INTRODUCTION

It has long been recognized that the nutritional status of humans and animals influences their susceptibility to infectious disease, with famine and pestilence closely linked throughout history.

In humans, generalized protein-energy malnutrition (PEM) depresses a range of non-immune and immune defenses against disease and is considered the commonest cause of immunodeficiency in humans worldwide (Chandra, 1996), even acquiring its own acronym, NAIDS (Nutritionally Acquired Immune Dysfunction Syndromes) (Beisel, 1996). The greatest effects of PEM are on cell-mediated immunity and some non-immune defenses (e.g. lysosyme and gastric acid secretion, normal flora), with more variable effects on humoral (antibody-mediated) immunity (Gershwin et al., 1984). The consequence of this is a marked increase in susceptibility to some (e.g. tuberculosis, pneumonia, bacterial and viral diarrhea, measles) but not all (e.g. tetanus, viral encephalitis) diseases (Chandra, 1996).

Specific deficiencies of single nutrients can also have profound immunosuppressive effects in animals and humans and may interact to exacerbate the effects of generalized PEM or other deficiencies (Kubena and Murray, 1996). The most important of these nutrients in humans are vitamins A and C, and the trace metals zinc and iron, but there are many others (Beisel, 1996; Dendurli and Chandra, 1998). Paradoxically, moderate dietary restrictions are associated in some instances with enhanced immune function and enhanced longevity, the latter thought to be due, in part, to nutritionally-induced changes in the maturation of the immune system (Watson, 1984).

For farm animals there has been a similarly long recognition of, and tradition of investigation into, the links between nutrition and susceptibility to infectious disease, with particular emphasis on interactions between nutrition and gastro-intestinal nematode infection in ruminants. The latter has been the subject of numerous comprehensive reviews, most recently Sykes (2001); Coop and Kyriazakis (1999); Van Houtert and Sykes (1996) and Coop and Holmes (1996).

While the focus on nutrition/infectious disease interaction in human health is on detailing and reversing the suppressive effects of frank under- or mal-nutrition on disease resistance, interest amongst animal scientists focuses more on the enhancement of immune competence and disease resistance status with nutritional interventions in “normal” animals. There is also considerable interest in nutritional intervention to support or maintain normal animal function in the face of infectious disease, rather than to specifically increase resistance. The latter concept is known as “resilience” and needs to be differentiated from nutritionally-induced “resistance” to disease (Riffkin and Dobson, 1979). The terms can be defined as follows:

Resistance - The ability of a host to reduce the establishment, survival or reproductive rates of a pathogen. Susceptibility is the inverse of resistance.

Resilience - The ability of a host to limit the adverse effects of infection with a pathogen by mechanisms other than resistance.

Important in any discussion of both concepts is the understanding that the interaction between infectious disease and nutrition works both ways with infectious
disease status often having a profound effect on the nutritional status of the host. Recognition of this duality in farm animals (Whitlock et al., 1943) and human medicine (Scrimshaw et al., 1959) occurred considerably later than initial recognition of the effects of nutrition on resistance to disease. The nutritional consequences of gastrointestinal parasitism in sheep have been recently reviewed (Sykes, 2000).

From the foregoing it is clear that nutrition is an important modulator of disease resistance, operating via non-immune mechanisms and both the innate and adaptive branches of the immune system. It is also a potentially important modulator of disease resilience. The remainder of the review will focus on the nutritional modulation of gastro-intestinal nematodiasis (GIN), primarily in sheep and goats for which it is probably the most important disease condition worldwide. Key issues which we hope to address in the review include:

- The pathological consequences of GIN and the basis for them. It is from an understanding of this, that insights into the role of nutrition in combating GIN arise.
- The mechanisms of resistance and immunity to large metazoan parasites such as nematodes, particularly those residing in the gut.
- The extent to which host nutrition can modulate the development of resistance to GIN and the factors that influence this modulation.
- The timing of changes in resistance induced by nutrition and the extent to which such changes persist beyond the period of differential nutrition.
- The nutrients or other dietary components which are most important in mediating effects on resistance.

Given the scope of these issues our emphasis will be upon highlighting key principles and relationships, and drawing broad conclusions, with the reader directed to more detailed sources of information in specific areas. As sheep are one of the animal models most widely used in the study of nutritional modulation of resistance to nematode infection, and are the species that we have worked with primarily, the review will have a special focus on this species.

**IMPORTANCE AND PHYSIOLOGICAL IMPACT OF GASTROINTESTINAL NEMATODIASIS**

Gastrointestinal nematodiasis is a major animal health problem of domesticated small ruminants in both temperate (McLeod, 1995) and tropical (Walkden-Brown and Banks, 1986) areas and is undoubtedly the most important disease of sheep and goats worldwide. In Australia alone, the cost of GIN to the sheep industry in 1995, in both lost production and costs of control, was estimated to be $US114 million for an industry with a farm gate value of $US2.1 billion (McLeod, 1995; SAUD converted to $US at $1AUD=$0.50 US). The loss of production induced by GIN is due to reduced feed intake and reduced efficiency of feed utilization for productive purposes such as growth, wool production and reproduction. GIN is also a significant health problem for cattle, buffalo and monogastric domestic species.

The most economically important species of nematode affecting domestic ruminants all belong to the Order Strongylida and come from the family Trichostrongylidea. The major genera involved are *Haemonchus*, *Trichostrongylus* and *Ostertagia*. As adults these nematodes inhabit the abomasum or anterior small intestine. All of them are ingested off pasture as infective 3rd stage larvae (L3) and proceed through moults to L4 and then adult. The different stage larvae and the adults occupy different niches in the gut with differing degrees of direct contact with host tissues. While there are many common features in the pathogenesis and immune response to these nematodes it is worth noting that each represents a unique “disease” and that the effects on the host, and the host response, vary with both parasite species and the stage of the life cycle involved.

The pathological consequences of GIN have been the subject of numerous reviews (Sykes, 2000; Coop and Kyriazakis, 1999; Fox, 1997; Coop and Holmes, 1996; McRae, 1993, Parkins and Holmes, 1989; Holmes, 1987; Sykes, 1983; Symons and Steel, 1978; Steel, 1974). The key distinguishing features of the pathogenesis of GIN are marked reductions in voluntary feed intake of the host, and profound disturbances in the metabolism of protein, energy and some major minerals due in large part to the mounting of a gut-based immune response. In addition to causing production loss, these and other pathological changes, can result in clinical disease distinguished by hypoproteinemia and edema, anemia, diarrhea, and osteoporosis, depending on the species of nematode involved.

**Effects on feed intake**

Reduced feed intake is a typical but not invariable consequence of GIN, being in the range of 10-30% (Van Houtert and Sykes, 1996; Poppi et al., 1990). It is associated with both acute and chronic infection by a range of parasite species, irrespective of the primary site of parasitism in the gut. For example, in ruminants effects have been reported for nematode infections of the abomasum (*Haemonchus* spp., *Ostertagia* spp. *Trichostrongylus axei*), small intestine (*Trichostrongylus colubriformis*, *Nematodirus* spp., *Cooperia* spp.) and large intestine (*Oesophagostomum* spp. *Chabertia ovina*) (Steel, 1978). The magnitude of the depression in feed intake varies widely, from complete anorexia to mild inappetence, depending on a number of factors. The level of infection is
important. Steel (1978) reported dose-dependant reductions in feed intake in lambs trickle infected with doses of *T. colubriformis* L₃ ranging from 300 to 30,000 per week. Peak depression in feed intake ranged from undetectable to 66% and occurred 10 weeks after the initiation of infection. Equivalent infections with *Ostertagia circumcincta* induced much smaller reductions in feed intake, illustrating parasite species differences for this effect.

While GIN is associated with reduced feed intake infected animals appear to become more selective in their choice of foods. Kyriazakis et al. (1994) reported that when offered a choice between high and low protein foods, housed infected animals increased the proportion of high protein food in the diet. However, despite the exhibition of a dietary preference, total protein intake in infected animals was still reduced compared to uninfected animals. Co-evolution with parasites appears to have also influenced ruminant grazing behaviour. Hutchings et al. (1999) showed that the feeding choices made by sheep are influenced by complex interactions between fecal contamination of pastures, their nitrogen content, the feeding motivation of the host and its infection and immune status with regard gastro intestinal nematodes. In their study sheep with greater levels of infection, as assessed by fecal egg count, selected for a greater proportion of clover and hence consumed diets with a higher protein content.

Reductions in feed intake associated with GIN occur during the development of immunity, but strong immunity is generally associated with a complete recovery of feed intake. The mechanisms mediating parasite effects on feed intake remain obscure despite considerable attention (eg. Dynes et al., 1998). However, our understanding of the complex intercommunication between the neural, immune and endocrine systems at both a local and systemic level is developing rapidly and has recently been reviewed for gastro intestinal parasitism (Palmer and Greenwood-Van Meerveld, 2001). These authors show that interactions between the host’s nervous and immune systems can redirect activity in neuronal circuits intrinsic to the gut into an special repertoire of defensive and adaptive motor programs. They suggest that signaling molecules from both the parasite and host are able to initiate this functional reorganization of the parasitized gut via direct effects on nerve cell function and neurotransmission pathways in both the enteric and central nervous systems of the host.

**Effects on nutrient digestion and metabolism**

Pair feeding experiments with parasitized animals quickly established that reduced feed intake is often the major factor which accounts for the productive consequences of GIN. More specifically, growth in infected animals is most limited by the reduction in metabolizable protein (MP) supply. Bown et al. (1991) demonstrated that impaired growth as a result of GIN could be completely overcome by abomasal infusions of casein whereas infusions of glucose were significantly less effective. Although infection of the abomasum is associated with increases in gastric pH of up to pH 6.5 (Sykes, 2001), and infection of the small intestine with pronounced villous atrophy (Sykes and Coop, 1970), effects on true digestibility of dietary protein and energy are either absent (Poppi et al., 1986) or transient and small (Kimambo et al., 1988), probably due to compensatory digestion and absorption distal to the site of infection. In contrast, absorption of phosphorus during small intestinal infection (Wilson and Field, 1983) and copper during abomasal infection (Bang et al., 1990) are impaired.

Most of the adverse effects of GIN not accounted for by reduced feed intake and MP supply, are associated with increased endogenous secretion of protein into the gut in the form of blood, plasma, increased mucus production and increased epithelial cell turnover (Kimambo et al., 1988; Rowe et al., 1988). Some of these effects are due solely to the direct pathological actions of the parasite (eg. blood loss induced by *Haemonchus contortus*) but the majority are closely associated with the inflammatory and adaptive host immune response to infection which is discussed later in this review. These losses can be substantial, varying between 20-125 g protein/d lost into the gut in sheep infected with *T. colubriformis* (Poppi et al., 1986). The variation in protein loss reflects different stages of infection. Of these total losses, leakage of plasma accounts for 5-16 g protein/d in sheep and 30-58 g protein/d in calves depending on parasite species and severity and stage of infection (Parkins and Holmes, 1989). Estimates of erythrocyte losses by the same authors were 31 ml/d for *H. contortus* infection in sheep and 39 ml/d for *Oesophagostomum radiatum* infection in calves. The remaining protein loss into the gut is of endogenous origin namely mucus or sloughed epithelial cells of the gut. However, due to relatively intact intestinal protein digestion, losses of endogenous protein at the terminal ileum are substantially lower (5-30 g protein/d) (Kimambo et al., 1988; Rowe et al., 1988).

What are the costs of this enteric recycling of endogenous protein? Surprisingly perhaps, the energetic costs are small with McRae et al. (1982) demonstrating, by use of calorimetry, that infection with *T. colubriformis* does not increase energy expenditure. This is not to say that GIN has no effects on energy metabolism as reductions in feed intake associated with GIN reduce the gross efficiency of energy utilization for production by increasing the relative proportion of energy intake used for maintenance. The lack of effect of infection on total energy expenditure despite a large increase in protein cycling through the gut suggests that protein synthesis in other pools within the body is
reduced accordingly. The key problem with GIN appears to be increased protein synthesis in the gastro-intestinal tract with concomitant reductions in amino acid availability for protein synthesis in other tissues (MacRae, 1993). In normal cattle, the gut comprises about 5% of the total protein in the body, but contributes 25-45% of whole body protein synthesis, whereas skeletal muscle represents about 45% of total body protein but accounts for only 16-22% of whole body protein synthesis (Lobley et al., 1980). Clearly then, increases in the protein synthetic capacity of the gut have the capacity to significantly influence protein accretion in other tissues, particularly if the increase in synthetic activity is for proteins ultimately secreted into the lumen of the gut rather than exported to other tissues. Recent studies using sophisticated tracer kinetic methods have shown that whole body protein synthesis is unaffected in sheep infected with *T. colubriformis* (Yu et al., 2000; Bermingham et al., 2000). However Yu et al. (2000) showed that sequestration and oxidation of leucine in the gut increased by 30% during weeks 5-13 of infection, with proportional reductions in availability in other tissues such as skeletal muscle. This supports earlier reports of reduced protein synthesis in wool follicles and skeletal muscle (eg. Symons and Jones, 1985) and together with a reduction in feed intake and MP supply, probably explains the greater part of both clinical and sub-clinical effects of GIN on animal productivity.

It would seem then, that gastrointestinal nematodes achieve their effects on the host by a combination of reduced feed intake, reduced retention of dietary N, impaired mineral digestion and metabolism and increased partitioning of protein and energy usage towards the gut at the expense of other body tissues.

**IMMUNE RESPONSES TO GASTROINTESTINAL NEMATODIASIS**

The efficacy of the mammalian immune system in dealing with infections by many viruses and bacteria is not matched by its efficacy against large metazoan parasites. This is particularly true for those residing in the gut, partially sequestered from the immune system, and with very limited tissue invasion as is the case for the most important trichostrongylid helminth parasites of grazing ruminants. This largely explains the chronic and endemic nature of much parasitic disease, in contrast to the epidemic or sporadic occurrence of much bacterial and viral disease. Nevertheless, complete immunity to some species of helminth is readily attained in housed sheep under experimental circumstances (Coyne and Smith, 1992; Barnes and Dobson, 1993). However, development and maintenance of immunity in grazing sheep has been more problematic (Bain, 1999; Kahn et al., unpublished). The difficulties of the immunological challenges posed by these parasites is exemplified by the absence of effective vaccines against them on the market, despite decades of effort expended in this area. Recent reviews of immunity and host resistance to gastrointestinal parasites include Balic et al. (2000); McClure et al. (2000), Meeusen (1999) and Stear et al. (1999) while older authoritative reviews include Rothwell (1989), Wakelin (1984), Barger et al. (1983) and Dineen (1978).

**Development of the host immune response**

In grazing ruminants, neonates unintentionally avoid infection as a result of the predominance of milk rather than pasture in the diet, and possibly by direct inhibitory effects of milk on larval establishment. The direct effects have been demonstrated for the abomasal parasite *O. circumcincta* and appear to be mediated through pH changes in the gut associated with milk diets (Zeng et al., 2001). Neonates are capable of mounting an immune response to infection with *T. colubriformis*. Emery et al. (1999) challenged lambs for the first 6 weeks of life with this parasite and reported enhanced immunity to subsequent challenge.

That suckling lambs are able to develop and express immunity to helminth parasites is also evidenced from selection line studies. Ward et al. (1999) reported significant differences in fecal egg count (FEC) as early as 65 days of age between a line of Merino sheep selected for increased resistance to *H. contortus* and a control line selected at random. Despite the immunocompetence of young lambs, it is young growing ruminants that are most susceptible to nematode infection. The development of maximal levels of resistance may not be until they are 8-14 months old (Van Houtert and Sykes, 1996) or later depending on a variety of host, parasite and environmental factors, which may also influence the extent of immunity in the adult.

**Expression of host immunity**

Effects of the host immune response include reduced establishment rate of incoming larvae, reduction in the size and fecundity of mature female nematodes in the gut, and expulsion of adult worms (Dobson et al., 1990ab,1992). Under experimental conditions in sheep, these responses develop sequentially with reduced establishment evident 5-7 weeks after the initiation of challenge, depressed fecundity evident by 7-10 weeks and adult expulsion not until 12-20 weeks (McClure et al., 2000). The rate of establishment of *T. colubriformis*, *H. contortus* and *O. circumcincta* in previously helminth naïve sheep is typically 40-60% but this reduces to 5% or less as immunity develops. Generally this occurs as a result of immune exclusion where larvae fail to penetrate the mucus layer.
covering the walls of the GI tract and are expelled from the animal (Miller et al., 1983). Balic et al. (2000) have postulated that ruminants reject incoming trichostrongylid larvae by two overlapping mechanisms. The first is the rapid expulsion noted above which occurs within 48 h of infection with larvae failing to penetrate the mucus layer. Rejection in as little as 30 minutes has been documented with sheep hyperimmune to H. contortus (Jackson et al., 1978). The primary effector cells for this response, which is a Type 1 hypersensitivity (allergic) response, are mast cells and globule leucocytes. The second mechanism is delayed expulsion which occurs when some larvae manage to penetrate the host tissues. This is mediated primarily by eosinophils and constitutes a delayed hypersensitivity type 2 response (Meeusen, 1999). It may take 3-14 days for expulsion to be achieved by this mechanism. It should be noted that under experimental conditions, multiple immunizing infections are required to activate either of these mechanisms.

Sheep that have developed full immunity to H. contortus not only reject incoming H. contortus larvae, but also prevent establishment of T. colubriformis larvae (Jackson et al., 1978). This cross immunity between parasite species is only evident during concurrent infections and specific infections with one species do not confer protection to other species in mono-specific infections (Balic et al., 2000).

The incidence of hypobiosis (arrested development) of incoming L_4 is also greater following the development of resistance to infection in cattle (Barger et al., 1983) and sheep (Dineen, 1978). However the regulation of hypobiosis is complex and varies between worm species, with changes in host immunity being but one factor influencing it.

Mechanisms of the host immune response

The immune response to nematode parasites is mediated largely by Type 1 hypersensitivity reactions, causing localised acute inflammatory changes. This effector system is better known for mediating the allergic reactions associated with asthma, hay fever, food and contact allergies in humans, and a range of allergic responses in animals. Indeed, because the efficacy of this system in mediating immune responses to parasitic disease is one of its few demonstrable benefits, it is believed that the system evolved specifically to deal with nematode parasites (Tizard, 1996). The major relevance of these mechanisms to the subject of this review is that they are largely responsible for the increase in endogenous protein secretion by the gut associated with GIN (together with frank blood loss caused by some parasites). It is beyond the scope of this review to detail the immunological mechanisms giving rise to the immune response. The reader is referred to detailed reviews in the area (eg. Balic et al., 2000; McClure et al., 2000; Meeusen, 1999; Rothwell, 1989), which nevertheless remains incompletely understood. A brief overview is provided below.

All specific immune responses involve host detection of foreign antigens by antigen sensitive cells, followed by processing of this antigen and presentation, in association with MHC (Major Histocompatibility Complex) encoded receptors, to lymphocytes of various classes. By means of production of specific cytokines these then mediate an effector response to eliminate the antigen. Different types of antigen elicit different effector responses, with the production of antibody by B lymphocytes predominating in the case of exogenous (free) antigen, and the activation of cellular responses in the case of endogenous (intracellular) antigen presented by infected host cells or tumor cells. In the case of gastrointestinal nematodes, surface or secreted/excreted antigens (thus exogenous) stimulate the Th2 subclass of helper T lymphocytes which produce a range of cytokines including IL-4, IL-5 and IL-10 resulting in the activation of antibody mediated (humoral) effector mechanisms as well as inducing local mast cell and eosinophil proliferation (Meeusen, 1999). While IgG (Gill, 1991; Douch et al., 1996) and IgA (Stear et al., 1999) levels are significantly elevated in immune animals, it is tissue-based IgE, the antibody class associated with Type 1 hypersensitivity reactions that appears to be the key effector antibody (McClure et al., 2000). IgE is produced primarily in lymphoid tissue associated with mucosal surfaces and binds to mast cells and globule leucocytes in the associated mucosa and connective tissue. Mast cells with bound specific IgE are said to be sensitized and the binding of antigen to IgE on a sensitised mast cell induces the production and release of numerous vasoactive inflammatory mediators including histamine, a variety of trypsin-like proteases, arachidonic acid derivatives (prostaglandins, prostacyclins, thromboxanes and leukotrienes), chemotactic factors attracting eosinophils and neutrophils and a range of cytokines including IL-4, IL-5, IL-6, IL-13 and TNF-α (Tizard, 1996). These agents cause local smooth muscle contraction, increased vascular permeability and are powerful inducers of exocrine secretory activity. They probably mediate much of the increased fluid flow into the gut lumen, increased mucus production and increased peristalsis that characterise the host response to gastrointestinal nematode infection. This mechanism is also responsible for the “rapid rejection” of incoming larvae in immune animals (Rothwell, 1989; Balic et al., 2000) and the “self cure” phenomenon of rapid expulsion of adult worms in a sensitized animal carrying adult worms and faced with a superimposed larval challenge (Dineen, 1978). Whether the villous atrophy and
increased epithelial cell turnover that characterize GIN have an immunological basis is unclear.

As noted by McClure et al. (2000) resistance to GIN is based upon a variety of mechanisms with a high level of redundancy. In addition to the IgE/mast cell mediated mechanisms, the relationship between circulating IgA concentrations and immunity to O. circumcincta in sheep (Stear et al., 1999) suggests that IgA may be acting either in mucus or in the gut lumen to inhibit parasite function. Similarly, elevated specific IgG levels have been associated with resistance to H. contortus in sheep (Gill, 1991) and high levels of IgG have been found in gastrointestinal mucus of sheep infected with H. contortus (Miller, 1987). Gut mucus plays an important role in mediating immune responses to gastrointestinal worm infection, both as an inhibitory medium in its own right, and as a vehicle for antibody and other effector compounds secreted during the immune response (Miller, 1987). Changes in gastrointestinal motility induced by nematode infection have adaptive significance and are due to complex interactions between the local neural and immune systems as reviewed by Palmer and Greenwood-Van Meerveld (2001).

Metabolic cost of the host immune response

Addressing this issue in their recent review McClure et al. (2000) concluded that there were significant production losses associated with the acquisition of immunity in sheep, particularly the expulsion of adult worm populations, but that protective immunity against ongoing challenge involved relatively minor metabolic costs. They suggested that this may be because prevention of larval establishment may be mediated primarily in gut mucus composition with little impact on host metabolism.

NUTRITIONAL MODULATION OF RESISTANCE TO GASTROINTESTINAL NEMATODIASIS

Periparturient females

A key host-related phenomenon affecting the immune response to GIN is the peri-parturient relaxation (PPR) of immunity that occurs in reproducing females. It is most important in sheep where a transient loss of immunity to intestinal nematode parasites begins around the time of lambing and continues for many weeks postpartum (Brunsden, 1970; O’Sullivan and Donald, 1970; Connan, 1976; Lloyd, 1983). This may result from one or a combination of more than one of the following factors: increased establishment rate of incoming larvae, resumed development of arrested larvae, increased egg production by established females (fecundity) and/or decreased mortality of established adult worms (O’Sullivan and Donald, 1970). The extent to which immunity in the periparturient ewe is diminished appears to be specific to the species of nematode involved. For example, an increase in the susceptibility of both the pregnant and lactating ewe to infection with T. colubriformis (O’Sullivan and Donald, 1973; Gibbs and Barger, 1986) and O. circumcincta (Brunsden, 1970; Gibbs and Barger, 1986; Jackson, et al., 1988) has been reported but it appears that, in comparison to the nonreproductive animal, there is no loss of immunity to H. contortus (O’Sullivan and Donald, 1973; Gibbs and Barger, 1986).

A number of causes for the transient loss of immunity have been suggested including immunosuppression due to changes in endocrine status, reduced levels of anti-parasite IgA in the gut as a result of an increase in the transport rate into mammary epithelium (Jeffcoate et al., 1992), stress of parturition and poor nutrition. For the purposes of this review evidence supporting a link between nutrient requirement and the loss of immunity in periparturient ewes is discussed.

The PPR coincides with an increase in the nutritional requirements of the ewe due to the demands of pregnancy and lactation. Metabolizable energy (ME) requirements of a 50 kg single-bearing ewe maintaining maternal live weight increase 3.0 fold by 3 weeks postpartum at peak lactation (Freer et al., 1997). Metabolizable protein requirements increase 5.4 fold over the same period (Freer et al., 1997; figure 1). It is apparent that during the latter stages of pregnancy and during lactation the requirement for MP increases at a rate greater than that for ME (figure 2). The MP:ME requirement during lactation exceeds that able to be provided by rumen fermentation which is variable but has been estimated at approximately 6.5 g/MJ (Egan and Walker, 1975).

![Figure 1](image.png)

**Figure 1.** Calculated requirements for ME (MJ/d), metabolizable protein (MP, g/d) during gestation and lactation for a 50 kg ewe maintaining maternal bodyweight and fed a diet providing 11.5 MJ/kg DM (Freer et al., 1997). Calculated milk yield is also shown.
There is evidence (Donaldson, 1997; Kahn et al., 1999; Houdjit et al., 2001) that the PPR, arising from a loss in immunocompetence to nematode parasites, is exacerbated by the combination of an increased requirement for protein relative to ME and increased competition for essential nutrients experienced during late pregnancy and lactation. Consequently, nutritional strategies that can increase the supply of MP may be expected to reduce PPR. Donaldson et al. (1997) infected single and twin bearing Coopworth ewes with *T. colubriformis* and *O. circumcincta* for the 7 weeks prior to parturition. Animals were fed diets providing 2 levels of ME (E1 and E2) which were calculated to promote 0 and 50 g/d gain in maternal body weight during pregnancy and -100 and 0 g/d during lactation. Within each level of ME, fishmeal was added (0 or 8%) to provide 2 diets calculated to supply differing levels of MP. The 2 levels of ME and MP produced 4 diets viz. E1P1, E1P2, E2P1 and E2P2. Worm burdens of ewes 3 weeks after parturition fed diets calculated to provide greater amounts of MP were reduced by 87% (12,020 vs 1,540) but ME supply had no effect (table 1).

To assess whether immuno-enhancement arising from increased MP supply also occurs in grazing ewes, Kahn et al. (1999) subjected 120 periparturient Merino ewes to one of three supplementation strategies viz. zero supplement or 250 g/ewe/d cottonseed meal pellets (92% DM: 396 g CP/kg DM; *circa* 50% rumen degradable protein) fed for the 5 weeks prior to the start of parturition or for the 6 weeks after the start of parturition. Animals were artificially infected with 9000 L₃ *T. colubriformis* and 3000 L₃ *H. contortus* prior to the trial. Supplementation reduced FEC⁰.⁵ with the effect reaching statistical significance for prepartum-fed ewes 3 weeks prior to parturition at which stage FEC⁰.⁵ was reduced by 50% (figure 3).

These data provide support for the hypothesis that the periparturient loss in immunity is due, at least in part to increased competition for nutrients, particularly MP, and that strategic protein supplementation will help overcome it. In applied terms such an approach to limiting GIN during this period is attractive because protein supplementation of ewes at this time is likely to produce economic benefits other than reduced worm burdens. These include increased birth weights, reduced lamb mortality and increased growth rates mediated by increased milk supply.

**Young animals**

As is the case for the periparturient ewe, young growing animals have an elevated requirement for nutrients, particularly MP. It is clear from the earlier discussion that GIN diverts amino acids away from productive functions (ie. growth) towards survival functions associated with removal of gastrointestinal parasites. As a result GIN imposes an untimely nutritional penalty. It is therefore not surprising that increasing the supply of MP has been demonstrated to be effective in improving growth (ie. resilience) and hastening the development of immunity to gastrointestinal parasites. Bown et al. (1991) identified that it was the supply of MP, not energy, which benefited resistance to

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**Table 1.** Mean worm burden of single and twin-bearing ewes 3 weeks post partum following 7 weeks of mixed species trickle infection (Donaldson et al., 1997). Animals were fed diets providing 2 levels of ME (E1 and E2) which were calculated to promote 0 and 50 g/d gain in maternal body weight during pregnancy and -100 and 0 g/d during lactation, respectively. Within each level of ME, fishmeal was added (0 or 8%, P1 or P2 respectively)

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<th>Diet</th>
<th>Single-bearing</th>
<th>Twin-bearing</th>
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<td></td>
<td><em>T. colubriformis</em></td>
<td><em>O. circumcincta</em></td>
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<tr>
<td>E1P1</td>
<td>172</td>
<td>6,743</td>
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<tr>
<td>E1P2</td>
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<td>E2P2</td>
<td>3</td>
<td>469</td>
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NUTRITION AND RESISTANCE TO PARASITES

Gastrointestinal parasites. Those authors infused isoenergetic amounts of either sodium caseinate or glucose into the abomasum of lambs infected with *T. colubriformis*. At 12 weeks post infection, animals which received the infusion of protein had significantly reduced worm burdens. Elevation of energy supply had no effect on development of resistance.

Van Houtert et al. (1995) reported that, in 6 month old Merino weaners infected with *T. colubriformis* and fed a roughage diet supplemented with either 0, 50 or 100 g/day fish meal (to increase MP supply), resistance developed most rapidly in animals fed the largest amounts of fishmeal such that worm burdens were significantly reduced by 15 weeks post infection.

More recently, Kahn et al. (2000a) re-examined the role of energy and MP in the development and expression of resistance using strategically formulated diets rather than abomasal infusions. The basis for the re-examination of the role of energy was the recognition that while abomasal infusions of glucose increase energy supply they do not increase production rates of volatile fatty acids which is normally associated with increased energy intake. In contrast to the findings of Bown et al. (1991) higher rates of digestible energy (DE) lowered burdens of *T. colubriformis* at 10 weeks post infection by circa 25% while the supply of MP was ineffective (table 2). The beneficial effects of DE on resistance to gastrointestinal parasites, suggests that changes to energy metabolism driven through changes in the production rates of volatile fatty acids, rather than through changes in glucose entry rates may be of greater relevance for the study of infected animals. These results, and others (eg. Kahn et al., 2000b) where increased MP supply did not lead to a greater resistance to *T. colubriformis* infection suggest that, with young growing sheep, more emphasis should be given to improved nutrition in general rather than to particular components of the diet.

Long-term effects of nutritional supplementation on resistance and production

The evidence presented so far indicates that resistance to GIN can be enhanced through nutritional manipulation but, in general, most observations have examined effects during a single infection cycle covering the period during which treatments have been applied. Long-term benefits of these treatments (ie. for months or years beyond the period of treatment) have been discussed by Nolan (1999) but otherwise have received little attention.

Datta et al. (1999) first suggested that nutritional enhancement of resistance may be retained for long periods after supplementation had ceased. Datta et al. (1998) fed young sheep (8-9 mo), trickle infected with *H. contortus*, isoenergetic diets that differed in crude protein (CP) content from 10-22% for 9 weeks. Diets were fed *ad libitum* resulting in differences in both ME intake (circa 15% difference between 19 and 10% CP diets) and MP supply (circa 112% difference between 19 and 10% CP diets). Significant effects of diet on FEC were observed during the 9 weeks of differential feeding (figure 4). Fecal egg count decreased with higher levels of CP. Fecal egg count of animals fed 19 and 22% CP diets was significantly lower than from animals fed 10 and 13% CP diets.

After the initial 9 week experimental period, animals were drenched to remove existing infections and grazed at pasture as a single flock. Fecal egg count was recorded

Table 2. Numbers of *T. colubriformis* recovered 10 weeks post infection from Merino weaners fed diets to provide for either a low (E1) or moderate (E2) digestible energy intake (DEI) and a low (P1) or moderate (P2) metabolisable protein (MP) supply (Kahn et al., 2000a)

<table>
<thead>
<tr>
<th>Level</th>
<th>DEI (MJ/kg live weight/day)</th>
<th>MP supply (g/kg live weight/day)</th>
<th>Adult female</th>
<th>Total(^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>E1</td>
<td>0.28</td>
<td>6,303(^a)</td>
<td>11,827(^a)</td>
<td></td>
</tr>
<tr>
<td>E2</td>
<td>0.34</td>
<td>4,513(^b)</td>
<td>8,541(^b)</td>
<td></td>
</tr>
<tr>
<td>P1</td>
<td>1.7</td>
<td>5,205(^b)</td>
<td>9,817</td>
<td></td>
</tr>
<tr>
<td>P2</td>
<td>2.7</td>
<td>5,612(^b)</td>
<td>10,552</td>
<td></td>
</tr>
</tbody>
</table>

\(^a\) Total is the sum of adult males, adult females and juveniles.

\(^b\) Main effect means within columns followed by different superscripts differ significantly (p<0.05).
periodically over a 16 month period. Quite remarkably, the ranking of FEC observed during the initial 9 week period remained the same over the following 16 month period. Data for the first 10 months after the experiment are shown in figure 4.

Given the importance of enhancing resistance to GIN over the long-term we (Kahn et al., unpublished) have completed a number of related experiments which have investigated the residual value of nutritional supplementation to resistance. As part of a larger investigation, twenty six Merino wether weaners (7 mo) were exposed to natural infection from pasture and were either unsupplemented or supplemented with 140 g/d cottonseed meal pellets (90% DM; 30% CP; *circa* 50% rumen undegradable protein) for 7 weeks. At the end of the supplementation period some of these animals were drenched, then grazed together at pasture and FEC determined at approximately 6 weekly intervals for the following 34 weeks.

Supplementation reduced FEC\(^{0.33}\) significantly when averaged over the 7 week experimental period (figure 5). Fecal egg count \(^{0.33}\) during the 34 week period after feeding ceased was unaffected by the initial period of supplementation. Indeed there was a consistent trend towards higher FEC in the previously supplemented animals (figure 6). Whereas the studies described above have used castrate male animals it is perhaps with female animals where long-term effects on resistance will be most valuable. Kaidong Deng et al. (2001) reported on the response in terms of resistance and resilience of young Merino ewes fed cottonseed meal pellets at two levels (170 or 85 g/hd/day) for 10 weeks immediately after weaning. Over the 10 weeks of feeding, supplementation lowered FEC\(^{0.33}\) significantly when compared to unsupplemented controls and this effect continued up to 8 weeks after supplementation ceased while the ewes remained in their respective experimental pasture plots. At week 18, the ewes were drenched to remove the resident infection and then grazed together as one flock and sampled at 29, 42 and 52 weeks. There was no carry-over effect of supplementation on FEC\(^{0.33}\).

Taken together these studies demonstrate that significant increases in host resistance to GIN are generally achievable during or shortly following periods of increased MP supply. However the longer term effects observed by Datta et al. (1999) have proven more difficult to reproduce and may involve very precise timing of supplementation in relation to the maturation of the host immune system, basal nutrient supply and their possible interaction with regards ongoing development of immunity to GIN.

![Figure 4](image_url.png)

**Figure 4.** Fecal egg count of Merino×Coopworth weaner sheep when (i) housed, trickle infected with *H. contortus* and fed diets differing in crude protein content (May 95); and (ii) at two intervals over the next 10 months following anthelmintic treatment and return to pasture as one group. Adapted from Datta et al. (1998; 1999).
Gastrointestinal nematodiasis is one of a large subset of human and animal infectious disease conditions that is profoundly affected by the nutritional status of the host. This is not surprising when one considers the pathophysiology of GIN, and the metabolic cost of mounting an inflammatory immune response in the gut. Indeed one of the most intriguing features of gastrointestinal parasitism is the extent to which the adaptive immune responses to infection, mounted by the host, contributes to the pathophysiology of the disease.

This review has shown that the key metabolic consequences of GIN are a reduction in feed intake, reduced retention of dietary N and a substantial shift in the partitioning of retained protein and energy towards the gut. To a greater or lesser extent all of these may be due, at least in part, to a complex host immune response and associated changes to local neural circuits. The primary immune mechanism, that of rapid expulsion of incoming larvae, is inflammatory and allergic in nature, and almost certainly contributes to the increased secretion of N into the gut lumen during GIN. This cycling of endogenous N through the gut lumen in turn contributes to the shift in partitioning of N to the gut and away from more productive functions.

Given the above, it is not surprising that the effects of GIN are greatest in young growing animals and periparturient females, animals with very high requirements for MP, both in absolute terms, and relative to requirements for ME. This offers livestock managers the opportunity of increasing MP supply to these animals to increase both their resilience and resistance to infection and clear responses are readily obtainable for both. However the economics of protein supplementation for disease resistance are marginal unless long term increases are obtained well beyond the period of supplementation. There is tantalizing evidence from a single experiment that such long term responses are obtainable, but to date they have not been repeated. Determining the conditions under which such responses can be attained is a fertile area for future research.

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