Nutritional Management of Transition Dairy Cows: Strategies to Optimize Metabolic Health^{*†}

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ABSTRACT

During the transition period, dairy cows undergo large metabolic adaptations in glucose, fatty acid, and mineral metabolism to support lactation and avoid metabolic dysfunction. The practical goal of nutritional management during this timeframe is to support these metabolic adaptations. The National Research Council addressed nutritional management of transition cows for the first time in 2001; however, a substantial amount of research has been reported since this publication was released. Results support 2-group nutritional strategies for dry cows to minimize overfeeding of nutrients during the early dry period but increase nutrient supply to facilitate metabolic adaptation to lactation during the late dry period. Increasing the amount of energy supplied through dietary carbohydrate during the prepartum period results in generally positive effects on metabolism and performance of transition cows. Recent research, however, suggests that the form of that carbohydrate (i.e., starch vs. highly digestible neutral detergent fiber) may be of lesser importance. Attempts to increase energy supply by feeding dietary fat sources or decrease energy expenditure by supplying specific fatty acids such as *trans*-10, *cis*-12 conjugated linoleic acid to decrease milk fat output during early lactation do not decrease the release of nonesterified fatty acids (NEFA) from adipose tissue. Although the view that nutritional means have limited ability to enhance hepatic export of NEFA as triglycerides in lipoproteins in ruminants has become dogma, recent evidence suggests that nutrients such as choline or specific fatty acids may enhance this process in transi-

tion cows. Adaptation of calcium metabolism to lactation is facilitated by nutritional strategies to decrease the cation-anion difference (DCAD) of the diet fed prepartum, although the degree to which the DCAD must be decreased to sufficiently prevent hypocalcemia remains controversial. Recent research also has provided possible physiological links between the associations of primary infectious disease with the occurrence of secondary metabolic disorders, thereby enabling investigation of factors affecting variation in response to nutritional management programs for transition cows on dairy farms. (**Key words:** periparturient cow, metabolism, immune function)

Abbreviation key: CLA = conjugated linoleic acids, CRC = controlled release capsule, DCAD = dietary cation-anion difference.

INTRODUCTION

Transition cow biology and management has become a focal point for research in nutrition and physiology during the past 15 yr. First, it was recognized that many of the metabolic disorders afflicting cows during the periparturient period are interrelated in their occurrence and are related to the diet fed during the prepartum period (Curtis et al., 1985). They determined that increased energy content of the diet fed during the prepartum period was associated with decreased incidence of displaced abomasum and that increased protein content of this diet was associated with decreased incidences of retained placenta and ketosis (Curtis et al., 1985). Although the strategy for prevention of milk fever was to feed a prepartum diet low in Ca at that time, Ca content of the prepartum diet was not related to the occurrence of milk fever in their study. These results led to substantial investigation of the biological relationships underpinning these epidemiological relationships.

Despite the prodigious output of research on the nutrition and physiology of transition cows, the transition period remains a problematic area on many dairy farms, and metabolic disorders continue to occur at economically important rates on commercial dairy farms (Burhans et al., 2003). Data recently summarized (Godden

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et al., 2003) indicate that approximately 25% of cows that left dairy herds in Minnesota from 1996 to 2001 did so during the first 60 DIM, with an uncertain additional percentage leaving by the end of the lactation due in part to difficulty during the transition period. The economic ramifications of the loss of cows early in lactation together with the comprehensive costs associated with occurrence of the various metabolic disorders in both clinical and subclinical form are large. Therefore, research attention will continue to focus on understanding the biology of transition cows and implementing management schemes on dairy farms to optimize production and profitability on these farms.

Excellent reviews have been written to describe the adaptations in energy, protein, and mineral metabolism that must occur for dairy cows to transition successfully to lactation (Grummer, 1993; Bell, 1995; Grummer, 1995; Horst et al., 1997; Drackley, 1999; Goff, 2000; Drackley et al., 2001) and the authors of NRC (2001) effectively integrated the metabolic adaptations described by these authors with nutritional recommendations. Hence, the purpose of this review is to briefly overview our knowledge of these metabolic adaptations and then to update knowledge summarized by the NRC (2001) with more recent research on transition cow nutrition and management. Furthermore, recent research integrating immune function with metabolism in dairy cows will be overviewed, with emphasis on the implications of this interrelationship for the successful implementation of programs for transition cows on dairy farms. Given our emphasis on incorporating the most recent information, we have chosen to include abstracted results to extend the peer-reviewed literature where appropriate. We acknowledge that this approach carries some risk and limitations, but believe that it is consistent with our intent to provide as current a view of this rapidly evolving area as possible.

METABOLIC ADAPTATIONS DURING THE TRANSITION PERIOD

The hallmark of the transition period of dairy cattle is the dramatic change in nutrient demands that necessitate exquisite coordination of metabolism to meet requirements for energy, glucose, AA, and Ca by the mammary gland following calving. Estimates of the demand for glucose, AA, fatty acids, and net energy by the gravid uterus at 250 d of gestation and the lactating mammary gland at 4 d postpartum indicate approximately a tripling of demand for glucose, a doubling of demand for AA, and approximately a fivefold increase in demand for fatty acids during this timeframe (Bell, 1995). In addition, the requirement for Ca increases approximately fourfold on the day of parturition (Horst et al.,

1997). The cow relies on homeorhetic controls to enable these changes in nutrient partitioning to occur.

Glucose Metabolism

The primary homeorhetic adaptation of glucose metabolism to lactation is the concurrent increase in hepatic gluconeogenesis (Reynolds et al., 2003) and decrease in oxidation of glucose by peripheral tissues (Benink et al., 1972) to direct glucose to the mammary gland for lactose synthesis. Reynolds et al. (2003) reported that net flux of glucose across the portal-drained viscera of cows was zero to slightly negative during the transition period and early lactation; the 267% increase in total splanchnic output of glucose from 9 d before expected parturition to 21 d after parturition resulted almost completely from increased hepatic gluconeogenesis. The major substrates for hepatic gluconeogenesis in ruminants are propionate from ruminal fermentation, lactate from Cori cycling, AA from protein catabolism or net portal-drained visceral absorption, and glycerol released during lipolysis in adipose tissue (Seal and Reynolds, 1993). The maximal calculated contribution of propionate to net glucose release by liver ranged from approximately 50 to 60% during the transition period; that for lactate ranged from 15 to 20%; and that for glycerol ranged from 2 to 4% (Reynolds et al., 2003). By difference, AA accounted for a minimum of approximately 20 to 30% during the transition period; the maximal contribution of Ala increased from 2.3% at 9 d prepartum to 5.5% at 11 d postpartum. These results are consistent with those of Overton et al. (1998), who reported that hepatic capacity to convert [1-¹⁴C]alanine to glucose was approximately doubled on 1 d postpartum compared with 21 d prepartum. Although AA are not likely to be quantitatively important in terms of the amount of milk that the AA pool will support during early lactation, these results lend support to the use of AA as an adaptational substrate pool for glucose synthesis during the immediate postpartum period.

Lipid Metabolism

The primary homeorhetic adaptation of lipid metabolism to lactation is the mobilization of body fat stores to meet the overall energetic requirements of the cow during a period of negative energy balance in early lactation. Body fat is mobilized into the bloodstream in the form of NEFA. The NEFA are utilized to make upwards of 40% of milk fat during the first days of lactation (Bell, 1995). Skeletal muscle uses some NEFA for fuel, particularly as it decreases its reliance on glucose as a fuel during early lactation. Given that plasma NEFA concentrations increase in response to increased energy needs

accompanied by inadequate feed intake, DMI and plasma NEFA concentrations usually are inversely related. Available evidence suggests that the liver takes up NEFA in proportion to their supply (Pullen et al., 1989; Reynolds et al., 2003), but the liver typically does not have sufficient capacity to completely dispose of NEFA through export into the blood or catabolism for energy; therefore, cows are predisposed to accumulate NEFA as triglycerides within liver when large amounts of NEFA are released from adipose tissue into the circulation (Emery et al., 1992).

It is likely that some triglyceride accumulates in liver of almost all high-producing cows during the first few weeks postpartum. What is uncertain is the threshold at which fat begins to have detrimental effects on other hepatic processes. Piepenbrink and Overton (2003b) reported that there is a negative correlation ($r = -0.4$) between triglyceride accumulation in liver and the capacity of liver slices to convert propionate to glucose *in vitro*. Cadorniga-Valino et al. (1997) demonstrated that lipid infiltration of isolated hepatocytes decreased gluconeogenic capacity from propionate. A subsequent experiment using a "physiological" mixture of fatty acids determined that lipid infiltration did not affect rates of gluconeogenesis but decreased ureagenic capacity (Strang et al., 1998).

The implications of decreased ureagenic capacity are not clear, but limited evidence suggests that this phenomenon may occur in dairy cows during the transition period. Zhu et al. (2000) determined that peripheral concentrations of ammonia doubled when liver triglyceride concentrations increased during the first 2 d postpartum. *In vitro* incubation with ammonium chloride strongly inhibited capacity of isolated hepatocytes to synthesize glucose from propionate (Overton et al., 1999). Therefore, it is conceivable that inhibition of gluconeogenesis may occur *in vivo* when triglycerides accumulate in liver. Perhaps the mechanism is modulated by ammonia supply to liver. Potential implications of this research for the management of transition dairy cows centers around carbohydrate and protein nutrition. As discussed previously, significant quantities of AA are needed for gluconeogenesis. However, we hypothesize that excess protein or asynchronous supply of ruminal N relative to carbohydrate supply may increase the ammonia load on the animal, and thereby affect the capacity of a triglyceride-laden liver to synthesize glucose. Furthermore, the specific nature of the potential link between impaired gluconeogenic capacity and ureagenic capacity has yet to be elucidated.

Calcium Metabolism

Reinhardt et al. (1988) reviewed basic Ca, P, and Mg homeostatic mechanisms in ruminants, and further re-

view of Ca and vitamin D metabolism in dairy cows were given by Horst et al. (1994). The skeleton contains 99 and 80% of total body Ca and P, respectively. Calcium pools are under strict homeostatic control, whereas the P pool is less regulated. Under noninflammatory physiologic conditions, serum Ca and P concentrations are under endocrine control regulated at the level of intestinal absorption, bone resorption or deposition, renal reabsorption and urinary excretion, salivary recycling, fetal deposition (pregnant animal), milk secretion (lactating animal), and fecal excretion. In the absence of inflammation, parathyroid hormone and 1,25-dihydroxyvitamin D are generally conservatory for the extracellular pool and are responsible for increasing intestinal absorption and renal reabsorption of Ca, and bone resorption of Ca and P. Although parathyroid hormone adds to the extracellular phosphate pool via bone resorption, it actually increases renal phosphate excretion and, more significantly, increases salivary phosphate secretion. Parathyroid hormone-related protein may also be important for the secretion of Ca (as well as Mg and P) into the milk of lactating animals (Thiede, 1994). Calcitonin is secreted by the thyroid gland in response to elevated serum Ca and results in increased bone mineral deposition, decreased intestinal absorption, and increased urinary Ca excretion. Study of mastectomized cows (Goff et al., 2002) indicated that the mammary gland and its concomitant lactogenesis are fully responsible for the periparturient hypocalcemia. In contrast, serum P concentration decreased irrespective of mastectomy, indicating that factors other than milk production at the time of parturition are responsible for periparturient hypophosphatemia.

Although circulating concentrations of regulatory hormones yield some information about macromineral homeostasis, these data alone may be insufficient to elucidate the mechanisms of macromineral dysregulation. For example, plasma concentrations of parathyroid hormone (Mayer et al., 1969) and 1,25-dihydroxyvitamin D (Horst et al., 1978) are actually elevated, while plasma calcitonin concentration is decreased (Mayer et al., 1975) immediately preceding, and during, most cases of hypocalcemic parturient paresis in dairy cows. Thus, factors at the tissue level other than hormone concentrations, such as receptor numbers, binding affinity, hormone clearance, and postreceptor signaling, may also be affected during cases of macromineral dysregulation (Horst et al., 1994). Nutritional strategies to minimize periparturient hypocalcemia are based on manipulation of these endocrine control-points by priming the absorptive and resorptive mechanisms of macromineral metabolism so that the cow can more efficiently manage the period of negative mineral balance associated with the onset of lactation (Horst et al., 1997).

NUTRITIONAL MANAGEMENT TO SUPPORT METABOLIC ADAPTATIONS DURING THE TRANSITION PERIOD

Grouping Strategies

The primary goal of nutritional management strategies of dairy cows during the transition period should be to support the metabolic adaptations described above. Industry-standard nutritional management of dairy cows during the dry period consists of a 2-group nutritional scheme. The NRC (2001) recommended that a diet containing approximately 1.25 Mcal/kg of NE_L be fed from dry off until approximately 21 d before calving, and that a diet containing 1.54 to 1.62 Mcal/kg of NEL be fed during the last 3 wk preceding parturition. The primary rationale for feeding a lower energy diet during the early dry period is to minimize BCS gain during the dry period; furthermore, Dann et al. (2003) reported recently that supplying excessive energy to dairy cows during the early dry period may actually have detrimental carryover effects during the subsequent early lactation period. The nature of these carryover effects is not known. One could speculate, however, that effects could be mediated through metabolic machinery responsible for tissue responsiveness to endocrine signals during the late prepartum period.

In general, available information supports feeding the higher energy diet for two to three weeks prior to parturition (Mashek and Beede, 2001; Corbett, 2002; Contreras et al., 2004). Results from 2 of these experiments indicated farm-specific negative effects on subsequent production and health if cows were fed the higher energy diet for the entire dry period (Contreras et al., 2004) or for an average of 37 d prepartum (Mashek and Beede, 2001). These responses may correspond to the negative carryover effects of overfeeding energy during the early dry period described by Dann et al. (2003).

Furthermore, recent results (Contreras et al., 2004) support managing cows to achieve a BCS of approximately 3.0 at dry off rather than the traditional 3.5 to 3.75 BCS—perhaps partially due to the decreased DMI associated with higher BCS during the prepartum period (Hayirli et al., 2002). Studies conducted with limited replication indicate increased DMI and milk yield for cows of BCS 2 to 2.5 at calving versus those with a BCS of 3.5 to 4 on a 4-point scale (Garnsworthy and Topps, 1982a, 1982b; Treacher et al., 1986; Garnsworthy and Jones, 1987). These results are also consistent with those of Domecq et al. (1997), who reported that as BCS of cows at dry off increased, milk yield during the first 120 DIM decreased; furthermore, thinner cows that gained BCS during the dry period yielded more milk during the first 120 DIM. Collectively, results published in the scientific literature support the concept that cows of mod-

erately lower BCS within a well-managed transition management system are more likely to have positive transition period outcomes than cows of greater BCS due to their propensity to have increased DMI and potentially increased milk yield during early lactation.

Strategies to Meet Glucose Demands and Decrease NEFA Supply During the Transition Period

Carbohydrate formulation of the prepartum diet.

A substantial amount of research has been conducted to examine carbohydrate nutrition of dairy cows during the dry period, specifically relating to the NFC content of the diet. A concept that has been perpetuated through the scientific literature (Rabelo et al., 2003) is that diets higher in NFC content than traditional dry cow diets must be fed prior to calving to promote development of ruminal papillae for adequate absorption of VFA produced during ruminal fermentation. This idea was based on one experiment in which dry cows were adapted from a diet containing a large amount of poor-quality forage to a diet containing a much larger proportion of grain (Dirksen et al., 1985). However, Andersen et al. (1999) reported that cows fed more typical diets during the prepartum period do not have meaningful changes in ruminal epithelium. Regardless of the effect on rumen epithelium, feeding diets containing higher proportions of NFC should promote ruminal microbial adaptation to NFC levels typical of diets fed during lactation and provide increased amounts of propionate to support hepatic gluconeogenesis and microbial protein (providing the diet contains sufficient ruminally degradable protein) to support protein requirements for maintenance, pregnancy, and mammogenesis.

Results from 7 experiments conducted during the past 10 yr that focused on NFC content of the prepartum diet are summarized in Table 1. Although the content of both the low- and high-NFC prepartum diets varied substantially across the experiments, most of these studies reported one or more positive outcomes when the higher NFC diet was fed relative to a paired lower NFC diet. Most of the researchers reported increased prepartum DMI in response to increasing the NFC content of the prepartum diet. These results are consistent with those summarized in the correlation dataset of Hayirli et al. (2002), who reported that prepartum DMI was positively correlated with NFC content of the prepartum diet.

The NFC content of the diet is only one factor that has an impact on the ruminal fermentability of carbohydrate in the diet. Accordingly, research attention also has focused on the fermentability of a given concentration of NFC in diets fed during both the prepartum and immediate postpartum periods. Dann et al. (1999) re-

Table 1. Effect of NFC¹ concentration in the prepartum diet on metabolism and performance.

Experiment	NFC, % of DM		Effect of high NFC ²
	Low	High	
Grum et al., 1996	18	28	↑ pre-DMI; ↑ pre-insulin
Minor et al., 1998	24	44	↑ pre-DMI; ↑ milk yield ³
Mashek and Beede, 2000	35	38	↓ pre-BHBA; ↑ pre-insulin; ↑ milk yield ⁴
Keady et al., 2001	13	28	↑ pre-DMI
Holcomb et al., 2001	25	30	↑ pre-DMI; ↓ peri-NEFA
Doepel et al., 2002	24	30	↑ post-DMI; ↓ peri-NEFA; ↓ liver TG ⁵
Rabelo et al., 2003	38	45	↑ pre-DMI; ↑ post-DMI ⁵ (d 1 to 20)

¹Nonfiber carbohydrate; $100 - [(NDF-NDICP) + CP + EE + Ash]$; NRC, 2001.

²pre = Prepartum; peri = periparturient; post = postpartum.

³Cows fed higher NFC prepartum continued on higher NFC diet postpartum.

⁴Higher NFC increased milk yield only in third lactation and greater cows.

⁵Statistical trend.

ported that increasing the fermentability of the NFC in the prepartum diet by replacing cracked corn with steam-flaked corn (39% total NFC content of the diet) tended to increase prepartum DMI, postpartum milk yield, and plasma insulin concentrations during the immediate postpartum period; NEFA concentrations were decreased during the prepartum period by increasing intake of fermentable carbohydrate. Ordway et al. (2002) fed diets containing approximately 36% NFC during the prepartum period and replaced 2.7% of diet DM as ground shelled corn with sucrose. Feeding sucrose tended to increase plasma glucose concentrations during the prepartum period, but did not affect peripartum performance or concentrations of NEFA during either the prepartum or postpartum periods.

Most of the experiments described above confounded NFC content and energy concentration of the prepartum diet, i.e., the increase in NFC content of the diet simultaneously increased NE_L content of the diet, and, given that cows typically consumed more of the higher NFC diet, they also consumed more energy during the prepartum period. We were interested in exploring the concentration of NFC in the diet independent of energy content of the prepartum diet and, more specifically, the impact of deriving energy from starch-based NFC compared with other carbohydrate sources (Smith et al., 2002, 2003). Of particular interest was the effect that feeding a diet high in nonforage fiber sources (i.e., beet pulp, soybean hulls) as a source of highly digestible NDF might have on performance and metabolism during the periparturient period. The high NFC diet contained 1.59 Mcal/kg of NE_L, 40% NFC, and 28% starch; the high nonforage fiber sources diet contained 1.54 Mcal/kg of NE_L, 34% NFC, and 18% starch. Dry matter intake between the 2 treatments during the prepartum and postpartum periods did not differ, and other aspects of performance and metabolism, including the dynamics of insulin action and glucose disposal in response to a glucose

challenge, were virtually unaffected by the source of dietary carbohydrate in the prepartum diet.

Although we did not assess the impact of energy supply in this experiment (Smith et al., 2002, 2003); results imply that the generally positive effects on performance and metabolism of feeding diets during the prepartum period that are moderately higher in NFC content are linked to energy supply from carbohydrate rather than NFC content of the diet per se. Therefore, the specific NFC content of the diet prepartum diet may have received unwarranted focus in research and also practical diet formulation in the dairy industry. This speculation is consistent with results reported recently by Pickett et al. (2003a), who measured positive effects on metabolism and performance when NDF from forage was replaced by NDF from nonforage fiber sources in diets fed during the prepartum period.

Direct supplementation with glucogenic precursors. Propylene glycol is a glucogenic precursor that has been used for many years as an oral drench in the treatment of ketosis. Available studies consistently demonstrate decreased concentrations of NEFA in plasma and usually demonstrate decreased concentrations of BHBA in plasma in response to propylene glycol administered as an oral drench (Studer et al., 1993; Grummer et al., 1994; Formigoni et al., 1996; Burhans et al., 1997; Christensen et al., 1997; Stokes and Goff, 2001; Pickett et al., 2003b). Incorporation of propylene glycol into the TMR did not affect concentrations of NEFA and BHBA in plasma (Christensen et al., 1997). Recently, Stokes and Goff (2001) reported that administration of an oral drench of propylene glycol for 2 d beginning at parturition decreased concentrations of NEFA in plasma and increased milk yield during early lactation. Subsequent experiments in which propylene glycol was administered as a drench beginning at parturition for either 2 (Visser et al., 2003) or 3 d (Lenkaitis et al., 2003) or as part of a combination drench administered for 3 d beginning at

parturition (Visser et al., 2002) reported no productive response to propylene glycol drench. Overall, research supports that bolus administration of propylene glycol will result in modest effects on metabolic variables; however, the lack of consistent production responses across experiments dictate that routine administration of propylene glycol is not indicated.

Propionate supplements consisting of propionate complexed to Ca or trace minerals potentially could be used to supply substrate for hepatic gluconeogenesis. Published responses to periparturient supplementation with propionate supplements have been mixed. Burhans and Bell (1998) reported that postpartum supplementation of 300 g/d of Ca propionate did not affect postpartum milk yield or plasma NEFA concentrations. Mandebvu et al. (2003) reported that feeding approximately 110 g/d of a propionate supplement on a commercial dairy farm did not affect milk yield, but transiently decreased plasma NEFA concentrations and urine ketone score. Beem et al. (2003) determined that feeding 113.5 g/d of Ca propionate during transition period did not affect DMI, milk yield, or plasma BHBA concentrations. Stokes and Goff (2001) reported that drenching cows with 0.68 kg of Ca propionate twice during the early postparturient period did not affect early lactation milk yield, or concentrations of NEFA and BHBA in plasma. Part of the reason for the lack of measured response to propionate supplements could be the amount of propionate provided relative to the amount produced in the rumen. Midlactation cows consuming 16 kg/d of DM from a diet containing 55% forage produced almost 1000 g/d of propionate in the rumen (Bauman et al. 1971). Given that cows in the first week of lactation typically will consume a comparable amount of a comparable diet, the additional propionate supplement likely only makes a small contribution to total propionate supply to the cow. Because Stokes and Goff (2001) did not detect metabolic responses (decreased NEFA and/or BHBA concentrations in plasma) in response to oral administration of a sizable (0.68 kg) bolus of Ca propionate, we speculate that there may also be differences in either ruminal metabolism or absorption kinetics of propylene glycol and the propionate supplements. Overall, existing research does not support use of propionate supplements either through the TMR or via bolus.

Monensin provided in controlled-release capsule (CRC) form during the transition period and early lactation has been shown to decrease the incidence of subclinical ketosis in dairy cows by 50% (Duffield et al., 1998b). In addition to decreased postpartum concentrations of serum BHBA, cows administered the monensin CRC also had increased concentrations of serum glucose during the postpartum period (Duffield et al., 1998a). Overconditioned cows (BCS > 4.0 at 21 d before expected

calving) supplemented with the monensin CRC produced significantly more milk than unsupplemented controls during early lactation (Duffield et al., 1999). In a subsequent experiment, cows administered the monensin CRC had decreased circulating concentrations of NEFA during the week immediately preceding calving; however, circulating concentrations of NEFA during the first week postcalving were not affected by administration of the monensin CRC (Duffield et al., 2003). In contrast, cows fed 300 mg/d of monensin from 28 d prior to calving until calving did not have altered concentrations of NEFA and glucose during the prepartum period compared with controls; however, cows fed 300 mg/d of monensin during the prepartum period had significantly lower circulating NEFA concentrations during the first week postcalving (Vallimont et al., 2001).

As demonstrated with growing steers, the net effect of monensin within the rumen is to increase ruminal propionate production at the expense of ruminal acetate and methane production so that propionate supply is increased and the overall energetic efficiency of ruminal fermentation is increased (Armentano and Young, 1983). Although this mechanism is consistent with observations on the increased circulating concentrations of glucose and reduction in incidence of subclinical ketosis described above, Markantonatos et al. (2002) determined that prepartum ruminal production of propionate was not affected by feeding 300 mg/d of monensin during the prepartum period of dairy cows. Furthermore, only modest effects of monensin on glucose kinetics during the prepartum period were measured (Arieli et al., 2001). It is uncertain whether the metabolic effect on subclinical ketosis and milk yield is mediated directly through glucose metabolism or NEFA metabolism; however, research supports consistent efficacy of monensin administered as a CRC or as a topdress. Given the fluctuations in DMI during the periparturient period, it is not known whether inclusion of monensin in a TMR will be as effective as administering via CRC.

Added fat in transition diets. It has been proposed that dietary fat may help to decrease concentrations of NEFA and help to prevent occurrence of ketosis (Kronfeld, 1982). Dietary long-chain fatty acids are absorbed into the lymphatic system and do not pass first through the liver. This fat can provide energy for peripheral tissues and the mammary gland. Kronfeld's hypothesis is that the increased energy availability would in turn decrease mobilization of body fat and decrease NEFA concentrations. Despite available information (Skaar et al., 1989; Grum et al., 1996; Burhans and Bell, 1998; Douglas et al., 1998; Bertics and Grummer, 1999), indicating that added fat fed to cows during the prepartum period does not decrease plasma NEFA concentrations, advancement of this hypothesis by various commercial in-

terests in the dairy industry has continued. Grum et al. (1996) determined that feeding fat (6.7% of diet DM) to cows during the entire dry period virtually abolished accumulation of triglycerides in liver during the immediate periparturient period; however, cows fed fat also had decreased DMI during the dry period. A subsequent experiment (Douglas et al., 1998) determined that the reduction in liver triglycerides was mostly attributable to the decreased DMI of cows fed added fat during the dry period. As indicated above, Doepel et al. (2002) reported that cows fed high-energy diets during the preparturient period had decreased periparturient concentrations of NEFA in plasma and tended to have decreased postparturient liver triglyceride concentrations. The increase in energy content of the preparturient diet was achieved by a combination of increasing NFC content as reported above and addition of tallow at 2.2% of DM. The preponderance of results reported above suggest that the results of Doepel et al. (2002) occurred as a consequence of changes made in the NFC content of the diet rather than in the fat content of the diet.

Anecdotal reports from some practitioners in the dairy industry have indicated beneficial effects of administering dietary fat by oral drench to cows during the immediate postparturient period, and dietary fat sources are commonly included in commercially available mixtures administered orally to fresh cows. Pickett et al. (2003b) administered 454 g/d of a commercially available fat supplement (82% fatty acids by weight) by oral drench for the first 3 d of lactation; administration of fat did not affect concentrations of NEFA and BHBA in plasma and triglycerides in liver during the postparturient period, and tended to decrease DMI and milk yield during the first 21 d of lactation.

Effects of specific fatty acids on NEFA supply. A substantial amount of research conducted during the past few years has focused on the metabolic roles of individual fatty acids. Interest in application of individual fatty acids in transition cow nutrition and metabolism to date has focused on one of two general areas. First, researchers have sought to determine whether feeding *trans*-10, *cis*-12 conjugated linoleic acid (CLA), a fatty acid known to decrease milk fat percentage and yield in cows in established lactation (Baumgard et al., 2001; Bauman and Griinari, 2003), will decrease energy output during early lactation and in turn decrease the extent and duration of negative energy balance during early lactation. Giesy et al. (1999) fed cows a mixture of CLA isomers in a Ca-salt form from d 13 through 80 postparturient. They reported few effects of CLA supplementation on cow performance during d 14 through 28 postcalving; however, milk yield was increased, and percentage and yield of milk fat were decreased, during d 35 through 80 postparturient. Energy balance was not

affected by treatment during either period. Bernal-Santos et al. (2003) fed cows a mixture of CLA isomers as Ca-salts from 14 d preparturient through 140 d postparturient. Milk fat percentage and yield decreased beginning during the third week postparturient. However, cows fed the rumen-protected CLA tended to produce more milk during early lactation and energy balance was also unaffected by treatment in this experiment. Castaneda-Gutierrez et al. (2003) reported similar effects on milk fat percentage and yield beginning during the third week postparturient in response to feeding CLA. Milk yield was not different among treatments in this experiment. Selberg et al. (2002) fed a source of *trans*-octadecenoic acid during the transition period and early lactation and reported that liver triglyceride concentration decreased in response to feeding the *trans*-octadecenoic acid source. In contrast, Bernal-Santos et al. (2003) reported that liver triglyceride concentration was not affected by feeding CLA. Given that these 2 fatty acids appear to have different effects on liver metabolism, research is required to characterize further the metabolic effects of these 2 fatty acids in transition cows.

Nutritional Strategies to Decrease Conversion of NEFA to Accumulated Triglyceride in Liver

In addition to nutritional strategies used to decrease the supply of circulating NEFA available for extraction by the liver, the potential exists to employ nutritional strategies to decrease the rate at which NEFA are converted to triglycerides within the liver. Although hepatic capacities for disposal of NEFA through mitochondrial or peroxisomal β -oxidation or export as triglycerides within VLDL are limited in ruminants compared with nonruminants (Grummer, 1993), recent evidence suggests that supplying specific nutrients to dairy cows during the transition period may increase rates of NEFA disposal, with resulting effects on performance.

Choline is a quasi-vitamin that has a variety of functions in mammalian metabolism. Its most significant functions are as a component of the predominant phospholipids contained in the membranes of all cells in the body (phosphatidylcholine), a component of the neurotransmitter acetylcholine, and as the direct precursor to betaine in methyl metabolism. Most of the potential application of choline within transition cow nutrition has focused on its role in lipid metabolism because phosphatidylcholine is required for synthesis and release of VLDL by liver. Choline deficiency in rats resulted in a sixfold increase in liver triglyceride content (Yao and Vance, 1990), and in vitro incubation of hepatocytes isolated from choline-deficient rats with either choline or Met increased concentrations of phosphatidylcholine in liver and release of VLDL (Yao and Vance, 1988). Feed-

ing choline in rumen-protected form to transition dairy cows tended to decrease the rate of accumulation of esterified products in liver slices *in vitro* (Piepenbrink and Overton, 2003c), implying that VLDL export was sensitive to choline supply also in dairy cows. Yields of milk and fat-corrected milk have generally increased in response to feeding rumen-protected choline during the transition period (Erdman and Sharma, 1991; Hartwell et al., 2000; Scheer et al., 2002; Piepenbrink and Overton, 2003c; Pinotti et al., 2003), suggesting that the metabolic changes in hepatic fatty acid metabolism translated into improved performance during early lactation.

Methionine and Lys are frequently considered to be the 2 most limiting AA for synthesis of milk and milk protein (NRC, 2001). These 2 AA also have potential roles in mitochondrial β -oxidation of fatty acids (carnitine biosynthesis) in liver and export of triglycerides as VLDL (apolipoprotein B100 biosynthesis; Bauchart et al., 1998). A potential role for Met in bovine ketosis has been speculated for more than 30 yr (McCarthy et al., 1968; Waterman and Schultz, 1972). Investigators that have sought to increase the supply of Met as either rumen-protected Met (Socha et al., 1994; Overton et al., 1996) or its analog [(2-hydroxy-4-(methylthio)-butanoic acid; Rode et al., 1998; Piepenbrink et al., 2004] beginning prior to parturition and continuing through early lactation generally reported increased milk yield during early lactation. These positive productive responses do not appear to relate directly to effects of Met and Lys on hepatic lipid or glucose metabolism (Pullen et al., 1989; Socha, 1994; Bertics and Grummer, 1999; Piepenbrink et al., 2004). Therefore, specific roles for Met and Lys in aspects of hepatic lipid and glucose metabolism remain speculative and unsubstantiated.

Linoleic and linolenic acids are considered to be essential in many species. Linolenic acid is a precursor to both docosahexaenoic and eicosapentaenoic acids—collectively, these fatty acids may have roles important for the secretion of apolipoprotein B100 and also for VLDL particle stability in cultured hepatocytes (Lang and Davis, 1990; Wu et al., 1997). Consistent with these effects, incubation of neonatal hepatocytes *in vitro* demonstrated a potential role of linolenic acid in decreasing cellular accumulation of triglycerides from palmitic acid (Mashek et al., 2002). Short-term cultures of liver slices from immediate postpartal cows displayed decreased capacity for fatty acid esterification when incubated with a mixture of linoleic and linolenic acids (Piepenbrink and Overton, 2003a). These initial results are intriguing—are the effects of linolenic acid and its products specific to VLDL export, or are there potential effects of these fatty acids on either mitochondrial or peroxisomal β -oxidation?

Restricted Feeding During the Dry Period

Despite the widely held concept that increased DMI during the prepartum period is a harbinger of increased DMI during the postpartum period and overall transition cow success (Grummer, 1995; Hayirli et al., 2002), several investigators have studied the potential to restrict energy intake of dairy cows during the prepartum period to precondition metabolism to negative energy balance. In general, cows fed balanced diets restricted to below calculated energy requirements (usually about 80% of predicted requirements) did not decrease their voluntary DMI during the days preceding parturition and increased postpartum DMI and milk yield at faster rates than cows consuming the same diets for *ad libitum* intake (Douglas et al., 1998; Holcomb et al., 2001; Agenas et al., 2003). Furthermore, feed-restricted cows typically had blunted periparturient NEFA curves compared with those fed for *ad libitum* intake (Douglas et al., 1998; Holcomb et al., 2001; Holtenius et al., 2003), and cows fed for *ad libitum* intake prepartum had decreased insulin sensitivity compared with those that were restricted-fed (Holtenius et al., 2003). Collectively these results are intriguing, but all experiments were conducted with cows that were individually fed. Achieving uniform restricted intake in the typical group-fed situation on commercial farms will be difficult to achieve.

The phenomena of improved health and performance when DMI of cows is restricted during the prepartum period so that voluntary DMI prior to calving is not decreased has led to increasing focus on the dynamics of the prepartum DMI curve (i.e., the rate and extent of decrease of DMI prior to parturition). Recently, Mashek and Grummer (2003) proposed that, although postpartum DMI and milk production appeared to correlate more strongly with total DMI from 21 d prepartum to 1 d prepartum, the change in DMI from 21 d prepartum to 1 d prepartum correlated more strongly with metabolic indices such as postpartum plasma NEFA concentrations and liver triglyceride accumulation. The metabolic events underpinning these relationships are not known. It is possible that tissue specific responses to endocrine signals may be affected by plane of nutrition during the prepartum period, given that overall concentrations of hormones typically are only modestly affected by dietary treatment during this timeframe (see experiments cited in Table 1).

Considerations for Prevention of Hypocalcemia

One of the more interesting relationships in the epidemiological study of Curtis et al. (1985) was the lack of association of Ca content of the diet fed prepartum with occurrence of milk fever. Indeed, the NRC (2001) effectively discounted the potential that diets sufficiently low

in Ca to prevent hypocalcemia could be fed during the prepartum period. In turn, they focused attention on the approach of adjusting cation-anion difference $[(\text{Na}^+ + \text{K}^+) - (\text{Cl}^- + \text{S}^{2-})]$ to prevent metabolic alkalosis and perhaps induce a compensated metabolic acidosis. Horst et al. (1997) hypothesized that this correction of metabolic alkalosis would prevent changes in the conformation of the receptor for parathyroid hormone on bone and facilitate mobilization of Ca from bone. Prepartal diets with a negative dietary cation-anion difference (DCAD) have repeatedly been shown to reduce subclinical and clinical hypocalcemia in cows predisposed to milk fever (Horst et al., 1997). Although the basic tenet of DCAD has not changed since their review, this area has been the subject of much research, and several aspects of this subject deserve mention.

The use of prepartum diets having a lower DCAD has repeatedly been shown to be effective in preventing milk fever in cows predisposed to milk fever (Block, 1984; Joyce et al., 1997). Nonetheless, several points should be noted that should affect decision making for feeding low DCAD diets. As pointed out by Roche et al. (2002), much of the controlled research concerning diets containing a decreased DCAD was conducted using animals that are highly predisposed to milk fever (e.g., Jersey cows in their third or greater lactation). Therefore, the effects of a low DCAD diet in breeds that are less susceptible to milk fever and in modern dairy herds that often exceed 40% first-lactation animals need to be considered in decision-making. Moore et al. (2000) reported that although inclusion of anionic salts in the diet of first-lactation Holstein cows effectively induced a compensated metabolic acidosis, Ca metabolism was not improved, prepartum DMI was reduced, prepartum circulating NEFA concentrations were increased, and more triglycerides accumulated in the liver. Furthermore, these authors reported anecdotally that compared to a control cow that twinned, cows carrying twins fed anionic salts to -15 meq/100 g of diet had dramatically decreased DMI and increased circulating NEFA and liver triglyceride concentrations.

Currently, controversy exists regarding whether sufficient alleviation of hypocalcemia can occur by decreasing the cation (Na and K) content of the diet fed during the prepartum period alone without adding anions through mineral- or acid- (HCl) based sources. Existing research in the literature is equivocal about whether a reduction in dietary K and a moderate DCAD are sufficient to avert milk fever or whether herds predisposed to milk fever might benefit from diets with a DCAD of -10 to -15 meq/100 g of DM. Goff and Horst (1997) indicated a reduction in dietary K to 1.1% DM was sufficient to avert clinical milk fever in multiparous Jersey cows; however, the incidence of subclinical hypocalcemia

was not reduced. Moore et al. (2000) reported that cows fed a diet containing a DCAD of 0 meq/100 g DM resulted in intermediate indices of Ca metabolism relative to cows fed diets containing either -15 or $+15$ meq/100 g DM; however, the feeding a diet with a 0 DCAD was not sufficient to prevent parturient hypocalcemia in Holstein cows.

A final area of research that does not directly fit into DCAD programs but has stimulated interest in the area of Ca metabolism is the inclusion of the sodium aluminum silicate Zeolite A in the diets of dairy cattle. Negative Ca balance induces Ca homeostatic mechanisms to be upregulated such that the severe decline in serum Ca at the onset of lactation is attenuated (Horst et al., 1997). Indeed restriction of prepartum Ca intake to less than 20 g/d has proven effective in preventing parturient paresis (Goings et al., 1974; Wiggers et al., 1975; Kichura et al., 1982); however, this dramatic restriction of dietary Ca is difficult to achieve with available feedstuffs. Zeolite A potentially binds Ca in the digestive tract thereby making it unavailable for intestinal absorption by the cow and, in theory, dramatically restricts Ca entry rate to induce negative Ca balance in the cow prior to the initiation of lactogenesis. Thilsing-Hansen and Jorgensen (2001) reported that dietary supplementation with Zeolite A prepartum prevented milk fever and subclinical hypocalcemia in Jersey cows. Similarly, Thilsing-Hansen et al. (2002) reported that although control cows were not hypocalcemic, cows fed Zeolite A prepartum had higher serum concentrations of 1,25-dihydroxyvitamin D about 1 wk prior to calving and had greater serum Ca levels on the day of calving. Although these initial results are promising, more research is needed on this supplement to determine actual *in vivo* Ca binding capacity and also to determine any potential negative effects on the bioavailability of micronutrients when cows are fed Zeolite A.

INTERRELATIONSHIPS BETWEEN METABOLIC ADAPTATIONS AND THE IMMUNE SYSTEM DURING THE TRANSITION PERIOD

As is evident from the results reviewed above on nutritional management strategies potentially employed in support of metabolic adaptations during the transition period, our knowledge base is sufficient to enable us to formulate diets on commercial dairy farms that should lead to transition cow success. Despite this knowledge, considerable inconsistency in terms of response exists on commercial dairy farms. Thus, it is apparent that overall success in transition cow programs on commercial farms requires investigation of transition cow management as an integrated system, with the dietary strategies discussed above as one component.

An emerging area within transition cow metabolism and management is the consideration of interrelationships with the immune system (Drackley, 1999; Drackley et al., 2001). In addition to the adaptations in classical metabolism described above, transition dairy cows also undergo a period of reduced immunological capacity during the periparturient period. As reviewed by Mallard et al. (1998), this immune dysfunction is not limited to isolated immune parameters; instead it is broad in scope, affects multiple functions of various cell types, and lasts from about 3 wk prior to calving until about 3 wk after calving. The consequence of immunosuppression is that cows may be hyposensitive to invading pathogens and therefore more susceptible to disease, particularly mastitis, during the periparturient period. Paradoxically, although leukocytes from immunosuppressed cows are functionally compromised and hyposensitive to pathogens, they are also hyperresponsive once activated and produce more proinflammatory cytokines (Sordillo et al., 1995).

Due in part to immunosuppression, IMI that occur during the dry or periparturient period can adversely affect udder health, resulting in decreased milk production, altered milk composition, and impaired mammary function (Oliver and Sordillo, 1988). Virulence factors produced by mastitis pathogens may influence mammary epithelial proliferation *in vivo*, which could be important during the periparturient period, when mammary tissue undergoes rapid differentiation and growth (Matthews et al., 1994). Perhaps slightly more obscure are the concerns that either a mammary infection during immunosuppression will predispose the animal to a greater risk of other pathologies or that other pathologies will increase the risk of mastitis at a time when the immune system is compromised. For example, Schukken et al. (1989) reported that cows with retained placenta were 3 times more likely to develop mastitis during hospitalization than animals without retained placenta. Of course, this does not establish a cause and effect relationship; rather, as the authors suggested, it could be that some common factor (e.g., the activity of peripheral leukocytes) predisposed the animals to both diseases. Indeed, Dosogne et al. (1999) reported that circulating percentages of polymorphonuclear neutrophils (leukocytes also important in defense of the mammary gland against mastitic pathogens; reviewed by Paape et al., 2002) were lower in cows with retained fetal membranes and that a greater percentage of neutrophils in these cows were immature—perhaps leading to impaired function. Kimura et al. (2002) utilized neutrophils isolated from cows with or without retained placenta in an *in vitro* system to evaluate neutrophil function and reported that neutrophils from cows with retained placenta had impaired cellular killing capacity and cotyledonary chemotactic

migration activity. These reports support the suggestion by Schukken et al. (1989) that a common factor such as neutrophil function may be important in the associative relationship between some metabolic and infectious diseases in lactating dairy cows. In the case of another common periparturient disease, however, Kehrli and Goff (1989) reported that hypocalcemia did not exacerbate immune suppression in periparturient cows.

In addition to interactions of immunity with metabolism, clinical mastitis has also been shown to reduce reproductive performance in lactating dairy cows (Barker et al., 1998). Furthermore, Schrick et al. (2001) reported that subclinical mastitis also decreased reproductive efficiency by increasing days to first service, days open, and number of services per conception. Immune activation via experimental means or natural infection of the mammary gland has been shown to affect multiple reproductive tissues at various times in the estrous cycle. Huszenicza et al. (1998) reported that mastitis infection occurring in the first 14 d after calving did not affect ovarian cyclicity, but that mastitis between d 15 through 28 delayed the time to first ovulation and first estrus. The authors also reported that gram-negative mastitis in already cycling cows during the luteal phase resulted in luteolysis, whereas mastitis during the follicular phase increased period of low progesterone, perhaps resulting in degeneration of the dominant follicle. During clinical gram-positive mastitis of cows in the luteal phase of their cycle, Hockett et al. (2000) reported elevated circulating cortisol concentrations and, following oxytocin administration, greater circulating prostaglandin $F_{2\alpha}$ concentrations. Such endocrine changes could result in luteal regression and decreased embryo viability.

The etiology of periparturient immunosuppression is multifactorial and not well understood, but seems to be due to physiologic changes associated with parturition and the initiation of lactation and to metabolic factors related to these events. Glucocorticoids are known immunosuppressants (Roth and Kaeberle, 1982), are elevated at parturition, and have therefore been postulated to play a role in periparturient immunosuppression. However, cortisol is elevated for only hours around calving and therefore its role in prolonged immunosuppression around the time of calving has been questioned. Some researchers (Preisler et al., 2000; Weber et al., 2001) have suggested that, although cortisol concentrations are only transiently elevated, changes in glucocorticoid receptor expression driven by changes in estrogen and progesterone at the time of parturition might contribute to immunosuppression for at least several days around calving.

Periparturient negative energy balance has also been implicated in contributing to immunosuppression. However, negative energy balance alone had little effect on

the expression of adhesion molecules on the surface of bovine leukocytes (Perkins et al., 2001). Furthermore, negative energy balance in midlactation cows did not affect the clinical symptoms associated with an intramammary endotoxin infusion (Perkins et al., 2002). These results are contrary to work in periparturient cows where the presence of a mammary gland (vs. mastectomized cows) and its attendant metabolic demands slowed recovery of neutrophil function, suggesting that the metabolic stress of lactation exacerbated periparturient immunosuppression (Kimura et al., 1999). Other work has investigated individual metabolic components associated with negative energy balance, and has concluded that while hypoglycemia alone is not likely to exacerbate periparturient immunosuppression (Nonnecke et al., 1992), hyperketonemia appears to have multiple negative effects on aspects of immune function (as reviewed by Suriyasathaporn et al., 2000).

Reports of the negative effects of ketosis on immune function may be related to or compounded by the impact of fatty liver on immune function. As previously discussed, triglyceride accumulation in the liver is reported to have metabolic effects whereby hepatic ureagenic and perhaps gluconeogenic capacity is reduced, but fatty liver also affects immune function. Andersen et al. (1996) reported that cows without fatty liver cleared bacterial endotoxin from circulation within 30 min of i.v. endotoxin administration, whereas cows with fatty liver were unable to clear the administered endotoxin even after 6 h. Furthermore, these authors reported that whereas 0 of 18 healthy cows had severe reactions to endotoxin administration, 1 of 4 cows with fatty liver died following endotoxin administration. Reid and Roberts (1983) reported preliminary results whereby cows with fatty liver displayed decreased neutrophil extravasation *in vitro* and Hill et al. (1985) reported that cows with fatty liver took significantly longer to resolve IMI than did cows without hepatic lipidosis. Other aspects of metabolic status were not reported in these studies, so it is unknown to what extent fatty liver was solely responsible for the reported results; however, it seems clear that indeed fatty liver and attendant metabolic perturbations negatively impact immune function in dairy cattle.

In addition to effects of metabolic dysfunction on immunological capacity, it is possible that perturbations of the immune system also may impact the normal adaptations of other aspects of metabolism during the transition period. In experiments conducted in our laboratory, Waldron et al. (2003a) reported that lactating cows subjected to activation of the immune system via endotoxin administration responded with dramatic changes in circulating concentrations of cortisol, glucagon, and insulin in order to maintain glucose homeostasis. Furthermore, immune system activation resulted in decreased concentrations

of circulating Ca and P (Waldron et al., 2003b). In light of these results, it is conceivable that a vigorous immune response during the periparturient period may also predispose cows to the development of secondary metabolic disorder. Therefore, attenuation of immune sensitivity (immunosuppression) during the transition period actually may be a normal and protective homeorhetic adaptation to lactation. Unfortunately, this potentially beneficial adaptation also allows for the establishment of more severe infections and greater inflammatory reactions when immune challenges do occur. These concepts must be evaluated in periparturient cows, and the biological magnitude of the potential interface of nutrient metabolism and immune function determined so that researchers can focus on methods to determine whether these interactions account for variation in response to nutritional management strategies across commercial dairy farms.

CONCLUSIONS AND IMPLICATIONS

Significant progress in understanding the metabolic adaptations that dairy cows make as they transition from a nonlactating to lactating state has enabled continual development of specific nutritional strategies to support these metabolic adaptations. Overall, research supports 2-group nutritional management schemes for dry cows to minimize overfeeding during the early dry period and to increase energy supply to dairy cows during the late prepartum period. Although confirming studies are required, recent evidence suggests that metabolism and performance of transition cows is more sensitive to total energy supplied by carbohydrate than the form of that carbohydrate (i.e., starch versus highly digestible NDF). Efforts to improve the energy status of dairy cows during the periparturient period and decrease NEFA release from adipose tissue by feeding added dietary fat sources or *trans*-10, *cis*-12 CLA have not resulted in improved metabolism or consistently improved performance. Although the dogma has been that there is little potential to nutritionally affect hepatic metabolism of NEFA extracted from the circulation, recent evidence suggests that nutrients such as choline and essential fatty acids may increase rates of hepatic export of NEFA as triglycerides in VLDL. Calcium mobilization in support of lactation can be facilitated effectively by lowering the DCAD of the diet fed during the prepartum period; however, the degree to which the DCAD must be lowered to sufficiently alleviate hypocalcemia remains controversial. Our understanding of periparturient nutritional physiology continues to evolve; however, the substantial variation in response to nutritional manipulation that occurs on commercial dairy farms is a reminder that transition cow management is a multifaceted issue. Recent results

have developed our understanding of changes in immune function during the periparturient period; events mediated via the immune system have the potential to impact metabolic adaptations to lactation and thus affect the outcome of nutrition programs on commercial dairy farms. Future research in transition cow biology and management will be most fruitful if conducted as an investigation of integrative biology rather than classical nutrition.

REFERENCES

- Agenas, S., E. Burstedt, and K. Holtenius. 2003. Effects of feeding intensity during the dry period. 1. Feed intake, body weight, and milk production. *J. Dairy Sci.* 86:870–882.
- Andersen, J. B., J. Sehested, and K. L. Ingvarsen. 1999. Effect of dry cow feeding strategy on rumen pH, concentration of volatile fatty acids, and rumen epithelium development. *Acta Agric. Scand. Sect. A Animal Sci.* 49:149–155.
- Andersen, P. H., N. Jarlov, M. Hesselholt, and L. Baek. 1996. Studies on in vivo endotoxin plasma disappearance times in cattle. *J. Vet. Med. A* 43:93–101.
- Arieli, A., J. E. Vallimont, Y. Aharoni, and G. A. Varga. 2001. Monensin and growth hormone effects on glucose metabolism in the prepartum cow. *J. Dairy Sci.* 84:2770–2776.
- Armentano, L. E., and J. W. Young. 1983. Production and metabolism of volatile fatty acids, glucose, and CO₂ in steers and the effects of monensin on volatile fatty acid kinetics. *J. Nutr.* 113:1265–1277.
- Barker, A. R., F. N. Schrick, M. J. Lewis, H. H. Dowlen, and S. P. Oliver. 1998. Influence of clinical mastitis during early lactation on reproductive performance of Jersey cows. *J. Dairy Sci.* 81:1285–1290.
- Bauchart, D., D. Durand, D. Gruffat, and Y. Chilliard. 1998. Mechanism of liver steatosis in early lactation cows—Effects of hepatoprotector agents. Pages 27–37 in *Proc. Cornell Nutr. Conf. Feed Manuf.* Cornell University, Ithaca, NY.
- Bauman, D. E., C. L. Davis, and H. F. Bucholtz. 1971. Propionate production in the rumen of cows fed either a control or high-grain, low-fiber diet. *J. Dairy Sci.* 54:1282–1287.
- Bauman, D. E., and J. M. Grinari. 2003. Nutritional regulation of milk fat synthesis. *Ann. Rev. Nutr.* 23:203–227.
- Baumgard, L. H., J. K. Sangster, and D. E. Bauman. 2001. Milk fat synthesis in dairy cows is progressively reduced by increasing supplemental amounts of trans-10, cis-12 conjugated linoleic acid (CLA). *J. Nutr.* 131:1764–1769.
- Beem, A. E., H. G. Bateman, C. C. Williams, C. C. Stanley, D. T. Gantt, Y. H. Chung, and F. R. Valdez. 2003. Effects of prepartum dietary energy concentration and Ca-propionate on transition performance. *J. Dairy Sci.* 86(Suppl. 1):105. (Abstr.)
- Bell, A. W. 1995. Regulation of organic nutrient metabolism during transition from late pregnancy to early lactation. *J. Anim. Sci.* 73:2804–2819.
- Bennink, M. R., R. W. Mellenberger, R. A. Frobish, and D. E. Bauman. 1972. Glucose oxidation and entry rate as affected by the initiation of lactation. *J. Dairy Sci.* 55:712. (Abstr.)
- Bernal-Santos, G., J. W. Perfield II, D. M. Barbano, D. E. Bauman, and T. R. Overton. 2003. Production responses of dairy cows to dietary supplementation with conjugated linoleic acid (CLA) during the transition period and early lactation. *J. Dairy Sci.* 86:3218–3228.
- Bertics, S. J., and R. R. Grummer. 1999. Effects of fat and methionine hydroxy analog on prevention or alleviation of fatty liver induced by feed restriction. *J. Dairy Sci.* 82:2731–2736.
- Block, E. 1984. Manipulating dietary anions and cations for prepartum dairy cows to reduce incidence of milk fever. *J. Dairy Sci.* 67:2939–2948.
- Burhans, W. S., and A. W. Bell. 1998. Feeding the transition cow. Pages 247–258 in *Proc. Cornell Nutr. Conf. Feed Manuf.* Cornell Univ., Ithaca NY.
- Burhans, W. S., E. A. Briggs, J. A. Rathmacher, and A. W. Bell. 1997. Glucogenic supplementation does not reduce body tissue protein degradation in periparturient dairy cows. *J. Dairy Sci.* 80(Suppl. 1):167. (Abstr.)
- Burhans, W. S., A. W. Bell, R. Nadeau, and J. R. Knapp. 2003. Factors associated with transition cow ketosis incidence in selected New England herds. *J. Dairy Sci.* 86(Suppl. 1):247. (Abstr.)
- Cadorniga-Valino, C., R. R. Grummer, L. E. Armentano, S. S. Donkin, and S. J. Bertics. 1997. Effects of fatty acids and hormones on fatty acid metabolism and gluconeogenesis in bovine hepatocytes. *J. Dairy Sci.* 80:646–656.
- Castaneda-Gutierrez, E., T. R. Overton, and D. E. Bauman. 2003. Dose response to supplementation with calcium salts of conjugated linoleic acid during the transition period and early lactation. *J. Dairy Sci.* 86(Suppl. 1):146. (Abstr.)
- Christensen, J. O., R. R. Grummer, F. E. Rasmussen, and S. J. Bertics. 1997. Effect of method of delivery of propylene glycol on plasma metabolites of feed-restricted cattle. *J. Dairy Sci.* 80:563–568.
- Contreras, L. L., C. M. Ryan, and T. R. Overton. 2004. Effects of dry cow grouping strategy and prepartum body condition score on performance and health of transition dairy cows. *J. Dairy Sci.* 87:517–523.
- Corbett, R. B. 2002. Influence of days fed a close-up dry cow ration and heat stress on subsequent milk production in western dairy herds. *J. Dairy Sci.* 85(Suppl. 1):191–192. (Abstr.)
- Curtis, C. R., H. N. Erb, C. H. Sniffen, R. D. Smith, and D. S. Kronfeld. 1985. Path analysis of dry period nutrition, postpartum metabolic and reproductive disorders, and mastitis in Holstein cows. *J. Dairy Sci.* 68:2347–2360.
- Dann, H. M., G. A. Varga, and D. E. Putnam. 1999. Improving energy supply to late gestation and early postpartum dairy cows. *J. Dairy Sci.* 82:1765–1778.
- Dann, H. M., N. B. Litherland, J. P. Underwood, M. Bionaz, and J. K. Drackley. 2003. Prepartum nutrient intake has minimal effects on postpartum dry matter intake, serum nonesterified fatty acids, liver lipid and glycogen contents, and milk yield. *J. Dairy Sci.* 86(Suppl. 1):106. (Abstr.)
- Dirksen, G., H. Liebich, and K. Mayer. 1985. Adaptive changes of the ruminal mucosa and functional and clinical significance. *Bov. Pract.* 20:116–120.
- Doepel, L., H. Lapierre, and J. J. Kennelly. 2002. Peripartum performance and metabolism of dairy cows in response to prepartum energy and protein intake. *J. Dairy Sci.* 85:2315–2334.
- Domecq, J. J., A. L. Skidmore, J. W. Lloyd, and J. B. Kaneene. 1997. Relationship between body condition scores and milk yield in a large dairy herd of high yielding Holstein cows. *J. Dairy Sci.* 80:101–112.
- Dosogne, H., C. Burvenich, and J. A. Lohuis. 1999. Acyloxyacyl hydrolase activity of neutrophil leukocytes in normal early postpartum dairy cows and in cows with retained placenta. *Theriogenology* 51:867–874.
- Douglas, G. N., J. K. Drackley, T. R. Overton, and H. G. Bateman. 1998. Lipid metabolism and production by Holstein cows fed control or high fat diets at restricted or ad libitum intakes during the dry period. *J. Dairy Sci.* 81(Suppl. 1):295. (Abstr.)
- Drackley, J. K. 1999. Biology of dairy cows during the transition period: The final frontier? *J. Dairy Sci.* 82:2259–2273.
- Drackley, J. K., T. R. Overton, and G. N. Douglas. 2001. Adaptations of glucose and long-chain fatty acid metabolism in liver of dairy cows during the periparturient period. *J. Dairy Sci.* 84(E. Suppl.):E100–E112.
- Duffield, T. F., S. LeBlanc, R. Bagg, K. Leslie, J. Ten Hag, and P. Dick. 2003. Effect of a monensin controlled release capsule on metabolic parameters in transition dairy cows. *J. Dairy Sci.* 86:1171–1176.
- Duffield, T. F., K. E. Leslie, D. Sandals, K. Lissemore, B. W. McBride, J. H. Lumsden, P. Dick, and R. Bagg. 1999. Effect of prepartum administration of monensin in a controlled-release capsule on milk production and milk components in early lactation. *J. Dairy Sci.* 82:272–279.
- Duffield, T. F., D. Sandals, K. E. Leslie, K. Lissemore, B. W. McBride, J. H. Lumsden, P. Dick, and R. Bagg. 1998a. Effect of prepartum administration of monensin in a controlled-release capsule on post-

- partum energy indicators in lactating dairy cows. *J. Dairy Sci.* 81:2354–2361.
- Duffield, T. F., D. Sandals, K. E. Leslie, K. Lissimore, B. W. McBride, J. H. Lumsden, P. Dick, and R. Bagg. 1998b. Efficacy of monensin for the prevention of subclinical ketosis in lactating dairy cows. *J. Dairy Sci.* 81:2866–2873.
- Emery, R. S., J. S. Liesman, and T. H. Herdt. 1992. Metabolism of long-chain fatty acids by ruminant liver. *J. Nutr.* 122:832–837.
- Erdman, R. A., and B. K. Sharma. 1991. Effect of dietary rumen-protected choline in lactating dairy cows. *J. Dairy Sci.* 74:1641–1647.
- Formigoni, A., M. Cornil, A. Prandi, A. Mordenti, A. Rossi, D. Portetelle, and R. Renaville. 1996. Effect of propylene glycol supplementation around parturition on milk yield, reproduction performance and some hormonal and metabolic characteristics in dairy cows. *J. Dairy Res.* 63:11–24.
- Garnsworthy, P. C., and G. P. Jones. 1987. The influence of body condition at calving and dietary protein supply on voluntary food intake and performance in dairy cows. *Anim. Prod.* 44:347–353.
- Garnsworthy, P. C., and J. H. Topps. 1982a. The effect of body condition of dairy cows at calving on their food intake and performance when given complete diets. *Anim. Prod.* 35:113–119.
- Garnsworthy, P. C., and J. H. Topps. 1982b. The effects of body condition at calving, food intake, and performance in early lactation on blood composition of dairy cows given complete diets. *Anim. Prod.* 35:121–125.
- Giesy, J. G., S. Viswanadha, T. W. Hanson, L. R. Falen, M. A. McGuire, C. H. Skarie, and A. Vinci. 1999. Effects of calcium salts of conjugated linoleic acid (CLA) on estimated energy balance in Holstein cows early in lactation. *J. Dairy Sci.* 82(Suppl. 1):74. (Abstr.)
- Godden, S. M., S. C. Stewart, J. F. Fetrow, P. Rapnicki, R. Cady, W. Weiland, H. Spencer, and S. W. Eicker. 2003. The relationship between herd rbST-supplementation and other factors and risk for removal for cows in Minnesota Holstein dairy herds. Pages 55–64 in *Proc. Four-State Nutr. Conf. LaCrosse, WI. Midwest Plan Service publication MWPS-4SD16*.
- Goff, J. P. 2000. Pathophysiology of calcium and phosphorus disorders. *Vet. Clin. N. Am. Food Anim. Pract.* 16:319–337.
- Goff, J. P., and R. L. Horst. 1997. Effect of dietary potassium and sodium, but not calcium, on the incidence of milk fever in dairy cows. *J. Dairy Sci.* 80:176.
- Goff, J. P., K. Kimura, and R. L. Horst. 2002. Effect of mastectomy on milk fever, energy, and vitamins A, E, and β -carotene status at parturition. *J. Dairy Sci.* 85:1427–1436.
- Goings, R. L., N. L. Jacobson, D. C. Beitz, E. T. Littledike, and K. D. Wiggers. 1974. Prevention of parturient paresis by a prepartum, calcium-deficient diet. *J. Dairy Sci.* 57:1184–1188.
- Grum, D. E., J. K. Drackley, R. S. Younker, D. W. LaCount, and J. J. Veenhuizen. 1996. Nutrition during the dry period and hepatic lipid metabolism of periparturient dairy cows. *J. Dairy Sci.* 79:1850–1864.
- Grummer, R. R. 1993. Etiology of lipid-related metabolic disorders in periparturient dairy cows. *J. Dairy Sci.* 76:3882–3896.
- Grummer, R. R. 1995. Impact in changes in organic nutrient metabolism on feeding the transition cow. *J. Anim. Sci.* 73:2820–2833.
- Grummer, R. R., J. C. Winkler, S. J. Bertics, and V. A. Studer. 1994. Effect of propylene glycol dosage during feed restriction on metabolites in blood of prepartum Holstein heifers. *J. Dairy Sci.* 77:3618–3623.
- Hartwell, J. R., M. J. Cecava, and S. S. Donkin. 2000. Impact of dietary rumen undegradable protein and rumen-protected choline on intake, peripartum liver triacylglyceride, plasma metabolites, and milk production in transition dairy cows. *J. Dairy Sci.* 83:2907–2917.
- Hayirli, A., R. R. Grummer, E. V. Nordheim, and P. M. Crump. 2002. Animal and dietary factors affecting feed intake during the pre-fresh transition period in Holsteins. *J. Dairy Sci.* 85:3430–3443.
- Hill, A. W., I. M. Reid, and R. A. Collins. 1985. Influence of liver fat on experimental *Escherichia coli* mastitis in periparturient cows. *Vet. Rec.* 117:549–551.
- Hockett, M. E., F. M. Hopkins, M. J. Lewis, A. M. Saxton, H. H. Dowlen, S. P. Oliver, and F. N. Schrick. 2000. Endocrine profiles of dairy cows following experimentally induced clinical mastitis during early lactation. *Anim. Reprod. Sci.* 58:241–251.
- Holcomb, C. S., H. H. Van Horn, H. H. Head, M. B. Hall, and C. J. Wilcox. 2001. Effects of prepartum dry matter intake and forage percentage on postpartum performance of lactating dairy cows. *J. Dairy Sci.* 84:2051–2058.
- Holtenius, K., S. Agenas, C. Delavaud, and Y. Chilliard. 2003. Effects of feeding intensity during the dry period. 2. Metabolic and hormonal responses. *J. Dairy Sci.* 86:883–891.
- Horst, R. L., J. P. Goff, and T. A. Reinhardt. 1994. Calcium and vitamin D metabolism in the dairy cow. *J. Dairy Sci.* 77:1936–1951.
- Horst, R. L., J. P. Goff, T. A. Reinhardt, and D. R. Buxton. 1997. Strategies for preventing milk fever in dairy cattle. *J. Dairy Sci.* 80:1269–1280.
- Horst, R. L., N. A. Jorgensen, and H. F. DeLuca. 1978. Plasma 1,25-dihydroxyvitamin D and parathyroid hormone levels in paretic dairy cows. *Am J. Physiol.* 235:E634–E637.
- Huszenicza, G., S. Janosi, M. Kulcsar, P. Korodi, S. J. Dieleman, J. Bartyik, P. Rudas, and P. Ribiczei-Szabo. 1998. Gram-negative mastitis in early lactation may interfere with ovarian and certain endocrine functions and metabolism in dairy cows. *Reprod. Domest. Anim.* 33:147–153.
- Joyce, P. W., W. K. Sanchez, and J. P. Goff. 1997. Effect of anionic salts in prepartum diets based on alfalfa. *J. Dairy Sci.* 80:2866–2875.
- Keady, T. W. J., C. S. Mayne, D. A. Fitzpatrick, and M. A. McCoy. 2001. Effect of concentrate feed level in late gestation on subsequent milk yield, milk composition, and fertility of dairy cows. *J. Dairy Sci.* 84:1468–1479.
- Kehrli, M. E., Jr., and J. P. Goff. 1989. Periparturient hypocalcemia in cows: effects on peripheral blood neutrophil and lymphocyte function. *J. Dairy Sci.* 72:1188–1196.
- Kichura, T. S., R. L. Horst, D. C. Beitz, and E. T. Littledike. 1982. Relationships between prepartal dietary calcium and phosphorus, vitamin D metabolism, and parturient paresis in dairy cows. *J. Nutr.* 112:480–487.
- Kimura, K., J. P. Goff, and M. E. Kehrli, Jr. 1999. Effects of the presence of the mammary gland on expression of neutrophil adhesion molecules and myeloperoxidase activity in periparturient dairy cows. *J. Dairy Sci.* 82:2385–2392.
- Kimura, K., J. P. Goff, M. E. Kehrli, Jr., and T. A. Reinhardt. 2002. Decreased neutrophil function as a cause of retained placenta in dairy cattle. *J. Dairy Sci.* 85:544–550.
- Kronfeld, D. S. 1982. Major metabolic determinants of milk volume, mammary efficiency, and spontaneous ketosis in dairy cows. *J. Dairy Sci.* 65:2204–2212.
- Lang, C. A., and R. A. Davis. 1990. Fish oil fatty acids impair VLDL assembly and/or secretion by cultured rat hepatocytes. *J. Lipid Res.* 31:2079–2086.
- Lenkaitis, V. E., L. L. Contreras, C. M. Ryan, and T. R. Overton. 2003. Effects of short-term drenching of transition cows with propylene glycol on early lactation performance and health. *J. Dairy Sci.* 86(Suppl. 1):225. (Abstr.)
- Mallard, B. A., J. C. Dekkers, M. J. Ireland, K. E. Leslie, S. Sharif, C. Lacey Vankampen, L. Wagter, and B. N. Wilkie. 1998. Alteration in immune responsiveness during the periparturient period and its ramification on dairy cow and calf health. *J. Dairy Sci.* 81:585–595.
- Mandevbu, P., C. S. Ballard, C. J. Sniffen, D. S. Tsang, F. Valdez, S. Miyoshi, and L. Schlatter. 2003. Effect of feeding an energy supplement prepartum and postpartum on milk yield and composition, and incidence of ketosis in dairy cows. *Anim. Feed Sci. Tech.* 105:81–93.
- Markantonatos, X., G. A. Varga, T. W. Cassidy, R. K. McGuffey, R. Tucker, and L. F. Richardson. 2002. Volatile fatty acid production rates of Holstein dairy cows provided monensin during the transition period. *J. Dairy Sci.* 85(Suppl. 1):105. (Abstr.)
- Mashek, D. G., and D. K. Beede. 2000. Peripartum responses of dairy cows to partial substitution of corn silage with corn grain in diets fed during the late dry period. *J. Dairy Sci.* 83:2310–2318.
- Mashek, D. G., and D. K. Beede. 2001. Peripartum responses of dairy cows fed energy-dense diets for 3 or 6 weeks prepartum. *J. Dairy Sci.* 84:115–125.

- Mashek, D. G., S. J. Bertics, and R. R. Grummer. 2002. Metabolic fate of long-chain unsaturated fatty acids and their effects on palmitic acid metabolism and gluconeogenesis in bovine hepatocytes. *J. Dairy Sci.* 85:2283–2289.
- Mashek, D. G., and R. R. Grummer. 2003. Feeding pre-fresh transition cows: should we maximize feed intake or minimize feed intake depression? *J. Dairy Sci.* 86(Suppl. 1):11. (Abstr.)
- Matthews, K. R., J. J. Rejman, J. D. Turner, and S. P. Oliver. 1994. Proliferation of a bovine mammary epithelial cell line in the presence of bacterial virulence factors. *J. Dairy Sci.* 77:2959–2964.
- Mayer, G. P., J. W. Blum, and L. J. Deftos. 1975. Diminished prepartal plasma calcitonin concentration in cows developing parturient hypocalcemia. *Endocrinology* 96:1478–1485.
- Mayer, G. P., C. F. Ramberg, D. S. Kronfeld, R. M. Buckle, L. M. Sherwood, G. D. Aurbach, and J. T. Potts, Jr. 1969. Plasma parathyroid hormone concentration in hypocalcemic parturient cows. *Am. J. Vet. Res.* 30:1587–1597.
- McCarthy, R. D., G. A. Porter, and L. C. Griel, Jr. 1968. Bovine ketosis and depressed fat test in milk: A problem of methionine metabolism and serum lipoprotein aberration. *J. Dairy Sci.* 51:459–462.
- Minor, D. J., S. L. Trower, B. D. Strang, R. D. Shaver, and R. R. Grummer. 1998. Effects of nonfiber carbohydrate and niacin on periparturient metabolic status and lactation of dairy cows. *J. Dairy Sci.* 81:189–200.
- Moore, S. J., M. J. VandeHaar, B. K. Sharma, T. E. Pilbeam, D. K. Beede, H. F. Bucholtz, J. S. Liesman, R. L. Horst, and J. P. Goff. 2000. Effects of altering dietary cation-anion difference on calcium and energy metabolism in peripartum cows. *J. Dairy Sci.* 83:2095–2104.
- National Research Council. 2001. *Nutrient Requirements of Dairy Cattle*. 7th rev. ed. National Academy Press, Washington, DC.
- Nonnecke, B. J., S. T. Franklin, and J. W. Young. 1992. Effects of ketones, acetate, and glucose on *in vitro* immunoglobulin secretion by bovine lymphocytes. *J. Dairy Sci.* 75:982–990.
- Oliver, S. P., and L. M. Sordillo. 1988. Udder health in the periparturient period. *J. Dairy Sci.* 71:2584–2606.
- Ordway, R. S., V. A. Ishler, and G. A. Varga. 2002. Effects of sucrose supplementation on dry matter intake, milk yield, and blood metabolites of periparturient Holstein dairy cows. *J. Dairy Sci.* 85:879–888.
- Overton, T. R., J. K. Drackley, G. N. Douglas, L. S. Emmert, and J. H. Clark. 1998. Hepatic gluconeogenesis and whole-body protein metabolism of periparturient dairy cows as affected by source of energy and intake of the prepartum diet. *J. Dairy Sci.* 81(Suppl. 1):295. (Abstr.)
- Overton, T. R., J. K. Drackley, C. J. Ottemann-Abbamonte, A. D. Beaulieu, L. S. Emmert, and J. H. Clark. 1999. Substrate utilization for hepatic gluconeogenesis is altered by increased glucose demand in ruminants. *J. Anim. Sci.* 77:1940–1951.
- Overton, T. R., D. W. LaCount, T. M. Cicela, and J. H. Clark. 1996. Evaluation of a ruminally protected methionine product for lactating dairy cows. *J. Dairy Sci.* 79:631–638.
- Paape, M., J. Mehrzad, X. Zhao, J. Detilleux, and C. Burvenich. 2002. Defense of the bovine mammary gland by polymorphonuclear neutrophil leukocytes. *J. Mammary Gland Biol. Neoplasia* 7:109–121.
- Perkins, K. H., M. J. VandeHaar, R. J. Tempelman, and J. L. Burton. 2001. Negative energy balance does not decrease expression of leukocyte adhesion or antigen-presenting molecules in cattle. *J. Dairy Sci.* 84:421–428.
- Perkins, K. H., M. J. VandeHaar, J. L. Burton, J. S. Liesman, R. J. Erskine, and T. H. Elsasser. 2002. Clinical responses to intramammary endotoxin infusion in dairy cows subjected to feed restriction. *J. Dairy Sci.* 85:1724–1731.
- Pickett, M. M., T. W. Cassidy, P. R. Tozer, and G. A. Varga. 2003a. Effect of prepartum dietary carbohydrate source and monensin on dry matter intake, milk production and blood metabolites of transition dairy cows. *J. Dairy Sci.* 86(Suppl. 1):10. (Abstr.)
- Pickett, M. M., M. S. Piepenbrink, and T. R. Overton. 2003b. Effects of propylene glycol or fat drench on plasma metabolites, liver composition, and production of dairy cows during the periparturient period. *J. Dairy Sci.* 86:2113–2121.
- Piepenbrink, M. S., A. L. Bork, M. R. Waldron, W. R. Butler, T. R. Overton, M. Vazquez-Anon, and M. D. Holt. 2004. Feeding 2-hydroxy-4-(methylthio)-butanoic acid to transition dairy cows improves milk production but not hepatic metabolism. *J. Dairy Sci.* 87:1071–1084.
- Piepenbrink, M. S., and T. R. Overton. 2003a. Hepatic palmitate metabolism of periparturient dairy cows as affected by nutrients supplied *in vitro*. *J. Dairy Sci.* 86(Suppl. 1):220. (Abstr.)
- Piepenbrink, M. S., and T. R. Overton. 2003b. Interrelationships of hepatic palmitate and propionate metabolism, liver composition, blood metabolites, and cow performance. *J. Dairy Sci.* 86(Suppl. 1):148. (Abstr.)
- Piepenbrink, M. S., and T. R. Overton. 2003c. Liver metabolism and production of cows fed increasing amounts of rumen-protected choline during the transition period. *J. Dairy Sci.* 86:1722–1733.
- Pinotti, L., A. Baldi, I. Politis, R. Rebucci, L. Sangalli, and V. Dell'Orto. 2003. Rumen-protected choline administration to transition cows: Effects on milk production and vitamin E status. *J. Vet. Med.* 50:18–21.
- Preisler, M. T., P. S. Weber, R. J. Tempelman, R. J. Erskine, H. Hunt, and J. L. Burton. 2000. Glucocorticoid receptor down-regulation in neutrophils of periparturient cows. *Am. J. Vet. Res.* 61:14–19.
- Pullen, D. L., D. L. Palmquist, and R. S. Emery. 1989. Effect of days of lactation and methionine hydroxy analog on incorporation of plasma fatty acids into plasma triglycerides. *J. Dairy Sci.* 72:49–58.
- Rabelo, E., R. L. Rezende, S. J. Bertics, and R. R. Grummer. 2003. Effects of transition diets varying in dietary energy density on lactation performance and ruminal parameters of dairy cows. *J. Dairy Sci.* 86:916–925.
- Reid, I. M., and C. J. Roberts. 1983. Subclinical fatty liver in dairy cows—current research and future prospects. *Irish Vet. J.* 37:104–110.
- Reinhardt, T. A., R. L. Horst, and J. P. Goff. 1988. Calcium, phosphorus, and magnesium homeostasis in ruminants. *Vet. Clin. North Am. Food Anim. Pract.* 4:331–350.
- Reynolds, C. K., P. C. Aikman, B. Lupoli, D. J. Humphries, and D. E. Beever. 2003. Splanchnic metabolism of dairy cows during the transition from late gestation through early lactation. *J. Dairy Sci.* 86:1201–1217.
- Roche, J. R., J. Morton, and E. S. Kolver. 2002. Sulfur and chlorine play a non-acid base role in periparturient calcium homeostasis. *J. Dairy Sci.* 85:3444–3453.
- Rode, L. M., C. D. Knight, K. A. Andrews, and K. M. Koenig. 1998. Effects of pre- and post-partum Alimet supplementation on milk production of dairy cows. *J. Dairy Sci.* 81(Suppl. 1):294. (Abstr.)
- Roth, J. A., and M. L. Kaerberle. 1982. Effect of glucocorticoids on the bovine immune system. *JAVMA* 180:894–901.
- Scheer, W. A., M. C. Lucy, M. S. Kerley, and J. N. Spain. 2002. Effects of feeding soybeans and rumen-protected choline during late gestation and early lactation on performance of dairy cows. *J. Dairy Sci.* 85(Suppl. 1):276. (Abstr.)
- Schrick, F. N., M. E. Hockett, A. M. Saxton, M. J. Lewis, H. H. Dowlen, and S. P. Oliver. 2001. Influence of subclinical mastitis during early lactation on reproductive parameters. *J. Dairy Sci.* 84:1407–1412.
- Schukken, Y. H., H. N. Erb, and J. M. Scarlett. 1989. A hospital-based study of the relationship between retained placenta and mastitis in dairy cows. *Cornell Vet.* 79:319–326.
- Seal, C. J., and C. K. Reynolds. 1993. Nutritional implications of gastrointestinal and liver metabolism in ruminants. *Nutr. Res. Rev.* 6:185–208.
- Selberg, K. T., C. R. Staples, and L. Badinga. 2002. Production and metabolic responses to dietary conjugated linoleic acid (CLA) and trans-octadecenoic acid isomers in periparturient dairy cows. *J. Dairy Sci.* 85(Suppl. 1):19. (Abstr.)
- Skaar, T. C., R. R. Grummer, M. R. Dentine, and R. H. Stauffacher. 1989. Seasonal effects of prepartum and postpartum fat and niacin feeding on lactation performance and lipid metabolism. *J. Dairy Sci.* 72:2028–2038.
- Smith, K. L., M. R. Waldron, T. R. Overton, J. K. Drackley, and M. T. Socha. 2002. Performance of dairy cows as affected by prepartum carbohydrate source and supplementation with chromium

- throughout the periparturient period. *J. Dairy Sci.* 85(Suppl. 1):23. (Abstr.)
- Smith, K. L., M. R. Waldron, T. R. Overton, J. K. Drackley, and M. T. Socha. 2003. Metabolism of dairy cows as affected by prepartum dietary carbohydrate source and supplementation with chromium throughout the periparturient period. *J. Dairy Sci.* 86(Suppl. 1):106. (Abstr.)
- Socha, M. T. 1994. Determining the methionine requirements of lactating cows. Ph.D. Diss. Univ. of New Hampshire, Durham.
- Socha, M. T., C. G. Schwab, D. E. Putnam, N. L. Whitehouse, N. A. Kierstead, and B. D. Garthwaite. 1994. Production responses of early lactation cows fed rumen-stable methionine or rumen-stable lysine plus methionine at two levels of dietary crude protein. *J. Dairy Sci.* 77(Suppl. 1):93. (Abstr.)
- Sordillo, L. M., G. M. Pighetti, and M. R. Davis. 1995. Enhanced production of bovine tumor necrosis factor- α during the periparturient period. *Vet. Immunol. Immunopathol.* 49:263–270.
- Stokes, S. R., and J. P. Goff. 2001. Evaluation of calcium propionate and propylene glycol administered into the esophagus at calving. *Prof. Anim. Sci.* 17:115–122.
- Strang, B. D., S. J. Bertics, R. R. Grummer, and L. E. Armentano. 1998. Effect of long-chain fatty acids on triglyceride accumulation, gluconeogenesis, and ureagenesis in bovine hepatocytes. *J. Dairy Sci.* 81:728–739.
- Studer, V. A., R. R. Grummer, S. J. Bertics, and C. K. Reynolds. 1993. Effect of prepartum propylene glycol administration on periparturient fatty liver in dairy cows. *J. Dairy Sci.* 76:2931–2939.
- Suriyasathaporn, W., C. Heuer, E. N. Noordhuizen-Stassen, and Y. H. Schukken. 2000. Hyperketonemia and the impairment of udder defense: A review. *Vet. Res.* 31:397–412.
- Thiede, M. A. 1994. Parathyroid hormone-related protein: a regulated calcium-mobilizing product of the mammary gland. *J. Dairy Sci.* 77:1952–1963.
- Thilising-Hansen, T., and R. J. Jorgensen. 2001. Prevention of parturient paresis and subclinical hypocalcemia in dairy cows by zeolite A administration in the dry period. *J. Dairy Sci.* 84:691–693.
- Thilising-Hansen, T., R. J. Jorgensen, J. M. Enemark, and T. Larsen. 2002. The effect of zeolite A supplementation in the dry period on periparturient calcium, phosphorus, and magnesium homeostasis. *J. Dairy Sci.* 85:1855–1862.
- Treacher, R. J., I. M. Reid, and C. J. Roberts. 1986. Effect of body condition at calving on the health and performance of dairy cows. *Anim. Prod.* 43:1–6.
- Vallimont, J. E., G. A. Varga, A. Arieli, T. W. Cassidy, and K. A. Cummins. 2001. Effects of prepartum somatotropin and monensin on metabolism and production of periparturient Holstein dairy cows. *J. Dairy Sci.* 84:2607–2621.
- Visser, B. M., J. G. Linn, S. M. Godden, and M. L. Raeth-Knight. 2002. Effects of prefresh diet and post parturition drenching on early lactation performance of multiparous Holstein cows. *J. Dairy Sci.* 85(Suppl. 1):186. (Abstr.)
- Visser, B. M., J. G. Linn, S. M. Godden, and M. L. Raeth-Knight. 2003. Effects of prepartum diet and postpartum drenching on production performance and blood parameters of early lactation primiparous and multiparous Holstein cows. *J. Dairy Sci.* 86(Suppl. 1):104. (Abstr.)
- Waldron, M. R., T. Nishida, B. J. Nonnecke, and T. R. Overton. 2003a. Effect of lipopolysaccharide on indices of peripheral and hepatic metabolism in lactating cows. *J. Dairy Sci.* 86:3447–3459.
- Waldron, M. R., B. J. Nonnecke, T. Nishida, R. L. Horst, and T. R. Overton. 2003b. Effect of lipopolysaccharide infusion on serum macromineral and vitamin D concentrations in dairy cows. *J. Dairy Sci.* 86:3440–3446.
- Waterman, R., and L. H. Schultz. 1972. Methionine hydroxyl analog treatment of bovine ketosis: Effects on circulating metabolites and interrelationships. *J. Dairy Sci.* 55:1513–1516.
- Weber, P. S., S. A. Madsen, G. W. Smith, J. J. Ireland, and J. L. Burton. 2001. Pre-translational regulation of neutrophil L-selectin in glucocorticoid-challenged cattle. *Vet. Immunol. Immunopathol.* 83:213–240.
- Wiggers, K. D., D. K. Nelson, and N. L. Jacobson. 1975. Prevention of parturient paresis by a low-calcium diet prepartum: a field study. *J. Dairy Sci.* 58:430–431.
- Wu, X., A. Shang, H. Jiang, and H. N. Ginsberg. 1997. Demonstration of biphasic effects of docosahexaenoic acid on apolipoprotein B secretion in HepG2 cells. *Arterioscler. Thromb. Vasc. Biol.* 17:3347–3355.
- Yao, Z., and D. E. Vance. 1988. The active synthesis of phosphatidylcholine is required for very low density lipoprotein secretion from rat hepatocytes. *J. Biol. Chem.* 263:2998–3004.
- Yao, Z. M., and D. E. Vance. 1990. Reduction in VLDL, but not HDL, in plasma of rats deficient in choline. *Biochem. Cell Biol.* 68:552–558.
- Zhu, L. H., L. E. Armentano, D. R. Bremner, R. R. Grummer, and S. J. Bertics. 2000. Plasma concentration of urea, ammonia, glutamine around calving, and the relation of hepatic triglyceride, to plasma ammonia removal and blood acid-base balance. *J. Dairy Sci.* 83:734–740.