ABSTRACT

Most of the metabolic diseases of dairy cows—milk fever, ketosis, retained placenta, and displacement of the abomasum—occur within the first 2 wk of lactation. The etiology of many of those metabolic diseases that are not clinically apparent during the first 2 wk of lactation, such as laminitis, can be traced back to insults that occurred during early lactation. In addition to metabolic disease, the overwhelming majority of infectious disease, in particular mastitis, becomes clinically apparent during the first 2 wk of lactation. Three basic physiological functions must be maintained during the periparturient period if disease is to be avoided: adaptation of the rumen to lactation diets that are high in energy density, maintenance of normocalcemia, and maintenance of a strong immune system. The incidence of both metabolic and infectious diseases is greatly increased whenever one or more of these physiological functions are impaired. This paper discusses the etiological role of each of these factors in the development of common diseases encountered during the periparturient period.

(Ke y words: milk fever, ketosis, displaced abomasum, immunosuppression)

INTRODUCTION

Efficient milk production continues to require the dairy cow to experience gestation and parturition each year. The transition from the pregnant, nonlactating state to the nonpregnant, lactating state is too often a disastrous experience for the cow. Most of the metabolic diseases of dairy cows—milk fever, ketosis, retained placenta, and displacement of the abomasum—occur within the first 2 wk of lactation.

The etiology of many of those metabolic diseases that are not clinically apparent during the first 2 wk of lactation, such as laminitis, can be traced back to insults that occurred during early lactation. In addition to metabolic disease, the overwhelming majority of infectious diseases—especially mastitis and also diseases such as Johne’s disease and salmonellosis—become clinically apparent during the first 2 wk of lactation. The well-being and profitability of the cow could be greatly enhanced by understanding those factors that account for the high disease incidence in periparturient cows.

The bovine fetal-placental mass and its demand for energy, protein, and minerals increase dramatically as gestational age increases. By the end of gestation, daily development of the fetus requires about 0.82 Mcal of energy, 117 g of protein, 10.3 g of calcium, 5.4 g of phosphorus, and 0.2 g of magnesium (1,33). However, the metabolic demands imposed on the cow by the formation of colostrum far exceed the demands of the fetus. The production of just 10 kg of colostrum on the day of calving requires that 11 Mcal of energy, 140 g of protein, 23 g of calcium, 9 g of phosphorus, and 1 g of magnesium be supplied from the diet or be brought to the mammary gland from body stores. The high demand for nutrients imposed on the body by the increased activity of the mammary gland cannot always be met, resulting in the development of such metabolic diseases as milk fever and the ketosis-fatty liver complex.

Parturition and the onset of lactation impose tremendous physiological challenges to the homeostatic mechanisms of the cow. This review attempts to describe what is known and, more importantly, what is unknown about the physiological changes occurring in the periparturient dairy cow and the relationship of those changes to the development of disease.

Mammary Gland Changes

The average cow is dried off at 7 mo of gestation. Several changes occur at dry-off that influence the response of the periparturient cow. During involution of the mammary gland, the secretory mammary
Physiology of the Rumen

Upon dry-off, cows are fed a high forage ration that is less energy dense and higher in neutral detergent fiber than the lactation ration. This change affects rumen function in two ways. The bacterial population shifts away from the lactate producers (bacteria possessing α-amylase, such as Streptococcus bovis and lactobacilli) as a result of the decrease in readily fermentable starches in the diet (68). Therefore, the population of those bacteria (primarily Megasphaera elsdenii and Selenomonas ruminantium) that are capable of converting lactate to acetate, propionate, or long-chain fatty acids, which can be used by the cow, declines. The higher forage diet increases the population of cellulolytic bacteria, but also increases populations of methane-producing bacteria, which are generally regarded as an inefficient use of dietary energy (38). Another effect of the lower energy diet of the early dry period is a reduction in length of papillae and in the absorptive capacity of the VFA in rumen mucosa. As much as 50% of the absorptive area may be lost during the first 7 wk of the dry period (11). The fresh cow, if abruptly switched to a high energy lactation diet, is at risk of developing rumen acidosis because the lactate producers respond rapidly to the milk flow ceases to flush bacterial invaders from the streak canal and before the gland is fully involuted (53). However, these IMI often do not result in clinical mastitis. Although many of these IMI are eliminated by the immune cells during the dry period, some are simply held in check until lactation begins. Clinical mastitis, especially coliform mastitis, is most likely to occur during the 1st mo of lactation (14, 52) and is the result of infection established during the dry period or during early lactation. Two important questions are raised. Why do IMI that are subclinical early in the dry period become clinical cases in early lactation, and why is the udder so susceptible to IMI during the periparturient period? At least part of the answer is that the activity of the immune system of the cow is depressed during the week before and the week after calving (Figure 1). Neutrophils obtained from cows during the 1st wk of lactation exhibit an impaired ability to ingest and kill bacteria (42, 46). The ability of lymphocytes to respond to mitogens and to produce antibody is also impaired around parturition (36, 39, 40, 41, 63). The serum concentrations of other components of the immune system of cows such as Ig, complement, and conglutinin are also decreased at parturition (40, 54). Thus, IMI that have been held in check during the dry period can overcome the weakened immune system to become clinical mastitis cases at parturition. Coupled with the recrudescence of existing IMI, the gland is also at increased risk for new IMI around parturition. As the mammary secretions change to colostrum, lactoferrin concentration declines, which increases the amount of iron that is available for bacterial growth (60). The keratin plug that seals the teat breaks down about 7 to 10 d before parturition (52), permitting bacteria easier access to the gland. At parturition, most dairy cows become hypocalcemic (some to the point of developing milk fever), which is suspected to impair the smooth muscle contraction that is vital to closure of the teat sphincter after milking. Why the immune system is depressed at parturition is currently unknown, although in another section of this review the possible effects of various endocrine and nutritional factors are discussed.

![Figure 1. Neutrophil function (iodination; △) and lymphocyte function (blastogenesis; ●) are impaired during the weeks immediately before and after parturition. Values are expressed as percentages of control steers. Adapted from data of Kehrli et al. (41, 42).](image-url)
higher starch diets and produce high amounts of lactate. The bacterial population that converts lactate responds only slowly to a change in diet, requiring 3 to 4 wk to reach levels that effectively prevent lactate from accumulating in the rumen. The acidity of lactate is 10 times stronger (pK_a = 3.86) than that of propionate (pK_a = 4.87), acetate (pK_a = 4.76), or butyrate (pK_a = 4.82), so its presence has a slightly greater effect on rumen pH than VFA have. Also, lactate and VFA are absorbed by rumen epithelium when in the free acid state only (as opposed to the dissociated state). As the pH of the rumen decreases, more VFA exists in the free acid state. Because the pK_a of lactate is lower than the pK_a of VFA, lactate is absorbed more slowly from the rumen than acetate, propionate, or butyrate. Perhaps more importantly, the poorly developed rumen epithelia of the unadapted cow are not able to absorb the VFA quickly enough to prevent an accumulation of organic acids within the rumen, causing rumen pH to fall to the point at which the protozoa and many of the bacteria within the rumen are killed or are inactive. The lactic acid and the endotoxins and histamine released as the rumen flora die are absorbed systemically and affect the microvasculature of the growing hoof wall, which can then result in clinical laminitis (48). Metabolic acidosis follows rumen acidosis if the amount of organic acid absorbed into the blood exceeds the ability of the liver and other tissues to metabolize the anions.

Normally, only a small amount of lactate is produced within the rumen, and all of this lactate is in the L-lactate form. An early hypothesis on the etiology of the “grain overload” syndrome attached a great deal of importance to the observation that, under conditions of grain engorgement, D-lactate is not absorbed from the rumen as efficiently as L-lactate and also that D-lactate was metabolized slowly by body tissues once it was absorbed. More recent research suggests that D-lactate is absorbed from the rumen (34) and metabolized by tissues (28) at the same rate as L-lactate.

Prevention of lactate accumulation within the rumen can be reduced by adapting the rumen flora to a high starch diet to induce high populations of those bacteria that are capable of converting lactate to acetate, propionate, or long-chain fatty acids. Fully adapting the rumen flora to a high starch diet requires about 3 to 4 wk (35). Increasing rumen papillae length and width increases rumen absorption of lactate and other VFA, which also helps prevent the decline in rumen pH (but, arguably, may exacerbate systemic metabolic acidosis). Full development of rumen papillae requires about 5 wk of concentrate feeding; the greatest increase in papillae length and rumen absorption capability occurs during the final 2 wk of adaptation (11). In the US, concentrate feeding usually begins 2 to 3 wk before cows calve, presumably to adapt the cow to the high grain diet normally fed during lactation. Grain feeding should probably be initiated 5 wk before calving to enable better development of ruminal papillae.

Abomasal Physiology

In the nonpregnant cow, the abomasum occupies the ventral portion of the abdomen, very nearly on the midline, with the pylorus extending to the right side of the cow caudal to the omasum. As pregnancy progresses, the growing uterus occupies an increasing amount of the abdominal cavity. The uterus begins to slide under the caudal aspects of the rumen, reducing the volume of the rumen by one-third at the end of gestation. This change also forces the abomasum forward and slightly to the left side of the cow, although the pylorus continues to extend across the abdomen to the right side of the cow (26). After calving, the uterus retracts back toward the pelvic inlet, which, under normal conditions, allows the abomasum to return to its original position. During left displacement of the abomasum, the pyloric end of the abomasum slides completely under the rumen to the left side of the cow. Three factors are thought to be responsible for allowing the abomasum to move to the left side of the cow. First, the rumen must fail to take up the void left by the retracting uterus. If the rumen moved into its normal position on the left ventral floor of the abdomen, the abomasum would not be able to slide under it. Second, the omentum attached to the abomasum must have been stretched to permit movement of the abomasum to the left side. These two factors constitute an opportunity for displacement. The third factor is abomasal atony. Normally, gases produced in the abomasum (from fermentation of feedstuffs or CO_2 released when bicarbonate from the rumen meets the HCl of the abomasum) are expelled back into the rumen as a result of abomasal contractions. These contractions are thought to be impaired in cows developing left displacement of the abomasum. The cause of abomasal atony is less clear.

A decline in plasma calcium concentration around parturition linearly decreases abomasal contractility, which is suspected to lead to atony and distension of the abomasum. At a plasma calcium concentration of
5 mg/100 ml, abomasal motility is reduced by 70%, and strength of contractions is reduced by 50% (10); at 7.5 mg/100 ml, the motility and strength of abomasal contractions were reduced by 30 and 25%, respectively. Clinical signs of milk fever (down cows) often are not seen until calcium is about 4 mg/100 ml. In a recent study (17) of plasma calcium concentrations of periparturient Holstein cows, 10 to 50% of cows remained subclinically hypocalcemic (plasma calcium <7.5 mg/100 ml) up to 10 d after calving, depending on management efforts to combat milk fever.

Volatile fatty acids within the abomasum also reduce abomasial contractility (3). A high grain, reduced forage diet can promote the appearance of VFA in the abomasum by reducing the depth of the rumen mat or raft (made up primarily of the long fibers of forages). The rumen mat captures grain particles so that they are fermented at the top of the rumen liqueur. The VFA produced at the top of the rumen liqueur are generally absorbed by the rumen with little VFA entering the abomasum. In cows that have an inadequate rumen mat, grain particles fall to the ventral portion of the rumen and reticulum where they are fermented or pass to the abomasum (where they can then be fermented to some extent). The VFA produced in the ventral rumen can pass through the ruminoreticular orifice to enter the abomasum before the rumen can absorb them. A thick rumen mat is generally present during the dry period when cows are fed a high forage diet, but the depth of the rumen mat is rapidly reduced in early lactation, especially if DMI declines markedly. Because the rumen mat also stimulates regurgitation of the cud and mastication, release of saliva, which promotes rumen buffering, decreases when cows are placed on a higher grain ration. Also, early in lactation, the underdeveloped ruminal papillae allow more of the VFA that are produced in the ventral rumen to escape the rumen than would the highly absorptive ruminal mucosa that are typical of later lactation.

**Energy Balance and the Ketosis-Fatty Liver Complex**

During early lactation, the amount of energy that is required for maintenance of body tissues and milk production exceeds the amount of energy the cow can obtain from dietary sources. As a result, the cow must utilize body fat as a source of energy. However, there is a limit to the amount of fatty acid that can be oxidized to completion by the tricarboxylic acid cycle of the liver or exported from the liver as very low density lipoprotein. When this limit is reached, triglycerides accumulate within the hepatocytes, impairing their function, and the acetyl-coenzyme A that is not incorporated into the tricarboxylic acid cycle is converted to acetoacetate and β-hydroxybutyrate. The appearance of these ketone bodies in the blood, milk, and urine is diagnostic of ketosis and usually becomes clinically evident from 10 d to 3 wk after calving. Gluconeogenesis becomes impaired, resulting in hypoglycemia. The cow becomes further depressed, reducing feed intake additionally and reducing milk production. The liver of an overconditioned cow is more limited in ability to oxidize fatty acids than the liver of a thinner cow. Of special interest is the rise in estrogens at parturition that can have deleterious effects on energy balance in the cow. Estrogen can enhance triglyceride deposition within the liver when nonesterified fatty acids are elevated in plasma (23). Numerous salient reviews (22, 44, 50, 69) offer hypotheses to explain why the liver has a limited capacity for the oxidation of fatty acids, including a lack of oxaloacetate to maintain a functioning TCA cycle, the lack of carnitine necessary for mitochondrial transport and oxidation of acetyl-coenzyme A, the lack of niacin, and a host of endocrine factors. However, identification of the biochemical defect that limits efficient oxidation of fatty acids remains elusive. This paper reviews the effects that some of the changes occurring at parturition can have on early lactation energy balance.

Recent research at Iowa State University (13) and the University of Wisconsin (2) demonstrates the importance of feed intake at calving on the etiology of the fatty liver-ketosis syndrome. In the average cow, DMI decreases precipitously by 30% on d 1 or 2 before calving and does not recover until 1 to 2 d after calving. Interestingly, liver biopsies taken several weeks before calving, at calving, and 4 wk into lactation showed that liver triglycerides were increased 3-fold by the day of calving. By 4 wk into lactation, the liver triglycerides were 4-fold higher than before calving. Total liver lipids were increased 2-fold at calving and were still 2-fold higher at 4 wk into lactation. Triglyceride and lipid accumulation in the liver is a much earlier phenomenon than previously assumed. Conversely, if DMI is not allowed to drop around the time of calving by forcing feed into the rumen through a rumen fistula, liver lipids and triglycerides increase only a small amount. Similar results were achieved by daily drenching of cows with propylene glycol (1 L/d) during the periparturient period (58).

Thus, energy intake must not be compromised during the day before calving. Any factor, such as milk fever, that exacerbates reduction in feed intake at
calving increases the energy deficit of the cow and the risk of fatty liver and ketosis (Figure 2). One factor limiting the amount of energy the cow can derive from the diet is the ability of the rumen during early lactation to produce and absorb VFAs, in particular, propionate. In the fully adapted rumen, little methane is produced, and a ration with higher energy density can be fed without causing rumen acidosis. Unfortunately, rumen acidosis is common and reduces feed intake in early lactation (47).

Induction of Parturition

Progesterone is the dominant hormone of pregnancy (Figure 3). Plasma progesterone concentrations increase steadily until approximately d 250 of gestation, when they peak at around 7 to 8 ng/ml. From d 240 until the day prior to calving, plasma progesterone concentrations decrease to about 3 to 4 ng/ml. On the day before parturition, plasma progesterone concentrations fall precipitously to nearly undetectable levels (27). Total plasma concentrations of estrogen are relatively low during early pregnancy (20 pg/ml, which is similar to the luteal phase of the estrous cycle). By midgestation, plasma estrogen has increased to around 300 pg/ml, which is about 10-fold higher than estrogen concentrations during the follicular phase of the estrous cycle. Estrogen concentrations remain steady until about d 240 of gestation, when plasma estrogens (primarily estrone) begin a slow increase. By 7 d before calving, plasma estrogen concentrations have risen to around 2000 pg/ml. Plasma estrogens, especially estrone, increase rapidly just before calving and peak at between 4000 and 6000 pg/ml (6).

The alteration in the relative concentrations of progesterone and estrogen that begins around 30 d before parturition is initiated by the fetus. The secretion of fetal cortisol stimulates the placenta to produce estrogen, perhaps utilizing progesterone as a precursor (56). Within 24 to 36 h of parturition, PGF$_{2\alpha}$ concentrations begin to rise, peaking at parturition; PGF$_{2\alpha}$ causes luteolysis and further inhibits synthesis of progesterone by the uterus, resulting in the precipitous drop in plasma progesterone occurring at calving. Plasma prolactin concentration increases rapidly the day before calving and is partly responsible for the rapid increase in colostrum synthesis just before parturition. Plasma cortisol concentrations (primarily of maternal adrenal origin) of the cow increase from 4 to 8 ng/ml 3 d before calving to 15 to 30 ng/ml at parturition and the day after calving. The response of cortisol secretion is even more pronounced in those cows that develop milk fever (19).

Endogenous opioid peptides circulate at only very low concentrations during early gestation. However, during the last month of gestation, $\beta$-endorphin concentrations in blood are increased and decline to baseline concentrations about 48 h after calving. Met-enkephalin concentrations rise rapidly at calving (12). It is thought that the rise in opioid peptides as parturition approaches reduces the perception of pain experienced by the cow during parturition. The endorphins and enkephalins are potent opioid receptor
agonists. Opiates are often used in the treatment of diarrheal diseases because of their ability to decrease motility of the gastrointestinal tract (37). Does the rise in endogenous opioids at parturition slow gastrointestinal motility and contribute to the depression of feed intake observed at calving or in the development of a displaced abomasum?

Expulsion of the Placenta

The fetal membrane villi should separate from the maternal caruncles within a few hours of calving. Numerous factors are thought to be important in determining whether the placenta is successfully expelled. Gross et al. (21) reported that injection of PGF$_{2\alpha}$ within 1 h of calving dramatically reduced the incidence of retained placenta during calvings induced by dexamethasone, suggesting that PGF$_{2\alpha}$ production is deficient in cows developing retained fetal membranes. However, other researchers (4) have not found prostaglandin treatment to be effective in prevention or treatment of retained fetal membranes, although those researchers did not give the prostaglandin treatment within 1 h of calving.

Binucleate giant cells comprise about 20% of the cells of the trophoblast (65). These cells produce placental lactogen (66). For cows that expel the placenta normally, these binucleate giant cells nearly disappear from the maternal-fetal interface. They remain in high numbers in cotyledons from cows with retained placenta (64). Numerous studies have been conducted to try to demonstrate a hormone deficiency or excess that is responsible for the retained fetal membrane syndrome, but no clear conclusions are evident (6). A great deal of epidemiological evidence exists that links milk fever with an increased incidence of retained fetal membranes (8). Hypocalcemia presumably prevents the uterine contractions that are necessary for expulsion of the placenta. Although uterine contraction may be a factor in expulsion of the placenta in those cases in which the placenta is free of the caruncles, in most cases, uterine contraction is actually stronger and more protracted in cows with retained placenta than in cows that expel the placenta normally (4).

In a series of interesting experiments, Gunnink (24, 25) demonstrated that leukocytes of cows that would expel the placenta normally had a strong chemotactic response to cotyledon material suspended in a Boyden chamber. In striking contrast, cows that failed to expel the placenta normally had peripheral blood leukocytes that exhibited little to no chemotraction to the cotyledon suspension. This inability to attack cotyledon material was evident several days before parturition in those cows that would develop a retained placenta. Gunnink (24, 25) proposed that, at the time of parturition, placental tissue becomes a dead foreign body that the body must recognize and then reject in order to complete separation of the fetal membranes. Perhaps immunosuppression at calving has implications for expulsion of fetal membranes in addition to susceptibility to infectious disease. In partial support of this theory, a loss in neutrophil chemotraction for fetal membrane tissue after parturition, but not before, has also been observed (5) for cows with retained fetal membranes. Cai et al. (5) also reported that neutrophil superoxide production was impaired before calving in those cows that would develop metritis after calving.

Endocrine and Nutritional Influences on Periparturient Immunosuppression

It is beyond the scope of this review to give a detailed survey of the literature that has examined the influence of various hormones and nutritional factors on the immune system. However, certain research findings provoke interesting conjecture. Progesterone has often been shown to inhibit many leukocyte functions (7); this inhibition is widely thought to be necessary to prevent rejection of the “foreign” fetus during gestation (62). Although progesterone is probably important in suppression of the immune system throughout gestation, progesterone is unlikely to be the cause of the severe immunosuppression that is observed at calving, because plasma progesterone concentration decreases as the periparturient immunosuppression occurs (39, 42). Some experiments (61) have found that estrogens stimulate the humoral immune response, but most workers (67) agree that estrogens have a strong suppressive effect on cell-mediated immunity. Glucocorticoids have long been used as powerful immunosuppressive agents. Thus, the immunosuppressive effects of plasma estrogen and cortisol increases that occur during the periparturient period would be likely suspects as causative agents of the immunosuppression observed at calving.

Chronic deficiencies of energy, protein, minerals, or vitamins have repeatedly been associated with increased disease susceptibility as a result of depressed immune function. Parturition and the onset of lactation impose great metabolic stress on the cow, causing relatively acute deficiencies of nutritional factors that are necessary for maintenance of the immune system; these deficiencies can last from 1 d to several weeks.
Partly because of poor development of the digestive tract, it is impossible for the high producing dairy cow to ingest enough feed to meet lactational demands for energy and protein. Therefore, in early lactation, the dairy cow is in negative energy and protein balance, which impairs immune function. Severe energy deficiency in early lactation can also cause ketoads to accumulate in the blood, further impairing lymphocyte function (15). At parturition, plasma concentrations of vitamin A (retinol) and vitamin E ($\alpha$-tocopherol) were found to decrease by 38 and 47%, respectively (20), to levels that would be diagnostic of chronic deficiency. Although a portion of the serum loss of these vitamins may be due to sequestration within colostrum, these vitamins also appear to have been consumed at a higher rate at calving as a result of increased immunologic and metabolic stress. Supplementation with vitamins A and E can improve immune responses of the periparturient cow (9, 29, 30, 55, 59). Supplementation has often been associated with a decrease in the incidence of mastitis in dairy cows (29, 51). It is important to note that the vitamin and mineral requirements of the periparturient cow generally have not been determined; requirements appear to be considerably higher than would be predicted from data obtained from cows outside the periparturient period. It is logical to conclude that any nutritional insults to the immune system would add to immunosuppression caused by hormonal changes associated with parturition.

**Hypocalcemia**

The onset of lactation places such a large demand on mechanisms of calcium homeostasis that most cows develop some degree of hypocalcemia at calving (18, 31). In some cases, plasma calcium concentrations become too low to support nerve and muscle function, resulting in parturient paresis or milk fever. The factors, such as dietary cation-anion difference and blood alkalinity, that determine the degree of hypocalcemia occurring at calving are reviewed in a companion paper. However, hypocalcemia already has some widespread effects that predispose the cow to other periparturient diseases (8).

Cows that develop milk fever have higher plasma cortisol concentrations than cows that do not develop milk fever (19, 32, 43); these higher concentrations may exacerbate the immunosuppression ordinarily present at calving (Figure 4). Hypocalcemia also results in loss of muscle tone in the uterus, and, we suspect, in the teat sphincter that, combined with the immunosuppressive effects of the excess cortisol, might account for the increased incidence of retained placenta and mastitis that occurs for cows with milk fever. Loss of uterine muscle tone is a major cause of uterine prolapse, and this disease process is almost always due to hypocalcemia (49).

Cows that have milk fever also exhibit a greater decline in feed intake after calving than do cows without milk fever (16, 45), exacerbating the negative energy balance commonly observed during early lactation. In addition, hypocalcemia prevents the secretion of insulin (43), which prevents tissue uptake of glucose. Reduced glucose uptake would exacerbate lipid mobilization at calving, thus increasing the risk of ketosis. The decline in feed intake that is associated with milk fever reduces rumen fill (so that rumen sits above the floor of the abdomen), reduces the depth of the rumen mat, allowing more VFA into the abomasum, and reduces abomasal contractility. All of these effects of hypocalcemia predispose the cow to displacement of the abomasum.

**CONCLUSIONS**

Adaptation of the rumen to the lactation diet, elimination of hypocalcemia, and immunomodulation to stimulate the immune system at calving would greatly reduce the incidence of periparturient disease in dairy cows. How this reduction can be achieved is unknown, but some areas seem promising for research. Adaptation of the rumen to the lactation diet may take up to 5 wk, but cows are usually fed a transition ration for just 2 to 3 wk before calving. It is
not possible to produce a probiotic bolus of \textit{M. elsdenii} and \textit{S. ruminantium} to speed the growth of the lactate-utilizing bacterial population? Great strides have been made in the prevention of milk fever in dairy cows by the use of anionic salts to adjust dietary cation-anion difference to increase blood acidity. However, further efforts need to be made to eliminate subclinical hypocalcemia, which accompanies most calvings. Immunomodulation may present the greatest challenge and opportunity. Obviously, some improvements in nutrition can be made to prevent the exacerbation of immunosuppression that seems to be caused by the hormonal changes that are associated with parturition. If the hormones that are responsible for periparturient immunosuppression can be identified, perhaps those hormones can be neutralized after delivery of the calf by administration of estrogen and glucocorticoid antagonists to the cow.

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