

Management of parasitic disease in livestock—can resistance be programmed by dietary manipulation?

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Summary

It is argued that parasitism may induce an indirect form of protein malnutrition in weaners which may not only impair their ability to mount effective immune responses to infective agents during the infection but may also impair metabolic processes in the liver and other organs and cause reduced production from animals in later life.

The presence of internal parasites increases the losses of endogenous protein into the gut, thereby reducing the availability of amino acids for use by organs and tissues. In young growing animals, the induced amino acid deficiency may impair the development and maintenance of immunity to parasites; however, various studies have shown that dietary protein supplementation helps to ameliorate their detrimental effects.

Recent studies in this laboratory have confirmed that protein supplementation soon after weaning enhanced growth rate and wool production of lambs relative to their unsupplemented controls and, in addition, showed that production was higher in those lambs given diets containing more than 160 g crude protein/kg dry matter than in those receiving iso-energetic, mineral-adequate diets with less protein. Notably, the positive ranking of production responses with dietary protein concentrations persisted for 69 weeks after the supplementation ceased when the lambs grazed as a single flock on improved pasture.

It is speculated that protein-dependent 'carryover' effects on production in farm animals may be the result of early-life 'nutritional programming' similar to that which has recently been found in human beings to affect disease susceptibility in later life.

Introduction

Internal parasites such as *Haemonchus contortus* and *Trichostrongylus colubriformis* produce effects in their hosts that are similar to those of protein malnutrition. When parasitised sheep are given additional dietary protein, however, they often maintain levels of production similar to those in unsupplemented,

uninfected controls (Steel 1978; Sykes 1978; van Houtert and Sykes 1996; Fox 1997). Uncertainty about the importance of ME deficiency relative to metabolisable protein (see, for example, Donaldson 1997) has arisen because it is difficult to devise diets that provide the host with ME without a confounding increase in metabolisable protein (MP) supply. The latter is the result of additional microbial protein outflow from the rumen promoted by the extra energy provided in the rumen by the supplement. In a definitive study, however, Bown *et al.* (1991) infused iso-energetic amounts of sodium caseinate or glucose into the abomasum of lambs artificially infected with *T. colubriformis* and found that only the caseinate reversed the debilitating effects of the infection. These results suggest that a specific protein deficiency was the major limitation to production. Thus, supplying additional MP to parasitised animals probably ameliorates a parasite-induced amino acid deficiency resulting from altered patterns of gut digestion and absorption (Rowe *et al.* 1988) and a decline in feed intake (Dynes *et al.* 1992). Exactly how amino acid insufficiency impairs the ability of animals to cope with infection is still uncertain. It seems likely, however, that in young growing animals and in those pregnant or lactating there may be competition for amino acids between tissues involved in muscle or foetal growth or milk production, and those involved with development or maintenance of immunity.

In practice, additional MP can be made available to ruminants by giving them dietary supplements containing protein in forms that avoid rumen degradation (e.g. protein in cottonseed meal or fish meal); van Houtert *et al.* (1995b), for example, demonstrated the beneficial effects of giving fishmeal as a supplement to Merino lambs on a basal diet of oat chaff and minerals and infected with *T. colubriformis* larvae. Faecal egg counts (FEC) were reduced by supplementation, and rejection of worms from the gut apparently occurred earlier (as determined by worm numbers in the gut at the time of slaughter) than in unsupplemented lambs. Liveweight gain was 43% higher in infected lambs that were supplemented than in those unsupplemented. In

lambs given 50 g fishmeal/d, gain was reduced by only 18%, and in those receiving 100 g fishmeal/d by only 11%, relative to control lambs.

Workers in our laboratory (Shaw 1995; Datta *et al.* 1998) also found that providing parasitised weaner lambs with additional MP improved their production during the period of supplementation, but protein supplements are relatively expensive. 'Carryover' effects, generated by a short period of supplementation and leading to higher production of animals in later life, would offset the high initial cost of supplementation and help to justify the use of supplements for young animals. One indirect carryover benefit is that supplemented sheep, with their improved immune response to parasites, excrete fewer nematode eggs and this reduces the intake of larvae by animals that subsequently graze in the same area. Immunity to internal parasites, once established, persists even during periods of protein malnutrition (van Houtert *et al.* 1995c) and confers other continuing production benefits provided the period between parasite challenges is not too long (Barnes and Dobson 1993). Apart from studies of the persistence of immunity, however, there are few other studies that provide information concerning continuing production benefits following short period of supplementation in early life.

There do not appear to be any reports of records of lifetime production from animals given dietary supplements only in their first year, but the probability that early-life nutrition can generate longer-term benefits for production seems high. In young humans, the provision of good nutrition *in utero* or in early life has been shown to have life-long effects on, for example, the development of diabetes in 64-year old men (Barker *et al.* 1993). Similar types of early nutritional 'programming', possibly affecting metabolic, neural and immunological systems, may also have long-term or even life-long beneficial or detrimental effects on production in farm livestock. The idea of 'nutritional programming' as a potential component of nutritional management of livestock is developed later in this paper.

Additional costs of protein and amino acid due to parasites

The additional requirements for MP in animals infected with parasites such as *H. contortus* and *T. colubriformis* are a consequence of their greater losses of endogenous protein into the abomasum and small intestine (in whole blood, plasma, sloughed epithelial cells and mucus). Although most of the nitrogen in these secretions is reabsorbed proximal to the ileum (Roseby and Leng 1974), the reabsorbed nitrogen is principally ammonia rather than peptides or amino acids. Further, using cannulated sheep, Poppi *et al.* (1986) and Steel (1978) demonstrated that even though most of the nitrogen in these endogenous proteins was digested and reabsorbed in the small intestine, an appreciable fraction,

especially in sloughed epithelial cells and mucus, reached the ileum. Once in the large intestine, this nitrogen was further digested and absorbed as ammonia, or was excreted in faeces. It seems clear that, in animals infected with internal parasites, peptide or amino acid nitrogen will be a smaller component of the total nitrogen absorbed from their intestines. In this connection, the first limitation to production could be a deficiency of a single amino acid such as methionine, cysteine or threonine. In this connection, mucus may be a particularly important channel of amino acid loss because it has a low apparent digestibility in the small intestine and, in addition, contains high concentrations of threonine relative to 'average' protein (Neutra and Forstner 1987).

In general, little is known about the requirements of animals for individual amino acids (or other nutrients) when coping with diseases. On the one hand, the protein cost of mounting and maintaining immunity to diseases is thought to be low relative to total daily protein requirements (see Klasing 1999) but on the other, individual nutrients may be needed to be diverted from general use to serve particular roles in diseased animals such as enabling them to mount immune responses (Reddy and Frey 1990; MacRae 1993). Lewis and Austen (1981), for example, have argued there may be a particular requirement for cysteine to form leucotrienes after mast cells have been activated by immuno-globulin E.

Provision of protein supplements to parasitised animals to provide them with extra MP may enable the animal (1) to mount a more rapid and stronger immune response to the parasites, i.e. to increase their 'resistance' to infection, or (2) to overcome the nutritional and physiological disturbances resulting from the presence of the parasites, i.e. to increase its 'resilience' (Coop and Kyriazakis 1999). The effects of improving nutritional status on host resilience are less well understood than effects on host resistance (van Houtert and Sykes 1996).

In their recent review, Coop and Holmes (1996) concluded that the main effects of protein supplementation on host resistance were to increase the rate of acquisition of immunity and the strength of the immune response, both factors being associated with an enhanced cellular immune response in the gastrointestinal mucosa. The infusion of protein into lambs infected with *Ostertagia circumcincta* reduced worm size and numbers in the gut and faecal egg counts (FEC) (Coop *et al.* 1995). Mucosal mast cell numbers and protease concentrations were also increased, suggesting that lambs receiving supplementary protein developed stronger immunity to the parasite. Coop and Holmes (1996) and van Houtert and Sykes (1996) also found that improved protein nutrition accelerated the development of immunity to other nematode larvae in lambs. Moreover, the immuno-responsiveness of lambs to nematodiasis was markedly boosted by giving higher protein diets (Kambara *et al.* 1993; Shaw *et al.* 1995).

Once sheep have mounted an immune response to a parasite, the immunity persists for some months at least. Sheep made resistant to *T. colubriformis* by artificial infection over 34 weeks still exhibited immunity when re-challenged 24 weeks later. No faecal worm eggs were excreted during the re-challenge infection. However, there was a small but significant increase in plasma-N leakage into the gut from days 4 to 9 after which leakage returned to the levels found in the controls. Re-challenge caused a rapid development of eosinophilia which peaked during week 6 of re-infection then declined to the levels in the control animals by week 8. Sheep are therefore able to re-activate their immunological mechanisms when re-challenged, with little associated nutritional penalty (Kimambo *et al.* 1988). In adult sheep, a period of inadequate nutrition causing weight loss between an initial challenge with *T. colubriformis* and a subsequent re-challenge did not appear to impair the immune response (van Houtert *et al.* 1995c). These studies suggest that, once animals have acquired immunity to parasites, the MP cost of re-activating the immune mechanism may be relatively small.

Resistance of the host to disease and parasites can depend on physical barriers (skin, mucous membranes, mucus), phagocytosis (neutrophils and macrophages), the complement system, immunoglobulins, cell-mediated immune responses, secretion of cytokines and non-specific humoral factors. All of these factors may be enhanced by good nutrition. Plane of nutrition may therefore affect an animal's resilience by acting directly on immuno-competent cells, or indirectly by altering metabolic, neurological or endocrine physiology. McGillivray (1967) showed that young growing pigs given protein-deficient diets had low antibody titres and poor resistance to infection. With decreasing dietary crude protein concentrations there was a linear decrease in antibody response to heat-killed *Salmonella pullorum*. Certain anti-nutrients can also lower immune responsiveness. For example, the hypersensitivity responses generated by certain soy proteins can cause depression in immuno-competence (Friesen *et al.* 1993).

Recent studies of the benefits of protein supplementation

As already discussed, production by parasitised lambs is improved when they are given dietary protein supplements. In this laboratory, we have confirmed that the detrimental effects of haemonchosis in lambs can be largely overcome by increasing dietary protein concentrations (Shaw *et al.* 1995). In subsequent studies with *H. contortus*-infected weaner lambs, Datta *et al.* (1998, 1999) investigated the nature of the response to additional protein when the lambs were given iso-energetic diets with a range of crude protein content concentrations and found that the strength of the immune response developed in the period of

supplementation to parasitic infection was dietary protein concentration dependent. Notably, gradations in immuno-responsiveness associated with increments in protein concentration in the diet persisted for more than a year after supplementation ceased. As there are few other studies of this type, our studies are summarised below and, from assessment of the results, it is suggested that some form of 'nutritional programming' may explain the extended carryover effects.

Five iso-energetic, mineral-adequate diets differing in crude protein concentration were formulated and the ability of penned crossbred lambs given these diets to cope with a moderate level of challenge from *H. contortus* was assessed over a period of 9 weeks (Phase 1). After the period of supplementation ceased, the performance of the same animals was recorded while they were grazing on improved pasture for a period of 69 weeks (Phase 2).

In Phase 1, the lambs were allocated to one of five dietary treatments (n = 12). Six lambs in each treatment were artificially infected by dosing them orally with 750 *H. contortus* third-stage (L3) larvae each Monday and Friday. The other six lambs were dosed with a solution containing no larvae (controls). The diets, composed of different proportions of oat chaff, barley, cottonseed meal and urea, were formulated to provide 9 MJ ME/kg dry matter but different protein concentrations, i.e. 100, 130, 160, 190 and 220 g crude protein/kg dry matter. All diets contained 10 g mineral mixture and were given *ad libitum*.

At the end of the 9-week Phase 1 (16 May 1995) the lambs were individually identified by ear tags, drenched with Ivermectin and Closantel to eliminate internal parasites and then put out as a single flock to graze on good quality pasture until 29 September 1996 (i.e. Phase 2). The results collected during Phase 2 were collated and examined according to the dietary groupings of the lambs during Phase 1. In accord with the drenching program used on the University farm, the sheep were drenched three more times during Phase 2, i.e. at the end of September 1995, and in March and August 1996. They were shorn on 29 September 1995 and on 9 September 1996.

Supplementation of penned sheep

Lambs given the diets with higher crude protein concentrations, in general, had lower FEC and higher feed intakes, higher liveweight gains, higher rumen fluid ammonia concentrations and higher packed cell volumes (PCV); the lower FEC and higher PCV suggested they had fewer gut parasites or higher rates of erythropoiesis, or both. The Phase 1 results confirmed the earlier conclusions of other workers: that extra dietary protein intake can, to a large extent, overcome the negative effects of *H. contortus* infections on lamb production. They further indicated that, under the conditions of this experiment, the optimal dietary crude protein was about 160 g/kg dry matter.

There was a significant diet x infection interaction such that feed intake and production were higher in parasitised animals on the higher protein diets than in those that were parasitised and unsupplemented. As a result of random allocation to treatments, the lambs with the higher intakes of crude protein, and presumably higher availabilities of amino acids for absorption from the small intestine, were the lightest at the start of the experiment but had the higher liveweight gains during this period. The liveweights and rates of weight gain of the lambs, grouped according to their dietary treatments during Phase 1 are shown in Figure 1.

It is not clear whether the growth rate responses to supplementary protein in Phase 1 were to the rumen degradable nitrogen (RDN) or the undegraded dietary protein (UDP) components in the diets. Diets containing 16% crude protein produced ammonia concentrations in excess of 250 mgN/L, and one hypothesis arising from the work was that higher rumen ammonia concentrations associated with the diets with higher RDN contents may have reduced the ability of the parasites to colonise the gut, or to develop to adult worms. There does not appear to be any relevant published information on this matter.

In attempting to elucidate the roles of protein supplementation on the resilience of lambs in Phase 1, we found that those that ingested the higher protein diets also had higher numbers of circulating eosinophils (starting at around week 3 of the artificial infection period), and higher antibody titres to *H. contortus* L3 antigen (see Figure 2). The antibody responses were ranked in increasing order with increasing crude protein content of the diets, indicating that these responses were dependent on dietary protein concentration and MP supply to the animals.

Supplementation 'carry over' effects in grazing sheep

Lambs in all treatment groups lost weight when first put out on pasture from 15 May 1995 to 17 July 1995 (see Figure 1). However, the lambs that had previously received the higher protein treatments lost liveweight less rapidly ($P < 0.05$) during the first 9 weeks on pasture. They then gained weight more rapidly ($P < 0.05$) for the remaining 60 weeks. There was no clear evidence of compensatory growth during the grazing period by the lambs whose growth had been restricted during the period of hand feeding (Figure 1), so that the benefits of the 9 weeks of supplementation remained until the end of Phase 2.

The sheep were shorn on 29 September 1995 and again on 9 September 1996. Those that were given the higher protein diets during Phase 1 produced more clean wool in Phase 2 in a one-year period that commenced several months after protein

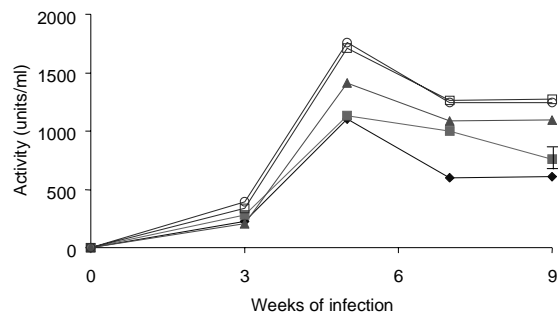


Figure 2 Serum antibody response to *H. contortus* L3 antigen in infected lambs when given mineral-adequate, iso-energetic diets with increasing crude protein concentrations: \blacklozenge = 10% CP; \blacksquare = 13% CP; \blacktriangle = 16% CP; \circ = 19% CP; \square = 22% CP. (Error bar indicates pooled SEM).

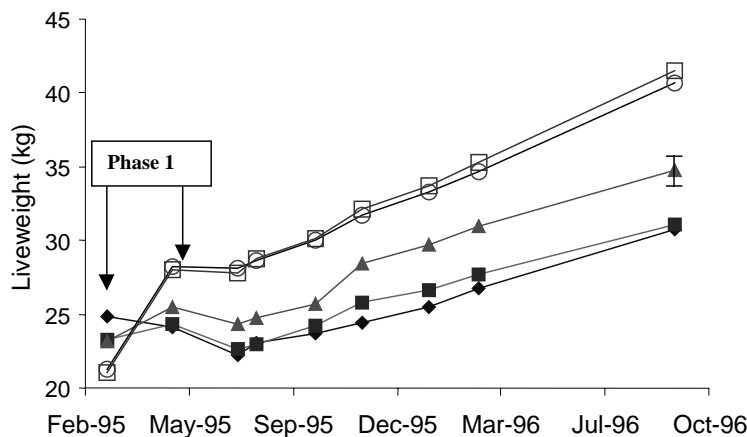


Figure 1 Liveweight of groups of lambs during a 9-week period of handfeeding (Phase 1, delineated by the arrows) and subsequently when at pasture. During Phase 1 only, the treatment groups received iso-energetic diets with different concentrations of crude protein: \blacklozenge = 10% CP; \blacksquare = 13% CP; \blacktriangle = 16% CP; \circ = 19% CP; \square = 22% CP. (Error bar indicates pooled SEM).

supplementation ceased. This advantage was, however, removed when the wool growth was adjusted for fleece-free liveweight at the start of the wool-growth period.

In Phase 2, *H. contortus* larvae were only found in the three faecal samples taken between July and September 1995 and in one sample collected in September 1996 and never exceeded 10% of the total larval numbers. The antibody response to this parasite in previously infected and uninfected groups was positively related to the protein content of the diets given in Phase 1 (Figure 3).

After each drenching in Phase 2, faecal egg numbers were undetectable in the samples taken one week after drenching and then in subsequent weeks the build-up of natural infection, as judged by FEC, was inversely related to the crude protein content of their diets during Phase 1. The lower egg outputs corresponded with higher antibody responses to *H. contortus* and *T. colubriformis* antigens in those sheep that had previously been on the higher protein diets. The results show that the dietary protein concentrations in Phase 1 produced effects on parasite resistance that were still present more than one year after supplementation ceased.

Those sheep that were artificially infected with *H. contortus* during Phase 1 not only had higher antibody responses specific to *H. contortus* during Phase 2, but also tended ($P < 0.1$) to have higher non-specific antibody responses to *T. colubriformis* antigen. This finding suggests there was nutritional programming of the immune response during Phase 1 which was not dependent on a specific parasite antigen.

Serum antibody responses to *T. colubriformis*, which was the predominant parasite cultured from the faeces of the grazing sheep in Phase 2, were also positively related to dietary protein concentrations during Phase 1 on all five occasions when serum samples were taken (Figure 4).

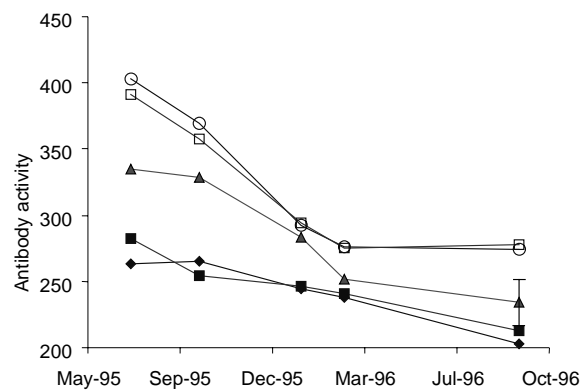


Figure 3 Serum antibody responses (units/ml) of lambs throughout Phase 2, with immunity to *H. contortus* acquired during Phase 1 and grouped according to their dietary treatments during Phase 1: ◆ = 10% CP; ■ = 13% CP; ▲ = 16% CP; ○ = 19% CP; □ = 22% CP. (n = 60, 12 animals per group; error bar indicates pooled SEM).

Speculations about 'nutritional programming'

The results obtained from the sheep during Phase 2 reflect their dietary history during Phase 1 and allow speculation that the lambs were nutritionally 'programmed' in some way during the period of hand feeding. This programming enabled them to be subsequently more productive.

Unfortunately, there appear to be no studies of the benefits of dietary supplementation of weaners for short periods on their lifetime production, although van Houtert *et al.* (1995b) obtained evidence of 'carry over' effects in young, grazing sheep in response to earlier protein (lucerne meal, sunflower meal) supplementation. The grazing phase of their study which included a period of dietary supplementation for some animals was terminated owing to drought, and the treatment groups were then maintained under management procedures designed to ensure the survival of all animals. About a year later, those previously supplemented produced more wool than their unsupplemented counterparts. The researchers hypothesised that the superior wool production from the supplemented group may have been due to their stronger immunity to larvae acquired from the pasture. Similar conclusions relating to 'carry over' results have been reached from studies with sheep (J. MacFarlane, pers. comm.) and goats (M. Knox, pers. comm.).

Hennessy *et al.* (1981) carried out an experiment with cattle that had some similarities with our studies. When weaner steers initially 180 kg on unimproved subtropical pasture were supplemented with protein-rich pellets for 140 days during winter and spring, they gained weight at 350 g/day whereas their counterparts in a control group given only a mineral supplement lost weight at 140 g/day (control group). At the end of a further 130 days without dietary supplementation in the

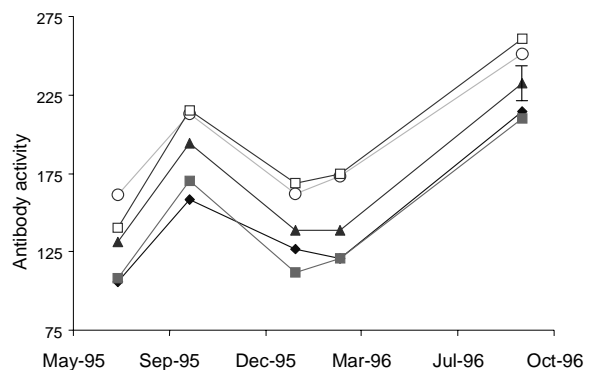


Figure 4 Antibody responses (units/ml) to *T. colubriformis* L₃ of lambs during a 69-week grazing period, grouped according to their dietary groups during earlier hand-feeding: ◆ = 10% CP; ■ = 13% CP; ▲ = 16% CP; ○ = 19% CP; □ = 22% CP. (n = 60, 12 animals per group; error bar indicates pooled SEM).

following summer, the previously protein-supplemented group at 265 kg was still appreciably heavier than the control group at 198 kg. The weight advantage was then maintained while both groups were set stocked together at 1.7 steers/ha on fertilized, improved pasture. At the end of this further 290 days, cattle in the protein-supplemented group averaged 357 kg and those from the control group 317 kg. This study provided no information on the immune status of the cattle or other changes that might explain the previously supplemented group maintained their higher growth rate. The foregoing discussion, however, suggests that the protein-supplemented animals may have better able to withstand parasitic and other disease challenges, and that this ability was, at least in part, responsible for their enhanced growth rate after the period of protein supplementation.

In summary, the studies above provide evidence of improved production from animals following periods of protein supplementation in early life. The roles played by the supplements are not clear but enhancement of immuno-competence of the previously supplemented animals, enabling those animals to resist better the effects of disease and parasitism in later life may have contributed to their higher production. This effect of early-life supplementation can be regarded as a form of 'nutritional programming'.

In light of the paucity of information on the longer-term effects of protein supplements it is not surprising that the suggestion being put forward here, namely that nutritional programming by provision of protein or specific amino acids in early life may affect the immune system, has received little attention (Moore 1998).

Peri-natal 'nutritional programming' affecting metabolism in later life

In the context of human nutrition, Hales and Barker (1992) have developed the 'thrifty phenotype' concept which implies that that metabolism can be 'programmed' in foetal and infant life with effects on metabolism extending throughout later life. According to this concept, the probability of an animal developing diseases in adult life is influenced by the rate of pre- and early post-partum nutrition. Undernutrition of the foetus modifies its subsequent metabolic function so that it can cope better with undernutrition, but the animal is then less productive if nutrition is later improved. These changes in metabolic characteristics in the young can persist into adult life.

This hypothesis is being tested by this group (see Desai and Hales 1997) using a rat model. Their studies of growth and metabolism in the offspring of rats fed a low-protein diet during pregnancy and/or lactation have shown:

- growth was retarded in offspring nursed by dams fed a low-protein diet
- organ growth, especially the liver, pancreas, muscle and spleen is permanently and selectively altered
- activities of key hepatic enzymes of glycolysis and gluconeogenesis were changed in a direction which would enable the liver to cope better with under-nutrition
- glucose tolerance was more prone to deteriorate with age
- life span of offspring exposed to maternal protein restriction only during the lactation period was increased, but
- life span of offspring was decreased after dams were subject to protein restriction only during gestation

These studies show that hepatic metabolism and even longevity can be programmed by peri-natal events. Whether or not nutritional programming can occur in weaner (as distinct from pre-weaned) livestock or affects their metabolism in later life is more problematic. However, there is enough evidence from our results described above, and also from work with cattle by (Hennessy *et al.* 1981) and sheep (van Houtert *et al.* 1995a) to suggest this hypothesis should be investigated further. During these investigations, it will be helpful to study carefully selected biochemical and metabolic processes rather than simply concentrating on immune function.

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