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Lactation and gestation in dairy cows: flexibility avoids nutritional extremes

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The modern dairy cow has been selectively bred to produce large amounts of milk. Partly as a result, food consumption is considerably less than milk energy output in early lactation. It is only at 2 months or more postpartum that intake increases to the point where positive energy balance is regained, the initial production being achieved by a substantial mobilisation of body reserves. These reserves are laid down before parturition, but it is certainly not the case that the pregnant cow will accumulate adipose tissue recklessly; in the last third of pregnancy well-fed cows in good body condition exhibit reduced, not increased, appetite. There is a fine balancing act to perform. Excessive body condition at parturition quickly leads to metabolic problems such as ketosis, but cows who subsequently become too thin have increased risk of metabolic diseases such as mastitis and lameness. The biological mechanisms regulating output of milk are reasonably well understood, those controlling appetite less well so, and there has been little attempt at systematic integration of the two. The transition from pregnancy to lactation represents a major challenge to homeostasis, made more complicated in multiparous cows by the fact that much of gestation is concurrent with lactation. Herein lies the potential for nutritionally-entrained flexibility. In the wild, concurrent pregnancy and lactation only occur when nutritional conditions are favourable. If conditions are poor, rebreeding will be delayed and lactation will continue, at an energetically-sustainable level, for much longer than its 'normal' duration. In this way the twin energetic burdens of pregnancy and lactation are separated, and extremes are avoided. Given the increasing public concern about stresses suffered by intensively-managed dairy cows, this case may be one where commercial dairying could learn useful lessons from nature.

Lactation: Energy balance: Dairy cows: Food intake: Milk yield

Strategies adopted by female mammals to meet the energetic costs of pregnancy and, particularly, lactation are many and varied, but inevitably involve one or more periods of increased food intake. It is equally inevitable that the control of intake must somehow be coordinated with the regulation of output, although the way in which this coordination is achieved is incompletely understood. Sometimes the coordination appears to fail; the early-lactation dairy cow does not take in as much energy as she puts out and is, therefore, in negative energy balance. This situation needs to be seen in the light of the overall strategy; there is another level of coordination to be achieved, between short-term dynamic regulation of energy balance and long-term control of body condition. A fundamental requirement is for the animal to be able to monitor its own energetic status, both in a dynamic sense and in terms of reserves. Leptin, an endocrine product of adipose tissue, is attracting considerable interest in this regard, and recent data pertaining to its role in lactating ruminants will be reviewed. The final part of the paper will deal with the options available to the cow. The biological objective is transfer of genes through to the next generation and beyond, so the more calves successfully reared to maturity the better. The emphasis has to be on successfully reared; rebreeding is pointless until the mother is ready to support that new investment and the first calf is ready to support itself. This factor means that lactation length is bound to be plastic, something hitherto largely unexploited by dairy farmers.

Abbreviations: GH, growth hormone; IGF, insulin-like growth factor.
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Extremes of metabolism

Output of milk

Following calving milk yield increases to reach a peak at about 8 weeks postpartum and then gradually declines, at a rate of about 2%/week, such that the lactation will normally last for about 10 months. Usually the cow will have been concurrently pregnant during most of this declining phase. The intensive lactation cycle typical of most milk production in the UK and elsewhere is based around the twin tenets of maximising peak milk yield and minimising calving interval. In the UK 'good' cows yield in excess of 30 kg/d at peak lactation whilst the best exceed 40 kg/d, both are expected to re-calve within 365 d or thereabouts, which means rebreeding at about peak lactation (Esslemont & Kossaibati, 2000). For evaluation purposes, commercial milk production is usually reported as 305 d lactation yields, calculated from monthly yield recording. On this basis the top UK herds aim for 10 000 kg per cow, whereas the national average is about 6500 kg per cow. As an illustration of the extreme case, a recent Symposium of the American Dairy Science Association (Anon, 2000) dealt with Management of dairy herds for 40 000 pounds of milk per year. The conversion from US pounds to kilogrammes is 0·454, so this objective equates to 18 000 kg, approaching three times the UK average! For the purposes of the present review daily output is more relevant than lactation yield. One of the best scientifically documented examples of extreme output of which I am aware is a study of Israeli Holsteins, a particular group of which achieved a peak yield of 60·0 (SE 2·9) kg/d (Bar-Peled *et al*. 1995).

Food intake

Food intake by dairy cows has been intensively researched; a recent review by Ingvartsen & Andersen (2000) cited about 344 references. Much of this effort has been directed to the construction of predictive models of intake which then enable the farmer to maximise feeding efficiency during lactation (for example, see Roseler *et al*. 1997), so most research deals with the lactating cow. Broster (1971), 30 years ago, stressed the importance of prepartum feeding, something which has recently been rediscovered and dubbed the 'transition period' (typically defined as the last 3 weeks of pregnancy and the first 3 weeks of lactation). Indeed, Drackley (1999) was moved to label this 'the final frontier' of lactation biology! Whilst Broster's (1971) observations were a step in the right direction, by concentrating on late pregnancy they still missed possibly the most fundamental teological point of lactation. The success of mammals is largely ascribable to the fact that, by drawing on body reserves to synthesise milk, the mother can rear young under conditions which would not directly support the nutritional requirements of those young (Pond, 1984). Part of the preparation for lactation, therefore, is the creation of these body reserves. When does this occur? Not in late pregnancy; the energetic demands of the growing fetus and mammary gland are greatest, by far, at this time (Bauman & Currie, 1980), so it would be folly for the mother to leave such a vital process until then. Rather, one would anticipate that as soon as there is a commitment to lactation (i.e. soon after conception or implantation) the storage process would commence. In support of this possibility, evidence of deposition of adipose reserves from early in gestation does exist in a variety of species, including sheep (Vernon *et al*. 1981). In the cow, however, whilst there is clear evidence of adipose mobilisation during early lactation, it is an unproven assumption that accretion occurs during pregnancy. Although deposition of adipose does not necessarily require increased food intake (Robinson, 1986), the endocrine environment of early pregnancy (low oestrogens, high progesterone) is stimulatory to appetite and the phenomenon of increased intake has been recognised for some time, at least in rats (Morrison, 1956). If the following quote from Johnson *et al*. (1966) is to be believed, the same is not true of cattle: '…suggestions of increased appetite accompanying pregnancy in dairy cattle are entirely unfounded'. The statement was based on food intake data obtained from mature cattle that were lactating as well as pregnant, and so may not be accurate, but the real surprise is the paucity of data on the subject. I am aware of only one study which has followed food intake of growing heifers from before conception through the whole of pregnancy (Ingvartsen *et al*. 1992). Analysis was done by body weight rather than by stage of pregnancy and, since the purpose was to construct a mathematical model of food intake, the only data reported are calculated intakes rather than actual intakes. However, it is recorded that the predicted intake of heifers mated at the first oestrous after 325 kg did not deviate from actual intake at body weights of 375 and 425 kg, nor was it any different from the intake of steers (castrated males) of the same body weight. The somewhat tentative conclusion must be that food intake did not increase during the early stages of gestation.

More recently, Ingvartsen (Ingvartsen *et al*. 1999; Ingvartsen & Andersen, 2000) has presented food intake data for heifers from week 17 of pregnancy onwards. The initial intake value of about 8 kg DM/d was similar to that previously reported for non-pregnant heifers, but by week 23 intake had risen approximately 50% to 12 kg DM/d, considerably in excess of what would be expected (on the basis of the earlier model) had they not been pregnant. This apparent evidence of increased intake to facilitate the creation of body reserves was not analysed statistically or commented on in either of the reviews. From week 26 onwards, intake fell gradually to reach a nadir at parturition. The extent to which intake decreases in late pregnancy is related to energy status; the greater the energy content of the diet, the less is eaten (Coppock *et al*. 1972). Presumably the cow moves towards a target body condition state at parturition; in other words, the creation of body reserves is a regulated process. Given that body reserves are so crucial to the subsequent lactation, it is somewhat curious that research has been directed at the later, adjustment, stage of this process, whilst ignoring the earlier, storage, phase.

There is a marked nadir in food intake around calving, followed by a gradual increase to a value about twice that of the non-pregnant heifer (16 kg DM/d). This increase is quite variable between cows, but in the great majority of cases does not keep pace with milk yield. Whereas output peaks at about 2 months, intake may take at least twice as long to

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reach its maximum. This lag of energy intake behind energy output was recognized some time ago (Bauman & Currie, 1980), but is arguably more relevant today, since yields have increased markedly in the last few decades. The net result is that high-yielding dairy cows are almost certain to be in negative energy balance for the first 2 months of lactation, and are likely to be so for about the first 4 months; in one recent study positive balance was still not restored after 20 weeks (Beever *et al*. 1998). This situation occurred despite the cows being fed a high-quality diet on which some individuals achieved an intake of > 28 kg DM/d.

In a gross sense, intake across the whole of a lactation correlates reasonably well with output; high-genetic-merit cows eat more than low-merit cows (Veerkamp *et al*. 1995), and multiparous cows eat more than heifers (Ingvartsen & Andersen, 2000). It would be a surprise if this situation was not so; dairy cows adhere to simple energetic laws, after all. If one focuses on particular periods, specific diets or compares different breeds, however, the relationship often breaks down because of variation in the way ingested nutrients are partitioned between mammary and storage tissues. Thus, high-merit cows on poor-quality diets will still yield more milk than low-merit cows, but they will do it by mobilising to a greater extent, rather than by eating more (Veerkamp *et al*. 1995).

The lactating heifer which then becomes pregnant will maintain its maximum intake at about 16 kg DM/d until about the last third of the concurrent pregnancy, thereafter intake will start to decline (Ingvartsen & Andersen, 2000). Milk yield, meanwhile, will have been declining for some considerable time. Thus, for much of the declining phase of lactation, intake runs ahead of output, as depleted body reserves are restored in readiness for the next lactation. Intake decreases further after drying-off; nevertheless, the amount consumed remains well above what was eaten at the same stage of the first pregnancy, in line with the increase in body weight. Similarly, food intake during the first few weeks of the second and subsequent lactations is higher than that of the heifer lactation (Ingvartsen & Andersen, 2000).

Mobilisation in early lactation

The metabolic impact of lactogenesis was neatly summarised by Bell (1995): 'The onset of lactation in the high yielding dairy cow imposes dramatic increases in requirements for glucose, amino acids and fatty acids that cannot be met by dietary intake.' It should be remembered that the pregnant cow is already investing considerable resources into the fetus; nevertheless, the postpartum mammary requirements for these precursors were estimated to be respectively 2·7, 2·0 and 4·5 times those of the growing conceptus (Bell, 1995). Furthermore, these values were calculated at 4 d into lactation, long before the peak output of milk, and at a time when food intake had hardly increased above its late-pregnant value. To complete the equation, Bell (1995) calculated the increment in dietary supply of glucose to be approximately half that actually required to support milk production, and showed that these early-lactation cows were in negative energy balance to the extent of −50·2 MJ (−12 Mcal/d). This level of deficit is not an extreme; in a more recent study by the same group cows milked three times daily in the immediate postpartum period had a deficit of −84 MJ (−20 Mcal)/d (Block *et al*. 2000). Reflecting the high mammary requirement, plasma glucose was 330 mg/l compared with 590 mg/l in 'control' cows which went through a normal pregnancy but were dried-off immediately postpartum. On the other hand, non-esterified fatty acids (products of adipose mobilisation) were four times higher in the lactating cows (882 μmol/l *v*. 218 μmol/l). The most extreme examples of tissue mobilisation to support lactation are presumed to occur in species such as fur seals, bears and baleen whales, which lactate whilst fasting (Oftedal, 2000). The composition of the milk of these species (low-sugar high-fat) is designed to minimise requirements for gluconeogenesis, whilst maintaining the supply of energy to the young. Nevertheless, it remains a fact that the entire energetic and substrate costs of the milk production must be met from body reserves. Calculations suggest that such animals can lose as much as one-third of their body fat and one-fifth of their body protein (Oftedal, 2000). Only a very few studies have quantified the actual loss of body tissues by dairy cows using slaughter and carcase analysis, and those studies have suffered from inadequate replication. Thus, Gibb *et al*. (1992) reported losses of fat that barely achieved statistical significance, yet amounted to one-third of the available body fat, in cows which were average rather than high yielders. By contrast, their estimate of tissue protein mobilisation was about 100 g/d, giving an overall depletion of 6·6% of the total body protein, whereas Bell *et al.* (2000) have suggested a daily requirement ten times this amount! Reasons for the discrepancy probably relate to the intervals studied; the 100 g/d estimate is for the whole of the period up to peak lactation, whereas the 1 kg/d estimate is for about the first week. Whilst mobilisation of fat may continue for several months, increased intake of high-protein diets means that metabolizable protein balance will be restored after about 3 weeks, even in high-yielding cows (Bell *et al*. 2000).

Clearly, the dairy cow has the capacity to mobilise considerable amounts of adipose tissue over fairly protracted periods and substantial quantities of protein, the latter only over short periods. For the most part this mobilisation will occur during early lactation, although it is worth remembering that the requirements of the third-trimester fetus are considerable and, in sheep at least, there is good evidence of mobilisation occurring for a considerable time prepartum (Robinson, 1986). It should also be borne in mind that mobilisation is but one aspect of a repertoire of metabolic adaptations affecting many tissues in support of lactation (Bauman & Currie, 1980; Vernon & Pond, 1997).

A specific example of an energetic extreme

A good example of carefully documented extreme input and output is to be found in an experiment conducted in an Israeli Kibbutz, under commercial farm conditions, where management levels were good, feed quality was high and the cows had been bred to produce high yields (Bar-Peled *et al*. 1995). The data are summarised in Fig. 1. Three

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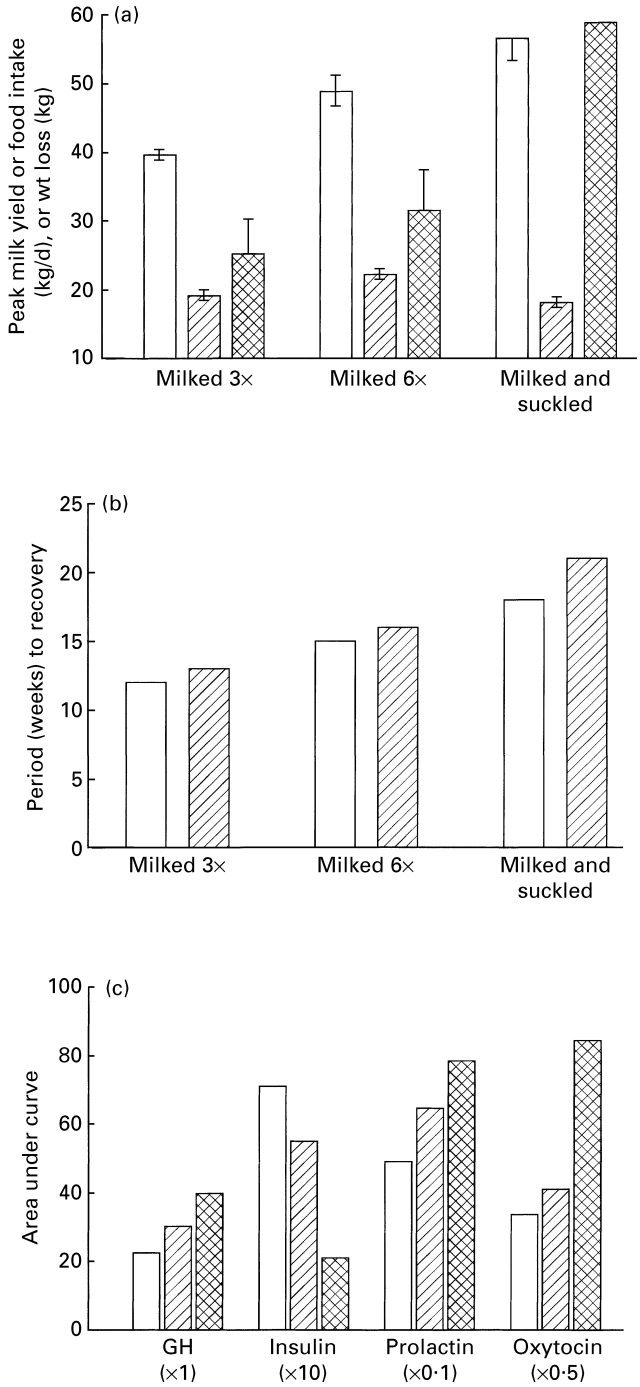

Fig. 1. Production and intake responses, tissue mobilisation and endocrine characteristics of high-yielding dairy cows milked three times daily (3×), six times daily (6×) or milked three times and suckled three times in early lactation. (a), Peak milk yield (▭), food intake averaged over the first 6 weeks of lactation (▨) and body weight loss during the first 6 weeks of lactation (▩). Values are means with their standard errors represented by vertical bars for nine cows per treatment group. (b), The number of weeks taken to recover body weight (▭) and body condition score (▨). (c), Area-under-curve values (arbitrary units) for hormone profiles in samples taken at 30 min intervals for 7 h during 1 d in week 6 of lactation: (▭), 3×; (▨), 6×; (▩), milked and suckled. Data are adjusted as shown to fit a common ordinate. GH, growth hormone. For b and c, values are means for nine cows per treatment group. (Data from Bar-Peled *et al.* 1995, 1998.)

groups of cows were milked either three times daily, six times daily or milked three times and suckled three times daily for the first 6 weeks of lactation. In the latter group total milk yield was estimated using the weigh–suckle–weigh technique to determine the intake of the two calves on 1 d of each week. Peak milk yields for the three groups were 40, 49 and 57 kg/d whilst DM intakes were 19, 22 and 18 kg/d respectively (Fig. 1(a)). The frequently-milked cows increased their intake significantly (by 16%; $P < 0{\cdot}05$), but this increase was insufficient to account for the increased yield (of 23%), so tissue mobilisation was greater. This mobilisation was evident as a slightly greater body weight loss (Fig. 1(a)) and a marked decrease in body condition score. Most surprisingly, the suckled cows did not increase their intake at all despite giving the highest milk yield. Their loss of body weight was over twice that of the control group and, at an average of almost 10 kg/week for the 6 weeks of the experiment, represented more than one-tenth of their starting weight. From week 7 of lactation onwards all the cows were milked three times daily. Another way of analysing the extent of tissue mobilisation is to measure the time taken for the original body weight and condition score to be restored; the longer this period, the greater the mobilisation. Fig. 1(b) clearly shows that mobilisation was greatest in the suckled cows and least in the controls. Further support for this finding was seen in plasma metabolite concentrations; glucose was highest in controls and lowest in suckled cows, whereas non-esterified fatty acids was highest in suckled and lowest in controls (Bar-Peled *et al.* 1998).

Problems created by metabolic extremes

Recently, the Farm Animal Welfare Council (1997) produced the *Report on the Welfare of Dairy Cattle*, and concluded: 'High metabolic turnover in cows can be associated with a greater risk of mastitis, lameness, infertility and other production diseases'. Dairy-cow fertility has decreased steadily as milk yield has increased (Webb *et al.* 1999). While this factor may be a serious economic concern, infertility induced by high metabolic turnover is a predictable physiological response rather than a pathological failing (Knight *et al.* 1999). Mastitis and lameness, on the other hand, are painful and debilitating diseases which can affect as many as one-third to half all cows (Kossaibati & Esslemont, 2000). There can be no doubt that disease is more prevalent in higher-producing cows. Relationships with genetic merit suggest this conclusion without being totally decisive (Pryce *et al.* 1997), but an association between disease incidence and peak lactation is incontrovertible, having been observed in a variety of production systems (Erb *et al.* 1984; Grohn *et al.* 1986). About 60% of health costs are incurred in the first 45 d of lactation. Some of this cost is due to diseases specifically associated with parturition, such as milk fever, ketosis, retained fetal membranes and metritis (Drackley, 1999), but these diseases occur relatively infrequently (single-figure incidences). Output-associated mastitis and lameness constitute a much bigger problem. The high risk period for diseases includes parturition, but extends through to peak lactation; in other words, exactly the time

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of the metabolic imbalance caused by the lag of intake behind output.

Control of intake and output

Endocrine factors

There are numerous reviews of the endocrine control of bovine lactation (Flint & Knight, 1997; Tucker, 2000) and of food intake in dairy cows (Ingvartsen *et al*. 1999; Ingvartsen & Andersen, 2000), as well as more general reviews of food intake regulation at systemic (Bray, 2000) and hypothalamic levels (Williams *et al*. 2000). Rather than attempt another comprehensive account, this section will highlight some of the principal endocrine factors involved in the control of milk yield, and will attempt to integrate their mammary role with any influence on food intake. The hormone data used will be those obtained in the Kibbutz experiment previously described (Bar-Peled *et al*. 1995), as shown in Fig. 1(c). The data are area-under-curve values for daily profiles, with adjustment to fit a common ordinate. Remembering that milk yield was lowest in controls and highest in suckled cows, positive relationships between milk yield and hormone concentration were evident for growth hormone (GH), prolactin and oxytocin, whilst insulin was negatively correlated (Bar-Peled *et al*. 1998). Food intake was increased in the frequently-milked cows but not in the suckled cows, a conundrum which will be explored below, since it is not immediately explained by the endocrine changes.

The positive relationship between yield and GH is to be expected. GH is the principal galactopoietic hormone in dairy cattle (Bauman *et al*. 1985), recombinant GH being marketed in several countries, including the USA, for use by dairy farmers to boost milk yield (Bauman *et al*. 1999). It is uncertain whether GH has a direct action on bovine mammary tissue; attempts to demonstrate specific binding of GH have consistently failed (Akers, 1985), although a recent immunocytochemical study has shown the receptor to be present on the membrane and in the cytoplasm of the secretory epithelial cell (Sinowatz *et al*. 2000). Indirect effects mediated through endocrine or paracrine insulin-like growth factor (IGF)-1 have been postulated to account for the mammogenic and galactopoietic roles of GH (Flint & Knight, 1997). However, its principal action is one of homeorhesis, repartitioning nutrients away from body stores and towards the mammary gland (Bauman, 1992). Injections of GH can increase food intake (Bray, 2000), and whilst there is no evidence of a direct cause and effect, cows treated with recombinant GH do show intake responses. Initially, mobilisation is increased, which can have the effect of reducing intake (Bareille & Faverdin, 1996), although in practice this effect is rarely seen. After a few weeks of recombinant GH treatment voluntary food intake increases (Chalupa & Galligan, 1989). This response is consistent and persists for as long as the treatment is continued (Bauman, 1992). Whilst it could be directly related to the increased output, the more likely explanation is that it is a response to the diminishing body reserves caused by the mobilisation. The lack of an intake response in the suckled–milked Kibbutz cows demonstrates that, whatever mechanism is involved, it can be overridden.

The metabolic adaptations of adipose tissue to lactation (increased lipolysis, decreased lipogenesis) are primarily regulated by insulin (Vernon & Pond, 1997), as are the glucose-sparing adaptations which ensure that as much glucose as possible is channelled to lactose production (Bell, 1995). Thus, insulin insensitivity develops in peripheral tissues (adipose, muscle) during late pregnancy and continues during lactation and, in addition, insulin secretion decreases. There is no direct effect of insulin on milk secretion. Food intake, on the other hand, is insulin-responsive, in as much as insulin infusion will depress appetite (Anil & Forbes, 1980). Insulin receptors are present in areas of the brain involved in appetite regulation, and in rats intracerebroventricular injection of insulin or insulin antibodies lowers or increases intake respectively (for review, see Ingvartsen *et al*. 1999). Given that insulin tends to correlate with relative extent of fatness, it has in the past been suggested as a candidate indicator of peripheral metabolic status (Williams *et al*. 2000). However, there is no direct evidence to suggest that insulin is involved in either the peripartum depression or subsequent increase in food intake of the dairy cow, and the differences in insulin cannot explain the anomalous food intake values of the suckled–milked cows in the Kibbutz experiment.

Prolactin release is stimulated by milking and basal levels are higher in lactating cows than in non-lactating cows when other factors such as time of year are taken into account (Koprowski & Tucker, 1973). However, the close relationship between yield and prolactin concentration seen in the Kibbutz data is not typical; for instance, we have compared high- and low-genetic-merit cows and found no difference in prolactin (Sorensen *et al.* 1998). Furthermore, prolactin depletion has only a small effect on bovine milk yield (Knight, 2001), whereas in many other species it is the principal galactopoietic hormone (Flint & Knight, 1997). Prolactin can affect food intake. Hyperphagic responses caused by lactation (in rats, Gerardo-Gettens *et al*. 1989) and by increasing daylength (in male reindeer (*Rangifer tarandus tarandus*), Ryg & Jacobsen, 1982) can be mimicked by prolactin injection. However, prolactin administration to dairy cows had no effect on either milk yield or food intake (Plaut *et al*. 1987).

Oxytocin is the milk ejection hormone, produced in response to suckling and acting on myoepithelial cells to cause contraction of secretory alveoli, dilatation of ducts and hence expulsion of milk. It has no direct action on milk secretion *per se* (Knight, 1994), but since milk yield is sensitive to the efficiency of udder emptying (Wilde *et al*. 1989) it will have an indirect galactopoietic effect. Oxytocin is produced by neurones in the paraventricular and supraoptic nuclei of the hypothalamus, both areas that are implicated in the control of appetite (Williams *et al*. 2000). It has long been considered capable of exerting a central anorexic effect in rodents (Verbalis *et al*. 1995), and there is limited data to suggest it has the same effect in cows (Svennersten *et al*. 1990). The role of oxytocin is by no means clear-cut. For instance, one report describes a stimulation of appetite after central administration in rats (Bjorkstrand & Uvnas-Moberg, 1996). It is not considered to be a major

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player in the same way as leptin or the recently discovered orexins (Williams *et al*. 2000). Nevertheless, it is the one hormone which could explain the anomaly in the Kibbutz cows; suckled cows had considerably higher oxytocin levels than the other two groups, and were the only cows to eat less than expected (Bar-Peled *et al*. 1995). The factor which is currently attracting most interest in relation to control of food intake is leptin. It is interesting, therefore, to note that a recent study has shown expression of leptin receptor on 'virtually all' oxytocin neurones in the supraoptic nucleus of the lactating rat hypothalamus (Brogan *et al*. 2000).

Leptin

Leptin is an endocrine product of adipose tissue, predicted several decades ago from parabiosis studies in obese (*ob/ob*) mice and positively identified in 1994 following the cloning of the *ob* gene (Zang *et al*. 1994). Although expressed in several other tissues including, apparently, the mammary gland (Chilliard *et al*. 2000), its concentration is closely related to fat mass and it exerts an anorexigenic or appetite-suppressing action at the level of the hypothalamus. Hence, in an era when human obesity is increasing dramatically, leptin has attracted very considerable interest as a regulator of metabolism or, more fancifully, as the 'lean' hormone. Reviews of leptin are numerous (for example, see Harris, 2000; Spiegelman & Flier, 2001) but are mainly clinically orientated. Many data exist for man and rodents, but little for ruminants due to the absence of reliable assays. This situation has been remedied recently with the introduction of specific ovine and bovine assays (Block *et al.* 2000; Delavaud *et al*. 2000; Thomas *et al*. 2001), and it is likely that within the next few years an abundance of data will appear concerned with leptin and dairy-cow energetics. Some interesting strands of information are already emerging, mainly in sheep. As expected, leptin correlates with body fatness and is lower during underfeeding (Delavaud *et al*. 2000). The effect of nutrition is particularly related to the energy content of the diet, and is greater in ewe lambs than ram lambs (Ehrhardt *et al*. 2000). The effects of pregnancy are less clear. There is evidence of increased leptin secretion in pregnant rodents (Chien *et al*. 1997), but a recent study failed to confirm this observation in sheep, although leptin was nutritionally regulated in much the same way as in non-pregnant animals (Thomas *et al*. 2001). Some of the sheep in this study were already catabolic well before parturition, and these animals had the lowest leptin values. It is tempting to speculate that the decreasing intake of the late-pregnant cow may be a consequence of increasing leptin. If so, one would then expect leptin to fall during lactation, in line with the increased intake. Recent measurements in sheep (A Sorensen, C Adams and RG Vernon, personal communication) show indeed that leptin is reduced from about 9 ng/ml to about 2 ng/ml during lactation, and a similar decrease is evident in cattle (Block *et al*. 2000). In a qualitative sense this decrease was predictable, but it occurs very soon after parturition, before fat has been mobilised and before food intake has increased, and there is then no further decrease during the period in which appetite gradually increases, so the two factors do not correlate. Experiments in lactating rats have produced a similar conclusion. Milk yield was varied by adjusting the number of suckling pups. This approach produced parallel changes in food intake, in the total absence of any change in leptin (R Denis and R G Vernon, personal communication). As more information emerges it becomes apparent that simple relationships between leptin concentration and intake do not exist; most obese human subjects have normal leptin concentrations. It is highly likely that leptin serves as a warning signal of too little fat rather than too much (Vernon, 2000), which for the mobilising cow could be a vital function. In an experiment where we forced lactating cows into extreme mobilisation we were able to demonstrate a fail-safe system which markedly and abruptly down regulated yield before the cow's health became compromised (Knight *et al*. 1999), but we could not identify what triggered this response; leptin, perhaps?

Conundrums and explanations

Declining food intake in late pregnancy is somewhat paradoxical in an animal which will need as many resources as possible to deal with the energetic demands of very high milk yield. It has been ascribed to sheer physical constraints imposed by the growing feto–placental unit, but this explanation is too simplistic. Late-pregnant cows fed high-concentrate diets show a greater depression than those on high-forage diets (Coppock *et al.* 1972); it is energy, not volume, which dictates intake. Food intake is negatively influenced by oestrogens, which increase during late pregnancy. Tempting as it is to ascribe a link between these observations, cause and effect has not been established (Ingvartsen *et al*. 1999). The critical experiments assessing food intake of late-pregnant cows of varying body composition have not been done; would a lean cow not show the prepartum decrease in intake? Probably not!

The bigger apparent conundrum is why intake lags behind output in early lactation, but if one restates the question, some obvious answers start to emerge. What advantages are conferred by relying on mobilisation rather than increased intake to fuel the first few weeks of lactation? The biggest threat to the wild ungulate is predation and, from this point of view, being fat is bad news. Having got fat whilst relying on the security provided by being part of a large herd, the more solitary lactating female will wish to lose weight rapidly for her own survival. Energetically, mobilisation confers approximately 80% efficiency, whilst digestion is only about 60% efficient, so at the time of greatest demand there is an energetic advantage (although the total energetic cost of depositing fat and then mobilising it is obviously much greater). There is less need for physical activity (foraging), and gut proliferation does not need to happen so rapidly, all of which confers more energetic efficiency. Perhaps the real conundrum is why so much effort is exerted by agricultural nutritionists and dairy famers in trying to persuade the early-lactation cow to eat more. She knows better!

Flexibility to avoid extremes

Much of the description up to this point has referred specifically to the first lactation cycle, but in considering flexibility

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it is important to think in lifetime terms about the factors that drive the mother to reproduce. Her objective is to maximise the chances of her genes surviving to the next generation and beyond, so the more young successfully reared the better. For an essentially monotocous species with a long gestation length, maternal investment theory (Trivers, 1974) predicts very considerable investment in lactation, as has been described. At some stage, however, the decision must be made to stop investing in the current offspring in order to start investing in the next one; in short, to rebreed. Most feral ungulates are highly seasonal. Reproductive activity is geared to the young being born in spring or early summer, such that peak lactation coincides with the greatest chance of abundant food. If young are to be reared successfully in consecutive seasons, it follows that the sum of gestation and lactation must be less than 12 months in duration, otherwise rebreeding must occur before the lactation has finished, such that lactation and gestation run concurrently. Quite obviously, the latter option will impose additional energetic costs on the mother, costs which cannot always be met in the wild. Muskoxen (*Ovibos moschatus*) have a gestation length (34 weeks) not dissimilar to cattle. They inhabit inhospitable arctic regions and exhibit highly seasonal breeding. The chances of a lactating muskox rebreeding are not high and are very dependent on body condition (Adamczewski *et al*. 1998). Similar conclusions have been drawn in red deer (*Cervus elaphus*); poor nutritional conditions result in rebreeding every second year, rather than every year (Loudon & Kay, 1984). If rebreeding fails, the mother can still fulfill her teleological drive by continuing to lactate and so invest in the first youngster, and subjective observations indicate that those muskoxen which do not rebreed pursue exactly this option (PF Flood, personal communication).

The essence of successful domestication is to improve conditions for the farmed species in order to gain greatest benefit from the desired characteristic(s). This approach brings us back to the principles of intensive lactation. The farmer supplies quality food all year round, while the cow responds with plentiful milk and a calf each year. The effect of many generations of domestication on the animal's physiology is apparent from the almost total lack of seasonality in reproductive cycles; especially remarkable given that annual cyclicity is still apparent in such things as hoof horn growth (MacCallum, 1999). The evidence of reducing fertility (by which is meant inability to rebreed early in lactation; Webb *et al*. 1999) shows, however, that reproduction is still very much constrained by the same output-related energetic factors which prevent the lactating muskox from rebreeding. This constraint is a problem if the desired outcome is another calf, but the economic value of dairy-breed bull calves is minimal, and the advent of reproductive technologies such as sexed semen and multiple-ovulation embryo transfer means that a dedicated industry could quickly remove the need for the dairy farmer to generate his own replacement heifers. Perhaps the time is ripe to learn lessons from muskoxen, and to redirect our efforts into concentrating investment in the current offspring. In other words, having got the cow to the point of producing milk, persuade her to carry on doing so for as long as possible at a level which is metabolically, energetically and commercially sustainable. This strategy is based on extended lactation, and to achieve it one has to know more about the biological factors which control lactation persistency.

Flexibility in lactation persistency

The 'normal' lactation length for a mouse is about 3 weeks. However, feral mice are communal nesters and will frequently suckle multiple offspring. If this practice is mimicked experimentally by regularly swapping the ageing litter of pups for a younger litter, the lactation can be extended almost indefinitely (Bruce, 1958), with milk yield maintained at about two-thirds of its peak lactation value (Shipman *et al*. 1987). By stimulating the release of galactopoietic hormones (particularly prolactin; Flint *et al*. 1984) and by removing milk in order to prevent feedback inhibition, vigorous suckling can largely prevent the usual decline in milk yield. How plastic is lactation persistency in ruminants? Goats implanted with perphenazine in the hypothalamic median eminence exhibit elevated prolactin release, and there is evidence of increased lactation persistency as a result (Vandeputte-Van Messom & Peeters, 1982). However, in a number of experiments using pharmacological and photoperiodic manipulations we have been unable to show similar effects (Brown, 1996; Alamer, 1998). McFadden (1997) reviewed bovine lactation persistency and identified factors such as better persistency of the heifer lactation, poorer persistency of higher-yielding cows, effects of season and nutrition and poorer persistency in concurrently pregnant cows. All this information was derived from an analysis of national databases, since until very recently there has been no systematic investigation of persistency in a controlled experimental fashion. Recent attempts at modelling extended lactation have adopted the same approach (Vargas *et al*. 2000). The problem is that virtually all farmers attempt to rebreed for 12-month calving intervals, so cows presenting with longer lactations are, by and large, there by default; they are the ones which have failed to rebreed. In reality, what is being modelled is calving interval, not extended lactation, because no attempt has been made to deliberately extend the lactation. A recent analysis of high-yielding Israeli dairy cows deliberately rebred for calving intervals of 12 or 14 months (heifers) or 11·5 and 13 months (cows) revealed greater profitability from the longer lactations, despite there being no intervention to improve persistency (Arbel *et al*. 2001). The different targets for heifers and cows is interesting; presumably there was insufficient confidence to attempt 14-month lactations in older cows which would be expected to have poorer persistency. A recent Swedish study has compared cows managed for 12-, 15- and 18-month calving intervals. Reproduction data have been published (Ratnayake *et al*. 1998), but production data have not as yet, although an early report referred to longer dry periods in the 18-month cows, suggestive of a failure to improve persistency (Bertilsson *et al*. 1998).

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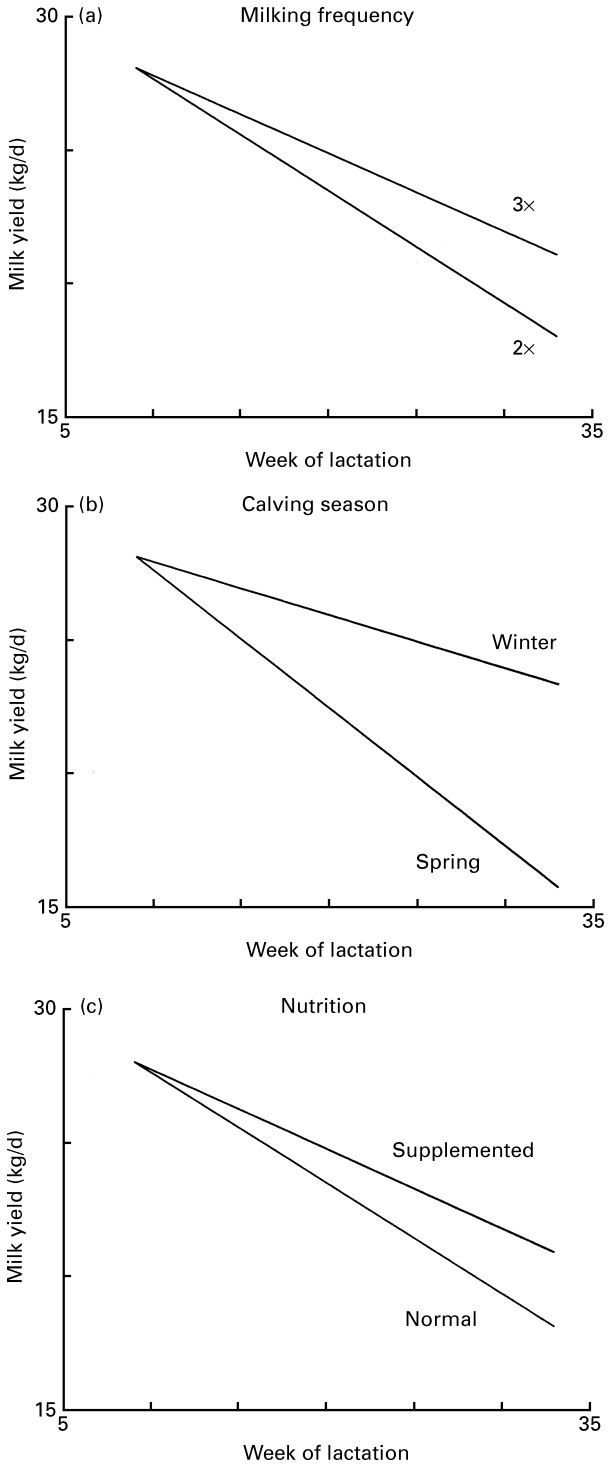

Fig. 2. Effects of (a) milking frequency, (b) calving season and (c) nutrition on lactation persistency in dairy cows. Treatments commenced in lactation week 9 and comprised three times daily (3×) or two times daily (2×) milking and additional concentrate supplement (supplemented) of 3 kg/d, with twelve cows per treatment group. For graphical presentation milk yield data were adjusted to a common start point and best-fit linear regression analysis was applied. Statistical evaluation was made of slopes fitted to actual data. (a) The difference between treatments was significant (ANOVA): $P = 0{\cdot}03$. (b) The difference between seasons was significant (ANOVA): $P < 0{\cdot}001$. (c) The difference between treatments was not significant (ANOVA): $P = 0{\cdot}07$. (From Sorensen & Knight, 2000.)

Control of lactation persistency

Our own recent data (Sorensen, 2000) has also indicated a potential for better profitability from longer lactations. The approach was rather different, in that management was based around lactation performance rather than rebreeding time. We examined the effects of milking frequency, nutrition and calving season on lactation persistency (Sorensen & Knight, 2000). The former treatments started at peak lactation, and Fig. 2 shows persistency slopes for the different treatments. It will be seen that persistency is plastic, and can be improved by milking more frequently, feeding more concentrate during declining lactation and by calving in the winter rather than the summer. We have previously observed a positive effect of milking frequency when applied together with GH in goats; indeed, in this case milk yield hardly declined at all during the 22 weeks of treatment (Knight *et al.* 1990). Measurement of mammary development and involution has shown that the reason milk yield declines after peak lactation is loss of secretory cells, rather than any decrease in the functionality of the cells that survive (Knight & Wilde, 1987). Cell loss is by apoptosis (Wilde *et al.* 1997), which is controlled through a complex interaction between prolactin, GH, IGF-1 and IGF-binding protein-5 (Flint & Knight, 1997). Briefly, IGF-1 is a survival factor for mammary cells, but sequestration by IGF-binding protein-5 prevents this action. GH stimulates intramammary release of IGF-1 and prolactin prevents local secretion of IGF-binding protein-5, so that when both hormones are present cells survive, but if either of the hormones is absent cells die by apoptosis. This interaction almost certainly explains why the frequent milking and GH combination is so effective, because frequent milking not only stimulates prolactin release but also increases mammary sensitivity through prolactin receptor up regulation (Bennett *et al.* 1990). Significantly, although those American dairy farmers who are using recombinant GH to increase milk yield are still being advised to calve their cows every year, many are achieving extremely persistent lactations (Van Amburgh *et al.* 1997).

Benefits of extended lactation

The biggest beneficiary would be the cow herself, through reduced lifetime exposure to the peak risk period of parturition and early lactation. The average productive life of a modern dairy cow is only 3 years, during which time she will calve three times. Switching to 18-month lactation cycles would mean only two calvings in the same period of time, a reduction of one-third in risk exposure. Since culling is heavily influenced by parity, it is probably the case that the cow on extended lactations would enjoy a longer life, and there would be less need for culling and replacement. This approach also means fewer calves being born, with a consequent reduction in unwanted bull calves. It is important to remember that the essence of extended lactation is continued production at a metabolically sustainable level, i.e. a cow working well within her capabilities and with ample time to replenish body reserves in readiness for future lactations. There are economic

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arguments in favour of extended lactation (Knight & Mainland, 1995; Galligan & Lormore, 2000), so the farmer would also benefit, and the milk retailing and processing industries would benefit from a more stable year-round supply of a more consistent product (Knight *et al*. 2000). For a more detailed account of the benefits, see Knight (1998).

Conclusions

The cow's investment in reproduction is considerable, the strategy employed being one of accretion of body reserves followed by intense mobilisation during the early stages of lactation and then increased intake initially to support the continued lactation and then to replenish reserves. By and large the long-term integration of intake and output is well regulated, as is short-term coordination, even if superficially it may appear otherwise. The period around parturition and early lactation is the most hazardous, and the feral ungulate will not take on this challenge (will not rebreed) if she is not equipped with sufficient body reserves to meet it. Instead, she will continue to lactate in order to invest in the current offspring. Extended lactation based on this principle could be an efficient and welfare-friendly alternative to intensive dairy production.

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