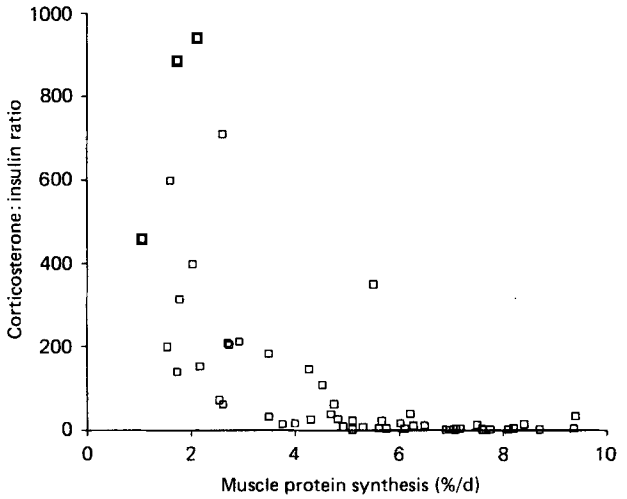
Letters to the Editors

Cortisol and growth in sheep

Sharpe *et al.* (1986) conclude from measurements on cortisol status and growth in sheep that the growth-promoting steroid, trenbolone, acts in part through modulation of cortisol metabolism, cortisol being an important modulator of growth through its antagonistic action on the insulin stimulation of muscle protein synthesis. These conclusions stem from their demonstrations that trenbolone reduces the maximum cortisol binding capacity of muscle and the negative correlation between the free cortisol:insulin ratio and weight gain. Their evaluation of the role of cortisol in normal growth regulation deserves some comment.

A glucocorticoid–insulin antagonism has certainly been shown to be an important factor for muscle protein balance not only where the hormone levels are directly manipulated (e.g. Odedra & Millward, 1982; Tomas *et al.* 1984) but also in conditions where the changes are purely physiological. Thus in fasted rats the acute restoration of muscle protein synthesis on refeeding is dependent on both an increase in insulin and a parallel fall in corticosterone, this latter change being necessary for full expression of insulin action (Millward *et al.* 1983). The accompanying figure shows corticosterone:insulin ratios, recalculated from published results (Millward *et al.* 1983), plotted against muscle protein synthesis during the first 3 h of refeeding fasted rats. Elevated ratios in the fasted rats fell to very low values (within 1 h) and these changes were causally related to the increase in protein synthesis. Such changes clearly relate to the switch between catabolic and anabolic states as do the inverse changes in corticosterone and insulin which were associated with catabolic changes in muscle metabolism in response to severe energy and protein restriction (Coward *et al.* 1977). Whilst such responses might account for any changes in normal growth in simple-stomached animals which were related to changes in the pattern of feeding (i.e. the feeding–fasting diurnal cycle), what must be asked is whether these glucocorticoid–insulin interactions could account for, or have any relevance to, variation in growth rates between well fed, growing, and especially ruminant animals which essentially are supplied with nutrients continuously.



The paper by Sharpe *et al.* (1986) offers little help with this problem. It appears to me that the significant correlation of the free cortisol:insulin ratio and weight gain reported in this paper was apparent only because of the marked increase in the ratio of animals in one subgroup which were severely growth restricted. Indeed, reduced food intake and growth of some of the trenbolone-treated animals clearly accounted for elevated cortisol in these animals and the similar correlation between the corticosterone:insulin ratio and growth within this group. If the analysis is restricted to those animals which exhibited no severe growth failure (say growth rates over 200 g/d) there is no such correlation. Thus this paper does not provide evidence that the cortisol:insulin ratio is related to variation in growth rates between *ad lib.* fed, normally eating, growing sheep. What it does confirm is that corticosteroids participate in the catabolic response to food restriction.

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Reply to letter by Millward

The main points of interest in our paper (Sharpe *et al.* 1986) were the results we obtained for the glucocorticoid binding capacity of sheep skeletal muscle under several experimental conditions, specifically the observation that treatment of lambs with trenbolone acetate reduced the binding capacity of muscle, a result recently confirmed by Galbraith *et al.* (1986). These authors also found that treatment of lambs with other androgenic agents does not have a similar effect to that of trenbolone. We also presented supplementary results on plasma cortisol and insulin concentrations which form the main subjects of Dr Millward's letter.

The objection raised by Dr Millward to our work is that he rejects a role for the glucocorticoids in the regulation of growth of normal, 'well-fed' animals. Whilst we agree that there is little direct evidence for this we would point out that reducing plasma corticosterone below normal physiological concentrations, by injection with an inhibitor of adrenal steroidogenesis, trilostane, has resulted in increased rates of weight gain in female rats (Sillence *et al.* 1985). These observations have been supported by unpublished work carried out in this laboratory.

With reference to the relevance of glucocorticoid concentrations to growth in ruminants, several studies have found a negative correlation between circulating levels of these hormones and the rate of weight gain in ruminant species (e.g. Purchas *et al.* 1971, 1980; Obst, 1974; Trenkle & Topel, 1978). In particular, the report by Barnett & Star (1981) showed a strong negative relation between integrated free cortisol concentrations and average daily gain in lambs, although no relation was found with total concentrations of the hormone. This work supports one of the main points of our paper, that often total concentrations of glucocorticoids may not reflect the actual levels of physiologically active ('free') hormone in the plasma. Quite clearly large changes in 'free' hormone concentration can occur with little apparent change in detectable total glucocorticoids (e.g. compare the concentrations of total and free cortisol in the control and trenbolone acetate-treated animals; Table 6, Sharpe *et al.* 1986). Indeed, a criticism of the work presented by Dr Millward in support of his theory that corticosterone:insulin ratios are involved in the regulation of muscle protein synthesis on refeeding fasting rats (Millward *et al.* 1983), could be that no account was made of any changes in transcortin capacity under these conditions. Such changes could, presumably, cause large fluctuations in free hormone concentrations which may, or may not, correspond to the observed changes in total hormone concentrations. We felt that the observed relation between free cortisol:insulin and weight gain was of sufficient interest to be included in our paper since this was one of the few studies which had measured 'free' as well as total hormone concentrations and because the relation corresponded to that proposed in the regulation of muscle protein synthesis (Millward *et al.* 1983). We were fully aware of the limitations of the regression analysis including the four treatment groups, which is why we included the raw data as Fig. 5 (Sharpe *et al.* 1986), rather than merely presenting a rather bald statement $r -0{\cdot}69$. Indeed, the final paragraph of the paper surely made clear our sentiments 'we appreciate the problems involved in correlating across the four treatment groups but do suggest that the relation between free cortisol:insulin and growth merits further study'. This may be especially true of the ruminant where the function of insulin may be quantitatively or even qualitatively different from that seen in other groups of animals (Harper *et al.* 1986; Weekes 1986).

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