subclinical losses, widely considered to be the source of greatest economic loss. However, if this is more universally adopted then it will be even a further disincentive for the pharmaceutical industry to invest into anthelmintic R&D.

So it has now become a generally recognized fact by researchers, and to an increasing extent by producers, that the anthelmintic arsenal for production livestock is unlikely to be expanded in the foreseeable future. Those associated with the sheep and goat industries, particularly in Australia and South Africa have realized for some time that the only way that these industries can cope with parasites in the face of escalating, or existing high level, of anthelmintic resistance is to 'live with worms'. Recognizing the importance of maintaining a level of parasitism in the flock is a good thing from the standpoint of inducing and maintaining naturally acquired immunity in grazing animals, as well as preserving anthelmintic susceptibility by not exposing the entire worm population to drug selection. Towards this goal, Australian researchers have developed a web-based interactive program called WormBoss for farmers to use for managing parasites in their flocks in the face of high level of anthelmintic resistance (see http://www.wormboss.com.au). Also most veterinary parasitologists would be well aware of the FAMACHA system developed by the South African researchers that is aimed at identification of only those animals in a flock that need anthelmintic treatment in *H. contortus* endemic areas (Malan et al., 2001). However, there still a need for cheap, reliable diagnostic methods to indicate individual animals needing treatment, where *Teladorsagia*/*Trichostrongylus* spp., dominate.

Development work is still proceeding on these procedures, which is largely financially underwritten by producer organizations and government funding agencies, but the manufacturers of anthelmintics for sheep and goats have shown both moral as well as financial support for this type of research.

Thus there is a paradigm shift in the way to deal with parasites in production animals—away from hard control and the chemical 'big hit' approach, to something more akin to parasite management, i.e. living with parasites. These novel control methods will assist in maintaining parasite infections below the economic threshold, related not only to efficiency of treatment, but to the epidemiology of parasite infection, animal management practices and other considerations (Ketzis et al., in press). However, to be seriously considered for adoption, livestock producers will need assurance that they will achieve a reliable benefit if and when a novel control method is used, provided of course that these are used correctly.

3.3. *Non-chemotherapeutic approaches*

Non-chemical approaches, such as worm vaccines and biological control using nematophagous fungi (specifically *Duddingtonia flagrans*) remain active research areas, which have received support both from the public and private industry. Both areas are non-chemotherapeutic, but no longer considered novel using the strict definition of 'novel' being 'new' or 'recent', as both have been researched now for several decades. Clearly there are commercial opportunities in both areas, provided they meet the criteria of being reliable. Judging from specific review presentations and scientific sessions on worm vaccines and biological control at both this conference and recent meetings with a similar theme (see proceedings/abstracts of WAAVP Conferences Christchurch, New Orleans; Novel Approaches to the Control of Helminth Parasites Workshop, Merida, etc.), it is apparent that further work remains to be done before commercial products will be available. The best way of achieving this is through R&D partnerships involving both the private and public sectors.

3.4. Anthelmintic plants

Under the non-chemotherapeutic umbrella for parasite control is the currently fashionable area of 'natural product' therapy. This has a solid basis, as modern pharmacopoeia – both medical and veterinary – have as their foundation, drugs derived from plants or synthetic analogues of herbal compounds. The origins are steeped in antiquity, particularly from Asian traditional medicine, but also important (but less publicized) is the ethno-medicine practices of Africa. The increasing popularity in the Western world seems to be matched by the skepticism of increasing numbers who consider that traditional, or ethno-medicine, which does not follow the conventional paradigms of scientific proof of efficacy, is without a place in the sophisticated modern world, often associated with superstition and in the domain of 'quacks' (Githiori et al., 2005). However, medicinal plants will continue to play an important role in the control of both human and veterinary diseases, not only in the developing countries, but apparently ever increasingly in the industrialised countries of the world. Thus, there needs to be some common dialogue established. Within the current control methods which rely on unproven remedies, such as herbal or homeopathic treatments, it is appropriate for scientists to reveal the presumed shortcomings of therapies chosen to meet political and/or emotional demands, rather than those based solely on scientific standards, while at the same time being able to recommend mutually acceptable alternatives (Geary et al., 2004). Although the negative epithet of 'bio-prospecting' seems to be linked with any activity of the pharmaceutical industry in this field, much will be gained by private industry researchers working with those in the public domain, including 'traditional healers' to elucidate the benefits, or otherwise, of natural product therapy (Githiori et al., 2005).

Considerable research interest is now being shown of crops containing plant secondary compounds (or nutracines), which are considered for their beneficial effect upon the health of production livestock, rather than on their direct contribution to the nutrition of animals (Waller and Thamsborg, 2004). Most interest has focused on the plants containing polyphenols, or condensed tannins. Initial enthusiasm that these compounds had a direct anthelmintic effect and/or by forming non-bio-degradable complexes with protein in the rumen acted as "natures protected protein", has now been tempered by the variable and inconsistent results from subsequent studies. There are many reasons which could account for this (Waller and Thamsborg, 2004), but in addition it is important that parasitologists becoming enthused by this research activity, recognize the enormous body of evidence assembled by animal nutritionists, that plants containing high levels of tannins are either unpalatable, or if acquired in quantity (such as animals deprived of any other food source), result in severe disturbances to ruminal/gut flora and thus are anti-metabolic to the animal (Brooker, 1999). However, further research in the area of nutraceutical plants and their effects on parasitised livestock is worthwhile persuing, with greatest opportunity for funding likely to be from the public sector.

3.5. Breeding programmes for worm resistance

In theory, genetically resistant hosts are the ultimate in sustainable parasite control, being a low-cost, permanent solution requiring no extra resources and incurring no additional costs. The problem is that for most species of ruminant livestock, those that have evolved to be highly resistant to parasite infection are not generously endowed with desirable productivity traits for wool, meat, or milk production. These innately resistant breeds are found in the tropics, where the formidable combination of malnutrition, environmental stress, long-term and often massive larval challenge and limited relief by way of effective anthelmintic treatment, have imposed the harshest conditions for selection, resulting in survival of the fittest. However, attempts are being made to identify those genes that encode parasite resistance in laboratory animal models (Behnke et al., 2000). With the aid of comparative genomic maps, the aim is to then identify the locations of similar genes in ruminants and develop transgenic animals in which genes for resistance are inserted into economically productive breeds.

Even with the more productive, but more parasite susceptible, sheep breeds that have evolved in the temperate regions of the world, within-breed selection for nematode resistance has made good progress, particularly in Australia and New Zealand. Resistance can be measured by a variety of techniques, but the most common method is by estimating worm egg counts in faeces. When conducted on young sheep, faecal egg counts represent a reasonably direct correlation with worm burden, which has been shown to be heritable. These concepts have been championed by researchers and now actively adopted by producers, e.g. Australian Merino Breeders Worm Control Network (Nemesis Programme); New Zealand Sheep Breeders Association (WormFEC Programme).

Irrespective of the benefits that have come from the use of host genetics to control nematode infections, progress is likely to be slow (generation interval of livestock is long), controversial (if transgenic animals are used) and uncertain (side-by-side evolution of parasites to changes in host genotype; inverse relationship between resistance and performance). Nevertheless the hard-won (in some cases several decades of selection), tangible benefits resulting from using worm resistance as an index in breeding programmes by large-scale producers of the Australian and New Zealand sheep industries are almost certainly going to have continuing appeal. However, whether resistance, or resilience, to worm infection should be the selection index of choice remain an issue of debate amongst researchers and thus a source of confusion amongst sheep breeders.

3.6. The changing profile of livestock production

In the context of current and future perspectives for industry in the development of novel methods of helminth control in livestock, it is very pertinent to look at this in relation to changes in international trade and environmental policies. Dismantling protective trade barriers and tariffs in Europe and North America for livestock products will be a drawn out and hard won process, despite the rhetoric of the G8 meetings. However, evidence is clear that grazing livestock production is shifting from the wealthier countries with temperate climates toward poorer and warmer regions of the world. To illustrate this, the numbers of cattle, sheep, goats and pigs have shown substantial increases in the 20 years up to 1995 in the developing world (see Schillhorn van Veen, 1999; Table 1). In contrast there has been a commensurate contraction in the same industries in the developed world, except for goats but the baseline for goat numbers in latter region is less than 5% of those in the developing world. Additionally it is expected that the world population will increase by a further 2.5 billion by the year 2020 and food demand in developing countries is expected to increase 80% for cereals and over 100% for meat. This increase poses tremendous challenges for the world economy and especially the rural/agricultural sector. Also a compounding factor in these extrapolations must be the realization that this expansion is precisely in those areas of the world which are accorded developing nation status by the United Nations, thus requiring particular assistance from the wealthy countries of the world (Fig. 5).

Livestock raised under conditions in the developing world will require more rigorous parasite control practices and this could well activate the apparently

Table 1
Changing demographics of livestock (millions) in the developing and developed countries of the world (1975–1995)

	Developing countries			Developed countries		
	1975	1995	% Increase	1975	1995	% Increase
Cattle	739	942	+27	448	364	−19
Sheep	523	639	+22	523	428	−18
Goats	389	607	+56	24	32	+33
Pigs	382	598	+56	302	302	0

From Schillhorn van Veen (1999).

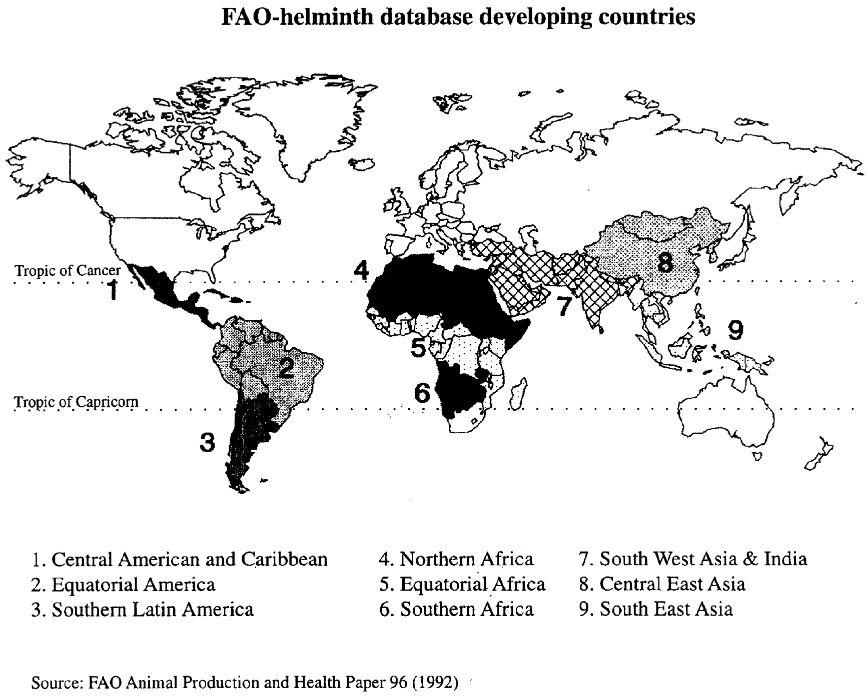


Fig. 5. Regions of the world accorded developing nation status by the Food and Agricultural Organization of the United Nations (source Anonymous, 1992).

dormant 'Development wing' of R&D activities for anthelmintics of the pharmaceutical industry (Geary et al., 2004). At the same time, rigid import restrictions based on livestock product quality are likely to always remain in place. Thus suggests that there will be an ever increasing need for expertise to assist countries with developing/emerging economies, to align their animal production to the standards of sustainability and product quality set by an increasingly more demanding and sophisticated consuming public.

4. Conclusion

The challenges to both the veterinary pharmaceutical industry and the publicly funded veterinary research industry to provide effective, sustainable methods of parasite control to the production livestock industries which in turn have to ensure that they are correctly adopted, have never been greater than at the present time. However, there are encouraging signs that these challenges are being met. What seems to be clear, at least in the public industry sector, is that the traditional approach of preserving research activities 'in-house' is now disappearing. Within the current environment of financial attrition and with it consolidation and contraction, progress in research – if not the very survival of research groups themselves – will only come about by more open collaboration and co-operation. Of course with this comes an urgent need for more sensible consideration by the managers of research scientists in specific institutions, of what is deemed to be 'intellectual property' or 'commercially sensitive' information. The temptation always will be to place a virtual blanket embargo on scientific disclosure of any kind by researchers, preventing them from dialogue with colleagues across institutes and at conferences, ultimately destining the researchers to scientific oblivion and by association, the research managers as well. However, there are encouraging signs of fruitful consortia being formed both within countries (e.g. Australian Sheep Industry Cooperative Research Centre) and between countries (e.g. European Commission Research Directorates), of research institutes who traditionally would have considered themselves as competitors, particularly for research funds. The prime aims of these research consortia are not simply the publication of results in the scientific literature, but in providing results as 'user friendly' products (e.g. see http://www.wormboss.com.au; http://www.wormcops.dk/), to assist the livestock industries in dealing with parasite control problems.

There are also encouraging signs of more active collaboration within the private industry sector towards the common goal of R&D of new drugs. Collaborations between relatively small, but highly focused biotechnology companies and the large multinational firms have been forged. Whereby the smaller company provides the target and the screening method, whilst the large pharmaceutical partner provides the chemical and developmental expertise (Geary et al., 2004). There is also a trend, particularly in Australia, where small veterinary/animal health companies are contracted to conduct evaluation trials necessary for assembling registration packages for new products of the large multinationals. These types of private industry collaborations are likely to extend to non-chemotherapeutics, if and when consistent, promising results come to fruition.

Additionally there is evidence that the producer organizations representing the production livestock industries are taking up the challenge of meeting the pressing needs of parasite control, in situations where both the pharmaceutical industry and governments accord these issues of low priority. For example in Australia, the Australian Wool Initiative Ltd. (AWI; http://www.woolinnovation.com.au) and the Meat and Livestock Australia (MLA; http://www.mla.com.au) are organizations created by producers, which financially support the development of new ways to control nematode parasites of sheep, where high levels of multiple anthelmintic resistance exist. These organizations provide the funding for situations outlined previously.

Thus it is my belief that the momentum for collaboration, both within and between industries, and across countries and continents, will continue. The vanguard for this will be through the scientists, extensionists, and technicians who should be allowed sufficient intellectual freedom and financial support to foster these activities. Open forums for discussion and sharing ideas are essential, and what better is the bi-annual WAAVP Conference? In this way I am confident that the 'industries' will meet the challenge for the development of novel methods of helminth control to serve the evolving livestock production systems of the world for the foreseeable future.

Acknowledgments

I wish to thank Drs. Ian Barger, Andrew Forbes, Timothy Geary, Arthur Redpath and Andrew Weatherley for reviewing this article and for their constructive suggestions.

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