Physiological and pathological adaptations in dairy cows that may increase susceptibility to periparturient diseases and disorders

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ABSTRACT

Dairy cows undergo tremendous metabolic and physiological adaptations around parturition to support lactation. The liver is central to many of these processes, including gluconeogenesis and metabolism of fatty acids mobilized from adipose tissue. Fat accumulation may impair normal functions of the liver and increase ketogenesis, which in turn may predispose cows to other metabolic abnormalities. Several aspects of dietary management and body condition may alter these adaptations, affect dry matter intake, and increase or decrease susceptibility to periparturient health problems. Overfeeding energy during the dry period is a prominent risk factor. Considerable progress has been made in recent years in describing the adaptive changes in the liver and other organs in normal and abnormal states, but this knowledge has not yet identified unequivocally the key steps that might be compromised during development of metabolic disorders. The potential role of signaling compounds, such as the inflammatory cytokines released in response to environmental stressors, infectious challenge, and oxidative stress, in the pathogenesis of periparturient disease is under investigation. New techniques such as functional genomics, using cDNA or oligonucleotide microarrays, as well as proteomics and metabolomics, provide additional high-throughput tools to determine the effects of nutrition, management, or stressors on tissue function in development of disease. Integrative approaches should be fruitful in unraveling the complex interactions of metabolism, immune activation, stress physiology, and endocrinology that likely underlie development of periparturient disease.

Key Words: Periparturient dairy cow, Transition period, Metabolic disorders, Liver, Metabolism.

RIASSUNTO

FENOMENI DI ADATTAMENTO FISIOLOGICO E PATOLOGICO CHE POSSONO AUGMENTARE LA SUSCETTIBILITÀ A MALATTIE E TURBE METABOLICHE NEL PERIPARTO DELLA BOVINA DA LATTE

Durante il periparto le bovine da latte sono sottoposte a importanti adattamenti metabolici e fisiologici per poter sostenere la lattazione. Il fegato risulta fondamentale in molti di questi processi, tra cui la gluconeogenesi e il metabolismo degli acidi grassi mobilitati dal tessuto adiposo. L’accumulo di lipidi può pregiudicare le normali funzioni del fegato ed aumentare la chetogenesi, la quale può predisporre le bovine ad ulteriori anomalie metaboliche. Parecchi aspetti relativi...
Introduction

Dairy cows undergo tremendous adaptive changes during the transition from late gestation to early lactation. The importance of the periparturient period in determining health, productivity, and profitability has been underscored by the intense interest in nutrition and management of dairy cows during the transition period over the last two decades. The fundamental basis of these physiological changes is to ensure provision of adequate nutrients for the calf, both prenatally and postnatally. Dairy production has capitalized on this metabolic drive by selecting for higher and higher milk production. As a result, the magnitude of metabolic challenge faced by modern dairy cows at parturition is staggering. As demonstrated in Table 1, requirements for net energy of lactation (NE\(_L\)) essentially double overnight as cows undergo parturition and commence lactation.

The fact that many cows are able to meet this challenge without difficulty implies that the metabolic adaptations necessary to support high milk production are a component of the genetic factors that accompany selection for high milk production. However, the fact that, on average, roughly one in every two to three cows calving succumbs to some health problem during the transition period (e.g., Jordan and Fourdraine, 1993; Duffield et al., 2002) underscores the fragility of the system. Hansen (2000) suggested that continued selection for high milk production along with concurrent selection for larger mature size and more angular appearance may have increased the susceptibility to digestive and metabolic disorders such as displaced abomasum and ketosis. Regardless, the

| Function      | -2 d  | +2 d  | -2 d  | +2 d  |
|---------------|-------|-------|-------|-------|
| Maintenance   | 46.9  | 42.2  | 38.9  | 35.6  |
| Pregnancy     | 13.8  | ---   | 11.7  | ---   |
| Growth        | ---   | ---   | 7.9   | 7.1   |
| Milk production | ---  | 78.2  | ---   | 62.3  |
| Total         | 60.7  | 120.4 | 58.5  | 105.0 |

Calculated from National Research Council (2001). Assumes precalving body weight for Holstein cows with average decrease for calf and fluid loss at calving, milk production of 25 kg/d for multiparous cow and 20 kg/d for primiparous cow, and milk containing 4% fat for each.
continued struggle with periparturient disease highlights the need for improvements in management to allow cows to achieve their genetic potential for milk production without jeopardizing their health (and the profitability of dairy producers). An improved mechanistic understanding of both physiological and pathological changes during the periparturient period may facilitate development of better feeding and management strategies.

Physiological and pathological changes associated with negative energy balance are important factors related to development of ketosis, displaced abomasum, and retained placenta (Duffield et al., 2002), and may impact the immune system to increase occurrence of infectious diseases such as mastitis and metritis (Dohoo and Martin, 1984; Kremer et al., 1993). The focus of this paper is on potential physiological and pathological mechanisms related to energy metabolism that may cause or predispose cows to periparturient disease. Many comprehensive reviews on various aspects of transition cow biology and management are available for more information (e.g., Bell, 1995; Grummer, 1993, 1995; Goff and Horst, 1997; Drackley, 1999; Bell et al., 2000; Ingvartsen and Andersen, 2000; Drackley et al., 2001; Ingvartsen et al., 2003; Jorritsma et al., 2003; Overton and Waldron, 2004). Emphasis here will be placed on recent investigations in our laboratory and on hypotheses that may be worthy of future investigation. As stated before (Drackley et al., 2001; Drackley, 2005), continued progress in this area will depend on multidisciplinary efforts encompassing nutrition and metabolism, endocrinology, immunology, and stress physiology.

**Physiological changes during the periparturient period**

**General aspects**

During the last 3 wk of pregnancy, nutrient demands by the fetal calf and placenta reach their maximum (Bell, 1995), yet dry matter intake (DMI) may decrease by 10 to 30% compared with intake during the early dry period. This in itself may not be cause for alarm, as decreased food or feed intake around parturition is a common finding in many mammalian species (Friggens, 2003). As parturition approaches, concentrations of progesterone in blood decrease and those of estrogen remain high or increase (Grummer, 1995). The high circulating estrogen may be one factor that contributes to decreased DMI around parturition (Grummer, 1993), although regulation of DMI in periparturient cows is complex and far from understood (Ingvartsen and Andersen, 2000; Grummer et al., 2004).

After calving, the initiation of milk synthesis and rapidly increasing milk production greatly increases demands for glucose for milk lactose synthesis, at a time when DMI has not reached its maximum. Because much of the dietary carbohydrate is fermented in the rumen, little glucose is absorbed directly from the digestive tract. Consequently, dairy cows rely extensively on hepatic gluconeogenesis to meet their systemic glucose requirements. Propionate production from the low DMI during the early postpartal period is insufficient to synthesize the total amount of glucose needed (Drackley et al., 2001). Amino acids from the diet or from skeletal muscle breakdown as well as glycerol from mobilized body fat must provide most of the remaining glucose synthesis (Reynolds et al., 2003).

The total intake of energy by cows after calving usually is less than energy requirements, even in healthy cows (Bell, 1995). The high ratio of growth hormone to insulin in blood of postpartal cows allows mobilization of long-chain fatty acids from adipose tissue triacylglycerol (TG) to attempt to make up the deficit between energy intake and requirements (i.e., negative energy balance). Fatty acids released from adipose tissue circulate as nonesterified fatty acids (NEFA), which are a major source of energy to the cow during this period. The concentration of NEFA in blood reflects the degree of adipose tissue TG mobilization (Pullen et al., 1989); therefore, as negative energy balance increases, more NEFA are released from body fat and the concentration of NEFA in blood increases.

Adipose tissue depots in the cow are oriented toward mobilization of NEFA at this time, rather than lipid deposition (McNamara, 1991). Adipose lipogenesis is essentially shut down, and the sensitivity to lipolytic signals (epinephrine and norepinephrine) is greatly enhanced. In recently completed research, we demonstrated that the increase...
of NEFA in blood in response to an intravenous epinephrine challenge was greatly increased at 7 d after calving relative to 10 d before calving, and was greater at 7 d than at 14 d postpartum (Underwood et al., 2003). Consequently, stressors and poor nutritional management that cause decreases in voluntary DMI will result in large increases in NEFA immediately after calving (Bertoni et al., 1998; Drackley, 1999).

As the concentration of NEFA in blood increases around calving or in early lactation, more NEFA are taken up by the liver (Emery et al., 1992; Reynolds et al., 2003). In the liver, NEFA can be 1) completely oxidized to carbon dioxide to provide energy for the liver, 2) partially oxidized to produce ketone bodies that are released into the blood and serve as fuels for other tissues, or 3) reconverted to TG. Ruminants have an inherently low capacity for synthesis and secretion of very-low density lipoproteins (VLDL) to export TG from the liver (Kleppe et al., 1988; Pullen et al., 1989), but a similar capacity to reconvert NEFA to TG (Kleppe et al., 1988; Graulet et al., 1998). Moreover, the hepatic tissue capacity to esterify NEFA to TG is increased at the time of parturition (Grum et al., 1996; Litherland et al., 2003). Consequently, cows fed typical diets during the dry period and peripartal period have an increased concentration of TG in the liver 1 d after calving (Skaar et al., 1989; Grum et al., 1996). This accumulation does not appear to begin appreciably before parturition (Vázquez-Añón et al., 1994; Van den Top et al., 1996), and usually reaches a maximum between 7 and 14 d after parturition (Van den Top et al., 1995, 1996; Rukkwamsuk et al., 1999) with a likely mean of about 10 days in milk (Figure 1).

If NEFA uptake by the liver becomes excessive, fatty liver may develop (Bobe et al., 2004). Negative energy balance and carbohydrate insufficiency in the liver after calving also lead to increased production of ketone bodies, which can result in clinical or subclinical ketosis (Duffield, 2000; Herdt, 2000; Drackley et al., 2001). Negative energy balance, intense mobilization of adipose TG, and ketogenesis are highly associated with periparturient disorders and diseases (Herdt, 2000; Jorritsma et al., 2003; Bobe et al., 2004). Increased concentrations of NEFA before calving and BHBA after calving were strongly related to development of displaced abomasum (LeBlanc et al., 2005). However,
TG accumulation in the liver may not accompany all periparturient disorders; for example, cows with retained placentas had no greater TG accumulation in the liver at 1 d or 14 d after calving than did healthy cows (Dann et al., 2005).

**Fatty acid metabolism in liver**

Previous research from our laboratory (Drackley et al., 1991) demonstrated that the proportion of total in vitro utilization of NEFA by liver slices represented by oxidation increased as energy balance decreased, whereas the proportion of total flux that was esterified decreased. Our recent research suggests that ad libitum feeding of high-energy diets during the dry period can increase esterification capacity and decrease oxidation capacity in liver tissue at 1 d postpartum, which would favor deposition of TG in liver (Litherland et al., 2003). Evidence for negative effects of dry period overfeeding on hepatic enzymes of NEFA oxidation also has been presented by others (Murondoti et al., 2004b).

Factors that regulate the disposition of NEFA between oxidation and esterification in the liver of dairy cows still are not well understood. The primary site of control in many non-ruminant species seems to reside at the mitochondrial membrane and governs whether NEFA enter the mitochondria for oxidation or are diverted to glyceride formation via microsomal esterification (Zammit, 1999). The latter occurs through activity of the mitochondrial form of glycerol phosphate acyltransferase (mGPAT), the first committed step of acylglyceride synthesis. We recently determined that the hepatic mRNA abundance for mGPAT decreased during the dry period to 1 d after calving and then increased sharply at 14 d postpartum (Loor et al., 2005). However, Van den Top et al. (1996), suggesting that NEFA influx to the liver or activity of β-oxidation were more important than maximal activities of esterification enzymes in determining TG accumulation.

Entry of NEFA into the mitochondria for β-oxidation to carbon dioxide or ketone bodies is controlled by the enzyme carnitine palmitoyltransferase (CPT-1). Activity of CPT-1 in ruminants is inhibited by malonyl-CoA, the product of acetyl-CoA carboxylase, and by methylmalonyl-CoA, which is produced during metabolism of propionate (Brindle et al., 1985; Knapp and Baldwin, 1990). Although ruminant liver does not actively synthesize fatty acids from acetate or glucose, the concentration of malonyl-CoA changes in concert with energy status (Brindle et al., 1985; Knapp and Baldwin, 1990) and thus may serve as an energy balance-sensitive regulatory mechanism for entry of fatty acids into the mitochondria via CPT-1.

We have recently investigated the activity of CPT-1 and its sensitivity to the key inhibitor molecule malonyl-CoA during the periparturient period. Total CPT activity in mitochondria isolated from liver biopsies was greater at d 1 and 21 postpartum than at d -21 (Dann et al., 2000). Activity of CPT-1 in mitochondria freshly isolated from liver biopsies was approximately 35% greater at d 1 and d 14 postpartum than at 30 d prepartum, but activity differed little between control cows and cows with ketosis induced by feed restriction beginning at 4 d postpartum (Dann and Drackley, 2005). Sensitivity of CPT-1 to inhibition by malonyl-CoA also did not differ between control and induced-ketosis cows; however, CPT-1 from cows fed ad libitum during the dry period was more sensitive to inhibition by malonyl-CoA than was CPT-1 from cows fed in restricted amounts during the dry period (Dann and Drackley, 2005).

We have also studied the activity of an auxiliary pathway of fatty acid β-oxidation that occurs in peroxisomes. Ruminant liver seems to possess a relatively greater capacity to initiate fatty acid oxidation in peroxisomes than does liver from rodents (Grum et al., 1994). This pathway may be a component of the adaptations of fatty acid metabolism in liver during the periparturient period (Grum et al., 1996, 2002). Increases in hepatic capacity for peroxisomal fatty acid oxidation
may help the liver cope with the large influx of mobilized NEFA and help to prevent excessive accumulation of fat in the liver. Peroxisomal \( \beta \)-oxidation capacity in liver during the periparturient period was increased for cows fed a high-fat diet during the dry period, but these cows also were in greater negative energy balance prepartum (Grum et al., 1996).

As discussed elsewhere (Drackley, 1999; Drackley et al., 2001), changes in enzymatic capacity for \( \beta \)-oxidation of NEFA in liver around parturition may be under transcriptional control by the nuclear receptor peroxisome proliferator-activated receptor-\( \alpha \) (PPAR\( \alpha \)) in ruminant liver as in other species. When activated by the binding of its ligand, such as long-chain fatty acids, PPAR\( \alpha \) dimerizes with the retinoid X receptor (RXR) protein and then binds to specific response elements in the promoter region of target genes to activate their transcription. Administration of the PPAR\( \alpha \) agonist Wy-14,643 to lactating goats increased hepatic peroxisomal \( \beta \)-oxidation activity to approximately three times that of controls (Cappon et al., 2002). Feeding calcium salts of trans-unsaturated fatty acids increased mRNA for PPAR\( \alpha \) in liver of early lactation dairy cows (Selberg et al., 2005).

In recent experiments, we used a bovine-specific cDNA microarray (Everts et al., 2005) to analyze hepatic RNA isolated from liver biopsies of periparturient dairy cows (Loor et al., 2005). Abundance of mRNA for several genes presumably under the control of PPAR\( \alpha \), including ACSL1, ACADVL, and CPT1A (encoding acyl-CoA synthetase, very-long-chain acyl-CoA dehydrogenase, and CPT-1, respectively) was increased sharply at d 1 relative to d 14 prepartum. Use of quantitative real-time polymerase chain reaction (RT-PCR) confirmed that abundance of mRNA for ACOXI, (which encodes acyl-CoA oxidase, the flux-generating enzyme of peroxisomal \( \beta \)-oxidation of fatty acids) increased more gradually after parturition in the same pattern of increase as PPAR\( \alpha \), the gene encoding PPAR\( \alpha \) (Loor et al., 2005). It is intriguing to speculate that periparturient TG accumulation in vivo could be decreased by enhancing the capacity to \( \beta \)-oxidize NEFA via activating PPAR\( \alpha \) with either natural ligands (e.g., fatty acids) or pharmacological compounds. Andersen et al. (2002) showed that improving energy balance in early lactation increased hepatic capacity for oxidation of long-chain fatty acids, which was associated with decreased TG accumulation.

**Fatty liver and liver function**

Maintaining optimal liver function may be central to the ability of cows to make a smooth transition into heavy milk production. Fat infiltration is a principal factor leading to development of so-called type II ketosis (Herdt, 2000). As the degree of fatty infiltration increases, normal functions of the liver are believed to be affected adversely, although convincing data demonstrating these effects directly remain to be presented. This topic has been reviewed recently (Bobe et al., 2004).

Fat infiltration impairs the ability of cultured liver cells to detoxify ammonia to urea (Strang et al., 1998). Ammonia decreases the ability of the liver to convert propionate to glucose (Overton et al., 1999), thus potentially linking fat accumulation to impaired gluconeogenesis in liver (Drackley et al., 2001). Although the urea cycle has tremendous adaptive capacity in nonruminants (Morris, 1992), Hartwell et al. (2001) recently reported that mRNA for several enzymes of the urea cycle were low at calving and were not affected by dietary protein supplementation. These authors speculated that limitations in adaptations of the urea cycle during the periparturient period might precipitate ammonia toxicity, especially if highly degradable protein sources were overfed during this period (Hartwell et al., 2001). Others have found that blood ammonia concentrations were positively correlated with the degree of fat accumulation in the liver of cows shortly after calving (Zhu et al., 2000), although this correlation diminished quickly with time. That the urea cycle enzymes may adapt with time postpartum is in agreement with the lack of correlation observed clinically between hepatic fat accumulation and blood ammonia in cows admitted to a veterinary clinic for treatment of displaced abomasum (J. Rehage, personal communication, 2002).

Fatty liver impairs the ability of the liver to detoxify endotoxin, and thereby renders the periparturient cow extremely sensitive to endotoxic shock and death (Andersen et al., 1996). In severe fatty liver, normal functions of the liver are markedly depressed, which results in the condi-
tion of “fatty liver syndrome” or “clinical fatty liver” (Morrow, 1976; Bobe et al., 2004). Extreme fatty liver increases convalescence and delays recovery from surgery to correct left displacement of the abomasum (Rehage et al., 1996). Fat infiltration per se evidently does not lead to liver failure (Rehage, 1996) but may be a contributing factor at least in some circumstances.

The impacts of hepatic lipid accumulation on gluconeogenesis have been somewhat controversial. The capacity of isolated liver slices to convert propionate to glucose was lower for cows with fatty livers and induced ketosis than for healthy controls (Mills et al., 1986; Veenhuizen et al., 1991). In hepatocytes isolated from calves and then induced to accumulate TG in vitro, TG accumulation decreased gluconeogenic capacity in one study (Cadorniga-Valino et al., 1997) but not in another from the same research group (Strang et al., 1998). Severely overfed cows that developed fatty livers after parturition had lower activity of phosphoenolpyruvate carboxykinase (PEPCK), the presumed rate-limiting enzyme in conversion of propionate to glucose (Rukkwamsuk et al., 1999), as well as other gluconeogenic enzymes (Murondoti et al., 2004a). Thus, impairment of hepatic gluconeogenic capacity and hence, decreased glucose production, might be a triggering mechanism for ketosis.

Mechanisms for the impairment of critical hepatic functions by TG accumulation are unclear. Possibilities include a reduction in bile flow or secretion (Bobe et al., 2004) and an increase in oxidative stress (Bernabucci et al., 2004). Lipid accumulation in liver of mice leads to subacute hepatic inflammation through activation of nuclear factor kappa-B (NF-κB) and downstream cytokine production (Cai et al., 2005), which could have multiple effects on both hepatic and extrahepatic tissue function.

**Glucose and amino acid metabolism**

At calving, the mammary gland rapidly increases its demand for glucose, which strains the ability of the cow to meet the total demands for glucose. Feed intake, and therefore propionate supply, increases less rapidly than milk production. During the first week after calving, we and others have estimated that the supply of glucose from fermentation of dietary carbohydrates consumed may fall short of glucose demands by as much as 500 g/d (Drackley et al., 2001). Glucogenic amino acids, particularly alanine and perhaps glutamine, and glycerol from body fat mobilization likely contribute to making up this shortfall. In support of this idea, we measured a three-fold increase in rates of muscle protein mobilization during the first week after calving compared with prepartum values (Overton et al., 1998). Likewise, the capacity of liver tissue to convert alanine to glucose was 198% of prepartum (21 d before calving) values on d 1 after calving, whereas capacity for conversion of propionate to glucose was increased by only 119% (Overton et al., 1998). Abundance of mRNA for the key regulatory enzymes involved (pyruvate carboxylase and PEPCK) changed in a similar manner in the liver (Greenfield et al., 2000; Hartwell et al., 2001). These changes seem to be in response to a glucose deficit per se, because we could reproduce them in male sheep by injecting phlorizin to cause excretion of glucose in the urine (Overton et al., 1999). In multicatheterized cows, little evidence was found for increased fractional contribution of amino acids other than alanine to glucose synthesis during the periparturient period (Reynolds et al., 2003).

In practical terms, amino acid contribution to glucose synthesis emphasizes the importance of dietary provision of metabolizable protein. Lack of response in milk production to increased rumen-undegradable protein supplementation, except in first-calf heifers (Van Saun et al., 1993; Santos et al., 2001), has been common in the literature (see Bell et al., 2000) and in our own experience (Underwood et al., 2001). Nevertheless, the importance of maintaining maternal stores of protein on long-term health, productivity, and reproduction is backed by strong indirect evidence (Bell et al., 2000).

**Immune function**

Function of the immune system is depressed during the transition period (Kehrli et al., 1989a,b). Decreased ability of the immune system to respond to infectious challenges likely is responsible for the high incidence of environmental mastitis around calving, as well as the high incidence of metritis (Mallard et al., 1998). Reasons for the
decreased immune function are not well understood. Vitamins A and E as well as a number of the trace minerals (selenium, copper, zinc) play a role in enhancing immune function. Evidence suggests that negative energy balance or protein balance may be a major contributing factor (Kremer et al., 1993; Goff, 1999). Several components of the immune system seem to be adversely affected by elevated concentrations of ketone bodies (Suriyasathaporn et al., 2000). These findings relate well to the common observation that cows which seem to be the most stressed by nutritional and environmental factors, as judged by excessive loss of body condition, are the most likely to become ill. In particular, an inadequate supply of metabolizable protein has been related to impaired function of the immune system (Houdijk et al., 2001). Evidence linking retained placenta to a malfunction of the immune system (Kimura et al., 2002) suggests that protein nutrition also might impact the incidence of retained placenta.

Fatty liver may further decrease function of the immune system (Breukink and Wensing, 1997). The incidence of fatty liver is strongly associated with the occurrence of infectious diseases (Boje et al., 2004). Accumulation of TG in the liver is associated with marked differences in both functional and phenotypical properties of neutrophils (Zerbe et al., 2000). Specifically, increased hepatic TG was associated with decreased expression of function-associated surface molecules and decreased both antibody-dependent and antibody-independent cytotoxicity of blood neutrophils. Similarly, in vitro functional characteristics of lymphocytes were altered in overconditioned cows relative to those in moderate or low body condition (Lacetera et al., 2005), although liver lipid content was not measured. Mitogen-stimulated lymphocytes from overconditioned cows secreted less IgM after calving and less interferon-γ before calving than did cells from cows in moderate or thin body condition.

Calcium metabolism

The sudden onset of milk synthesis in the mammary gland results in a tremendous demand for calcium. As a result, blood calcium concentrations can drop precipitously at calving, leading to milk fever. Smaller decreases in blood calcium, called subclinical hypocalcemia, are believed to be contributing factors in disorders such as displaced abomasum and ketosis by decreasing smooth muscle function, which is critical for normal function of the digestive tract (Goff and Horst, 1997). Hypocalcemia also leads to increased secretion of cortisol, which is believed to be a factor in increased incidence of retained placenta (Goff, 1999). Until the ability of the digestive tract to absorb calcium can increase, calcium must be obtained by resorption from bone. Metabolic acidosis caused by a negative dietary cation-anion difference (DCAD) favors mobilization of calcium from bone, whereas high dietary potassium concentrations and positive DCAD suppress this process (Horst et al., 1997).

Periparturient nutritional management in relation to physiological or pathological adaptations

It is not the focus of this paper to review various nutritional management strategies for periparturient cows. Nevertheless, a few comments on various aspects of this topic in relation to the periparturient physiological or pathophysiological changes are warranted. Although it is unlikely that dry period nutrition per se causes metabolic disorders, certain nutritional factors certainly appear to predispose cows to health problems.

Close-up groups and diets

The close-up or pre-calving diet approach is today’s version of the “steam-up diet”, a concept that has been in existence since at least 1928 (Boutflour, 1928). It seems logical that use of separate pre-calving and post-calving diets, especially when fed as total mixed rations (TMR), should help maintain DMI around calving and promote more rapid increases in DMI after calving, with a lower incidence of postpartum health disorders. The general concept of diet changes during the transition is that nutrient density is increased gradually from that fed to cows during the first few weeks after dry-off to the higher nutrient density required for postpartal cows. Because DMI of cows may decline by 10 to 30% during the last 7 to 14 d before calving, it has been assumed that increased nutrient density may allow mainte-
nance of the same intake amounts of key nutrients such as protein despite lower total DMI. The typical decrease in DMI before calving would result in the need to increase contents of crude protein and NE\textsubscript{L} by about 2 percentage units and 0.84 MJ/kg of DM, respectively, in the pre-calving diet.

Current interest and support for the close-up diet of higher nutrient density (i.e., more cereal grains and less forage) stems from an elegant experiment by Bertics et al. (1992). In that experiment, researchers prevented the normal drop in DMI by force-feeding the refusals into one group of cows fitted with ruminal cannulas. The diet was a 50:50 mixture (DM basis) of corn silage and alfalfa silage, supplemented with vitamins and minerals. Force-fed cows had greater plasma glucose concentrations 2 d before calving, less liver TG accumulation at 1 d after calving, and tended (P < 0.11) to produce more 3.5% fat-corrected milk (46.1 vs. 41.7 kg/d) during the first 28 d of lactation. Of interest, however, is that by d 14 after calving, force-fed cows had greater plasma NEFA concentrations and by d 28 had similar liver TG concentrations.

While implementation of close-up diets has been adopted enthusiastically by the dairy industry in the North America, surprisingly few data are available to support their actual effectiveness in decreasing the incidence of health problems or increasing milk yield. VandeHaar et al. (1999) fed close-up diets with energy densities of 5.4, 6.1, and 6.7 MJ/kg to cows during the last 28 d before calving. While prepartum DMI tended (P < 0.11) to be increased by about 1.5 kg/d for cows fed the highest energy diet compared with cows fed the lowest energy density, there was no difference in postpartum DMI, milk production, energy balance, or loss in body condition. Although numbers of cows were too small to make reliable inferences about health data, the number of health problems actually was numerically greater for the high density diet (11) than for the lowest density diet (5). Other studies have shown no differences in postpartum responses to widely differing nutrient intakes during the close-up period (Dewhurst et al., 2000; Holcomb et al., 2001; Agenäs et al., 2003).

Close-up diets seem to have proven beneficial in the field in many situations. However, the aspects associated with the improved management of a group of close-up cows may be more important than the particular diet that is fed. Regardless, producers should be cautioned not to extend feeding of the close-up diet too long. Overfeeding high-starch rations (high in corn silage and grains) during the entire dry period is detrimental to cow performance and metabolic responses. Our own research (Douglas, 2002; Dann et al., 2003a,b; Douglas et al., 2006) as well as research from others (Holtenius et al., 2003) indicates that this appears to be true even if cows are not visibly overconditioned, which is well known to be detrimental (Fronk et al., 1980; Van den Top et al., 1995). Evidence is accumulating that increasing nutrient density of the pre-calving diet by addition of cereals actually may increase the pre-calving decline in DMI (Rabelo et al., 2003; Grummer et al., 2004).

Non-nutritional components of a good close-up program may be as important, or more important, than specific nutritional strategies. The importance of low-stress and comfortable environments for transition cows is discussed below. The questionable nutritional impact of the close-up group has been underscored again by a recent experiment from our laboratory, in which cows (n = 36 to 38 per group) had essentially equal DMI and milk production after calving when fed the same close-up diet at either ad libitum intake or in restricted amounts sufficient for only 80% of calculated pre-calving NE\textsubscript{L} requirements (Dann et al., 2003b).

Dry matter intake

Regulation of DMI during the periparturient period is complex and largely not understood (Ingvartsen and Andersen, 2000; Grummer et al., 2004). Based on high correlations between DMI 1 d before calving and DMI at 21 d after calving (Grummer, 1995), a major focus on maximizing prepartum DMI has developed in the field. Given the lack of significant differences, or in fact even improvements in postpartum DMI for cows that were restricted-fed (Agenäs et al., 2003; Douglas et al., 2006) or limit-fed (Holcomb et al., 2001) during the dry period, this relationship may have been overemphasized or misinterpreted. Relationships between prepartum and postpartum DMI and the accumulation of lipid in the liver after calving were analyzed (Drackley, 2003) using cows from a
previous data set (Douglas, 2002; Douglas et al., 2004, 2006). Our hypothesis was that the change in DMI before calving was more highly related to postpartum DMI and fat accumulation in the liver than to the absolute DMI.

In that analysis (Drackley, 2003), DMI for wk 3 postpartum was not correlated with DMI prepartum, but DMI for wk 1 postpartum was correlated with DMI for wk –1 (r = 0.44, P < 0.01). In contrast, DMI for wk 3 postpartum was correlated (P < 0.01) with percentage changes in DMI during the last 3 wk (r = 0.43) or last 2 wk (r = 0.41) prepartum. The DMI for wk 1 postpartum was correlated (P < 0.01) with percent changes in DMI during the last 3 wk (r = 0.34), last 2 wk (r = 0.49), or last week (r = 0.39) prepartum. Contents of total lipid and TG in liver at d 1 postpartum were negatively related to decreases in DMI during the last 3 wk (r = –0.63 and –0.63), last 2 wk (r = –0.67 and –0.65), and last 1 wk (r = –0.42 and –0.38) prepartum (Figure 2). Thus, it appears that changes in DMI prepartum, and not the absolute DMI per se, are more highly related to poor intakes and fatty livers after calving. Similar conclusions have been drawn by others (Grummer et al., 2004). These data emphasize the importance of good management that maintains cows healthy and comfortable before calving. In this way, high DMI may be more of an indicator of the overall comfort and well-being of the close-up cows rather than a cause for its success.

**Dietary carbohydrates**

Adequate fiber of sufficient particle size is needed to maintain good rumen function, prevent displaced abomasum, and achieve high DMI. On the other hand, excessive NDF content may limit intake. Cows during the last 3 wk before calving seem to consume no more than about 0.8 to 0.9% of their body weight as NDF (J.K. Drackley, unpublished data). Sufficient nonfiber carbohydrates (sugars and starch provided by grains) must be present to optimize rumen fermentation and provide adequate energy in the form of propionic acid for glucose synthesis and suppression of ketogenesis.

Considerable emphasis has been placed in recent years on increasing the starch content of close-up or pre-fresh groups (Grummer, 1995; Minor et al., 1998; VandeHaar et al., 1999). Starches promote relatively greater ruminal pro-

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**Figure 2.** Accumulation of total lipid in liver at 1 d postpartum is increased as the degree of DMI depression during the last 2 wk prepartum increases. Points represent data from individual cows (n = 50). From Drackley (2003) based on data in Douglas (2002).
duction of propionate, which triggers insulin release that may restrain body fat mobilization. Increasing starch also tends to improve total DMI, diet digestibility, and ruminal fermentation over forages alone (Grummer, 1995), at least over the short-term in the close-up diet. Another proposed benefit of additional grains in the prepartum diet is to adapt the ruminal tissues and the rumen microbial population to the type of diet that will be fed after calving (Goff and Horst, 1997). Grain feeding increases length of the rumen papillae in comparison to feeding only poorly digestible roughages (Dirksen et al., 1985). It has been proposed that rumen papillae elongate in the presence of increased concentrations of volatile fatty acids, thereby increasing the absorptive surface in the rumen and helping to prevent acidosis after calving. However, recent research has indicated that this likely is not a large factor in transition success of cows fed more typical close-up diets (Andersen et al., 1999; Ingvartsen et al., 2001; Reynolds et al., 2004).

Use of a prepartum “VFA load” strategy by feeding an allotment of barley grain altered VFA concentrations and pH in the rumen but did not affect rumen epithelium (Andersen et al., 1999) and did not positively affect DMI or milk production postpartum (Ingvartsen et al., 2001).

Other methods exist to increase energy intake by pre-fresh cows. Simply using higher quality forages can have a major impact on ration energy density. High-fiber by-product feeds such as soybean hulls, beet pulp, corn gluten feed, and wheat middlings that are highly digestible also can improve total energy intake. While fermentation of fibrous feeds typically is thought to result in more acetate than propionate production in the rumen, greater fermentability still increases total energy supply and supply of propionate for glucose production. Relative effects of cereal grains and corn silage versus highly digestible fibrous concentrates and higher quality grass or legume forages is a topic of current research. For example, pre-calving diets based on either high starch or high fibrous byproducts showed few differences in postpartum performance (Smith et al., 2005). Maintenance of a healthy forage fiber mat to stimulate rumination and minimize potential for acidosis may be of large importance during the peripartal period.

**Dietary fat**

Because of its high energy density, supplemental fat would seem to be a logical ingredient for minimizing the negative energy balance around and after calving, but increasing evidence indicates that cows may not respond as expected during the transition period. A summary of research indicated that fat supplementation during early lactation decreased DMI by an average of 0.3 kg/day but the response was variable among studies (Chilliard, 1993). While rumen-inert fat supplements often increase milk production for early lactation cows and may improve subsequent reproductive performance (Staples et al., 1998), fat supplementation does not seem to increase milk yield until after the first few weeks of lactation (Grummer, 1995). Furthermore, supplemental fat appears to be ineffective at suppressing body fat mobilization during the negative energy balance of early lactation (Chilliard, 1993). Therefore, additional long-chain fatty acids provided in the diet may further imbalance the relative proportions of glucogenic and ketogenic metabolites available to the cow during the periparturient period (Drackley, 1999; Ingvartsen et al., 2003). Consequently, fat supplementation in the early postpartum diet is not recommended if early postpartum cows can be grouped separately and fed a separate diet containing no supplemental fat.

Our research group has been interested in the potential use of supplemental fat during the dry period to restore body condition to thin cows and as a possible metabolism modifier. While dietary fat appears to affect some aspects of metabolism of fatty acids in the liver (Grummer, 1996; Douglas et al., 2004, 2006), the overall effect on production and feed intake was minimal (Douglas et al., 2004). Other studies in which supplemental fat was fed at more typical levels before calving also show no responses in DMI or milk production (Skaer et al., 1989; Allen et al., 1995; Salfer et al., 1995; Burhans and Bell, 1998). These results stand in contrast to the documented benefits of fat supplementation, particularly of rumen-inert fats, during established lactation (Staples et al., 1998). The discrepancy, as discussed above, likely is a function of additional long-chain fatty acids benefiting cows when body fat is not being mobilized intensively, but further imbalancing the mixture...
of metabolic fuels and substrates present during the periparturient period (Drackley, 1999).

The potential remains for appropriate fat supplementation strategies to manipulate liver metabolism. In particular, supplements designed to increase escape of polyunsaturated fatty acids (PUFA) to the intestine might be beneficial. In a recently reported commercial field trial (Sanchez et al., 2003), cows fed a supplement of calcium soaps of soybean oil (rich in linoleic acid and also supplying linolenic acid) pre- and postpartum had a tendency (P < 0.10) for fewer incidents of milk fever, displaced abomasum, mastitis, and abortion than cows receiving similar amounts of tallow or calcium soaps of palm oil. Hepatic phospholipids and TG can be enriched with PUFA if intestinal supply is increased. For example, we (Douglas et al., 2002) infused soybean oil into the abomasum of cows for 40 d before expected parturition. Concentrations of linoleic acid in hepatic phospholipids at d 1 postpartum were more than doubled relative to controls or cows administered saturated fatty acids.

Body condition and energy intake

Dairy cows, like other mammals, undergo a normal cycle of body energy storage and mobilization, with increased body fat storage during mid-gestation and increased body fat mobilization during early lactation. Over the long term, dairy cows appear to strive to maintain some normal degree of body fatness (Friggens, 2003). Evidence for this phenomenon includes the classic study by Garnsworthy and Topps (1982) and our own recent data (Douglas et al., 2006), showing that cows that are forced away from their desired body condition (either fatter or thinner) before calving eventually converge to a similar body condition score by 4 to 8 wk after calving. Management systems must recognize this basic phenomenon, and not try to circumvent the genetically programmed metabolic patterns during the lactation cycle. However, management or environmental circumstances that force cows away from their optimal body condition (i.e., too thin, too fat) may result in increased risk for health problems (Ingvartsen et al., 2003).

It is well known that overconditioned cows (>4.0 on a 5-point scale) are at greater risk for development of metabolic problems (Morrow, 1976; Fronk et al., 1980; Reid et al., 1986; Van den Top et al., 1995; Smith et al., 1997). Overconditioned cows have poorer DMI after calving (Fronk et al., 1980; Bines and Morant, 1983) and readily break down their excessive stores of body fat (Reid et al., 1986; Rukkwamsuk et al., 1998). Overconditioned cows lose more muscle fiber area after parturition than thin cows, suggesting greater mobilization of body protein as well as fat (Reid et al., 1986). Obesity leads to increased susceptibility to the complex of metabolic disorders and infectious diseases known as the "fat cow syndrome" (Morrow, 1976). Overconditioning results in impairment of the immune system (Lacetera et al., 2005) and also results in greater indices of oxidative stress (Bernabucci et al., 2005).

Assuming that management of post-parturient cows is satisfactory, a thinner cow should have a better appetite after calving than a heavier cow. In the experiment from our laboratory mentioned earlier (Douglas, 2002; Douglas et al., 2006), we fed two diets during the dry period either at ad libitum intake or at restricted intake. Cows were housed individually in tie-stalls during the dry period. Diets contained the same calculated energy density (NE\textsubscript{L} of 6 MJ/kg) and were either high fat (4% of DM) or control. Cows fed ad libitum consumed about 157% of NRC (1989) NE\textsubscript{L} requirements for dry cows and restricted cows were offered only enough feed to meet 80% of NRC recommendations. Body condition score at dry-off averaged about 3.0 (5-point scale). Cows fed either ration ad libitum gained about 0.2 body condition score units during the dry period, whereas restricted cows lost about 0.5 body condition units from dry-off to calving. Cows fed either ration in restricted amounts had less TG in liver on d 1 after calving, and had faster rates of DMI increase after calving. Cows fed for ad libitum intake during the dry period produced about 2 kg/d less than restricted-fed cows (not significant). Of interest is that cows in both ad libitum and restricted groups reached the same body condition by about 5 wk after calving.

Results of this experiment indicated that under our controlled conditions, there was no advantage to feeding higher-energy diets during the dry period to try to add body condition to...
cows in moderately thin body condition going into the dry period. Earlier research also supports this concept (Kunz et al., 1985).

The current working hypothesis under investigation in our laboratory is that extended periods of feeding diets high in starch and/or total energy to dairy cows during late gestation induce changes analogous to insulin resistance in other species, even in the absence of visible overconditioning. In support of this hypothesis, we recently fed cows either a moderate energy diet or a low-energy diet for ad libitum intake during the first 5 wk of the dry period (Dann et al., 2003a; Dann, 2004). Cows fed the high energy diet had about 2.5 times the insulin concentrations as cows fed to meet NRC (2001) energy requirements during the dry period, with similar glucose concentrations and serum NEFA that were suppressed only by 29%. During the close-up period (3 wk before parturition), cows that previously had overconsumed energy during the far-off dry period had greater NEFA concentrations (323 vs. 230 µmol/L) than cows previously fed to meet energy requirements. Holtenius et al. (2003) reported that cows fed a higher energy allowance during the dry period had a greater degree of insulin resistance before and after calving, which allowed greater NEFA concentrations. In contrast, cows that were limit-fed under requirements had lower NEFA concentrations in the periparturient period, similar to results of Douglas et al. (2006). Earlier Holtenius et al. (2000) reported that elevated glucose concentrations, such as might occur in overfed cows with insulin resistance, had altered abomasal function that would be consistent with greater likelihood for abomasal displacement. In our experiments, liver slices from overfed cows had a lower capacity for oxidation of fatty acids, and greater esterification capacity, compared with cows fed the lower energy diet (Litherland et al., 2003). In addition, microarray analysis of gene expression patterns revealed extensive differences in hepatic gene expression between overfed and underfed cows (Loor et al., 2004). To fully interpret these studies, data are needed on whether overfeeding energy during late gestation may result in preferential accumulation of fat in internal fat depots.

Non-nutritional factors in relation to pathological adaptations during the periparturient period

Obviously nutrition is not the only factor that determines transition success or failure. This is evidenced by the wide variability in response among cows within a herd and among herds on similar nutrition programs. Furthermore, both research and field experiences provide examples of success and failure on vastly different nutritional approaches to the periparturient period (Drackley, 1999). For cows fed reasonably well-balanced diets during the prepartal period, cow comfort and management, infectious challenges, and the resultant stresses on cows when these are sub-optimal likely are the major determinants of periparturient disease. Similar viewpoints have been expressed by others (Bertoni et al., 2001), and are embodied in the concept of “production diseases” (Drackley, 2005).

The periparturient period and its metabolic challenges constitute a potentially stressful period for the dairy cow, if stress is defined as the impacts of external stimuli (physiological, environmental, and psychological) that challenge homeostasis (Moberg, 1985). Cows face a major challenge to maintain homeostasis during the sudden and marked increase of nutrient requirements for milk production at a time when DMI, and thus nutrient supply, lags far behind. The metabolic constraints imposed by decreased DMI as parturition approaches, coupled with the immunosuppression that occurs during this time (Mallard et al., 1998) and other stressors associated with calving and the start of lactation, likely contribute to the high incidence of infectious diseases and metabolic disorders encountered during the transition period. While many of the physiological changes discussed to this point represent the concept of “homeorhesis” in adaptation to lactation (Bauman and Currie, 1980), these responses may be modulated by additional stressors during the periparturient period.

In addition to the metabolic challenges and potential for “nutritional stress” if periparturient nutrition is sub-optimal, cows may face additional stressors from the natural environment and from deficiencies in management (Grant and Albright, 2001). These may include heat stress, overcrowding, infectious challenge, poor ventilation, poor
footing, uncomfortable stalls, poor management of grouping and cow movement, and rough handling. Research has suggested the importance of minimizing stress responses for cattle health, well-being, and productivity (see reviews by: Friend, 1991; Ingvartsen and Andersen, 1993). For example, preventing steers from lying down resulted in decreased feed efficiency and decreased concentrations of insulin-like growth factor-1 in blood (Ingvartsen et al., 1999). Haley et al. (2000) demonstrated that comfort of stalls was inversely related to total time spent lying, but that cattle were more reluctant to change positions in uncomfortable stalls once lying in them. Isolation in unfamiliar surroundings resulted in increased vocalization, cortisol concentrations, and heart rate in cattle (Rushen et al., 1999). Individual cows respond differently to stressors (Hopster et al., 1998) and the responses may vary with the extent, duration, and severity of the stressor (Hydbring et al., 1999). Rectal temperature was increased by isolation of dairy cows in a novel environment (Hopster et al., 1998).

Little is known in general about the effects of stress during the transition period. Periparturient cows may be unduly affected by heat stress conditions (Huhnke and Monte, 1976), leading to greater drops in prepartum DMI and slower increases of postpartum DMI. Collier et al. (1982) studied the effects of heat stress during late gestation on calf birth weight and subsequent milk production. Dry cows provided with shade gave birth to heavier calves and produced more milk than cows not provided with shade. Biological response criteria to stressors such as crowding, poor ventilation, poor footing, and poor stall design have not been well established for dairy cows. Overcrowding is common in free-stall barns and moderate overcrowding has been reported not to affect milk production if feeding management is good; however, recommendations are that overcrowding should be avoided in the pre- and postpartum pens (Grant and Albright, 2001). Doubling the amount of feeding space from 0.5 to 1.0 m per cow in a free-stall barn provided at least 60% more space between animals and resulted in 57% fewer aggressive interactions while feeding (De Vries et al., 2004). Changes in spacing and aggressive behavior in turn resulted in increased feeding activity throughout the day; increases in feeding activity were particularly evident for subordinate cows. Given the overriding importance of DMI in determining the extent of negative energy balance in the first weeks after calving (Drackley, 2005), such efforts to minimize stressor-induced limitations in DMI should be emphasized on farms.

Direct mechanistic evidence is not available for the role of stressors in increasing periparturient disease, but several potential mechanisms can be proposed. A likely candidate linking the effects of various infectious, environmental, social, and nutritional stressors is release of pro-inflammatory cytokines (tumor necrosis factor-α [TNFα], interleukin-1β [IL-1β], and interleukin-6 [IL-6], among others) and their associated signal-transduction mechanisms. Psychological stressors can induce inflammatory or acute-phase type responses as in humans and other species (Black, 2002). In other species, increases in adipose tissue mass result in greater local production of TNFα (e.g., Morin et al., 1998) and IL-6 (e.g., Bastard et al., 2002) in adipose tissue depots, thus potentially linking inflammation to overfeeding as well as infection or stressors. Muscle also produces TNFα and IL-6 (Steensberg et al., 2002). Evidence for and speculation about the role of inflammation in periparturient disease have been discussed by several authors (e.g., Bertoni et al., 1996, 2001; Drackley, 1999; Ametaj et al., 2002; Calamari et al., 2002; Fürll and Leidel, 2002; Katoh, 2002; Ametaj, 2005).

Using a bovine cDNA microarray, we have recently obtained evidence that mRNA abundance in liver for several proteins involved in the inflammatory response was increased at d 1 postpartum compared with either -14 or +14 d relative to parturition (Loor et al., 2005). For example, mRNA for the positive acute phase protein serum amyloid A1 (SAA1) was over five-fold greater at d 1 postpartum than at d -65 prepartum, but then decreased to late-lactation values by d 14 postpartum. Using quantitative RT-PCR, mRNA for SAA1 was shown to be over 3-fold greater by d -14, suggesting that proinflammatory pressure was being exerted before parturition even in healthy cows. Whether prepartum nutritional status modulates these inflammatory responses is currently under investigation in our laboratory.

Stressors and the resultant cytokine release...
might impact peripartal dairy cows in several ways. First, DMI may be decreased (Bertoni et al., 2001; Kushibiki et al., 2003; Waldron et al., 2003a). Thus, stressors (of physiological or psychological nature), infection, or endotoxin released from the rumen because of feeding practices all could stimulate inflammatory processes, with the resulting cytokine release contributing to decreased DMI before parturition. In turn, the decreased DMI could increase body fat mobilization, resulting in elevated NEFA concentrations and increased hepatic lipid accumulation. Second, nutrients may be diverted away from the critical functions of fetal growth, lactogenesis, and preparation of support functions for lactation to support the stress response (Moberg, 2000). Third, activation of the sympathetic nervous system and release of stress hormones, such as glucocorticoids and epinephrine, generally are antagonistic to milk production (Munksgaard and Lovendahl, 1993; Kushibiki et al., 2003), insulin and glucagon (Waldron et al., 2003a), and the thyroid hormones (Kushibiki et al., 2003). Fourth, hormones and cytokines associated with the stress response may alter secretion of hormones important for lactogenesis, such as growth hormone (Munksgaard and Lovendahl, 1993; Kushibiki et al., 2003), insulin and glucagon (Waldron et al., 2003a), and the thyroid hormones (Kushibiki et al., 2003). Fifth, many stressors result in direct activation or permissive facilitation of lipolysis and thus increase NEFA concentration (Kushibiki et al., 2002, 2003), which could lead to fat infiltration in the liver. Moreover, factors secreted in response to infection, stress, or trauma, most likely the cytokines, result in increased lipid synthesis in liver even in the face of similar NEFA concentrations in blood (Herdt et al., 1983). The mechanism of this putative hepatic effect of cytokines remains unclear, however, because administration of endotoxin to midlactation cows did not greatly alter metabolism of palmitate by liver slices (Waldron et al., 2003a). Fat accumulation in liver appears to decrease endotoxin clearance (Andersen et al., 1996), which could result in a futile cycle that sustains or worsens the negative effects of endotoxin in the cow.

A sixth mechanism by which environmental or behavioral stressors may impact periparturient cows involves greater suppression of immune function via increased cortisol concentrations (Kushibiki et al., 2003; Waldron et al., 2003a). As a result, cows under stress could become more susceptible to infectious diseases (Hopster et al., 1998). Seventh, research implicates endotoxins or cytokines in the etiology of hypocalcemia (Waldron et al., 2003b), which potentially could lead to milk fever or the decreased smooth muscle function that may underlie displaced abomasum or other disorders. Finally, the pro-inflammatory cytokines are involved in disruption of the normal metabolic adaptations to lactation and result in wasting of muscle tissue, increased fat mobilization, increased fat deposition in the liver, and induction of the acute phase response in liver. Pro-inflammatory cytokines decrease synthesis of some proteins (albumin, retinol binding protein, apolipoproteins) while synthesis of others (fibrinogen, globulins, haptoglobin, ceruloplasmin, c-reactive protein, serum amyloid A, calcitonin-gene related peptide, lipopolysaccharide binding protein) is increased (Johnson et al., 1997; Ingvartsen and Andersen, 2000; Schroedl et al., 2001). These changes could result in a re-prioritization in homeorhetic responses that diverts biological resources from lactogenesis.

All of the systems invoked to deal with stress produce changes in biological function, and these changes may directly affect the animal’s well-being and productivity. These changes could result in the shift of important nutrients away from desired biological processes that support growth and or lactogenesis. For example, energy being used for growth in a first-lactation cow may be diverted to cope with the stressor; optimal mammary development and milk production may not be realized and life-long productivity may be hindered. For many day-to-day stressors, the biological cost of the response is inconsequential. However, in the face of prolonged, severe, or multiple stressors, the biological cost of the response may become significant to the animal (Moberg, 2000), thereby diverting enough resources to place the cow at greater risk for developing various pathologies, such as infectious disease. For example, the significance of the biological costs and economic losses due to these responses is observed with the increased incidence of respiratory infection (shipping fever) that results from the stress of transporting cattle long distances (Blecha, 2000).
It is now well accepted in the field of stress physiology that the effects of multiple stressors are additive. For example, steers grazing endophyte-infected fescue pasture showed significant decreases in plasma prolactin as a result of the toxin (Filipov et al., 1999). When steers then were challenged with endotoxin to simulate infection, responses in plasma cytokines and cortisol were significantly greater in the calves that were grazing the toxic fescue. Thus, deficiencies in management that may not have a major impact by themselves on dairy cow health and productivity (i.e., “subclinical stressors”) could cumulatively result in pronounced negative effects. For example, one might envision that the multiple stressors of overcrowding first-lactation heifers with mature cows in the pre-calving pen of an uncooled barn during heat stress conditions might be disastrous for the younger cows. The principles of stress physiology discussed above consider that animals may reach a “breakpoint” response if the cumulative effects of acute, chronic, or immune stressors reach some critical threshold (Elsasser et al., 2000). Beyond this, the animal’s health and productivity is compromised as a result of diversion of nutrients to support the stress response, altered endocrine status, and detrimental effects of products of the activated immune system.

This concept may explain why “outbreaks” of metabolic disorders often follow a period of excessive rain and mud, or are more frequent during summer heat stress. It also may explain why producers struggling with management during farm expansion, or producers operating under generally poor management, have greater problems with disease in periparturient cows.

Conclusions

Considerable progress has been made in the descriptive biology of dairy cows during the periparturient period, and in identifying dietary and environmental factors that place cows at greater risk for periparturient diseases and disorders. More elusive, however, has been direct evidence for why adaptive mechanisms often fail and cows develop metabolic disorders. Although attractive as a plausible explanation, the role of stressors and inflammatory responses in the etiology of periparturient disease in dairy cows remains largely speculative. Continued investigation into the potential roles of stress and immune challenge during the peripartal period in determining metabolic changes, postpartum feed intake, and incidence of diseases and health disorders would seem to be of enormous importance (Drackley, 2005). Progress will require the approach of integrative biology using broad interdisciplinary expertise and incorporating new developments from human biomedical research, including the “omics” techniques such as functional genomics, proteomics, and metabolomics.

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