

Metabolic consequences of intestinal parasitism

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Clinical and subclinical intestinal parasitism is characterized by impaired production (Sykes & Coop, 1976; Steele, 1978) with poor growth rates in young animals and loss of body weight in older animals. Sheep also incur severe reductions in wool growth. A number of comprehensive reviews prepared over the last decade characterize and contrast the magnitude of such impairment across a range of intestinal roundworms and consider the factors which contribute to this problem (Armour & Ogbourne, 1982; Bremner, 1982; Sykes, 1983; Holmes, 1986; Parkins & Holmes, 1989; Poppi *et al.* 1990).

Laboratory-based experiments designed to investigate the aetiology of different infections have followed two distinct approaches. They have involved administration of either a massive single dose of parasite larvae (e.g. 30 000–100 000; Steele, 1972; Roseby, 1973), or smaller doses of larvae given daily, or perhaps two to three times per week, in a so-called 'trickle infection' approach (Sykes & Coop, 1976; Jones & Symons, 1982). The latter regimen was adopted to more closely simulate the way animals incur infestation under practical conditions and it has provided a clearer picture of the aetiology and the subsequent immunological resistance which accompanies any subclinical condition. It has also shown the way in which the severity of infection relates to dose rate of larvae and nutritional state of the animal.

As the present review will address mainly the metabolic consequences of subclinical parasitism, it will relate predominantly to experimental data obtained from animals subjected to 'trickle infection', mainly with the intestinal roundworm *Trichostrongylus colubriformis*, where very few clinical symptoms other than parasite eggs in the faeces and high eosinophil counts in the blood are seen.

THE TIME-COURSE OF INFECTION

Most studies have adopted larval dosing procedures which continue for 14–15 weeks (Sykes & Coop, 1976; MacRae *et al.* 1982; Poppi *et al.* 1986); however, Kimambo *et al.* (1988a) dosed lambs daily with *T. colubriformis* larvae for 34 weeks. The growth rates of these animals and of non-parasitized control lambs pair-fed are shown in Fig. 1. These findings confirmed the earlier findings (e.g. Sykes & Coop, 1976; Poppi *et al.* 1986) that from weeks 4–14 of dosing infected animals underwent a severe growth check. After this period, however, growth restarted in the infected (now resistant) animals. Faecal egg numbers increased from week 3, peaked between weeks 7 and 8, and decreased to negligible levels by weeks 12–14 of dosing. Blood eosinophil counts which, at least in part, arise from IgE activation of serosal mast cells (Lewis & Austin, 1981) increased steadily from weeks 4–5, peaked at weeks 12–16 of dosing, but stayed at significant levels thereafter, confirming the development of the immunity. Kimambo *et al.* (1988b) then rested the animals for 6 months following the 34-week dosing before rechallenging them with the same numbers of daily larvae for a further 10 weeks. The animals showed no detectable effects of this subsequent challenge, except for a very rapid rise in blood eosinophils showing resistance had been retained over the rest period.

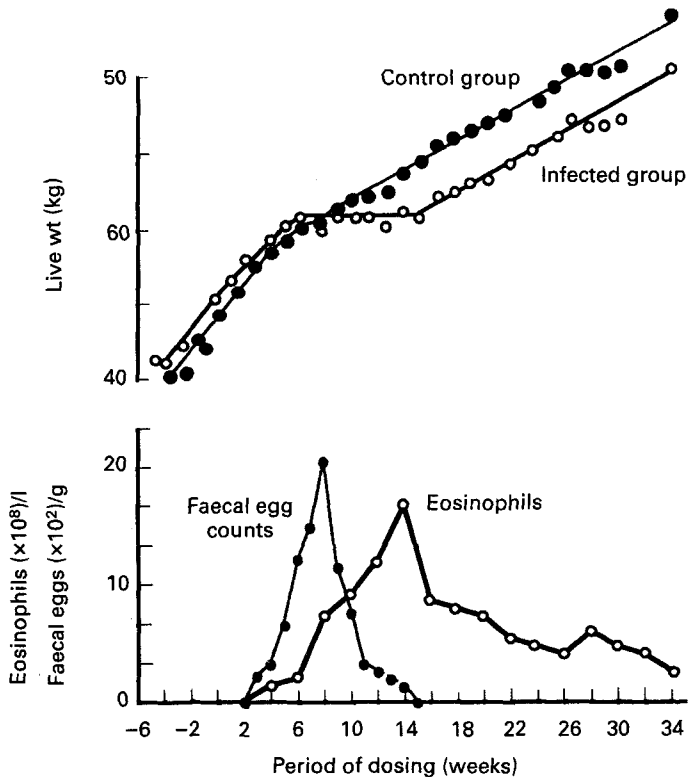


Fig. 1. Growth curves of lambs (n 5) dosed daily with 2500 *Trichostrongylus colubriformis* larvae for 34 weeks and of pair-fed control animals (n 5). Also shown are the faecal egg counts (no. of eggs $\times 10^2$ /g) and blood eosinophil concentrations ($\times 10^8$ /l) of the infected animals. (From values of Kimambo *et al.* 1988a.)

Most of the studies which report the effects of infection on digestive and/or metabolic function relate to the primary infection period between weeks 4 and 14 of dosing. During this period the majority of infections involve some loss of appetite, e.g. the pair-fed control animals had a 50% reduction in live-weight gain in Fig. 1 (Kimambo *et al.* 1988a), but this cannot explain fully the lower growth rate or the reduction in wool growth (Symons, 1985). In consequence, considerable attention has focused on the digestive and metabolic consequences which contribute to this loss of production.

ENERGY METABOLISM OF INFECTED ANIMALS

Early findings on subclinical *T. colubriformis* infections (animals given 2500 larvae/d for 15 weeks) indicated little effect on digestibility but a reduction in the efficiency of utilization of both energy and nitrogen (Sykes & Coop, 1976). Subsequent studies, however, using respiration chambers to determine energy expenditures in infected and pair-fed control animals indicated a significant reduction in the digestibility of the ration and, hence, in the metabolizable energy (ME) available to the infected animal between weeks 2 and 12 of dosing. Regression of energy expenditure *v.* ME intake indicated the

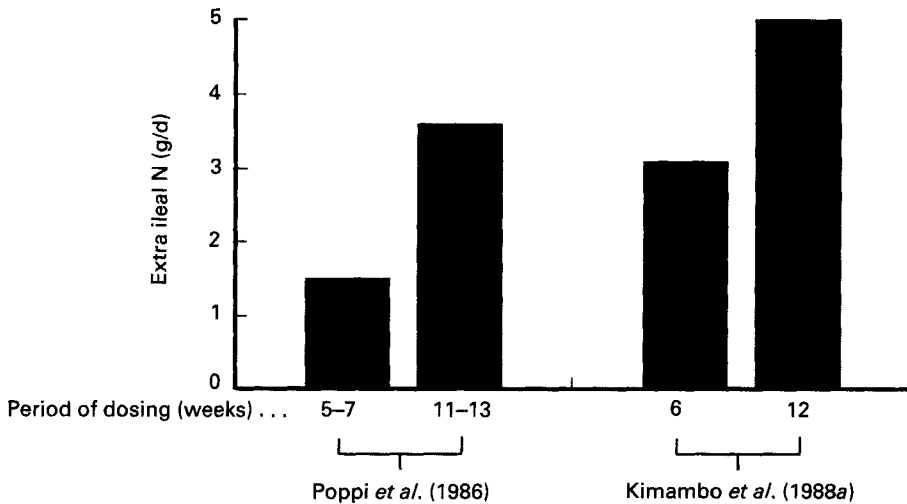


Fig. 2. Increased flow of nitrogen at the terminal ileum of lambs dosed with *Trichostrongylus colubriformis* (2500 g larvae/d).

relationship for the infected animals was indistinguishable from that of the pair-fed control lambs (MacRae *et al.* 1982).

PROTEIN METABOLISM OF INFECTED ANIMALS

The reduction in metabolizability of the ration was concomitant with a much more serious problem relating to the N and P metabolism of the infected animals. The N balance of infected lambs was 3–4 g N/d less than that of the pair-fed control lambs and blood P concentrations were approximately 50% of normal.

Using cannulation techniques to determine digesta flow, Poppi *et al.* (1986) found that the amount of N at the terminal ileum of infected animals was significantly elevated ($P < 0.05$) during weeks 5–7 and 11–13 of dosing (see Fig. 2). This was later confirmed by Kimambo *et al.* (1988a) (see Fig. 2). To test whether this was the result of either a reduced capacity to digest and absorb protein within the small intestines or enhanced secretion of endogenous N components into the lumen, Poppi *et al.* (1986) infused ^{35}S -labelled microbial protein into the abomasum and $^{51}\text{CrCl}_3$ -labelled plasma protein into the circulation. They concluded that the major factor was probably sloughed epithelial cells, and mucin secretion, which was estimated as elevated 42–150% depending on the resorbability of these desquamated and secreted proteins; the findings showed no change in absorption of ^{35}S -labelled amino acids and although plasma leakage was elevated by 1–2 g N/d this was assumed to be largely resorbed before the terminal ileum.

Kimambo *et al.* (1988a) made similar observations during weeks 6 and 12 of dosing, but the effect was reduced by week 18 and had virtually disappeared by weeks 28–33 of dosing. Interestingly, when subsequently Kimambo *et al.* (1988b) rechallenged their rested sheep for 10 weeks, no digestive or metabolic problems associated with the rechallenge could be detected.

PHOSPHORUS METABOLISM OF INFECTED ANIMALS

A major consequence of intestinal parasitism appears to be a reduced absorption of P from the small intestine (Wilson & Field, 1983; Poppi *et al.* 1985; Bown *et al.* 1989), leading to reduced bone formation, low plasma P levels and reduced salivary P secretions. The reasons for this in sheep dosed with *T. colubriformis* larvae are not fully understood, but may relate to the reduced intestinal motility in the upper regions of the duodenum (Gregory *et al.* 1985) and the consequent precipitation of digesta P out of solution, as Ca and Mg complexes, at pH 6–8 in the upper small intestine (Poppi *et al.* 1985). Low P absorption and the consequent low salivary P secretion has been linked to inappetence in sheep (Field *et al.* 1975; Milton & Ternouth, 1982) and indeed most experimentally-induced parasitisms induce varying degrees of anorexia. However, the major effect of the failure to absorb P (Poppi *et al.* 1985) is to severely impair bone mineralization which results in the characteristic stunted skeletal development of infected animals.

CONSEQUENCES OF THE PRIMARY INFECTION ON GASTROINTESTINAL (GI) TRACT PROTEIN METABOLISM

In order to consider the consequences of the presence of the parasites in the GI tract on the metabolic functioning of the tract and of other organs and tissues, it is first necessary to consider the complexity of protein metabolism within the different body components in the normal animal. Loblely *et al.* (1980) identified the disparity between the proportional distribution of protein mass in different body components of cattle and the corresponding rates of protein synthesis. Thus, whereas skeletal muscle, which represents 45% of protein mass, accounts for only 16–22% of total whole-body protein synthesis, the GI tract, which comprises only 5% of total protein, contributes 25–45% to total synthesis. These distributions are similar in young sheep (Attaix *et al.* 1987) and when allied with rates of protein deposition in animals of similar growth (J. C. MacRae, unpublished results) a general picture of the relative protein turnovers which occur in a number of body components in the lamb can be compiled (see Fig. 3).

Broadly, tissues can be divided into two distinct types in the growing animal. First, in tissues such as skeletal muscle (and skin) protein degradation proceeds at only 60–70% of synthesis and, thus, approximately 30–40% of the protein which the tissues synthesize is accreted. Such peripheral tissues may be considered as 'protein stores'. In other tissues, however, such as the GI tract and the liver, the rates of synthesis and degradation are greater with only low net accretion (but considerable production of export protein). In the case of the weaned lamb the GI tract accounts for 0.27 (77 g/d) of the whole-body protein synthesis yet net accretion is only 1 g protein/d. Thus, 76 g of the protein are degraded and/or secreted.

The representation in Fig. 3 of the degraded GI tract protein recycling directly back to the body amino acid pool is, therefore, oversimplistic and the structure of the tissue needs to be considered. The proteins of the GI tract comprise two distinct types, those of the serosa involved in propulsion of digesta through the tract and those of the mucosal epithelia which assist in nutrient absorption. The mucosal cells are continuously differentiated in the crypt regions of the epithelium and then migrate to the tips of the villi over a period of 36–48 h where they are desquamated into the lumen. Whilst the simple recycling concept illustrated in Fig. 3 could apply to the serosal proteins, a

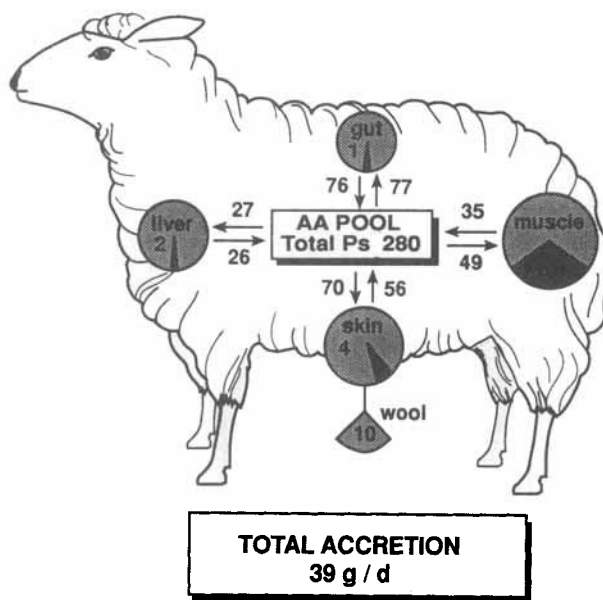


Fig. 3. Protein turnover (g/d) in different body components of young weaned lambs (calculated from values of Attaix *et al.* (1987) and J. C. MacRae (unpublished results)).

considerable proportion of the mucosal proteins, along with the digestive secretions and mucins require redigestion to amino acids and resorption of these before they are again available to the body. The efficiency of this salvage process is difficult to determine, but is not qualitative since Bown *et al.* (1986) estimated resorption of plasma proteins at 85%, while only 70% of ^{35}S -labelled microbial protein introduced into the tract is recovered (Poppi *et al.* 1986). The unresorbed residues will enter the large intestine and be excreted either in the faeces or, if sufficient energy is available for secondary microbial fermentation, via the urine as urea following ammonia release in the hind-gut, absorption and hepatic ureogenesis. Either way, this loss is detrimental to the N economy of the animal.

If the redigestion/resorption efficiency remains constant then the magnitude of the 'leakiness' or net loss will be proportional to the rate of intestinal protein synthesis. This rate has been shown to be influenced by physiological and nutritional state, e.g. the transition at weaning increased the rate of GI tract protein synthesis in lambs from 49 to 77 g/d (Attaix *et al.* 1987). No direct measurements have been reported of the rates of GI tract protein synthesis during the primary infection phase of parasitism in farm animals, but in guinea-pigs infected with *T. colubriformis* the rate of small intestine protein synthesis increased by 10% ($P < 0.06$) in the first third (the main area of infection) and by 40% ($P < 0.001$) in the section distal to this region. The enhanced flow of N into the large intestine, as indicated in Fig. 2, is clear evidence that excess leakage results from this increased turnover of cellular proteins plus, probably, enhanced intestinal secretions of mucin and/or digestive enzymes.

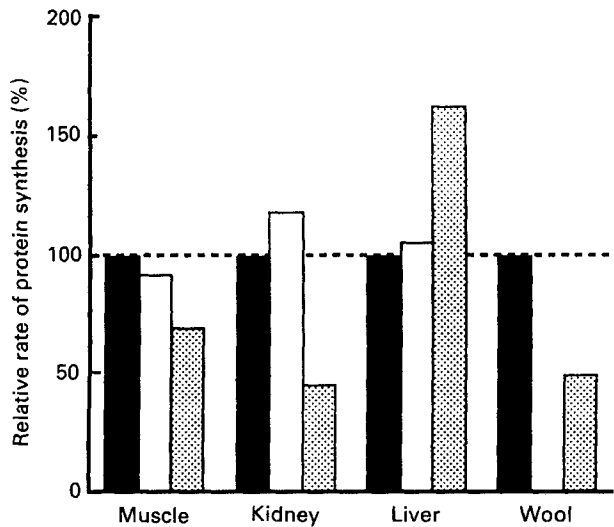


Fig. 4. Relative rates of protein synthesis in skeletal muscle, liver, kidney and wool of *ad lib.*-fed control sheep (■; 100%), sheep infected with *Trichostrongylus colubriformis* (▣) and sheep pair-fed to the intake of the infected animals (▤). From values of Symons & Jones (1975) and Jones & Symons (1982).

CONSEQUENCES OF THE PRIMARY INFECTION ON THE PROTEIN METABOLISM OF OTHER TISSUES

Increased protein and amino acid loss via the GI tract will reduce the amount available for other tissues. Symons & Jones (1975) and Jones & Symons (1982) found lowered rates of protein synthesis in skeletal muscle, liver and wool of sheep infected with *T. colubriformis*, compared with control animals fed *ad lib.* (Fig. 4). These were mainly the result of inappetence, but even relative to pair-fed controls the rates in muscle, kidney and skin were still markedly reduced. Liver values were more equivocal, the incorporation of tritium-labelled leucine being higher per unit RNA and DNA in the infected animals ($P=0.06$ and $P=0.055$ respectively). The technique employed would underestimate serum protein synthesis which would need to be enhanced both to offset the extra leakage into the intestine and to contribute to the immunological resistance which develops in these animals. However, these findings substantiate previous reports in guinea-pigs and in mice infected with *T. colubriformis* or *N. dubius* (Symons & Jones, 1971) and helped explain the observations of Sykes & Coop (1976) that the protein content of body tissue gain is considerably reduced in infected animals, from 114 and 124 g/kg live-weight gain in *ad lib.*- and pair-fed control animals respectively to 80 g/kg live-weight gain in infected animals.

Thus, the overall metabolic consequence of the intestinal infection seems to involve the diverting of protein synthesis away from muscle and bone (the 'storage' tissues) and towards the repair, replacement and reaction to damage of the gut wall, to mucus production and to plasma or whole blood loss.

CONSEQUENCES OF INFECTION ON THE AVAILABILITY OF INDIVIDUAL AMINO ACIDS FOR TISSUE PROTEIN SYNTHESIS

The aforementioned penalties may be exacerbated by alterations in the supply of individual amino acids. The amino acid composition of material absorbed from the small intestine is similar to mixed muscle protein, but is different from digestive secretions such as proteolytic enzymes and mucin, especially for valine, threonine, serine and proline (MacRae & Lobley, 1991). Thus, any elevation in digestive secretion losses will decrease the availability of these amino acids for protein synthesis and gain in other tissues. Most serious is the high concentration of threonine (280 mmol/mol), serine (130 mmol/mol) and proline (130 mmol/mol) in intestinal mucus (Neutra & Forstner, 1987), which is reported to be resistant to proteolytic degradation and poorly resorbed from the small intestine (Lindsay *et al.* 1980).

Another implication of the immunological resistance phase of infection relates to the availability of sulphur-amino acids for leukotriene production (Lewis & Austen, 1981). These compounds are thought to be involved in the ability of the host animal to impede larval development through inhibition of smooth muscle contraction and paralysis of larvae. Douch *et al.* (1983) first observed the larval migration inhibitory properties of mucus from sheep resistant to *T. colubriformis* larvae and identified that the factor responsible had properties similar to the slow-reacting substance of anaphylaxis (SRS-A). The major constituents of SRS-A are the cysteine-rich leukotrienes LTC₄, LTD₄ and LTE₄ thought to be produced from arachidonic acid by serosal cells following IgE activation of mast cells (Lewis & Austen, 1981). Kimambo & MacRae (1988) subsequently detected this same migration inhibitory factor in abomasal and intestinal mucosa of resistant animals, and also in the ileal digesta during larval challenge. Each of these leukotrienes contains a cysteine residue and if produced in greater quantity during the development and maintenance of immunological resistance this could reduce the net availability of this sulphur-amino acid for other tissues.

Interestingly, Barger *et al.* (1973) observed that sheep resistant to *T. colubriformis* produce 17–18% less wool when subjected to a larval challenge; wool is rich in cysteine (10% of the total amino acid mixture, approximately fourfold higher than that in most other body components; see MacRae & Lobley, 1991). Also, in the experiments of Kimambo *et al.* (1988a), once the lambs had developed resistance they started to regain weight, but, although they received the same quantity of feed daily as the pair-fed controls which were several kilograms heavier, the resistant animals exhibited no catch-up growth, implying some kind of nutritional penalty associated with their immunological status.

NUTRITIONAL SUPPLEMENTATION

It follows from the previously described considerations that amino acid supply for protein gain in the storage organs, such as muscle, bone and skin (wool), is severely restricted during the primary infection phase of parasitism and this may continue for specific amino acids in the immunologically-resistant animal. It is not surprising, therefore, that where animals have received supplemental protein, either by increasing the protein:energy value of the diet (Abbott *et al.* 1988), or by infusion of protein into the abomasum (Bown *et al.* 1986), this has reduced faecal output and worm burdens,

enhanced the onset of immunity, and offset the growth check associated with *Haemonchus contortus* (Abbott *et al.* 1988) and *T. colubriformis* (Bown *et al.* 1986) infections (see Holmes, 1986).

While it may appear less probable that P supplementation will increase the availability to tissues since the ability to absorb P is impaired by infection (Wilson & Field, 1983; Poppi *et al.* 1985), Coop & Field (1973) were able to increase live-weight gain in parasitized animals by increasing the P content of the diet from 1.9 to 2.7 g/kg dry matter. They observed also a possible enhancement of the host immune response on the higher P diet in that at slaughter, after 14 weeks of infection, worm burdens were reduced from 11 000 on the low-P diet to 1250 on the high-P diet.

CONCLUSIONS

Intestinal parasitism diverts amino acids towards protein metabolism in the GI tract and this has major consequences for other organs and tissues. The inefficient absorption of enhanced digestive secretions, particularly mucus, and sloughed mucosal proteins represents a net drain on the N economy of the host animal and may cause amino acid imbalances. Impaired P absorption inhibits bone mineralization and may induce inappetence in infected animals. Supplementation of diets with protein and P appears to offset the growth check and may also enhance the onset of the immunological resistance in infected animals.

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