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Nutrient partitioning between reproductive and immune functions in animals

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The physiological processes that underlie the reproductive cycle impose considerable metabolisable protein (MP) demands on a female, especially during the periparturient period. When MP supply falls short of MP demand (i.e. MP becomes scarce), certain, if not all, bodily functions are expected to be penalised. It has been proposed that partitioning of scarce MP is prioritised to reproductive rather than to immune functions. In other words, at times of MP scarcity, the penalty on expression of immunity would be expected to be greater than that on reproduction. This hypothesis forms a nutritional basis for the occurrence of periparturient breakdown of immunity to parasites (BIP), which can be observed in many host–parasite systems. In the present review we explore this nutritional basis, using periparturient sheep infected with the abomasal nematode *Teladorsagia circumcincta* as an example, and attempt to quantify its occurrence. Evidence supporting the nutritional basis of periparturient BIP is reviewed, covering experiments in which nutrient supply (from both exogenous and endogenous sources) and/or nutrient demand were manipulated. Quantitatively, MP requirements for expression of immunity to *T. circumcincta* were estimated to be about 1 g/kg metabolic body weight (body weight$^{0.75}$) per d, approximately 5 % of the maximum MP requirements of periparturient sheep. The major component of this requirement was assumed to be for replenishing irreversible plasma protein losses into the gastrointestinal tract. Although confirmation of this estimate is required, such estimates may be used to improve the known MP requirements of periparturient animals, enabling the extent and the consequences of periparturient BIP to be minimised.

Nutrient partitioning around parturition: Immunity to parasites: Protein requirements of sheep

The physiological processes that underlie the reproductive cycle impose considerable nutrient demands on a female. For example, energy and protein requirements can increase between two- and tenfold during lactation (Blaxter, 1989; Jessop, 1997), levels that are rarely encountered during the rest of an animal's life. This demand is serviced in many ways, e.g. quantity of food consumed increases and nutrients may be mobilised from sites within the female's body. In addition, changes in metabolic activities of tissues, e.g. brown adipose tissue, can spare nutrients for reproductive processes (Trayhurn, 1985). Nutrients are not only needed for reproductive functions during a reproductive cycle, but also for the so-called maintenance functions, which include resting metabolism and thermoregulation. Nutrient use for the former is obligatory to sustain life and may increase as the mass of active tissue increases with development of the uterus and mammary gland. Thermoregulatory costs are likely to be reduced when compared with those of a non-pregnant non-lactating animal, due to the increased heat production associated with reproduction.

Traditionally, immune functions have been regarded as part of maintenance. However, there is an increasing body of evidence that at least some aspects of immunity are sensitive to changes in nutrient supply (Coop & Holmes, 1996; van Houtert & Sykes, 1996; Coop & Kyriazakis, 1999, 2001). It has been suggested that such evidence allows immune functions to be considered separately from maintenance functions, which are expected to be relatively

Abbreviations: BIP, breakdown of immunity to parasites; FEC, faecal egg count; Ig, immunoglobulin; MP, metabolisable protein.
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Table 1. Examples of studies on periparturient breakdown of acquired immunity to parasites in species other than small ruminants

Host	Parasite	Reference
Pig	*Oesophagostomum dentatum, Hyostrongylus rubidus*	Connan (1967)
Cow	*Ostertagia ostertagi*	Kloosterman *et al.* (1984)
Rabbit	*Andrya cuniculi, Trichostrongylus retortaeformis, Nematodiroides zembra*	Molina *et al.* (1999)
Dog	*Toxocara canis*	Lloyd *et al.* (1983)
Rat	*Nippostrongylus brasiliensis*	Connan (1972)
Mouse	*Trichinella spiralis*	Ngwenya (1977)
	Trichuris muris	Selby & Wakelin (1975)
	Plasmodium berghei	van Zon & Eling (1980)
Horse	*Gardia* spp.	Xiao & Herd (1994)
Deer	*Ostertagia* spp., *Chabertia* spp., *Oesophagostomum* spp.	Lancaster & Andrews (1991)
Man	*Plasmodium falciparum*	Lloyd (1983)

insensitive to (moderate) changes in nutrient supply (Coop & Kyriazakis, 1999). An increasing number of experimental studies indicate that there may be competition for nutrient resources between the immune system and the reproductive effort (developing conceptus or mammary gland). As a consequence, immune functions may be penalised and a breakdown of immunity to parasites (BIP) can occur. As such, periparturient BIP may have a nutritional basis.

In the present review we begin by briefly referring to a recently-developed nutrient-partitioning framework, which introduced the nutritional basis for periparturient BIP (Coop & Kyriazakis, 1999). We will also summarise the immune responses involved in the expression of acquired immunity to gastrointestinal nematodes. We then explore the nutritional basis of periparturient BIP, initially in a qualitative descriptive way, and then in a more quantitative way. We will focus on periparturient sheep infected with the abomasal nematode *Teladorsagia circumcincta*, as sheep usually show a clear and repeatable periparturient breakdown of immunity to this parasite (O'Sullivan & Donald, 1973; Leyva *et al*. 1982; Jackson *et al*. 1988). However, periparturient BIP is not limited to sheep infected with this specific nematode, but is more likely to be a general phenomenon in mammals (Table 1). We will also focus on the role of metabolisable (available) protein (MP) as a scarce nutrient, although it might be argued that similar concepts could apply to other nutrients. It is less likely that BIP results from competition for metabolisable energy; changes in the supply of metabolisable energy did not affect BIP in sheep (Bown *et al*. 1991; Donaldson *et al*. 1998). Last, we will briefly broaden the nutritional basis of BIP to other nutrients, other hosts and other parasites.

A nutrient-partitioning framework

The principles of the nutrient-partitioning framework have been drawn from the idea of evolutionary fitness, and relate to the perceived goals of parasitised animals for nutrient allocation in terms of survival and reproductive fitness when nutrient resources are scarce (Coop & Kyriazakis, 1999). These authors have argued that animals will be expected to give the highest priority to the allocation of scarce nutrients for maintenance functions, as this action will guarantee survival of individuals in the short term. The second-highest priority for scarce nutrient allocation would be for reproductive effort, as this will ensure survival of the species in the long term. The high priority for maintenance and reproductive effort imply that immune functions, and especially those associated with the expression of acquired immunity to parasites, have a relatively low priority for the allocation of scarce nutrients in comparison with reproductive effort (Coop & Kyriazakis, 1999). In other words, at times of nutrient scarcity, the penalty on expression of immunity would be expected to be greater than that on reproduction. Had immunity been given a higher priority than reproduction for the allocation of scarce nutrients, then the penalty on reproduction would be expected to be greater than that on expression of immunity. For example, parasitised ewes would then be expected to give birth to lighter lambs than non-parasitised ewes. The latter does not seem to be the case (Leyva *et al*. 1982; Thomas & Ali, 1983).

Expression of acquired immunity to gastrointestinal nematodes

The expression of acquired immunity to gastrointestinal nematodes has been studied extensively in rodents (Rothwell, 1989; Else & Finkelman, 1998; Claerebout & Vercruysse, 2000). Briefly, on activation, specific T lymphocytes (T-helper 2 cells) produce cytokines, which induce inflammatory responses (e.g. eosinophilia, mucosal mastocytosis and globlet cell hyperplasia) in gut epithelium (cellular immune response). Mucus from globlet cells can paralyse the nematodes. Mast cells release a range of compounds, including proteases, and then transform into globule leucocytes. These proteases break down junctions between epithelial cells, causing increased permeability, allowing molecules from the systemic circulation to leak into the lumen. This process may facilitate parasite expulsion through the development of a microenvironment detrimental to parasite survival. In addition to this cellular immune response there is a humoral immune response, with production of parasite-specific immunoglobulins (Ig; IgA, IgG_1 and IgE). These Ig play an important role in mast cell activation (IgE), may directly bind to nematodes (IgA) and mediate in physical entrapment of the nematode in superficial mucus (IgG_1).

Most of these cellular and humoral effector mechanisms in rodents may operate in ruminants as well, although nematode expulsion in ruminants is less well understood (Claerebout & Vercruysse, 2000). For example, the involvement of T-helper 2 cells has not been shown in ruminants.

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The amounts of circulating or local lymphocytes and Ig, as well as globlet cell- and globule leucocyte hyperplasia, usually, but not necessarily, correlate positively with nematode expulsion (Claerebout & Vercruysse, 2000). The reasons why some studies do observe such correlations between different effector arms of the immune system (cellular *v.* humoral) and nematode expulsion, whilst others do not, are not well understood, but a potential role for nutrient availability cannot be excluded.

Periparturient breakdown of acquired immunity to gastrointestinal nematodes in sheep

The expression of acquired immunity to gastrointestinal nematodes in adult ewes is usually highly effective; the majority of the incoming infective larvae, which are ingested during grazing contaminated pastures, are either rapidly rejected or their development is inhibited. Inhibited larvae may lay dormant in the mucosa for many months. Thus, adult ewes usually harbour a small number of adult nematodes which produce eggs that are excreted in the faeces of the host. As a consequence, the number of nematode eggs in their faeces (faecal egg count; FEC) is often low or zero (Yakoob *et al.* 1983; Gibbs & Barger, 1986). However, FEC are often temporarily elevated during the periparturient period; this finding was first reported about 70 years ago (Taylor, 1935). It has long been suspected that a transient reduction in immunity causes the increased FEC around parturition (Crofton, 1954). The consequences of this BIP in sheep have been well documented. Parasitised periparturient ewes usually carry more adult nematodes, excrete more nematode eggs via the faeces and have less mucosal mast cells and globule leucocytes in the gastrointestinal mucosa than parasitised non-reproducing ewes. We will argue that these consequences are likely to have originated from a scarce supply of MP.

A nutritional basis for periparturient breakdown of immunity to parasites: scarcity of metabolisable protein

Many of the components of the immune system, such as Ig, cytokines and mast cell protease, are proteinaceous in nature (Lewis & Austen, 1981; MacRae, 1993; Coop & Holmes, 1996). This factor implies that a certain amount of MP would be required to mount and maintain an effective immune response. Thus, scarcity of MP supply to the immune system may result in BIP. Such scarcity would be expected to occur especially at times when prioritised bodily functions have high protein demands, such as reproductive effort during the periparturient period (Coop & Kyriazakis, 1999).

It can be hypothesised that an increased supply of, or a decreased demand for, MP reduces the periparturient BIP. Recent outcomes of protein supplementation studies in parasitised periparturient sheep (Donaldson *et al.* 1998; Kahn *et al.* 1999; Houdijk *et al.* 2000, 2001*a*,*b*) and parasitised lactating goats (Chartier *et al.* 2000) support this view. Protein supplementation resulted in decreased FEC and worm burden, and an increased concentration of globule leucocytes in the abomasal mucosa of periparturient ewes.

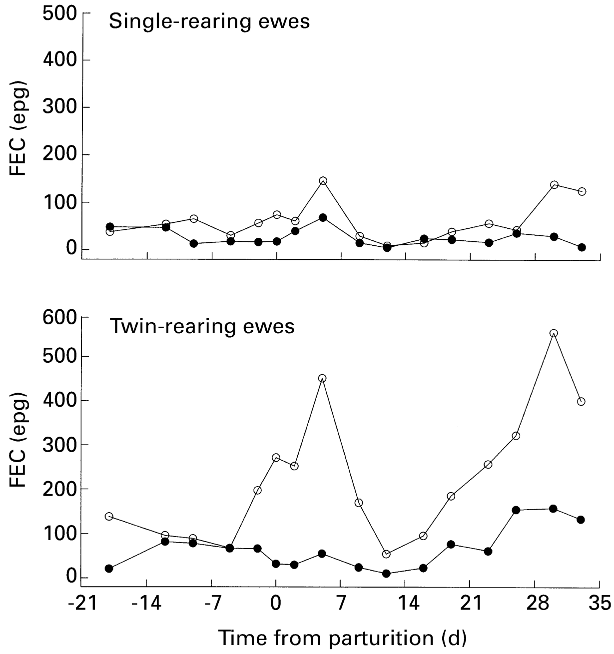

Fig. 1. Backtransformed mean faecal egg count (FEC, expressed as no. of nematode eggs per g faeces (epg)) of single- or twin-rearing ewes fed *ad libitum* foods that were calculated to provide either scarce (○) or adequate (●) amount of metabolisable protein. The ewes were infected with *Teladorsagia circumcincta* at a rate of 10 000 3rd stage infective larvae per d for 3 d per week from day –49 onwards. (Redrawn from Houdijk *et al.* 2001*a*.)

In addition, parasitised single-rearing ewes and goats usually have lower FEC and smaller worm burdens than their twin-rearing counterparts (Romjali *et al.* 1997; Baker *et al.* 1998; Donaldson *et al.* 1998; Houdijk *et al.* 2001*a*). High-yielding dairy goats may have a higher extent of BIP than low-producing goats (Hoste & Chartier, 1993; Chartier *et al.* 2000). Similar effects may be expected from genetic selection for an increased reproductive effort (Rauw *et al.* 1998).

In contrast, changes in supply of, and demand for, MP do not always affect periparturient BIP, although these contradictions can be explained. For example, feeding foods that were calculated to limit MP supply did not affect periparturient BIP in *ad libitum*-fed single-rearing ewes infected with *T. circumcincta* (Fig. 1; Houdijk *et al.* 2001*a*). However, feeding the same food to their twin-rearing counterparts resulted in periparturient BIP. The single-rearing ewes achieved higher than expected levels of food intake in this experiment. In contrast to the twin-rearing ewes, an increased MP supply did not improve performance of the single-rearing ewes (e.g. milk production). This finding implied that the single-rearing ewes were not limited by MP, even when fed the scarce-MP food. These results suggest that, if hosts are able to do so, increased feed intake may overcome BIP to a certain extent.

The effect of changes in supply of dietary MP on periparturient BIP may also depend on the presence of labile body protein (protein reserves), which may act as an endogenous source of MP (Jessop, 1997). We have recently shown that body protein may overcome the consequences of dietary MP

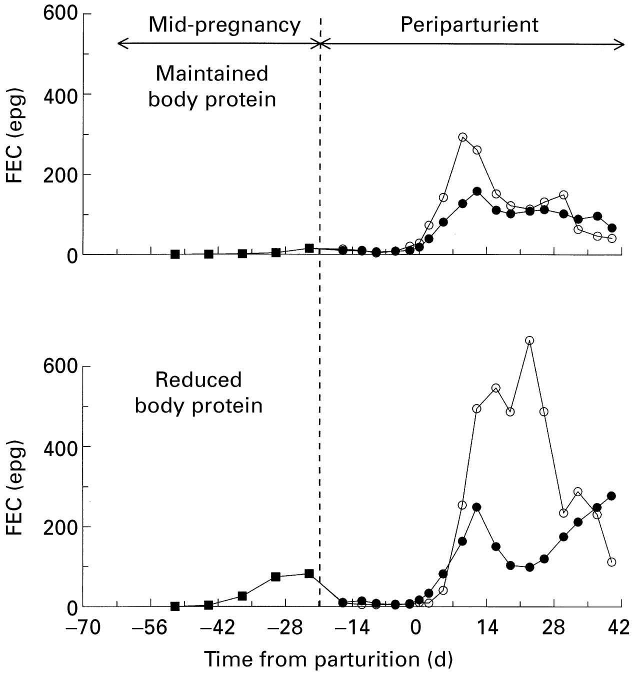

Fig. 2. Backtransformed mean faecal egg count (FEC: expressed as no. of nematode eggs per g faeces (epg)) of twin-bearing and -rearing ewes offered a scarce (○) or adequate (●) amount of metabolisable protein during the periparturient period, following mid-pregnancy feeding strategies to (a) maintain or (b) reduce body protein. The ewes were infected with *Teladorsagia circumcincta* at a rate of 10 000 3rd stage infective larvae for 3 d per week from day –63 onwards. (Redrawn from Houdijk *et al.* 2001*b*.)

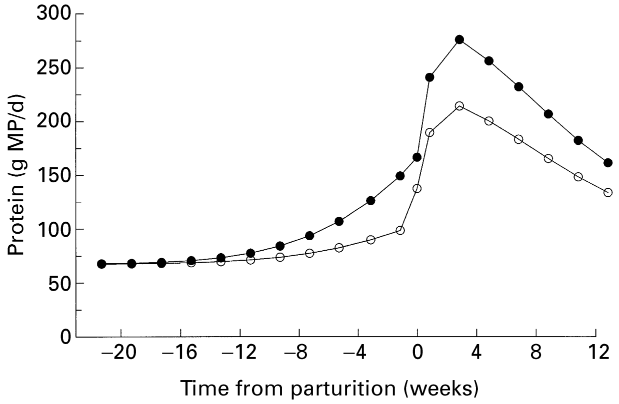

Fig. 3. Estimated metabolisable protein (MP) requirements of a 60 kg ewe bearing and rearing singles (○) or twins (●). (Calculated from Agricultural and Food Research Council, 1993; Groenewald *et al.* 1996.)

scarcity on periparturient BIP (Fig. 2; Houdijk *et al.* 2001*b*). Periparturient dietary MP scarcity did not affect periparturient BIP in ewes infected with *T. circumcincta* when the ewes were fed to maintain body protein during mid-pregnancy. In contrast, dietary MP scarcity exaggerated the extent of periparturient BIP in similarly-infected ewes fed to reduce body protein during mid-pregnancy.

Nutrient allocation to reproductive and immune functions has so far been dealt with in a qualitative descriptive way. This approach was considered a logical first step, i.e. to identify whether a nutritional basis of periparturient BIP existed in the first place. There is now a growing body of evidence in favour of the existence of the latter, and some apparent contradictions have been accounted for. We next wish to quantitatively explore this nutritional basis of periparturient BIP, by addressing MP requirements for expression of immunity to parasites in relation to MP requirements for reproduction.

Metabolisable protein requirements for reproduction

In qualitative terms, certain generalisations can be made as to the pattern of MP requirements during a reproductive cycle across mammals. During pregnancy there is an MP requirement for growth of the fetus, uterus, placenta and mammary gland. During lactation MP is required for continuing development of the mammary gland and for the production of milk. Quantitatively it is more difficult to generalise, since different reproductive strategies have evolved for different species. These strategies vary in the relative effort invested in pregnancy with respect to lactation, seen in the extent of development of the young at parturition, as well as in the length and intensity of lactation.

The MP requirements during the reproductive cycle have been well characterised for farm animals. Fig. 3 shows such data for a 60 kg sheep bearing and rearing one or two lambs. Depending on litter size, MP requirements increase to three to four times that of non-pregnant and non-lactating animals, with a maximum of approximately 13 g MP/kg metabolic body weight (body weight$^{0.75}$) per d. The physiological changes that arise from attempting to meet the increased MP requirements are major. The increased voluntary intake leads to hypertrophy of the gut (Hammond & Diamond, 1992) and increases in cardiac output and blood flow to the gut and mammary gland (Sakanashi *et al.* 1987). These factors, together with hormonal changes (Bauman, 2000), result in an increase in potential MP supply to the mammary gland. For some animals these changes ensure sufficient supply of MP to meet the increased requirement of lactation. However, in many circumstances MP supply falls short of that required, e.g. due to the maximum amount of food offered, maximum rate at which food can be processed, or the nutritional quality of the food. To some extent, MP supply from body protein may overcome this shortfall.

With regard to MP supply from body protein, Naismith & Morgan (1976) proposed a biphasic nature to protein use during gestation. Protein would accumulate in the body during the first half of pregnancy, and be drawn upon (thus acting as a reserve), when needed during the latter half of pregnancy and during early lactation. This process has been shown to take place in rats (Naismith *et al.* 1982), human subjects (Motil *et al.* 1989) and cattle (Trigg & Topps, 1981). It has been estimated that at times when protein reserves are present up to approximately 25 % of the body protein, principally from muscle and skin, can be mobilised (Botts *et al.* 1979; Pine *et al.* 1994*b*). Net fractional rates of loss of such labile protein can be as high as 13 %/d during early lactation in rats (Pine *et al.* 1994*a*). Allowing for differences in metabolic time, this rate of loss would be equivalent to a protein loss of approximately 2·5 g/kg body

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weight$^{0.75}$ per d in sheep, potentially meeting about 20 % of the maximum MP requirements of lactating sheep.

Coop & Kyriazakis (1999) have suggested that animals give the highest priority of scarce MP allocation to maintenance, defined as maintenance of body protein (Emmans & Fisher, 1986). However, we have discussed that animals may lose body protein to support reproductive and immune functions at times of dietary MP scarcity (Jessop, 1997; Houdijk *et al*. 2001*b*). Dividing body protein into that which is essential for tissue integrity and that which can potentially be mobilised may solve this paradox. We would propose that maintenance of essential body protein is given the highest priority for scarce nutrient allocation, whilst the maintenance of labile body protein would get a low priority, lower than that for reproductive and immune functions.

Metabolisable protein requirement for expression of immunity

The estimation of MP requirements for expression of immunity to gastrointestinal nematodes may be derived by comparing whole-animal quantities of effector cells and/or molecules in non-infected naive sheep and infected immune sheep. This estimation will be done for sheep expressing immunity to *T. circumcincta*. We have based this estimation on quantitative data relating to circulating lymphocytes and Ig, mucosal mast cells and sheep mast cell proteases, and plasma loss (see Table 2). Our estimation of the MP requirement for the expression of immunity to *T. circumcincta* in sheep is based on several assumptions related to the conversion of the data obtained to whole-animal quantities, protein contents and half-life of effector cells and/or molecules, and the efficiency for protein synthesis from MP supply (Table 2). Accurate measurements to confirm or improve these assumptions are required. We also wished to include MP requirements for mucus production. It is well known that the secretion of mucus plays an important role in the expression of immunity to gastrointestinal nematodes (Miller, 1984), and the amount of mucus produced per d may be considerable. However, appropriate quantitative data to estimate the latter are not (yet) available.

A series of measurements were taken from the gastric lymph of sheep infected with *T. circumcincta* (Smith *et al*. 1981, 1983, 1984). At a systemic level, the most pronounced differences between infected immune sheep and parasite-free sheep were an increased concentration of lymphocytes and IgA in the gastric lymph. It was calculated that the amount of MP required to maintain this difference would be about 50 mg/kg body weight$^{0.75}$ per d (Table 2). At a local level, in the mucosa of the gut wall one of the most striking aspects of expression of immunity to gastrointestinal nematodes is mucosal mast cell hyperplasia and the release of sheep mast cell protease (Miller, 1984). Our estimations suggest that the associated demand for MP is <1 mg/kg body weight$^{0.75}$ per d.

One of the key features of an infection with gastrointestinal nematodes is the leakage of considerable quantities of plasma into the gastrointestinal tract (Holmes, 1993). Whilst this factor has long been thought to be associated with primary infections, substantial plasma leakage has also been measured in solidly-immune sheep challenged with *T. circumcincta* (Yakoob *et al*. 1983). These sheep had low FEC and few adult nematodes present at slaughter, but had almost twice as much plasma leakage as their non-infected counterparts. Thus, although the concept is perhaps controversial, we have considered plasma leakage as an integral part of the expression of immunity to gastrointestinal nematodes. Plasma leakage may be seen as a mechanism for the delivery of circulating Ig and other compounds to the site of infection (Miller, 1996). A large amount of the lumen N originating from plasma leakage can be expected to be salvaged in more distal parts of the gastrointestinal tract (Kimambo *et al*. 1988; Jackson, 1998). However, such salvaged N may to some extent be excreted in the urine, presumably after being broken down to NH_3 and converted into urea (Taylor *et al*. 1989). In addition, it has also been shown that such N leakage matched a decreased N retention in growing sheep (Rowe *et al*. 1988). Thus, we have considered all plasma N leakage into the gut as an irreversible loss which needs to be replenished, resulting in an estimated MP requirement approximately 650 mg/kg body weight$^{0.75}$ per d (Table 2). This value may be an underestimation. Plasma leakage remains to be determined in parasitised periparturient animals in which blood flow rate through the gut, and hence the potential for plasma leakage, may be increased compared with non-reproducing animals.

Table 1. Estimation of the requirement for metabolisable protein (MP) to maintain the expression of immunity to *Teladorsagia circumcincta* in sheep*

	Parasite-free sheep	Infected immune sheep	Requirement for MP (mg/kg MBW per d)†
Total cell flow in lymph (no. of cells/d)	6.9×10^9	21.8×10^9	19·8
Flow of IgA in lymph (mg/d)	36	888	32·5
Mucosal mast cells (no. of cells/0·2 mm^2)	54×10^6	345×10^6	0·3
Sheep mast-cell proteases (μg/g tissue)	0·5	171·7	0·2
Plasma loss (ml/d)	40	190	655·3
Total			708·1

MBW, metabolic body weight (body weight$^{0.75}$); Ig, immunoglobulin.
*Compiled from Smith *et al.* (1981, 1983, 1984), Yakoob *et al.* (1983), Huntley *et al.* (1987) and Parkins & Holmes (1989).
†The following assumptions were made, or taken from Fell *et al.* (1972), Frandson (1986), Agricultural and Food Research Council (1993) and Klasing & Calvert (1999): lymph represents 10% total blood volume, packed cell volume of blood is 0·33, blood volume is 8% body weight, immune cells weigh 2×10^{-10} g and contain 18% protein, half-life of IgA and lymphocytes is 7 d, half-life of mucosal mast cells is 1·5 d, efficiency for protein synthesis is 0·85, plasma contains 60–75 g protein/l, abomasum volume is 1·4 litres, abomasal folds and glands increase the abomasal surface by a factor of 10, the abomasum weighs 250 g of which 20% is mucosa.

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Without taking into account the MP requirement for mucus production, the MP requirement for the expression of immunity to *T. circumcincta* in sheep was estimated to be approximately 0·7 g/kg body weight$^{0·75}$ per d, which is about 5 % of the maximum MP requirements for the non-infected twin-rearing ewe. This value indicates that the potential supply of protein from labile body protein (see p. 518) is probably sufficient to meet the MP requirement for the expression of immunity to *T. circumcincta*. The latter confirms our previously-discussed findings that body protein may overcome effects of MP scarcity on BIP in periparturient ewes infected with *T. circumcincta* (Houdijk *et al.* 2001*b*).

Our estimate of MP requirements for expression of immunity to *T. circumcincta* may be relatively small, but may need to be drawn from a much larger pool of MP if the required amino acid profile differs from that supplied. We have assumed that protein supply and demand are in balance in terms of amino acid composition. For ruminants, the amino acid composition of MP is still uncertain and, at present, there is only limited information available on the amino acid composition of proteins involved in the expression of immunity. For example, it has been suggested that immune cells have a relatively high requirement for glutamine (Calder, 1995) and for cysteine and methionine (MacRae, 1993; Takahashi *et al.* 1997; Dröge & Breitkreutz, 2000). Likewise, a relatively large amount of phenylalanine and tryptophan is required for the acute-phase protein response which is usually associated with responses to systemic infections or trauma (Reeds *et al.* 1994).

Our estimate of the MP requirement for the expression of immunity to *T. circumcincta* suggests that the MP requirements for parasitised periparturient ewes rearing twins may be about 5 % higher than current estimates of protein requirements for non-infected ewes (Agricultural and Food Research Council, 1993). This value is somewhat lower than that of about 20 % suggested elsewhere (Sykes, 2000). Whilst our estimate may well be an underestimation, the latter was derived from experiments that were not designed to assess nutrient requirements, and as a consequence may be an overestimation due to the assumption that the highest level of MP supplied via the diet was equal to the MP requirement. Although arbitrary, we would suggest that periparturient BIP may largely be overcome by increasing the MP supply by about 10 %. However, there is no accurate data-set available (yet) that uses a sufficient number of appropriately chosen levels of dietary MP supply with which we could confirm these estimates. Currently, we are performing an experiment in which periparturient ewes infected with *T. circumcincta* are fed at 65, 80, 95, 110 or 125 % of the MP requirements. Such experiments will provide data to confirm estimates for the MP requirements of infected periparturients ewes and to model MP allocation to reproductive effort and to immunity to *T. circumcincta*. The optimal level of dietary MP intake for maximum expression of immunity in periparturient animals is expected to be higher than that for reproductive effort only (Fig. 4). This difference stems from the hypothesis that expression of immunity has a lower priority for the allocation of scarce nutrients than reproductive effort (Coop & Kyriazakis, 1999).

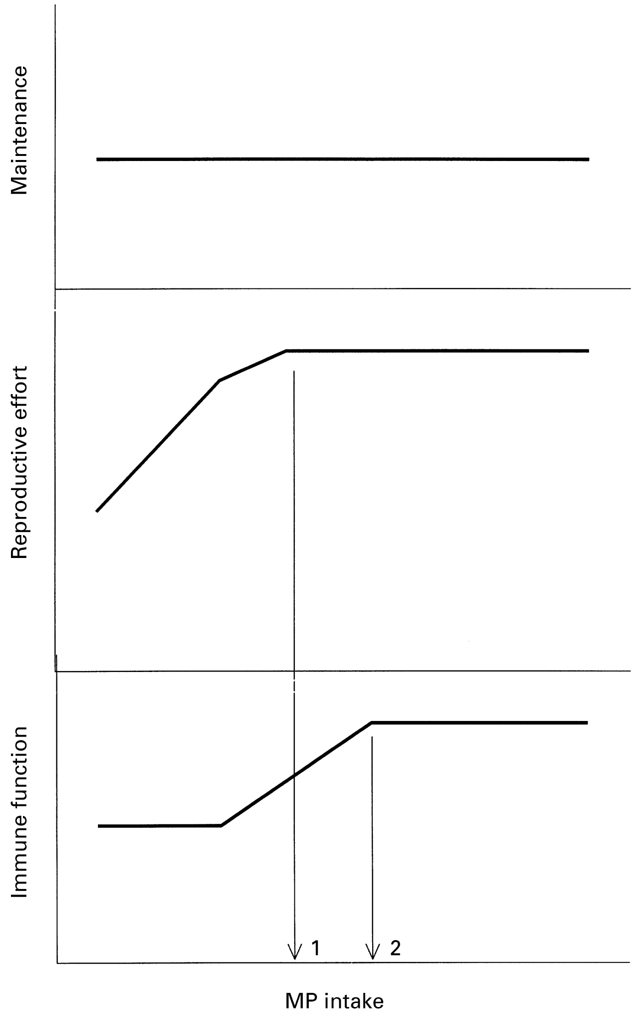

Fig. 4. Conceptual framework for the partitioning of metabolisable protein (MP) to maintenance functions, reproductive effort and immune functions. Maximal reproductive effort is reached at 1 and minimum breakdown of immunity to parasites is reached at 2. The latter would be the estimated MP requirements of the parasitised periparturient animal.

Our estimation of the MP requirement for the expression of immunity to gastrointestinal parasites may be used to test the nutrient-partitioning framework on which our initial hypotheses were based. Coop & Kyriazakis (1999) proposed that the majority of scarce MP would be allocated to the prioritised reproductive effort rather than to immune functions. A consequence of the resulting BIP is that parasite burden and tissue damage increase. Since tissue damage may hamper maintenance functions, scarce nutrient allocation to tissue repair is expected to have a high priority (Coop & Kyriazakis, 1999). However, if the host aims to prioritise scarce nutrient allocation to its reproductive effort, then the nutrient requirement for the repair of tissue damage would need to be lower than the nutrient requirement for the expression of immunity to parasites. MP requirements for tissue repair following a *T. circumcincta* infection are unknown, but may be derived from measurements of the amino acid metabolism of the infected gastrointestinal tract, as recently done by Yu *et al.* (2000) for another type of parasitic infection. To allocate such measurements to tissue repair, data should be obtained during the first few weeks of infection, i.e. before the expression of immunity starts to occur.

We have estimated the MP requirement for the expression of immunity in a specific case, i.e. immunity to *T. circumcincta* in sheep. Data from chickens challenged with lipopolysaccharides, which are antigenic components of bacterial cell walls, may be used to estimate MP requirements for immunity to other types of infections (Klasing & Calvert, 1999). These authors estimated that the immune response following a lipopolysaccharide challenge required lysine at a rate of approximately 435 µmol/kg body weight per d. Quantitatively, the most important host response to such a challenge is an increase in plasma acute-phase proteins, which contain on average 7 % lysine (Reeds *et al.* 1994). It can be calculated that the MP requirement for immune responses to a lipopolysaccharide challenge in chickens is about 0·8 g/kg body weight$^{0 \cdot 75}$ per d. In addition, protein loss over a range of infections in man was also of the same order (Powanda, 1977). Although more data are needed for confirmation, these estimations suggest that host MP requirements for the expression of immunity to a wide range of infections may all be of the same order of magnitude, despite the different underlying immune mechanisms.

Broadening the nutritional basis for breakdown in immunity: other nutrients, other hosts and other parasites

In the present review we have focused on MP scarcity as a cause of breakdown of immunity to *T. circumcincta* in periparturient sheep. However, there are no reasons why the concepts could not be expanded to other nutrients, other hosts and other parasites. For example, several other nutrients are known to influence immune functions, including vitamins (e.g. vitamin A), minerals (e.g. Zn and Fe) and fatty acids (Chandra, 1997; Miles & Calder, 1998). In theory, scarcity of any of these nutrients may cause some extent of BIP. We would argue that the importance of nutrients in causing BIP depends on which nutrient will be first limiting for the expression of immunity. However, it should be noted that since isolated deficiencies of nutrients are rare (Chandra, 1997), an increased supply of a specific nutrient may not necessarily overcome BIP.

In contrast to changes in MP supply, BIP in sheep is unlikely to be influenced by (moderate) changes in the metabolisable energy supply (Bown *et al.* 1991; Donaldson *et al.* 1998). This contradiction between metabolisable energy and MP is not well understood. Effects of energy or protein nutrition may be difficult to appreciate in isolation, since changes in energy and protein nutrition are often correlated. This issue could be readily elucidated in parasitised rodents. In contrast to ruminants, it is relatively easy to feed single-stomached animals isoenergetic foods with different protein contents as well as isonitrogenous foods that supply different amounts of non-protein energy. Such foods have recently been used to distinguish the effects of protein and non-protein energy on mammary activity in lactating rats (Goodwill *et al.* 1996).

It has been shown repeatedly that in growing sheep protein supplementation enhances the expression of immunity, resulting in decreased FEC and increased nematode expulsion (for references, see Coop & Kyriazakis, 1999, 2001). Similar examples can be found in growing goats (Papadopoulos *et al.* 2000), rats (Cummins *et al.* 1987) and mice (Boulay *et al.* 1998). It might be argued that their non-supplemented counterparts, in which the expression of immunity is penalised, experience some extent of breakdown of the potential expression of immunity to parasites. For example, van Houtert *et al.* (1995) observed that the concentrations of eosinophils in the blood and mucosal mast cell proteases in the gut were lower in non-supplemented, parasitised growing sheep than in their protein-supplemented counterparts. However, compared with non-infected controls, the non-supplemented parasitised sheep had higher concentrations of both blood eosinophils and gut mast cell proteases. This finding indicates that the potential for expression of immunity was present in the parasitised sheep, although MP scarcity may have reduced its effectiveness.

Another example of BIP in growing animals is the so-called type II ostertagiosis. This condition can be observed in calves housed for the winter after their first grazing season (Berghen *et al.* 1990). During type II ostertagiosis inhibited larvae suddenly re-emerge, with pathophysiological consequences for the host. It is a quite common agricultural practice to keep winter-housed calves on a relatively low plane of nutrition. Under such conditions body reserves form an additional source of nutrients for the host. It might be hypothesised that as long as a certain level of body reserves are present BIP would not occur, since MP requirements for the expression of immunity may be met from mobilised body protein (see p. 520). Timing and severity of bovine type II ostertagiosis in housed calves on a low plane of nutrition may thus depend on body condition in general, and labile body protein in particular.

Recent observations on interactions between parasitism, nutrition and reproductive effort in breeding birds support the nutritional hypothesis for the occurrence of BIP at times of high nutrient demands for the reproductive effort. An increased food supply (voles, *Microtus agrestis*) resulted in a decreased level of parasitism in nestling owls such as tawny owls (*Strix aluco*; Appleby *et al.* 1999) and in kestrels (*Falco tinnunculus*; Wiehn & Korpimaki, 1998). An increased brood size resulted in an increased prevalence of haematozoan parasites in great tits (*Parus major*; Norris *et al.* 1994; Richner *et al.* 1995), and reduced ability to mount an antibody response to Newcastle disease virus vaccine in the collared fly catcher (*Ficedula albicollis*; Nordling *et al.* 1998). It has been shown also that the negative correlation between brood size and susceptibility to *Trypanosoma* spp. in Tengmalm's owls (*Aegolius funereus*; Ilmonen *et al.* 1999) and in kestrels (Wiehn *et al.* 1999) was present only at times of moderate vole supply and not at times of vole abundance. Although these observations support the nutritional basis for BIP, it is highly unlikely that protein scarcity is the causal factor in the case of vole-eating owls.

Whilst BIP has been extensively reported for growing and periparturient animals, BIP in adult non-periparturient

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animals have only been reported sporadically. For example, Poelvoorde (1973) reported on rising FEC in housed adult boars. In contrast, it is well known that protein–energy malnutrition forms at least part of the basis of the reduced immunity in elderly human subjects (Chandra, 1991). However, effects of ageing and mal-nutrition are often confounded. MP scarcity in adult non-reproducing animals may be difficult to induce due to the presence of labile body protein. The latter may be the reason why BIP is not easily observed in adult non-reproducing animals. A study with mature animals that have been fed at a level designed to reduce body protein would provide a strong test for the existence of a nutritional basis for BIP; can BIP be induced in immune non-reproducing adult animals by feeding a limiting amount of MP?

Finally, there is evidence that the extent of periparturient BIP differs between species of gastrointestinal nematodes in sheep (O'Sullivan & Donald, 1970, 1973; Gibbs & Barger, 1986; Jackson *et al*. 1988; Barger, 1993). In general, peri-parturient sheep show a more pronounced breakdown of immunity to the abomasal nematode *T. circumcincta* than to *Trichostrongylus* spp. (nematodes that reside in the small intestine). In addition, a breakdown of immunity towards the small intestinal nematode *Nematodirus* spp. does not seem to occur at all. The reason for such differences in the extent of BIP between nematodes and their underlying mechanisms are unclear. Possible explanations may lie in the site of infection (abomasum *v*. small intestine) and the type of immune response evoked. Aspects to explore may include a possible higher priority for the host to maintain a certain degree of immunity in the small intestine, since this site is also a preferred site of attachment or invasion for bacteria. In relation to the type of immune response, protein scarcity seems to affect non-specific defences and cellular immunity to a much larger extent than it affects humoral immunity (Calder & Jackson, 2000). Future research would be needed to establish if, and to what extent, dependency on cellular immune responses differs between different parasites. A different extent of dependency on cellular immune responses may account, at least in part, for the different extent of periparturient breakdown of immunity to different parasite species. The latter may be extended to breakdown of immunity to bacteria, and may provide information that accounts for the suggestion that immunity to bacteria is much less labile than immunity to nematodes (Waller, 1993).

Conclusion

In the present review we have explored the concept of a nutritional basis for periparturient BIP, which was introduced in a recently developed nutrient-partitioning framework. According to this framework periparturient BIP could be due to reproductive functions taking priority over immune functions for the use of scarce nutrients. Such scarcity arises from an imbalance between nutrient supply and demand. It is hypothesised that an increased supply of, or a decreased demand for, nutrients lowers the extent of periparturient BIP. This view is supported by experimental evidence on changes in MP supply and demand in peri-parturient ewes infected with the abomasal nematode *Teladorsagia circumcincta*. From the limited information available we estimated that the MP requirement for the expression of immunity to this parasite is about 1 g MP/kg body weight$^{0.75}$ per d. This value needs to be confirmed, but it may be used to improve the known nutrient requirement of periparturient animals in order to minimise the extent and the consequences of periparturient BIP.

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