Immunity to gastrointestinal nematode parasites in domestic stock with particular reference to sheep: A review

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ABSTRACT

One alternative to control of gastrointestinal nematode parasitism with anthelmintics may lie in genetic selection for resistance to infection and/or disease. Heritabilities for faecal egg count suggest that good selection responses can be achieved with Romney sires. Research must now identify markers that will accurately predict resistant and susceptible animals. To do this successfully, mechanisms associated with immune-competence, -tolerance and -expulsion and host resistance to these nematodes must be elucidated more fully.

This review examines local and systemic humoral and cell-mediated immunities to some of the GI nematode parasites infecting sheep, goats and cattle, with emphasis to sheep. Additional literature is presented indentifying some of the factors that may modify any responses; factors such as host nutrition, hormonal and reproductive status and genetics.

The overwhelming conclusion must be that significant large voids exist in our understanding of the processes of immunity exerted by domestic stock to combat infection with nematode helminths. Furthermore much latitude has been taken describing and interpreting observations since many are postulated from studies involving laboratory host-parasite models.

Keywords Nematodes; gastrointestinal; sheep; parasites; immunity; humoral; cell-mediated; affector; effector; mechanisms

INTRODUCTION

During the last decades we have witnessed renewed interest in aspects of research into gastrointestinal (GI) nematode parasitism in farmed ruminants and specifically, host-parasite interactions. Researchers have focused, with increasing interest, on genetic variation associated with faecal egg counts (FEC) and "responsiveness" of sheep, and to a lesser extent cattle, to infection by various GI lumen-dwelling nematode genera, in particular *Haemonchus, Osteragia* and *Trichostrongylus.* The inference is that much of the more recent experimentation is indirectly selecting for immunological responsiveness and therefore resistance to infection by species of these genera.

In fact, it appears that much of our current understanding of immune responses to these parasites has been produced using various rodent-parasite models in laboratory studies. (The reader is directed to the following reviews concerned with small laboratory animal-parasite models - Soulsby (1960), Ogilvie and Love (1974), Butterworth (1977), Mitchell (1979), Dineen (1978) and Wakelin (1985)). Although significant advances have been made in studies of effector and affector mechanisms involved in immune responses to parasites in rodents, little application and much speculation still exists with respect to immune responses to nematode parasites of the GI tract.

The present manuscript will endeavour to summarise current understanding of immunity to GI nematode parasites in farmed stock with emphasis on sheep, and to illustrate briefly some environmental features that may confuse, alter and compromise immune mechanisms.

It is not our intention at this time to summarise the broad and obviously complex interacting components of immunity in ruminants. For an overview we refer you to Hohenboken *et al.* (1986).

Effector Components of Immunity

Although nematode parasites inhabiting the gastrointestinal tract of sheep are generally considered lumenal dwellers, both larval and adult phases appear to induce definite immunological responses in their ruminant host. These responses, although not completely understood in terms of effector and affector components, fall into 3 classical responses:

1. Cell-mediated immunity;
2. Humoral or antibody immunity, and
3. Phagocytic immunity.

Clearly though, immune responses may be local and/or systemic in nature acting dependently or independently of each other and ultimately producing a highly complex interaction between host and parasite. To simplify what we understand as immune responses to GI nematode parasites each class of immune response will be treated separately illustrating the most significant facts and/or speculations that have been reported to this time

Cell-mediated immunity (CMI)

Cell-mediated immunity (CMI) is generally considered to be an integral part of inflammatory responses to tissue invasion. Researchers presently believe that mucosal inflammation may be an important initial effector mechanism of expulsion of worm burdens during self-cure and that immunoglobulins of the IgE class and mast cells play roles in the process (Wakelin, 1978).

Attention has been devoted to globule leucocytes and their roles in GI nematode infections. There is some evidence to link globule leucocyte numbers with resistance to infection by *T. colubriformis* in sheep (Dargie, 1982). These cells accumulated as degranulated mast cells in the abomasal and intestinal walls of sheep infected with *Haemonchus contortus, Trichostrongylus* spp and/or *Ostertagia* spp. Smith and Christie (1979) noted that these cells were more numerous in the abomasal walls of sheep resistant to infection by *Haemonchus contortus* whereas worm-free animals had few.

Research with *T. colubriformis* in guinea pigs supports the limited work completed with ovine definitive hosts. Dineen and Adams (1971) showed that T-cell lymphocytes were required for the primary response to *T. colubriformis* when they thymectomised these rodents. Subsequently Rothwell and Dineen (1972, 1973) showed that the CMI in guinea pigs was characterised by eosinophils, basophils and mast cells. Rothwell (1975a) subsequently revealed that self-cure in guinea pigs was accompanied by increased basophils and eosinophils in both blood and bone marrow. These granulocytes as well as mast cells accumulated locally at infected sites where they apparently degranulated. Rothwell concluded that increases of eosinophil numbers and histamine concentrations in the small intestinal mucosa may be the consequence of an effector stimulus, namely *T. colubriformis*. The precise mechanisms and effectors of expulsion are not known. The significance of histamine has been questioned from time to time and this will be dealt with later in this paper.

Efforts to discover the nature of the effector mechanism(s) for CMI have been vast, and innumerable studies remain to be undertaken in the ovine host. Briefly, most authors speculate that most CMI phenomena are T-cell mediated, and indeed the T-cell may be the basis for many features of resistance to infection (Rothwell, 1975b; Riffkin and Dobson, 1979; Dineen and Windon, 1980; Wakelin, 1985). Adams and Cripps (1977) summarised the significance of the lymphocyte to immunity to GI nematode infection. After noting that *T. colubriformis* affected lymphocyte behaviour, they concluded that induction and dissemination of immune responses require that lymphocytes migrate to the site of antigenic stimulation. Numbers of inflammatory cells may be mediated by T-lymphocytes since lymphocyte proliferation has been identified *in vitro* using antigens of *H. contortus* and *T. colubriformis* (Riffkin and Dobson, 1979; Dineen and Windon, 1980). In an earlier study, Wagland and Dineen (1965) had shown that injection of lymphoid tissue markedly enhanced immunity of guinea pigs to *T. colubriformis*. Recently, Mackenzie *et al.* (1984) found that administration of a cell-free leucocyte lysate enhanced immunological responsiveness after Ross *et al.* (1978) showed enhanced expression of immunity to *H. contortus* with leucocyte lysates from immune sheep.

Two cautionary notes should be raised that will be expanded upon later. Clearly CMI (and for that matter, humoral immunity), can be significantly affected by environmental host and parasite affector mechanisms. Secondly, it should be noted that resistance (and susceptibility) have non-immunologically based components; innate resistance to infection may well be in this class.

Humoral immunity

Humoral immunity to GI nematodes in sheep, although noted earlier, was obviously advanced and interest was kindled by Stewart who, publishing data from numerous trials, showed clearly that the host recognised *H. contortus* and *T. colubriformis* parasite antigens when he detected complement fixing antibody circulating in sheep after larval challenge (Stewart, 1950a,b). Stewart (1950a,b) also noted that acquired resistance was strengthened with serial challenge and that serum antibody titre rose at the time of self-cure FEC decline. Recent efforts by researchers in Australia to differentiate "responsive" and "non-responsive" sheep have used titre of circulating complement-fixing antibodies to assist with genetic selection studies. Present trials have been designed to quantify variation between sires and dams by measuring lamb progeny resistance to infection by *T. colubriformis* (Windon and Dineen, 1981, 1984; Windon *et al.*, 1984).Smith (1977), Smith and Christie (1978) and Charley *et al.* (1981), studied antibodies to *H. contortus* larvae in hyperinfected and irradiated larvae vaccinated sheep. More recently, Charley-Poulain *et al.* (1984), in continued efforts to characterise antibody responses of sheep to *H. contortus*, found only low systemic IgG and IgM titres to egg derived antigens after primary infection. A second infection produced only slight antibody increases of doubtful significance. If these results reflect poor worm antigenicity or antibody complexing with antigens in circulation, the lack of response may be due to antigen purity (Charley-Poulain *et al.*, 1984). Smith and Christie (1978) also encountered difficulties in detecting circulating antibodies (IgG subclass), even though their efforts showed local IgA and IgG antilarval antibodies to *H. contortus*.

The eosinophil and eosinophilia during infection have received considerable attention by workers because of the killing potential of this granular

leucocyte (Butterworth, 1977). As early as 1963, circulating eosinophilia was documented by Gallagher in sheep infected with trichostrongyles and this was further described by Huxtable and Rothwell (1975). Tissue eosinophilia is thought to be mediated by mast cell degranulation and stage specific IgE, both having roles in releasing chemotactic factor(s). Eosinophils may, in this case, become killer cells, induced by antibody adherence to tissue-dwelling phases of the nematodes during ecdysis. At this time of infection, neutrophils are numerous and parent mast cells (and globule leucocytes) accumulated in the gut wall (Leid and Williams, 1979). Macrophages may also be numerous in inflamed regions of the gut but their primary role is to phagocytose cellular and parasite debris. The roles and significances of eosinophils and neutrophils in immunity to *T. colubriformis* are still unclear after Dineen *et al.* (1978) and Dineen and Windon (1980) found that quantities of both in tissues were positively correlated with worm counts. They concluded that since globule leucocytes negatively correlated with parasite numbers the latter were involved in the immune resistance mechanism whereas the former 2 cell-types were not.

Although investigations relating GI nematode infections in sheep to local antibody interactions have been extremely limited, local immune responses have been identified at the mucosal surface (Smith, 1977; Duncan *et al.*, 1978; Smith and Christie, 1978; Smith and Angus, 1980; Charley-Poulain *et al.*, 1984). IgA and IgG can be detected in the abomasal mucosa as early as 6 days after larval challenge with *H. contortus* (Smith, 1977; Smith and Christie, 1978). Charley-Poulain *et al.* (1984) detected musocal-bound IgA, IgG and IgM coincident with self-cure (approximately 10 days after a challenge dose of 1000 L_3 *H. contortus* was given.) These researchers showed that local IgA (antilarval) rose with falling FEC and concluded that IgA concentrations were directly influenced by local antigens. Probably the most important observations these workers made were that IgA levels fell very rapidly after self-cure and L_3 and L_3L_4 antigens were most stimulatory for IgA production. The former observation further supports the argument that threshold levels of immunological stimulation must be attained for expression of resistance to infection, or ultimately self-cure (Dineen, 1963; Dineen, Donald, Wagland and Offner, 1965; Dineen, Donald, Wagland and Turner, 1965; Michel, 1963; Windon *et al.*, 1984). The implication is that self-cure is the result of increasing larval intake and therefore is worm burden and larval challenge dependent. Additionally, this evidence suggests that local immunity may not be of a 'protective' nature that would be reasserted with subsequent exposures.

Thus, the sheep is assaulted with a complex of what Soulsby (1960) terms 'protective' and 'non-protective' parasite-based antigens from the moment of ingestion of larvae. A highly complex series of immunological (and non-immunological) responses is mounted to combat the foreign body and resulting tissue damage. Stimuli may be highly specific in inducing numerous effector mechanism(s)/responses with immunological bases. However, the general consensus is that the final effector for expression of immunity to infection (resistance) is likely non-specific (Dineen *et al.*, 1977) with CMI, HI and PI components.

Modification and Modulation of Immunity

It appears probable that many environmentally related features, host and parasite, may directly or indirectly influence the effectiveness of specific and non-specific immune responses mounted by the host. Only some of the more important factors with animal production implications will be discussed at this time. Generally, they fall into 2 categories depending whether the basis of an affector mechanism is host or parasite. Only various host affector factors will be discussed at this time.

Nutrition

Mineral deficiencies have been known to affect blood leucocyte activities and antigen-antibody binding on various diseases (see Miller, 1985). Only recently, Yong *et al.* (1985) demonstrated that copper deficiency could have a role in CMI to *Trichostrongylus* spp, even though white blood cell (WBC) numbers were not obviously altered. Although selenium appears to be associated with immunocompetence, the mechanism remains elusive. Another trace element, zinc, when in deficient concentration may induce thymus atrophy. This will interfere with T-cell dependent immunity and can result in depressed expression of humoral immunity as a result of fewer IgM and IgG plaque-forming cells.

Macro-elements have also been implicated in host-disease interactions. Magnesium apparently can influence serum and plasma levels of IgG and antibody-producing cells in mice, whereas decline of phosphorus concentration in serum has been positively correlated with peripheral leucocyte numbers (see Miller, 1985).

It is generally accepted that animals on elevated planes of nutrition naturally express better resistance to infection and to disease, directly related to patho-physiological impairment (Symons and Steel, 1978). Many studies have shown that dietary protein influences GI nematode establishment and expression of parasitic disease (Poeschel and Todd, 1969; Jackson and Christie, 1979, 1984; Abbott *et al.*, 1985a,b). Furthermore, in his recent review of the subject, Coop (1981) noted that GI parasitism compromises animal growth and production by various mechanisms including malabsorption, alteration of digestibility and induction of inappetence. He pointed out that although anthelmintic administration removes worm burdens and improves nutrient utilisation, appetite may remain seriously affected thereby

compromising dietary protein intake. Inconsequence, depression of dietary protein and mineral uptake and absorption will have far reaching implications beyond the traditionally recognised skeletal, body and tissue components. As well blood protein concentratons and ultimately CMI and HI may be seriously affected.

Recent work by Wagland *et al.* (1984) documents that, within dietary groups, CF antibodies against worm antigents correlated to resistance as measured by numbers of eggs produced/female worm/day and total worm counts. They found that animals on the higher plane of nutrition had elevated titres, at the same time when FEC was considerably lower. A negative correlation between live weight gain and antibody titre was observed with the overall conclusion that development of immunity competes with live weight gain for limiting essential resources. These results also prompted these researchers to conclude that the "inflammatory response" could be an essential effector for expression of resistance to infection. Finally, they suggested that a genetic link between resistance to infection and animal productivity is unlikely.

Lactation

Lactating ewes have long been observed to be highly susceptible to GI nematodes. The phenomenon is commonly referred to as peri-parturient rise (PPR). Brown *et al.* (1981/a,b) proposed that the condition resulted from deficiency of IgA producing cells in the gut. Smith *et al.* (1983) however, recently observed that neutrophils and eosinophils continued to be present in large numbers in gastric lymph, thereby showing that gut damage (induced by *Ostertagia circumcincta* in this case) continued to elicit a strong local inflammation. Furthermore, they observed that localised lymphocyte numbers and IgA concentrations were not depressed in lactating as compared to dry ewes. These data suggest T-cell mechanisms and not local components may be more important in depressing (or suppressing) immunity in these animals. Data collected by O'Sullivan and Donald (1973) appear to conflict with those of Smith *et al.* (1983), since the former found depressed globule leucocyte numbers in the mucosa of pregnant and lactating ewes. This is further confused by Ogilvie *et al.* (1977) who observed with *Nippostrongylus brasiliensis* in rats that T-cells enhanced expulsion of worms. Dineen and Kelly (1972) extended this further noting in rats that lymphocytes 'primed' by *N. brasiliensis* did not differentiate into effector cells, an impairment that remains unsolved.

As a consequence of well-designed experiments, Chen and Soulsby (1976) showed that CMI, and in particular the blastogenic activity in leucocytes, was suppressed in ewes infected with *H. contortus* during lactation. Subsequently Soulsby (1981) was prompted to suggest that parturition was accompanied by a general suppression of inflammatory processes coinciding with increasing FEC and worm burdens. The actual mechanism(s) of this suppression remain unresolved for the large part, in all likelihood a complex host-parasite interaction.

Hormonal Involvement

Observations pertinent to this review are indeed few. However, the first noteworthy ones were those published by Dodson (1961) who found that when oestradiol was given to castrated rats *N. brasiliensis* burdens were depressed. This was followed with another observation that declining worm numbers coincided with onset of oestrus in females, while the decline of worm numbers was much more gradual.

These earlier results prompted a series of experiments by Dineen and Kelly (1972) and Kelly and Dineen (1973) who concluded that lactogenic hormones in rats directly or indirectly inhibit differentiation of sensitised lymphocytes to effector cells integral to worm expulsion.

Recently, Swanson *et al.* (1984) further expanded on these earlier works. These investigators found that gonadectomy performed on mice had completely different outcomes when male or female animals were used. Castrated males had lower worm burdens while their female counterparts yielded larger burdens. Further, female worms from the male mice produced lower egg counts than those from female mice. Further experimentation revealed that egg outputs were affected by testosterone implant therapy and that this treatment resulted in worm counts comparable to those of intact shams.

Immunochemistry

Recent immunochemical/biochemical studies published by Douch *et al.* (1983, 1984) open an entirely new and exciting avenue of study. As a result of these studies a mucus-bound substance having larval activity/obility inhibitory (LMI) properties has been postulated and is presently being isolated, purified and characterised. Previously, immediate hypersensitivity reactions mediated by histamine, 5HT and prostaglandins from mast cells were believed to be responsible for self-cure (Stewart, 1953; Rothwell, *et al.*, 1974; Richards *et al.*, 1977) in laboratory models. Douch *et al.* (1984) have shed doubt on this theory while observing no significant differences in histamine levels to correlate with differences in FEC whereas LMI substance levels were substantially elevated in sheep with low FEC at times of peak larval challenge on pasture.

Genetics

Clearly, the most conclusive evidence that host breed and breeding profoundly alter susceptibility arises from studies involving cattle and susceptibility to

various parasites in tropical zones. Frisch (1981) and Albers (1981) provide summaries for anyone interested.

Associations between haemoglobin type and susceptibility to GI helminths have received considerable attention. However, results have been inconsistent and apparently are dependent upon the parasite species involved. While various authors have noted increased resistance and ability to more readily self-cure associated with HbA type (Evans *et al.*, 1963; Jilek and Bradley, 1969; Allonby and Urquhart, 1976; Altaif and Dargie, 1978), Windon *et al.* (1980) found no supporting evidence. There is some evidence to suggest that animals that convert from HbA to HbC during anaemic stress resulting from excessive decline of blood haemoglobin (7%) are very susceptible to *H. contortus* (Altaif, 1975).

Studies involving sheep remain inconclusive with most studies undertaken in uncontrolled field trials. Urquhart (1968) noted breed differences with respect to responsiveness to *H. contortus* between Blackface and East African Merino given similar doses of larvae. Preston and Allonby (1979) reported that breed influenced susceptibility of sheep to *H. contortus* in Kenya. In Florida, Jilek and Bradley (1969) had earlier found that Florida Native sheep showed higher blood haemoglobin concentrations, packed cell volumes and resistance to natural infection when compared to Rambouillet grazing the same pastures. Recently, Donald *et al.* (1982) found that Border Leicester x Merino ewes exhibited lower PPR than Merino counterparts. A similar observation was noted by Courtney *et al.* (1984) who found no evidence in St Croix, 3/4 St Croix and Florida Native sheep of PPR that was present in Finn-Dorset x Rambouillet crosses and Rambouillet.

Sex

Evidence that susceptibility to GI nematodes is dependent on host gender is mounting steadily since Dobson (1961) showed variation between sexes of mice infected with *N. dubius (N. brasiliensis)* (Bawden, 1969; Dineen and Windon, 1980; Windon and Dineen, 1981; Windon *et al.*, 1984). Evidence suggests that ewe lambs are more responsive as measured by serum antibody levels that ram lambs to challenge following a vaccinating dose (Windon and Dineen, 1981; Windon *et al.*, 1984).

Reproductive Maturity

Susceptibility of the neonate to infectious agents including nematode parasites has received considerable attention. Both peri-natal resistance as well as passive colostral immunity must be included in the present discussion. Peri-natal resistance to parasitic infection is difficult to define and has received very minimal attention. This seemingly reflects the opinion that this has little bearing on the ultimate degree of immunity or expression of immunity since it would appear that active immunity is far more important for host resistance to infection. Mackenzie *et al.* (1984) suggest that innate resistance is largely non-immunological. The subject of peri-natal immunity was addressed by Riffkin and Dobson (1979) who found that lymphocytes of worm free lambs responded to larval and adult *H. contortus* antigens by undergoing blast transformation. Furthermore, Adams (1983) showed that effector mechanisms were capable of activation within 7 days of lamb birth. Neonatal responsiveness is significantly lower than that of an adult. Granberg (1980) showed that *in vitro* induction of cytotoxic lymphocytes in sheep (CMI) was deficient in neonatal lambs (14% of adult levels and rising to 80% by 6 months of age). Clearly, most are of the opinion that antibodies appear in a step-wise manner with exposure to antigens but that at an early age, continual challenge is essential to maintain antibody levels. The question of effectiveness and persistance of colostral antibody immunity has been put in serious doubt by Dineen *et al.* (1978) who observed that protection against *T. colubriformis* was not conferred from the dam after comparing colostrum-deprived lambs with those given colostrum.

Although neonates show immunity and immune responsiveness to many antigens apparently T-cell dependent mechanisms (CMI) have only been demonstrated in animals after a number of months. In his Ph.D. thesis, Valera-Diaz (1970) showed anti-*Haemonchus* IgA in ewe colostrum but that resistance to infection could not be transferred. He concluded that IgA might provide immediate local protection but that long-standing protection would not be achieved by infusion of these dam-based antibodies.

CONCLUSION

It is still anyone's guess whether mechanisms found in rodent models apply to farm stock since extensive application and examination of mechanisms identified by laboratory-rodent models have yet to be undertaken. During the last 10 to 15 years various researchers have become deeply involved in documenting mechanisms of immunity of farm animals to GI nematode parasites, but only the surface appears to have been touched.

Immunity to these parasites appears to be a very complex interactive series of events that often may be altered or affected by numerous environmental and host factors. The 3 major immune mechanisms are:

1. Cell-mediated immunity (CMI);
2. Humoral immunity (HI); and
3. Phagocytic immunity (PI).

All have been recognised in various farmed ruminants. However, there are many more inroads to be made before data can reveal the integrated and highly complex phenomena that produce resistance to these nematodes.

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