



Invited review: The influence of immune activation on transition cow health and performance—A critical evaluation of traditional dogmas

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ABSTRACT

The progression from gestation into lactation represents the transition period, and it is accompanied by marked physiological, metabolic, and inflammatory adjustments. The entire lactation and a cow's opportunity to have an additional lactation are heavily dependent on how successfully she adapts during the periparturient period. Additionally, a disproportionate amount of health care and culling occurs early following parturition. Thus, lactation maladaptation has been a heavily researched area of dairy science for more than 50 yr. It was traditionally thought that excessive adipose tissue mobilization in large part dictated transition period success. Further, the magnitude of hypocalcemia has also been assumed to partly control whether a cow effectively navigates the first few months of lactation. The canon became that adipose tissue released non-esterified fatty acids (NEFA) and the resulting hepatic-derived ketones coupled with hypocalcemia lead to immune suppression, which is responsible for transition disorders (e.g., mastitis, metritis, retained placenta, poor fertility). In other words, the dogma evolved that these metabolites and hypocalcemia were causal to transition cow problems and that large efforts should be enlisted to prevent increased NEFA, hyperketonemia, and subclinical hypocalcemia. However, despite intensive academic and industry focus, the periparturient period remains a large hurdle to animal welfare, farm profitability, and dairy sustainability. Thus, it stands to reason that there are alternative explanations to periparturient failures. Recently, it has become firmly established that immune activation and the ipso facto inflammatory response are a normal component of transition cow biology. The origin of immune activation likely stems from the mammary gland, tissue trauma during parturition, and the gastrointestinal tract. If inflammation becomes pathological, it reduces

feed intake and causes hypocalcemia. Our tenet is that immune system utilization of glucose and its induction of hypophagia are responsible for the extensive increase in NEFA and ketones, and this explains why they (and the severity of hypocalcemia) are correlated with poor health, production, and reproduction outcomes. In this review, we argue that changes in circulating NEFA, ketones, and calcium are simply reflective of either (1) normal homeostatic adjustments that healthy, high-producing cows use to prioritize milk synthesis or (2) the consequence of immune activation and its sequelae. **Key words:** inflammation, hypocalcemia, ketosis, insulin, homeorhesis

THE PERIPARTURIENT PERIOD

Early lactation is a unique physiological state in which nutrient consumption often does not meet maintenance and milk production costs, creating a negative energy balance (NEB; Drackley, 1999). Milk energy output increases more rapidly than the increase in consumed energy. The magnitude of NEB varies, but nadir usually occurs within the first 10 DIM, and cows return to calculated positive energy balance between 30 and 100 DIM (Moallem et al., 2000; Coffey et al., 2002). To support milk synthesis during NEB, significant alterations in carbohydrate, lipid, protein, and mineral metabolism are implemented.

A thorough appreciation of how important glucose is to milk synthesis is required to understand why these changes (energetics in particular) occur. Glucose is the precursor for lactose synthesis, and lactose is the primary osmoregulator driving milk volume (Neville, 1990). For every 1 kg of milk produced, approximately 72 g of glucose is required (Kronfeld, 1982). During established lactation, hepatic glucose output is exquisitely orchestrated to precisely meet peripheral tissue (e.g., mammary, muscle, adipose, central nervous system) glucose requirements (Baumgard et al., 2017). However, inadequate feed intake during the periparturient period means that the contribution of diet-derived gluconeogenic precursors to hepatic glucose output is insufficient to meet the mammary gland's increasing

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requirement, as more than 90% of glucose made by the liver is utilized by the mammary gland in early lactation (Bell, 1995). Consequently, multiple tissues coordinate efforts in an attempt to compensate for the dietary shortage by becoming insulin resistant, a hormonal scenario that allows for tissue catabolism and mobilization of AA and glycerol (gluconeogenic precursors) from skeletal muscle and adipose tissue, respectively (Bell, 1995; Bell and Bauman, 1997).

In addition to providing gluconeogenic building blocks, both adipose tissue and skeletal muscle coordinate metabolism during the transition period to increase the supply of and reliance upon lipid fuel. During NEB, somatotropin (increased during NEB; Bell, 1995) promotes nonesterified fatty acid (**NEFA**) export from adipose tissue by accentuating the lipolytic response to β -adrenergic signals and by blunting insulin-mediated lipogenesis and glucose utilization (Bauman and Vernon, 1993). Further, early-lactation hypoglycemia heightens the stimulation of lipolysis by catecholamines (Clutter et al., 1981). Reduced systemic insulin sensitivity coupled with a decrease in circulating insulin allows for adipose lipolysis and NEFA mobilization (Bauman and Currie, 1980; Rhoads et al., 2004), which represent a substantial energy source for both peripheral tissues (skeletal muscle in particular) and the mammary gland. However, some tissues (i.e., the brain) and cell types are unable to oxidize NEFA and thus require the energy within fatty acids to be converted into ketones.

The exact mechanisms regulating all aspects of hepatic ketogenesis remain unclear, especially in ruminants (Baird, 1982). However, it is likely that 2 biochemical sequences of events partially control ketone production simultaneously. First, fatty acid β -oxidation generates large quantities of NADH and reduced flavin adenine dinucleotide (Berg et al., 2002), a scenario that presumably meets (in part) the hepatocyte's ATP requirements and thus decreases key tricarboxylic acid (**TCA**) enzymes (isocitrate dehydrogenase and ketoglutarate dehydrogenase). This would slow the cycle and create a buildup of acetyl CoA. Second is the salient explanation put forth by Sir Hans Krebs more than 55 yr ago. Ketone synthesis is enhanced when the TCA cycle intermediate oxaloacetate (**OAA**) supply is limited. Increased gluconeogenesis in early lactation causes cataplerosis (removal from the TCA cycle) of OAA to support phosphoenolpyruvate production (an early step in gluconeogenesis). Simultaneously, a large amount of acetyl CoA originates from β -oxidation of adipose-derived NEFA (Krebs, 1966). When OAA is plentiful, it combines with acetyl CoA to make citrate, and the TCA cycle progresses. The unavailability of OAA is now the metabolic crossroad between carbo-

hydrate and lipid metabolism, and accumulated acetyl CoA enters into ketogenesis (Krebs, 1966), an enzymatic pathway inhibited by insulin (Sato et al., 1995).

Skeletal muscle oxidation of fatty acids and ketones reduces their glucose uptake; this is referred to as the Randle effect (Randle, 1998). The aforementioned changes effectively partition glucose toward the mammary gland because glucose's contribution as a fuel source to extramammary tissues is markedly decreased (Bell, 1995), and the mammary gland's glucose consumption is insulin independent (Zhao and Keating, 2007). These metabolic adjustments essentially create a coordinated unidirectional glucose flow from the liver to the mammary gland. Ultimately, the normal homeorhetic adaptations described above empower "metabolic flexibility" (Baumgard et al., 2017) to prioritize milk synthesis at the expense of tissue accretion (Bauman and Currie, 1980).

In addition to energetic metabolism, Ca homeostasis is substantially altered at lactation onset due to a marked increase (>65%; DeGaris and Lean, 2008) in Ca requirements to support colostrum and milk synthesis (Horst et al., 2005). Eucalcemia is typically under tight homeostatic control via the action of the calcitropic hormones parathyroid hormone (**PTH**) and 1,25-dihydroxyvitamin D. The parathyroid gland detects hypocalcemia and secretes PTH, which increases renal Ca reabsorption (i.e., reduces urinary Ca loss), increases osteocytic and osteoclastic bone Ca release, and stimulates renal production of 1,25-dihydroxyvitamin D (also known as calcitriol). Calcitriol acts synergistically with PTH at the kidney and bone and also increases active transport of dietary Ca across the intestinal epithelium (as reviewed by Horst et al., 1997). It has long been hypothesized that the mammary gland's sudden Ca demand is so extensive and acute that it often exceeds these homeostatic mechanisms, resulting in clinical or subclinical hypocalcemia (**SCH**; Horst et al., 2005; Goff, 2008).

In the 1980s, it was demonstrated that precalving metabolic alkalosis predisposed cows to milk fever via diminishing tissue responsiveness to PTH, and adding dietary anions markedly reduced the incidence of clinical milk fever (Goff et al., 1991). Mechanisms by which metabolic acidosis improves Ca homeostasis have not been fully elucidated but may include improved tissue responsiveness to PTH (Goff et al., 2014) and decreased urinary Ca excretion via TRPV5 inhibition and a corresponding enhanced gastrointestinal Ca absorption via increased TRPV6 (Martín-Tereso and Martens, 2014). Other prepartum dietary strategies to minimize postpartum clinical hypocalcemia include low-Ca diets (Thihsing-Hansen et al., 2002) and Ca-

chelating compounds (Goff, 2008). Implementing these dietary strategies has successfully reduced rates of clinical hypocalcemia; however, SCH remains common, afflicting ~25% of primiparous and ~50% of multiparous cows (Reinhardt et al., 2011). Thus, the inability to strictly maintain Ca homeostasis continues to occur in the early postpartum period.

METABOLIC DISORDERS AND INFECTIOUS DISEASE: TRADITIONAL DOGMAS

Maintaining cow health and productivity during the transition period represents a significant obstacle to the dairy industry. Coinciding with the changes mentioned above in energetic and Ca homeostasis is an increased risk of metabolic disorders and infectious diseases such as ketosis, fatty liver, milk fever, displaced abomasum (DA), retained placenta (RP), mastitis, and metritis (Goff and Horst, 1997; LeBlanc, 2010; Berge and Vertenten, 2014). Approximately 75% of disease typically occurs during the first month postpartum (LeBlanc et al., 2006), and because they occur within a short window of time, the disorders are predictably interrelated (Curtis et al., 1984; Markusfeld, 1986; Gröhn et al., 1989). Not surprisingly, a disproportionate amount of culling occurs early in lactation. This animal welfare issue has profound implications for farm profitability, the social license to operate, and industry sustainability.

Research characterizing periparturient disorders by alterations in a single circulating metabolite began as early as the 1920s. Milk fever was identified by decreased circulating Ca (Hayden and Scholl, 1923; Sjollesma and Van Der Zande, 1923; Dryerre and Greig, 1925), and ketosis was identified by increased circulating acetone (Stinson, 1928; Sampson et al., 1933). In the late 1950s and 1960s, ketosis was further characterized by changes in NEFA (Radloff et al., 1966; Radloff and Schultz, 1967), and the severity of NEB was proposed as the primary cause (Shaw, 1956). Associations between increased NEFA, hyperketonemia, and hypocalcemia and the incidence of disease became a topic of intensive investigation beginning in the 1980s (Curtis et al., 1983; Dohoo and Martin, 1984; Markusfeld, 1987; Geishauser et al., 1997; Kaneene et al., 1997; Cameron et al., 1998; Duffield, 2000; Duffield et al., 2009; Berge and Vertenten, 2014), and hypocalcemia was later considered a gateway disorder leading to ketosis, mastitis, metritis, DA, impaired reproduction, and decreased milk yield (Curtis et al., 1983; DeGaris and Lean, 2008; Goff, 2008; Chapinal et al., 2012; Martinez et al., 2012; Ribeiro et al., 2013; Neves et al., 2018a,b).

A common observational approach in the aforementioned research is to obtain blood samples from cows during the transition period and retrospectively clas-

sify them according to health status. Once retroclassified, differences in circulating metabolites, minerals, and hormones can be evaluated between groups (e.g., diseased vs. healthy, high vs. low performers, pregnant vs. open, high NEFA vs. low NEFA). Another common method is to simply correlate circulating variables with a performance metric or health variable. Despite not using traditional intervening or controlled experimentation, increased NEFA, hyperketonemia, and hypocalcemia are presumed to have a causal relationship with poor transition cow success (Figure 1; Cameron et al., 1998; LeBlanc et al., 2005; Quiroz-Rocha et al., 2009; Ospina et al., 2010a; Chapinal et al., 2011; Huzzey et al., 2011).

We believe that there are multiple flaws in the theory connecting NEFA, ketones, and Ca with negative outcomes in the postpartum dairy cow. In addition to not having causal substantiation and having limited biological plausibility, many of the theory's principles counter evolutionary adaptations associated with milk synthesis, reproduction, and species survival. Below, we outline the inadequacies of the rationale for causation and provide evidence demonstrating that changes in circulating NEFA, ketones, and Ca are not responsible for negative outcomes but rather are simply reflective of either normal metabolic changes that healthy cows enlist to achieve high production or the metabolic downstream consequences of immune activation-induced hypophagia.

Correlation Does Not Equal Causation

Causality and correlation are incorrectly interchanged when an observational relationship between 2 events is claimed to be inevitable rather than coincidental. Dozens of peer-reviewed articles have demonstrated an association between metabolites and transition cow problems, but importantly numerous inconsistencies exist. For example, a variety of papers indicate no relationship between NEFA, ketones, and Ca and negative outcomes (Burke et al., 2010; Bicalho et al., 2014, 2017; Abdelli et al., 2017; McArt and Neves, 2020). The consistency of an effect is crucial when making causal inference from observational and field research. Second, as already mentioned, these tenets are largely based on associations and not cause-and-effect relationships garnered from controlled and intervening experimentation. Even from a relationship perspective, assessing the strength or robustness of the associations is difficult due to variability in analysis and statistical methods. In particular, different metabolite thresholds are set for different outcomes and time points (e.g., pre- vs. postpartum, wk 1 vs. wk 2) within observational studies. In addition, inconsistent association metrics (e.g.,

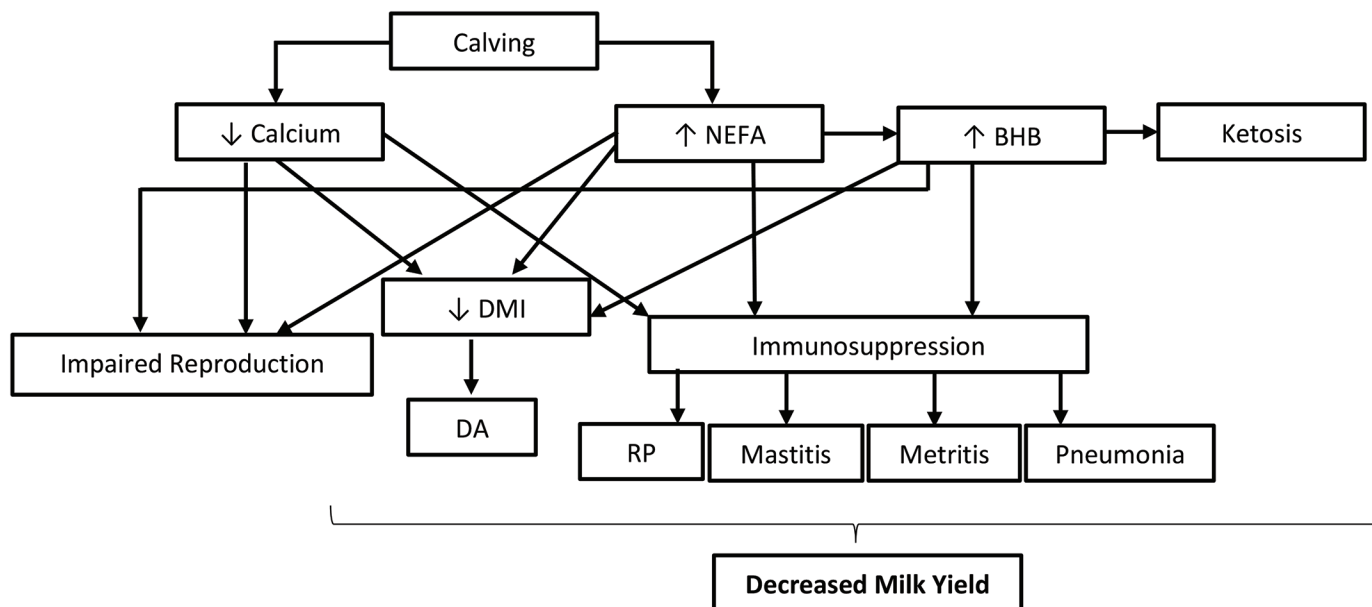


Figure 1. Traditional mechanisms by which hypocalcemia and increased nonesterified fatty acids (NEFA) and hyperketonemia are thought to cause poor transition cow health and performance. DA = displaced abomasum; RP = retained placenta.

odds ratio, relative risk, hazard ratio) are used to assess the relationship. A partial summary of the association studies was recently compiled by McArt et al. (2013) and Overton et al. (2017). Although these reports illustrate the large number of studies demonstrating a relationship of the metabolites (NEFA, BHB, Ca) with health and performance, they also indicate substantial variability in metabolite thresholds and association strength. For example, the association (as measured by odds ratios) between postpartum BHB and DA incidence ranged from 1.1 to 27.6 across studies (McArt et al., 2013). Interestingly, several reports demonstrated both a negative association of elevated NEFA and ketones with health outcomes and a positive association with milk yield (Lean et al., 1994; Duffield et al., 2009; Ospina et al., 2010b; Furken et al., 2015; Belay et al., 2017; Bach et al., 2019). The conflicting relationships described above exemplify the dogma's limitations and highlight the boundaries of retrospective classification and epidemiology. Additionally, emphasis on association metrics (e.g., odds ratios, relative risks) can lead to a non sequitur (Davies et al., 1998), epitomized by the skewed exegesis of how animal-derived food products influence human health (Taubes, 2001).

Immunosuppression Is Complex

Arguably, the best line of evidence in support of the dogma is extrapolated from the purported role of elevated NEFA, hyperketonemia, and hypocalcemia in

immunosuppression and its predisposing role in disease (Ducusin et al., 2003; Lacetera et al., 2004; Hammon et al., 2006; Scalia et al., 2006; Martinez et al., 2012, 2014; LeBlanc, 2020). For example, in vitro incubation of isolated circulating neutrophils with increasing NEFA and BHB concentrations negatively affects leukocyte function, such as neutrophil oxidative burst (Hoeben et al., 1997; Scalia et al., 2006; Grinberg et al., 2008; Ster et al., 2012) and lymphocyte antibody secretion (Lacetera et al., 2004). Additionally, chemotaxis and myeloperoxidase activity were impaired in neutrophils isolated from periparturient cows with elevated NEFA and ketones (Suriyasathaporn et al., 1999; Hammon et al., 2006). Inducing hypocalcemia via Ca chelators reduced neutrophil phagocytosis in vitro (Ducusin et al., 2001) and in vivo (Martinez et al., 2014). Furthermore, leukocytes isolated from hypocalcemic cows have reduced intracellular Ca stores (Ducusin et al., 2003; Kimura et al., 2006), a change that would interfere with Ca signaling and impede leukocyte activation (Lewis, 2001). Consequently, the metabolic and mineral profile dominating the periparturient period is presumed to adversely affect immune function, and the resulting immune suppression predisposes cows to a variety of disorders and diseases (Goff and Horst, 1997; Aleri et al., 2016; Figure 1). However, there are inconsistencies (in vivo and in vitro) in how these metabolites and Ca affect leukocyte function (reviewed by LeBlanc, 2020). For example, Scalia et al. (2006) reported reduced neutrophil reactive oxygen species production but no

change in neutrophil phagocytosis when incubated with increasing NEFA concentrations in vitro. Incidentally, most ex vivo research evaluating increasing NEFA concentrations on leukocyte function uses very low levels of albumin and thus are not replicating in vivo conditions. Similarly, Ster et al. (2012) observed no difference in blood mononuclear cell proliferation or interferon- γ production with BHB concentrations ≥ 1.0 mmol/L and no effect on oxidative burst up to 10 mmol/L. Further, no relationship was observed between BHB concentrations and neutrophil killing ability (Hammon et al., 2006). Rodent studies have even shown that ketone bodies may have a protective effect and limit reactive oxygen species-induced damage during bacterial inflammation (Wang et al., 2016). In addition to the aforementioned discrepancies, extending in vitro results to whole-animal biology has obvious limitations, and this is especially pertinent when considering the immune system. For example, most leukocyte function is integrally dependent on an intracellular metabolic shift from oxidative phosphorylation to aerobic glycolysis (discussed below; Palsson-McDermott and O'Neill, 2013), and it is highly unlikely that in vitro conditions can mimic the extracellular endocrine and energetic milieu accompanying normal immune activation. Additionally, we now realize that almost all periparturient dairy cows (even the seemingly healthy ones) experience some degree of immune activation and inflammation (discussed more below; Humblet et al., 2006; Bertoni et al., 2008), and the inflammatory milieu that accompanies it has suppressive effects on leukocyte function (Oh et al., 1990; Raju et al., 2019). This is particularly important when considering neutrophils because they continue to mature while in circulation, and this aging can affect their functional properties (Adrover et al., 2016; Rosales, 2018). Even more concerning is that inflammation causes the bone marrow to release immature and incompetent neutrophils, including neutrophil progenitor cells (Leliefeld et al., 2016). Thus, the normal homogeneity of circulating neutrophils in a healthy animal becomes increasingly heterogeneous during immune activation (Zonneveld et al., 2016), and this would very likely influence ex vivo neutrophil function metrics. Consequently, it is not clear whether ex vivo function assays during the transition period reflect immunosuppression or simply the pathology and leukocyte footprint associated with normal immune activation. In other words, some arms may appear immunosuppressed, whereas others are activated. Continued research into the immune system consistently reveals how little we know, how complex the interactions are (especially with metabolism), and how oversimplified our interpretation may have been.

NEB and BW Loss During Lactation Are Normal

Adipose tissue mobilization to support lactation is a highly conserved response (McNamara, 1997; Oftedal, 2000). Interestingly, in certain mammals such as bears, seals, dolphins, and baleen whales (i.e., the blue whale), lactation occurs concurrently with a prolonged fast; consequently, these mammals rely almost entirely on adipose tissue reserves to meet their energy demands (Oftedal, 2000; Crocker et al., 2001; Fowler et al., 2016, 2018). In fact, baleen whales will sustain a 6- to 7-mo lactation without eating and will mobilize $\sim 33\%$ of their fat stores, which is equivalent to 16 tons of BW (Oftedal, 2000). In seals, greater than 90% of the energy requirements for lactation are powered by lipid stores (Crocker et al., 2001; Fowler et al., 2018), and these mammals may lose more than 50% of their body fat reserves (Crocker et al., 2001). This is even more impressive considering most sea mammals are unable to perform ketogenesis (Jebb and Hiller, 2018). Evolutionarily closer to the cow, deer go through periods of insufficient intake after parturition and rely on reserves to support lactation, even during ad libitum feeding (Sadleir, 1982). Regardless, the species-conserved reliance on NEFA to support lactation further exemplifies the importance of this strategy. In fact, the extent to which cows incorporate adipose tissue mobilization during early lactation pales compared with many other species (Collier et al., 2005). Consequently, interpreting BW loss and tissue mobilization outside the bounds of proper biological context could lead to a pessimistic judgment.

NEFA and BHB Do Not Directly Inhibit Feed Intake

Regulation of feed intake is an extremely complex topic, exemplified by the fact that pharmaceutical interventions to reduce human caloric consumption have yet to be successful. Theories attempting to explain ruminant appetite control include energy requirements (Conrad et al., 1964), gut fill and hepatic oxidation (Allen et al., 2009), and endocrine regulation (Ingvarsen and Andersen, 2000; Kuhla et al., 2016). Pertinent to this review, the detrimental effects of elevated NEFA and hyperketonemia on health and performance are partially attributed to their alleged suppressive effect on feed intake (Baird, 1982; Ingvarsen and Andersen, 2000; Hayirli et al., 2002; Ingvarsen, 2006; Hammon et al., 2009; Allen, 2020). This is an especially prevalent mindset in veterinary medicine as clinicians often anecdotally claim that ketones depress periparturient cow feed intake. However, this purported effect is largely based on association (see above) and is in contrast with

the normal biology accompanying a healthy and successful transition (high circulating NEFA and BHB). Furthermore, results of several infusion studies suggest appetite is largely unaffected by ketones and lipids. In an elegant series of controlled experiments, it was demonstrated that intravenous BHB infusion did not affect feed intake (Zarrin et al., 2013, 2014a,b) and that infusing propionate, but not lipid, decreased DMI in mid-lactation cows (Stocks and Allen, 2014). When examining different fuel sources infused cerebrally, Davis et al. (1981) found that glucose and glycerol reduced feed intake, whereas BHB did not. Furthermore, infusing ketones intravenously actually increased feed intake (Carneiro et al., 2016a,b). This type of experimentation needs to be interpreted within homeostatic and homeorhetic context because administering a fuel would intuitively decrease energy consumption when the animal is in positive energy balance (Conrad et al., 1964), and this concept is reinforced by intervening experimentation (Chelikani et al., 2003). Regardless, from an evolutionary perspective, it is bioenergetically difficult to hypothesize why NEFA and BHB would decrease appetite. Adipose tissue mobilization and partial conversion of NEFA into ketones is a key metabolic strategy animals use to conserve skeletal muscle and ultimately survive NEB (Sherwin et al., 1975). The importance of ketogenesis to surviving malnutrition is highlighted by the fact that mutations in the gene regulating ketone synthesis (mitochondrial HMG-CoA synthetase) result in hypoglycemic-induced coma within days (Thompson et al., 1997). Reliance on stored lipid during energy insufficiency is so conserved that even microorganisms have the capacity to stow and oxidize NEFA (Nunn, 1986) and convert fatty acid energy into ketones (Wang et al., 2014). Thus, even the simplest of life forms have been utilizing these basic and uncomplicated ancient fuels (NEFA and ketones) since the beginning of time. If NEFA and ketones actually blunted the urge to eat, a starving animal would be anorexic, a scenario that would hasten their demise. In summary, animals have ebbed and flowed into and out of NEB (because of, e.g., food insecurity, hibernation, migration, and lactation) for eons, and oxidizing NEFA and ketones is absolutely essential to survival.

High-Producing Cows Are Hypoinsulinemic

A key strategy (maybe the most integral part) to successfully initiating lactogenesis and sustaining galactopoiesis is the development of insulin resistance in both skeletal muscle and adipose tissue and the decrease in pancreatic insulin secretion (Bauman and Currie, 1980; Baumgard et al., 2017). As already mentioned,

this allows adipose tissue mobilization and the exiting NEFA to be used by most cell types and tissues as a way to spare glucose for milk synthesis. Thus, it is not surprising that (1) higher producing cows are more hypoinsulinemic than their lower producing herdmates throughout lactation (Koprowski and Tucker, 1973; Hart et al., 1975, 1978, 1979; Jordan et al., 1981; Collier et al., 1984), (2) periparturient insulin concentrations are inversely related to whole lactation performance (Zinicola and Bicalho, 2019), (3) insulin clearance (removal from the circulating pool) is increased by genetic selection for milk yield (Barnes et al., 1985), and (4) administering insulin or insulin-sensitizing agents decreases milk yield (Kronfeld et al., 1963; Schmidt, 1966; Chang and Young, 1992; Yousefi et al., 2016).

Although not directly focusing on insulin per se, evaluating how feeding controlled-energy diets (low-quality forage) before calving affects energetic metabolism and production provides additional conceptual framing on how important metabolic flexibility is to normal lactation. Parturient low-energy diets successfully reduced postcalving NEFA, ketones, and liver fat content, but this was unsurprisingly accompanied by a substantial reduction in ECM or FCM yield (Janovick and Drackley, 2010; Silva-del-Río et al., 2010). Additionally, regardless of diet, cows that had increased postcalving circulating ketones (1.2–2.9 mmol/L) produced more milk (>3 kg/d) than cows whose ketone concentrations were considered healthy (<1.2 mmol/L; Lean et al., 1994; Vanholder et al., 2015; Rathbun et al., 2017). Clearly, mobilizing adipose tissue and converting NEFA into ketones is a physiological adaptation that mammals utilize to prioritize milk synthesis, and attempts to blunt or intervene with this homeorhetic process predictably come at the expense of milk yield.

The Confusing Insulin Status of Ketosis

Given insulin's incredibly potent regulation of intermediary metabolism, high milk production associated with associated with excessive adipose tissue mobilization-induced ketosis should be accompanied by severe hypoinsulinemia (Hove, 1978). Accordingly, most periparturient hyperketonemic cows are simultaneously hypoinsulinemic (Hove, 1978; Brockman, 1979), and it has been suggested that hypoinsulinemia is a prerequisite for ketosis development (Hove, 1974). However, sometimes there are no differences in circulating insulin between ketotic cows and healthy controls (Oikawa et al., 2019; L. H. Baumgard, unpublished data), and actually ketosis is sometimes accompanied by hyperinsulinemia (Kronfeld, 1971; Holtenius and Holtenius, 1996; Herdt, 2000). Further, hyperinsulinemia is thought to occur be-

fore clinical signs of ketosis (Rukkwamsuk et al., 1998, 1999). This is a peculiar pathological endocrine profile as insulin would normally prevent ketosis on multiple levels: (1) blunting adipose tissue mobilization, (2) reducing hepatic gluconeogenesis and thus minimizing depletion of the TCA cycle's OAA pool, (3) decreasing fatty acid transport into the mitochondria via carnitine palmitoyltransferase 1 (CPT1) downregulation, (4) negatively governing the rate-limiting enzyme of ketone synthesis (HMG-CoA synthase), and (5) increasing peripheral tissue ketone utilization (Jarrett et al., 1974). Incidentally, despite inappetence, immune activation is also characterized by acute hyperinsulinemia (discussed below). As a result, there are numerous metabolic and endocrine footprints clearly associated with ketosis, a controversial concept originally proposed by Holtenius and Holtenius (1996) and supported by Herdt (2000).

Inconsistent Success in Treating Ketosis

Given hyperketonemia's purported crucial role in transition cow pathophysiology, it stands to reason that clinical intervention should increase productivity. In fact, administering propylene glycol to subclinical hyperketonemic cows did increase milk yield in some instances (Emery et al., 1964; McArt et al., 2011; Lomander et al., 2012) but not in others (Hoedemaker et al., 2004; Liu et al., 2009; Bors et al., 2014; Østergaard et al., 2020; Capel et al., 2021). Explanations for the inconsistencies are not clear; however, one explanation for a positive effect may be that the additional endogenous glucose produced with propylene glycol administration temporarily alleviated the glucose burden of a transition dairy cow that is simultaneously inflamed. A reason for not observing an effect on milk yield is that the cows were healthy and the hyperketonemia was a crucial adjustment they were using to prioritize milk synthesis. Additionally, ketones blunt adipose tissue mobilization (in a negative feedback loop; Björntorp, 1966); therefore, therapeutically reducing ketones during subclinical ketosis could do more harm than good. Regardless, the collective body of evidence does not fully support the notion that medically treating hyperketonemia benefits milk synthesis. Incidentally, using steroids as part of a regimen to remediate ketosis needs a thorough re-examination, considering their role in immunosuppression.

In summary, transition cow health problems, sub-optimal milk production, premature culling, and poor reproduction remain key hurdles to profitable dairy farming. During the last 50 yr, dairy scientists have increasingly viewed elevated circulating NEFA and ketones and hypocalcemia as pathological and causal toward negative outcomes. This tenet is largely based

on observational studies, epidemiology, correlations, and ex vivo immune cell function assays. However, it is becoming more evident that periparturient diseases and disorders cannot be explained by the severity of changes in these simple metabolites. Interpreting biomarkers as causal agents of metabolic disorders deviates from the purpose of epidemiological studies. We believe that the postcalving changes to energetic and Ca metabolism reflect normal biological processes that healthy cows use to maximize milk synthesis or severe dysregulation of these processes arising from inflammation-induced changes enlisted to prioritize health (Figure 2).

INFLAMMATION

Regardless of health status (Humblet et al., 2006), inflammation is observed in almost all cows during the transition period (Ametaj et al., 2005; Bionaz et al., 2007; Bertoni et al., 2008; Mullins et al., 2012). Immune activation appears to be a double-edged sword, as a proper amount is required to healthfully navigate the periparturient period. In part, an active immune system is a normal constituent of dry-off and parturition arising from nonpathogenic sources such as tissue damage and remodeling (i.e., sterile homeostatic inflammation). Examples include mammary gland involution (Atabai et al., 2007), adipose tissue remodeling (Kosteli et al., 2010), and placental expulsion (Challis et al., 2009). In these situations, the immune system is activated via molecular patterns of nonpathogenic origin with the primary goal of remodeling tissue to support a new physiological state. It is unclear how much these nonpathogenic sources of inflammation contribute to systemic inflammation observed in poorly transitioning dairy cows. Cows are exposed to a myriad of physiological, environmental, and psychological stressors between dry-off and the early postpartum period that disrupt barrier integrity at epithelial interfaces (e.g., uterine, mammary, intestinal, and lung), which are constantly exposed to pathogens and colonized by commensal microorganisms. When microorganisms breach the epithelial barrier, underlying immune cells and tissues react quickly to prevent further infection. Immune cells respond after recognizing pathogen-associated molecular patterns (PAMP) via pathogen recognition receptors (PRR). These PRR are present on leukocytes and other cells, including adipocytes (Vailati Riboni et al., 2015), skeletal muscle (Frost and Lang, 2005), hepatocytes (Xu et al., 2017), endometrial cells (Sheldon and Roberts, 2010), mammary epithelial cells (Ibeagha-Awemu et al., 2008), and intestinal epithelial cells (Malmuthuge et al., 2012). Interaction of the PAMP with the PRR triggers a signaling cascade culminating in inflammatory cytokine production (Lu et al., 2008). Immune activa-

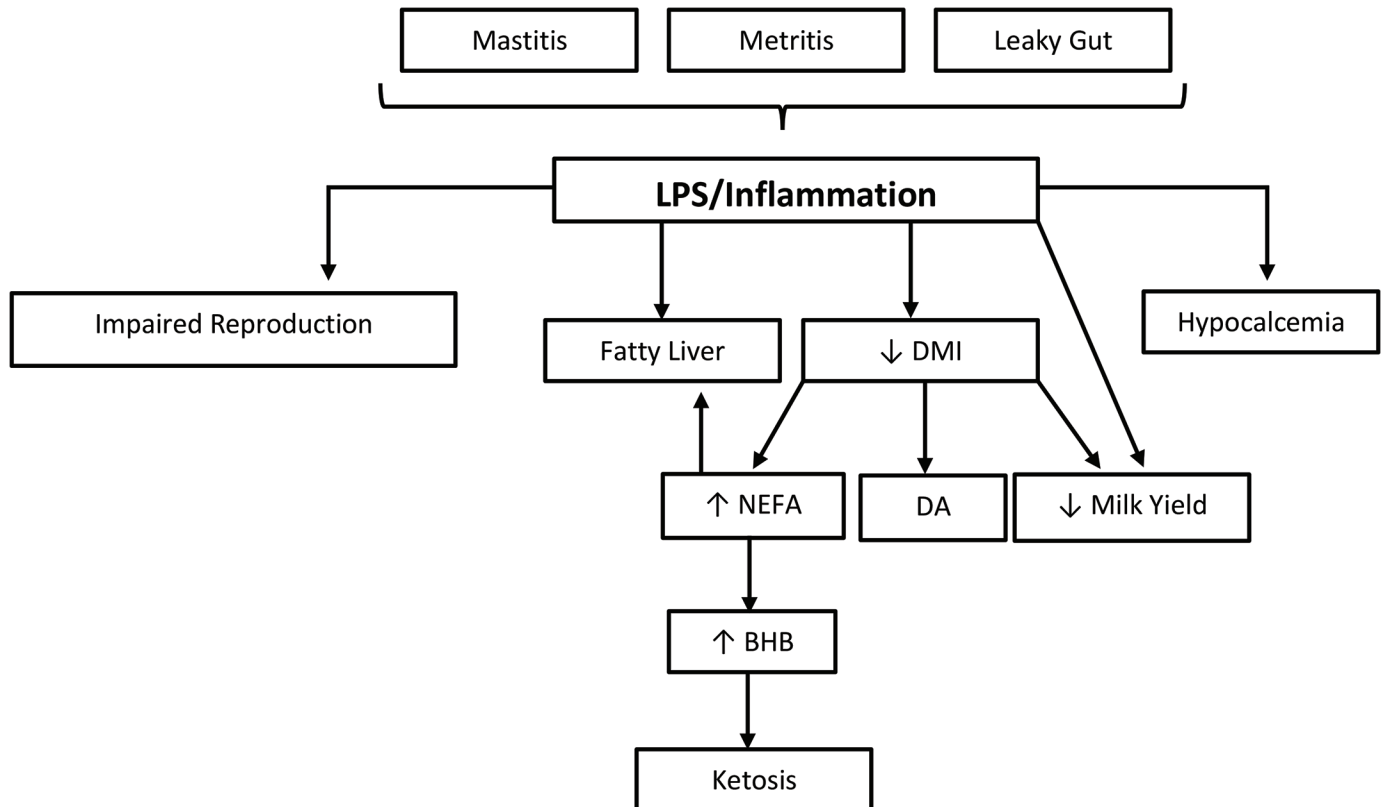


Figure 2. Potential downstream consequences of immune activation. In this model, decreased feed intake, hypocalcemia, excessive nonesterified fatty acids (NEFA), hyperketonemia, and hepatic lipidosis are not causative of poor transition cow performance and health but rather reflect prior immune stimulation. DA = displaced abomasum.

tion can be experimentally modeled via administering LPS, the antigenic component of gram-negative bacteria, which is recognized by the toll-like receptors (TLR; Kumar et al., 2011) and elicits a well-characterized and robust immune response (van Miert and Frens, 1968; Waldron et al., 2006; Eckel and Ametaj, 2016). Other models utilizing specific pathogens or PAMP also exist (i.e., live bacteria, lipoteichoic acid), and much of what we know about immune system effects on metabolism stem from these well-controlled and repeatable models. However, it is important to remember that the source of inflammation underlying these responses in practical situations arises from a wide variety of immunogenic and pathogenic components at 3 prominent sources in the transition cow: the uterus, mammary gland, and gastrointestinal tract.

Sources of Pathogenic Inflammation in the Transition Cow

Uterus. Bacteria present within the uterine lumen were originally thought to originate exclusively from contamination with environmental pathogens during

and after parturition (Sheldon et al., 2006); however, it is now established that a uterine microbiome exists (Karstrup et al., 2017; Moore et al., 2017). Both bacteria adapted to the uterus (part of the existing microbiome before parturition) and bacteria originating from the environment contribute to metritis (Sheldon et al., 2019). Infiltration of environmental microorganisms is restricted by anatomical barriers, including the vulva, vagina, and cervix; however, dilation of these structures during and after parturition reduces their ability to prevent pathogen entry. Tight junction (TJ) proteins connect adjacent uterine epithelial cells separating the apical and basolateral components of the endometrium and prevent bacteria from penetrating the underlying stroma (Sheldon et al., 2019). Epithelial cells recognize pathogens via PRR, which triggers inflammatory cytokine and antimicrobial peptide production (Davies et al., 2008). Interestingly, both apical and basolateral PRR activation triggers cytokine secretion apically, and this aids in immune cell recruitment to the infection site (Sheldon et al., 2019).

During parturition, the protective uterine epithelium is often physically injured. Damaged or dying cells

release damage-associated molecular patterns, which activate the immune system (independently of bacterial infiltration) to help clear unhealthy tissue. This damaged tissue creates an opportunity for bacteria to access the underlying stroma. Bacterial infiltration of the stroma induces cell damage and cytolysis, stimulating further release of damage-associated molecular patterns (Sheldon et al., 2019); these are recognized by epithelial and stromal cells via PRR, which intensifies the inflammatory response (Blander and Sander, 2012). Despite extensive defense mechanisms, increased circulating inflammatory cytokines are frequently observed in naturally metritic cows (Barragan et al., 2018), and increased circulating LPS occurs in severe metritis (Mateus et al., 2003). As alluded to above, the act of parturition independently triggers inflammation, and the severity of dystocia likely predisposes cows to a higher risk of pathogen entry into local and systemic circulation. In summary, both the act of parturition and bacterial contamination can contribute to local and systemic inflammation in dairy cows.

Mammary Gland. The mammary gland is highly susceptible to bacterial infections, making it a prominent source of pathogen infiltration in the transition period. Intramammary infections are most prevalent during early involution (i.e., dry-off) and colostrogenesis (Ballou, 2012). Abrupt milking cessation at dry-off engorges the udder with milk, increasing intramammary pressure and disrupting physical defense mechanisms within the streak canal (i.e., the keratin plug; Tucker et al., 2009); allowing microorganisms to colonize the mammary gland (Bradley and Green, 2004). Additionally, nonpathogenic inflammation is also involved with tissue remodeling and mammary involution (Monks et al., 2002). Regardless, bacterial infections often remain quiescent throughout the dry period and clinical disease is not observed until the periparturient period (Bradley and Green, 2004). Interestingly, a previous report estimated that approximately 65% of early-lactation clinical coliform mastitis cases originated during the dry period (Smith and Schoenberger, 1985).

Bovine mammary epithelial cells synthesize and secrete milk while simultaneously maintaining a semi-permeable barrier between blood and milk components. Integrity of the blood–milk barrier is reliant on TJ proteins, which connect adjacent epithelial cells (Burton and Erskine, 2003). Lipopolysaccharide, released during gram-negative bacterial proliferation within the teat and gland cistern, is recognized by resident leukocytes and mammary epithelial cells via TLR4 (Ibeagha-Awemu et al., 2008). Proinflammatory cytokines, produced in response to TLR4 activation, signal recruitment of effector leukocytes into the mammary

gland and disrupt TJ integrity (Burton and Erskine, 2003; Xu et al., 2018). Furthermore, leukocyte pathogen elimination triggers epithelial cell damage (Wellnitz et al., 2016). Altogether, these changes can disrupt the blood–milk barrier, resulting in systemic inflammation and potentially both endotoxemia and bacteremia; this occurs in an alarming number of gram-negative bacterial infections (Wenz et al., 2001). Interestingly, TJ can also be disrupted by stress events such as feed restriction (Stumpf et al., 2013; Kvidera et al., 2017d). Consequently, the mammary gland is a likely culprit in immune activation both after and before parturition.

Gastrointestinal Tract. The intestinal epithelium serves a dual purpose of nutrient absorption and protection from pathogens and other antigens present within the gastrointestinal tract. The importance of proper barrier function cannot be overstated as the intestine is continuously exposed to potential pathogens and toxins and has an enormous surface area (~400 m² in humans; Mani et al., 2012; Murphy, 2012). The gastrointestinal tract harbors trillions of microorganisms (Hooper and Macpherson, 2010), and it has been estimated that the human intestinal tract contains >1 g of LPS (Erridge et al., 2007). To put this into context, 1 g is 4,000-fold greater than that necessary to cause a >90% decrease in milk yield in a 700-kg cow (Kvidera et al., 2017b; Horst et al., 2018, 2019). Microbial exposure is certainly more extensive in ruminants due to pregastric fermentation and the relative size of the alimentary tract. The stratified squamous epithelium lining the reticulorumen and omasum is composed of 4 distinct strata that serve both metabolic and barrier integrity roles. In contrast to the reticulorumen and omasum, the lower gut is composed of a simple columnar epithelium, which consists of both absorptive epithelial cells and a myriad of immune-related cells with extensive defense mechanisms to protect the epithelial barrier (the intricate details of which are reviewed by Steele et al., 2016). More than 75% of all lymphocytes are located in the gastrointestinal tract of a healthy animal (van der Heijden et al., 1987), highlighting the threat in its paradoxical absorption and gatekeeping roles.

Dairy cows are exposed to numerous situations that can negatively affect intestinal barrier integrity, including heat stress (Baumgard and Rhoads, 2013; Koch et al., 2019), SARA (Emmanuel et al., 2007; Khafipour et al., 2009), and feed restriction (Zhang et al., 2013; Kvidera et al., 2017a,d; Horst et al., 2020b). Potential mechanisms by which heat stress and rumen acidosis may affect barrier integrity have been described in detail elsewhere (Baumgard and Rhoads, 2013; Steele et al., 2016). Interestingly, stress alone is associated with gastrointestinal hyperpermeability (Pohl et al., 2017)

and systemic inflammation (Proudfoot et al., 2018). In response to stress, the hypothalamic-pituitary-adrenal axis is activated, which in turn stimulates nervous system and peripheral tissue production of corticotropin-releasing factor (**CRF**) and subsequent release of adrenocorticotropic hormone from the anterior pituitary gland (Charmandari et al., 2005). Receptors for CRF are widely expressed in both the central and peripheral nervous system, where they interact with enteric neurons and epithelial immune cells (Larauche et al., 2009; Li et al., 2017). Administering CRF induces intestinal barrier dysfunction (Teitelbaum et al., 2008) and initiates systemic inflammation (Cooke and Bohnert, 2011; Cooke et al., 2012). The negative consequences of CRF on the epithelium seem to be mediated by intestinal resident mast cell degranulation and release of histamine, proteases, and cytokines, which negatively affect intestinal barrier function (Moeser et al., 2007; Overman et al., 2012). Mechanistically, the effects of CRF on barrier integrity are not fully elucidated but likely are a consequence of disrupted TJ complexes (Groschwitz et al., 2013). In addition to hypothalamic release, CRF is produced and released by intestinal cells (including immune and enterochromaffin cells), and the localized production can also affect intestinal epithelial function (Albert-Bayo et al., 2019). Stress-mediated effects on the gut barrier may explain why so many seemingly unrelated situations (e.g., heat stress, cold stress, weaning, acidosis, feed restriction) share a common consequence of leaky gut and systemic inflammation.

Hepatic Response to Inflammation

The liver is the first organ to filter blood from the portal-drained viscera, intimately tying it with any gut-derived inflammatory challenges. During inflammation, the liver shifts priority from metabolism to defense as it is a critical organ in the immune response. This change is known as the acute phase protein (**APP**) response, and it involves reduced synthesis of proteins integral in normal liver metabolism (e.g., albumin, cholesterol, retinol-binding protein, transferrin, and paraoxonase) and increased synthesis of proteins, which aid in the immune and detoxification response (Strnad et al., 2017). Acute phase proteins are classified as either negative or positive based on their directional change (Kushner and Mackiewicz, 1987); circulating positive APP increase in response to inflammation, whereas negative APP concomitantly decrease. In coordination with APP production, the liver plays a key role in detoxifying bacterial components and excreting them via bile. Interestingly, more than 60% of intravenously

infused bacteria are hepatically sequestered within 10 min of infusion (Yan et al., 2014).

Positive APP aid in pathogen elimination, removal of toxic substances, and maintenance of a balanced inflammatory response (Ceciliani et al., 2012) and can be further classified as minor, moderate, or major depending on the magnitude of increase observed following immune activation. Common positive APP evaluated in ruminants include serum amyloid A (**SAA**), haptoglobin (**Hp**), and LPS-binding protein (**LBP**; Ceciliani et al., 2012). The temporal pattern of the APP differs such that LBP and SAA typically increase more rapidly, whereas the Hp response is delayed. Serum amyloid A and Hp are major APP produced primarily by hepatocytes but also by various extrahepatic tissues, including the mammary gland, pancreas, gastrointestinal tract, and ovary, among others (Lecchi et al., 2012). During inflammation, SAA displaces ApoA1 from high-density lipoproteins and subsequently scavenges cholesterol from dying cells (Coetzee et al., 1986; Sato et al., 2016). Furthermore, SAA can facilitate bacterial opsonization and leukocyte chemotaxis (Shah et al., 2006; De Buck et al., 2016) and has antimicrobial activity in the mammary gland (Parés et al., 2020). Haptoglobin's most well-known function is binding hemoglobin released during hemolysis, thereby protecting hemoglobin from oxidative damage (Buehler et al., 2009) and reducing iron availability to bacteria (Eaton et al., 1982). Interestingly, Hp has potent anti-inflammatory actions that are crucial for immune tolerance and for maintaining a balanced inflammatory response (Raju et al., 2019). In particular, Hp inhibits leukocyte activities such as respiratory burst by binding to receptor ligand sites (Oh et al., 1990; Arredouani et al., 2005). In other words, it appears that Hp is a component of a negative feedback loop preventing an unchecked proinflammatory cytokine storm or systemic inflammatory response syndrome.

Lipopolysaccharide-binding protein is a moderate APP produced primarily by hepatocytes but also by adipose tissue (Rahman et al., 2015), the gastrointestinal tract, and the mammary gland (Rahman et al., 2010). Lipopolysaccharide-binding protein facilitates LPS presentation to CD14 for TLR4 activation. Although the LPS-CD14-TLR4 interaction can occur independently, LBP markedly enhances macrophage responsiveness (i.e., cytokine production) to LPS (Martin et al., 1992). Although classically known for its role in LPS recognition, LBP can also recognize other PAMP such as lipoteichoic acid (Schröder et al., 2003). Interestingly, constitutive levels of LBP promote immune activation, whereas acute phase levels are anti-inflammatory and inhibit cytokine production in rodents and

humans (Lamping et al., 1998; Zweigner et al., 2001). Furthermore, recombinant LBP decreased LPS-induced cytokine production in a bovine mammary epithelial cell line (Sun et al., 2015). Lipopolysaccharide-binding protein exerts its anti-inflammatory action by facilitating the transfer of LPS to lipoproteins, which are directed to the liver for biliary excretion (Lamping et al., 1998). As a result, LPS binding to leukocytes is markedly reduced, which in turn attenuates the inflammatory response (Lamping et al., 1998; Eckel and Ametaj, 2016). In summary, the liver is critical in the immune response because it produces APP, which helps remove the inflammatory insult without leading to overinflammation. This reprioritization of liver function from a metabolic to an immune organ is just one of the many whole-body physiological shifts used to support the immune system.

IMMUNOMETABOLISM

During infection, nutrients and energy are redirected from profitable purposes to support the immune system. Immunological costs contribute to economic consequences, including decreased growth, inefficient feed utilization, poor reproduction, and treatment expenses. An activated immune system markedly disrupts the normal orchestration of metabolism as a strategy used to ensure its quick and effective response. Having a better appreciation of the shifts in whole-body and tissue-specific metabolism that accompany an immune response is essential for understanding the potential etiology it plays in transition cow disorders.

Warburg Effect

In most nonproliferating, differentiated mammalian cells, energy is produced via the combined processes of glycolysis, the TCA cycle, and oxidative phosphorylation, which generates approximately 36 to 38 ATP molecules per molecule of glucose. The fate of pyruvate (the end product of glycolysis) is most often dependent on oxygen availability. In the presence of oxygen, pyruvate continues oxidative degradation through the TCA cycle and oxidative phosphorylation. During hypoxia, pyruvate is shunted toward lactate production to net 2 ATP and regenerate NAD^+ , allowing glycolysis to continue (Berg et al., 2002). However, in 1923, Otto Warburg demonstrated that highly proliferative cancer cells switch to and rely on glycolytic metabolism even in the presence of oxygen, a metabolic process known as aerobic glycolysis or the Warburg effect (Warburg, 1923; Palsson-McDermott and O'Neill, 2013). It was later noted that this same phenomenon occurred in essentially all rapidly proliferating cells, including im-

mune cells (Warburg et al., 1958; Vander Heiden et al., 2009).

Rapidly proliferating cells use the Warburg effect to support growth. Although ATP production from aerobic glycolysis is inefficient, it supplies energy at a much faster rate compared with oxidative phosphorylation (Pfeiffer et al., 2001), and this was traditionally thought to be the primary advantage of the Warburg effect. However, it is unlikely that an enhanced ATP requirement is the primary reason cells initiate the metabolic switch, as ATP availability is apparently not limiting growth in these rapidly proliferating cells (Vander Heiden et al., 2009). Rather, glucose oxidation by aerobic glycolysis generates intermediates needed to support biosynthetic pathways and provides a way to maintain cellular redox balance (NAD^+/NADH). For example, nucleotide, AA, and NADPH production occurs through the pentose phosphate pathway, whereas fatty acids needed for membrane lipid production are synthesized from citrate in the cytosol. Thus, the intracellular advantages of the Warburg effect are multifactorial.

Metabolic reprogramming occurs in activated leukocytes of both innate and adaptive immunity and is intimately related to the nature of the immune response, leading to an extensive increase in glucose utilization (Borregaard and Herlin, 1982; O'Neill and Pearce, 2016). Activated monocytes, neutrophils, and T- and B-lymphocytes express GLUT1, GLUT3, and GLUT4 on the plasma membrane, and insulin augments GLUT3 and GLUT4 expression (Maratou et al., 2007). The insulin receptor is expressed on most activated immune cells (Walrand et al., 2006), and insulin increases glucose uptake and modulates immunity (Estrada et al., 1994; Walrand et al., 2004, 2006; Calder et al., 2007; Ratter et al., 2021). Bovine monocytes and polymorphonuclear leukocytes also express GLUT1, GLUT3, GLUT4, and the insulin receptor on the plasma membrane (Nielsen et al., 2003; O'Boyle et al., 2012; Garcia et al., 2015). Endotoxin stimulation increases GLUT3 and GLUT4 expression on bovine monocytes (O'Boyle et al., 2012), which may allow for competitive uptake among cells when glucose concentrations in the microenvironment are low (i.e., early lactation), especially considering GLUT3 has a higher affinity for glucose than GLUT1, the main glucose transporter in mammary tissue (Zhao and Keating, 2007).

Leukocyte Glucose Consumption

Accurately assessing glucose consumption by the immune system in vivo is difficult due to the ubiquitous and fluctuating distribution of leukocytes. Early investigators demonstrated increased whole-body glucose

utilization during endotoxin administration (Lang et al., 1985). However, interpreting changes in whole-body glucose disposal is complicated by the fact that it represents the net effect of tissues that increase glucose uptake and those that decrease their glucose dependence. Mészáros et al. (1987) used tracer technology to evaluate tissue-specific differences following endotoxin administration and found that glucose utilization was increased most significantly in immune-rich tissues (i.e., liver, spleen, skin). Additionally, when different cell fractions within the liver were examined, glucose consumption did not change in parenchymal cells but markedly increased in Kupffer cells and neutrophils (Mészáros et al., 1991). The aforementioned studies clearly demonstrate that endotoxin-mediated changes in whole-body glucose disappearance reflect increased leukocyte utilization. Better understanding of the effect of immunoactivation on whole-animal physiological glucose consumption has practical implications for animal agriculture, as glucose is an incredibly important fuel for productive purposes. Therefore, we used an LPS-euglycemic clamp as a whole-body proxy of quantifying the amount of glucose consumed by an activated immune response and discovered that the glucose requirement of the immune system was consistent (~ 1.0 g/kg of $BW^{0.75}$ per hour) across physiological states and species (Kvidera et al., 2016, 2017b,c; Horst et al., 2018, 2019); this amount is equivalent to >2 kg of glucose/d in lactating cows. The uniformity in the glucose requirement across different ages, physiological states, and species suggests the extent of fuel utilization by activated leukocytes is a conserved response. Glucose is an essential fuel for the transition cow in particular because the transition-related inflammation and onset of milk synthesis occur simultaneously. Thus, if a cow is unable to clear an infection or resolve inflammation, shutting down milk synthesis as a means of sparing glucose for the immune system takes priority. In acute immune challenges, this crucial strategy can spare >700 g of glucose within a 12-h period (Kvidera et al., 2017b).

COORDINATED SYSTEMIC RESPONSE TO IMMUNE ACTIVATION

Considering the enormous importance of an effective immune response, it is not surprising that almost every tissue and system contributes to the war effort of fighting an infection. The orchestrated control of metabolism during an immune insult is not dissimilar to the coordinated adaptations mammals enlist to partition nutrients (sparing of glucose) toward the mammary gland during healthy lactation. But instead of supporting a dominant physiological state, these metabolic

adjustments are used to spare glucose for the most paramount of priorities: an activated immune system.

Carbohydrate Metabolism

Immune activation induces marked alterations in whole-body glucose dynamics as a result of increased leukocyte glucose requirements. Endotoxemia causes whole-body insulin resistance (Lang et al., 1985; Vernay et al., 2012), which specifically reflects a reduction in insulin-mediated glucose uptake by peripheral tissues such as skeletal muscle and adipose (Spitzer et al., 1980; Lang et al., 1990). Some reports indicate increased adipose tissue glucose uptake (Lang et al., 1992); however, this is likely explained by the presence of resident macrophages that utilize glucose (Weisberg et al., 2003). Drastic reductions in milk synthesis also occur quickly following endotoxin administration and represent an additional method that cows use to spare glucose for the immune system (Kvidera et al., 2017b). Endotoxin administration triggers a biphasic response in circulating glucose, with an initial transient hyperglycemic period followed by chronic hypoglycemia (Blackard et al., 1976; Kvidera et al., 2017b). Hyperglycemia results from increased hepatic glucose output via glycogenolysis and gluconeogenesis, although the latter process is typically delayed (Spitzer et al., 1985; Waldron et al., 2003a, 2006). Increased hepatic glucose output is facilitated by characteristic increases in glucagon and cortisol. Epinephrine may also play a role; however, the liver becomes less sensitive to epinephrine-mediated increases in glucose turnover during immune activation (Hargrove et al., 1989) as a result of downregulation of adrenergic receptors (Gurr and Ruh, 1980). Interestingly, despite being in a catabolic state and anorexic, LPS-infused animals are hyperinsulinemic, a response that is conserved across most species. Glucose infusion exacerbates hyperinsulinemia (Blackard et al., 1976); however, we observed no difference in insulin concentrations between cows infused with LPS alone and those infused with LPS in combination with glucose (Kvidera et al., 2017b). In addition, hyperinsulinemia persists even during hypoglycemia (Kvidera et al., 2017b) and when hyperglycemia is prevented by pre-LPS fasting, results indicating that hyperglycemia is not the primary stimulus for increased pancreatic insulin secretion during an infection (Hand et al., 1983; Kvidera et al., 2017c). Immune activation-induced hyperinsulinemia may help explain why ketotic cows are sometimes hyperinsulinemic relative to their healthy counterparts despite being anorexic. The connection between immune activation and ketosis is further discussed below. The mechanism by which LPS increases insulin remains unclear but likely involves direct effects of LPS on the

pancreas (Vives-Pi et al., 2003) or secondary effects by the secretagogue glucagon-like peptide 1 (Nguyen et al., 2014). Together, the peripheral tissue insulin resistance and increased hepatic glucose output provide glucose at a rate exceeding the immune system's requirement, culminating in transient hyperglycemia. However, once the immune system becomes fully engaged, leukocyte glucose consumption outpaces these strategies, often resulting in substantial hypoglycemia. In fact, if administered at a high-enough dose, LPS can cause lethal hypoglycemia (Lang et al., 1985, 1993).

Lipid Metabolism

Hypertriglyceridemia, a well-characterized response to infection in monogastrics, develops as a result of reduced triglyceride (TG) clearance or increased TG hepatic production (Takeyama et al., 1990; Memon et al., 1992). In response to large LPS doses, hypertriglyceridemia occurs as a result of decreased muscle and adipose tissue clearance mediated by reduced endothelial lipoprotein lipase (Bagby and Spitzer, 1980). In contrast, in response to low LPS doses, it reflects increased hepatic production (Feingold et al., 1995). As mentioned previously, increased circulating TG likely represents a strategy to promote LPS detoxification, as lipoproteins can help efficiently detoxify LPS. In ruminants, LPS-induced changes in TG concentrations are poorly described, as both increased (Ballou et al., 2008; Graugnard et al., 2013) and decreased (Wang et al., 2017) levels have been reported. Discrepancies in the response may be explained by sampling time, as the increase in TG appears to be short lived (Ballou et al., 2008; Graugnard et al., 2013). The mode of action for transient hypertriglyceridemia in ruminants remains unclear, but increased hepatic secretion is unlikely as ruminants are thought to have poor capacity to export very-low-density lipoprotein (Kleppe et al., 1988).

The lipolytic response to LPS is variable as both increased and decreased NEFA concentrations have been reported. In general, administering LPS increases circulating NEFA, but the response is delayed and dampened compared with noninflamed animals on the same plane of nutrition (Kvidera et al., 2017b). In lactating cows, the blunted NEFA response is most likely explained by an immediate LPS-induced reduction in milk synthesis, which spares energy, whereas feed-restricted cows maintain a much higher level of production requiring greater adipose mobilization. Other potential factors contributing to the blunted NEFA response include antilipolytic effects of increased insulin (Vernon, 1992) and increased circulating lactate, which sensitizes adipocytes to insulin action (Ahmed et al., 2010). Increased NEFA have also been observed in response to inflammatory

cytokine infusion (Kushibiki et al., 2003; Yuan et al., 2013). In immune-activated rodents, NEFA delivered to the liver rapidly accumulates into TG, resulting in fatty liver (Lanza-Jacoby and Tabares, 1990; Endo et al., 2007; Stienstra et al., 2010); the role of LPS in fatty liver development is discussed in detail later (see "Fatty Liver"). Even though hepatic NEFA uptake and TG synthesis are increased, the partial oxidation of NEFA via ketogenesis is downregulated in rodents (Takeyama et al., 1990; Maitra et al., 2009). Reduced ketogenesis is hypothesized to occur via a reduction in gene expression of peroxisome proliferator-activated receptor- α (Maitra et al., 2009), which regulates enzymes involved in fatty acid oxidation, including carnitine palmitoyltransferase 1, acyl-CoA oxidase, and ATP-citrate lyase (Maitra et al., 2009). However, in ruminants administered LPS, ketogenesis appears to remain functional (Waldron et al., 2003a), yet BHB concentrations markedly decrease. In well-fed ruminants, most BHB is produced by the rumen epithelium (Pennington, 1952); thus, decreased BHB concentrations are at least partially explained by LPS-induced reduced feed intake. This explains why BHB decreases in feed-restricted animals as well (Horst et al., 2018, 2019). Additionally, increased peripheral tissue BHB clearance during immune activation in lactating cows likely helps explain decreased BHB (Zarrin et al., 2014a; Rodriguez-Jimenez et al., 2020). Most research evaluating how immune activation governs lipid metabolism is conducted in mid- and late-lactation cows, and it is unclear how accurately these studies can model the inflamed periparturient dairy cow.

Protein Metabolism

Administering LPS in rodents markedly increases muscle protein degradation (Jepson et al., 1986). Immune activation induces muscle proteolysis as a means of providing AA to support gluconeogenesis (Wannemacher et al., 1980) and APP synthesis (Iseri and Klasing, 2013, 2014). The extent of skeletal muscle protein catabolism to assist APP synthesis far exceeds the true requirement due to dissimilarities in the AA composition between muscle and APP (Reeds et al., 1994). Amino acids not incorporated into APP are deaminated and the carbon skeletons are utilized for glucose synthesis, whereas the amino groups enter ureagenesis. As a result, BUN concentrations consistently increase in monogastric immunoactivation models. In ruminants, changes in circulating BUN are more variable as the increase may be masked by changes in rumen ammonia flux, which is altered due to decreased substrate availability and variations in ruminal microbiota composition and function (Galyean et al., 1981). In agreement with this, we observed no change in circulating BUN within 12 h

of LPS administration in lactating cows (Kvidera et al., 2017b) but did detect increased BUN 18 h postinfusion (Horst et al., 2018, 2019). A more reliable marker of muscle protein mobilization, 3-methylhistidine (Blum et al., 1985), is increased in cows exhibiting a more pronounced inflammatory response postpartum (Zhou et al., 2017). In addition to supporting glucose and APP synthesis, AA released from muscle (particularly glutamine and arginine) may also be directly utilized as a fuel source for activated leukocytes (Newsholme and Newsholme, 1989; Newsholme et al., 1999). In summary, skeletal muscle catabolism plays a key role in the homeorhetic response to immunoactivation.

Ca Homeostasis

In addition to altering energetics, infection markedly reduces circulating Ca. Hypocalcemia is a species-conserved response to infection in humans (Cardenas-Rivero et al., 1989; Dias et al., 2013), calves (Tennant et al., 1973; Elsasser et al., 1996), dogs (Holowaychuk et al., 2012), horses (Toribio et al., 2005), pigs (Carlstedt et al., 2000), and sheep (Naylor and Kronfeld, 1986). Unsurprisingly, cows administered LPS also become hypocalcemic (Griell et al., 1975; Waldron et al., 2003b; Kvidera et al., 2017b; Al-Qaisi et al., 2020), as do cows challenged with SARA (Minuti et al., 2014; Stefanska et al., 2018). Although infection-induced hypocalcemia is common and repeatable, the role Ca plays during the inflammatory state remains relatively obscure.

Recently, we studied the effects of ameliorating hypocalcemia following an LPS challenge in lactating dairy cows (Al-Qaisi et al., 2020; Horst et al., 2020a). Administering Ca (both orally and intravenously) successfully alleviated the severity of LPS-induced hypocalcemia. Using the LPS-eucalcemic clamp technique, we calculated that the total Ca disappearance from the circulating pool was ~20 g during an acute (12-h) model of immune activation (Horst et al., 2020a). Despite both models (oral and intravenous Ca) relieving the magnitude of hypocalcemia, the ramifications on productivity were strikingly different. Providing oral Ca before and after LPS administration increased milk yield and feed intake (Al-Qaisi et al., 2020). Conversely, maintaining eucalcemia (via intravenous infusion) intensified the inflammatory response and had deleterious effects on production (Horst et al., 2020a). Coincidentally, LPS-induced severe hypocalcemia did not influence neutrophil function, nor did rescuing eucalcemia affect neutrophil function metrics (Horst et al., 2020a). An ostensible explanation for the incongruous results may be the administration route. Intravenous Ca appears detrimental to hormonal Ca regulation compared with oral boluses, and others have suggested that it should

not be used to treat SCH (Wilms et al., 2019). It is likely that secondary signals accompanying alimentary Ca absorption might explain why oral Ca improved multiple metrics following immunoactivation and the intravenous route did not.

Even though the results of the eucalcemic clamp were unexpected, they are actually consistent with the literature on sepsis. Septic humans become hypocalcemic (Zaloga, 1992), and Ca administration increases the incidence of organ failure and mortality (Malcolm et al., 1989). It appears that infection-induced hypocalcemia is a protective strategy enlisted to facilitate a noninflammatory route to remove circulating endotoxin and should not be considered pathologic (Skarnes and Chedid, 1964; Collage et al., 2013; Eckel and Ametaj, 2016). When circulating Ca concentrations are decreased, LPS aggregation is inhibited, which allows the transfer of LPS to lipoproteins for biliary excretion (a noninflammatory route of LPS clearance). In contrast, during eucalcemia, LPS disaggregation is inhibited (Skarnes and Chedid, 1964), and, consequently, LPS is recognized by cells containing TLR4 receptors (resulting in a hyperinflammatory response). This mechanism may explain why changes in Ca homeostatic regulators (i.e., PTH, calcitonin, and vitamin D) favor a hypocalcemic state during infection (Nielsen et al., 1997; Waldron et al., 2003b; Holowaychuk et al., 2012). The relationship between immune activation and hypocalcemia has practical relevance for the transition period and is further discussed below.

ROLE OF INFLAMMATION IN TRANSITION COW PERFORMANCE

We do not believe it is coincidental that immunoactivation-induced disruptions in energetic and Ca metabolism closely resemble changes observed in poorly transitioning cows (Figure 1), as hypothesized by James Drackley and his colleagues more than 20 yr ago (Drackley, 1999; Drackley et al., 2001). Bertoni et al. (2008) demonstrated that cows with the most severe inflammatory profile were at a substantially higher risk of developing transition disorders. In addition, essentially all of the major transition cow diseases and disorders (i.e., metritis, mastitis, ketosis, milk fever, and RP) are preceded by a heightened inflammatory response (Huzzey et al., 2009; Dervishi et al., 2015, 2016a,b; Zhang et al., 2015, 2016; Abuajamieh et al., 2016).

Appetite

Depressed feed intake before calving is a well-characterized response and is an important determining factor in the severity of NEB that ensues (Hayirli et al., 2002).

Inflammatory mediators released during an immune response have potent anorexic effects (Kushibiki et al., 2003) and thus likely contribute to depressed feed intake surrounding calving (Kuhla, 2020). Anorexia is a universally conserved response to infection (Aubert et al., 1997; Wang et al., 2016; Kvidera et al., 2017b,c) and occurs even in insects (Adamo, 2005; Shakhar and Shakhar, 2015). In support of this, cows exhibiting an earlier and larger reduction in feed intake before parturition had a concomitantly more robust increase in Hp concentrations (Trevisi et al., 2002; Figures 2 and 3). Furthermore, cows with poor liver functionality or activity (a proxy of inflammation) had lower feed intake, decreased rumination time, an exacerbated NEB, and increased NEFA and BHB (Trevisi et al., 2010, 2012; Zhou et al., 2016).

Immune activation- and inflammation-induced reductions in feed intake and rumination may increase the opportunity for abomasal migration and subsequent DA. In fact, endotoxin administration during the periparturient period increases the incidence of DA (Zebeli et al., 2011), corroborating inflammation's role in the disorder. In addition to DA, inflammation has also been associated with ketosis development. We and others have previously demonstrated that cows that develop ketosis postpartum (and no other overt health event) had higher concentrations of LPS, cytokines, APP, and lactate before disease diagnosis (Abuajamieh et al., 2016; Zhang et al., 2016), and these changes could be observed as early as 8 wk before calving (Zhang et al., 2016). Additional indicators of inflammation such as increased markers of liver impairment (e.g., glutamic-oxaloacetic transaminase and bilirubin), decreased negative APP (e.g., retinol), increased neutrophil and monocyte activation markers, and decreased circulating Zn have also been observed in ketotic cows relative to their healthy herdmates (Rodriguez-Jimenez et al., 2018; Mezzetti et al., 2019). Shen et al. (2019) detected increased hepatic expression of inflammatory genes (e.g., nuclear factor- $\kappa\beta$, proinflammatory cytokines, inducible nitric oxide synthase) and circulating cytokines in ketotic cows; however, the authors concluded that ketosis caused inflammation rather than vice versa. We believe that inflammation before calving accentuates the reduction in feed intake, stimulates increased adipose tissue mobilization, creates an additional drain for glucose, and thus subsequently promotes ketone synthesis. Evidence suggests that inflammatory cytokines may also act directly on the adipocyte to stimulate lipolysis (see "Lipid Metabolism"), further increasing the opportunity for ketone body production. Therefore, decreased feed intake, increased NEFA, and hyperketonemia are likely consequences of immune activation and are not themselves causative of transition disorders

(Figures 2 and 3). It is important to note that increased NEFA and ketones in the absence of inflammation and poor lactational performance should not be considered problematic, as these are necessary mechanisms that healthy cows enlist to spare glucose for lactogenesis and galactopoiesis.

Fatty Liver

Fatty liver is traditionally thought to occur when excessive adipose tissue mobilization and corresponding hepatic NEFA uptake exceed the liver's capacity to fully utilize them (Herdt, 1988). Triglycerides are believed to rapidly accumulate because of the ruminant liver's poor capacity to export very-low-density lipoprotein (Kleppe et al., 1988). In nonruminants, hepatic steatosis is commonly observed during intestinal hyperpermeability pathologies (Ilan, 2012; Hamarneh et al., 2017) and can be induced by inflammatory cytokine infusion (see "Lipid Metabolism"). Inflammatory cytokines produced in response to LPS recognition negatively affect hepatic lipid trafficking (Lanza-Jacoby and Tabares, 1990; Endo et al., 2007; Stienstra et al., 2010). Inflammation's role in hepatic lipid metabolism is confirmed by LPS and cytokine recognition interference experiments that ameliorate liver fat accumulation (Endo et al., 2007; Spruss et al., 2009; Jin et al., 2017; Jia et al., 2018). It is generally believed that increased hepatic NEFA delivery and inflammation must coincide for progression of fatty liver disease, which is a concept known as the 2-hit hypothesis (Day and James, 1998; Csak et al., 2011), a scenario that clearly occurs in periparturient dairy cows. Therefore, strong evidence demonstrates a role of immune activation and inflammation in fatty liver development.

In transition cows, heightened circulating inflammatory markers precede fatty liver (Ohtsuka et al., 2001; Ametaj et al., 2005, 2010), suggesting that the same relationship between hepatic inflammation and lipid accumulation likely exists in ruminants. Additionally, daily TNF- α infusion in late-lactation cows altered hepatic lipid handling and increased hepatic TG storage (Bradford et al., 2009). Graugnard et al. (2013) demonstrated an exacerbated increase in liver TG content in cows that were overfed prepartum and administered intramammary LPS postpartum. However, no change in liver TG content was observed with continuous TNF- α infusion in late lactation (Martel et al., 2014) or repeated infusions in early-lactation cows (Yuan et al., 2013). Reasons for the inconsistencies are not clear, but infusing a single antigen (LPS) or cytokine (TNF- α) likely does not model the complexities associated with a natural infection. Regardless, effects of immune activation on adipose tissue mobilization

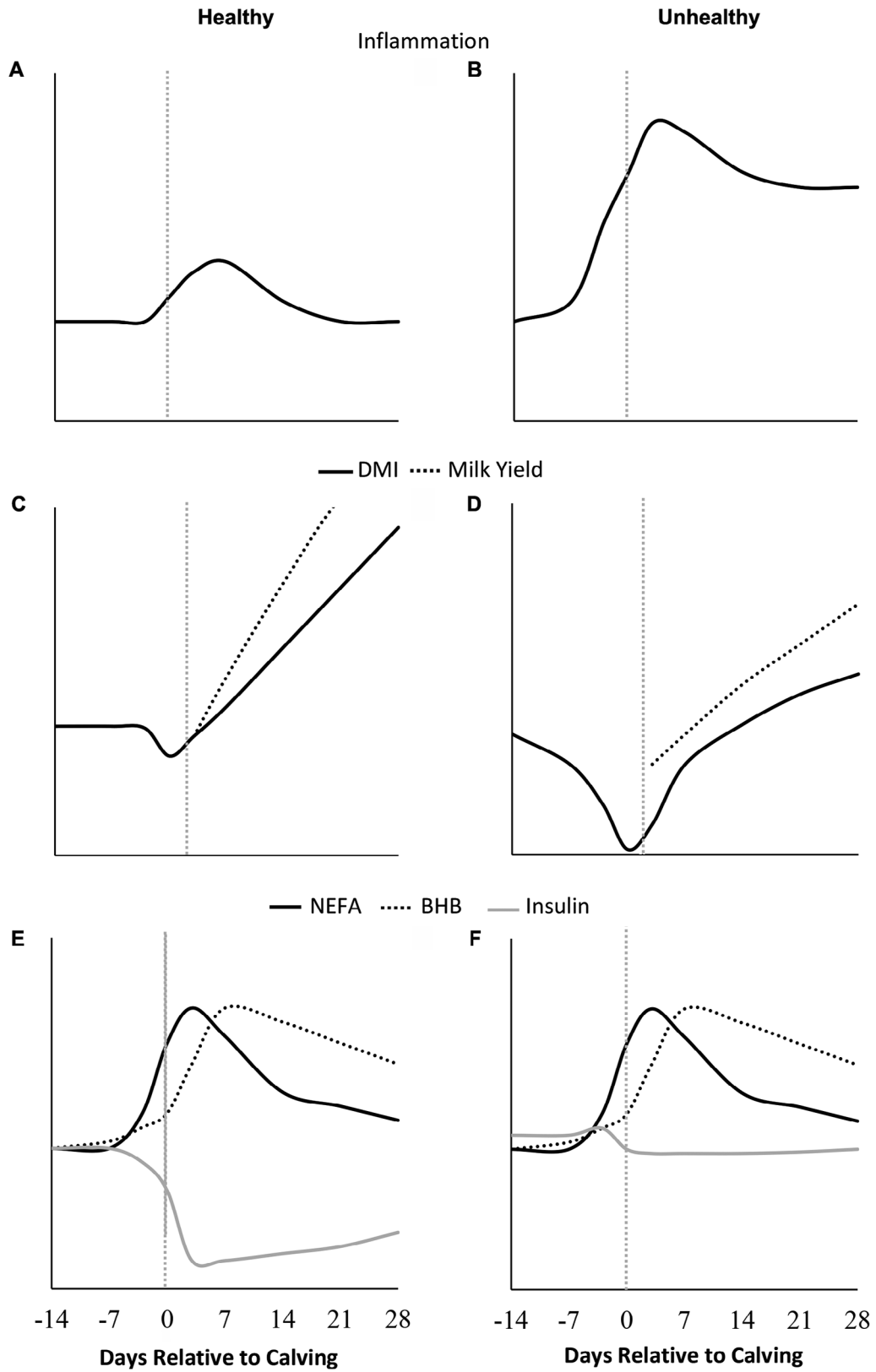


Figure 3. Examples of the temporal pattern of inflammation (A and B), feed intake and milk yield (C and D), and metabolism (E and F) in healthy and unhealthy (immune-activated) cows. The vertical dashed line represents parturition, and the x-axis represents time. NEFA = nonesterified fatty acids.

(both by direct action on adipocytes and as a result of decreased feed intake) and hepatic NEFA delivery coupled with inflammation-induced alterations in hepatic lipid handling may culminate in fatty liver in transition cows. An additional mechanism by which inflammation may increase fatty liver is preferential shunting of lipoprotein–LPS complexes to hepatocytes at a rate exceeding biliary excretion. Collectively, the body of evidence strongly suggests that immune activation and inflammation are key participators in periparturient hepatic steatosis.

Milk Fever

Clinical hypocalcemia incidence has been markedly reduced with the introduction of therapeutic and prophylactic strategies (Charbonneau et al., 2006; Reinhardt et al., 2011); however, SCH remains prevalent. It has recently been recognized that the temporal pattern of circulating Ca differs markedly across SCH cases such that it is sometimes transient, whereas other times it is persistent or delayed (Caixeta et al., 2017; McArt and Neves, 2020). For example, McArt and Neves (2020) retroclassified cows into groups based on their post-calving temporal Ca concentrations: normocalcemia, transient SCH, persistent SCH, or delayed SCH. Interestingly, cows experiencing transient SCH produced more milk and were as healthy as normocalcemic cows, whereas the opposite (i.e., higher health risk and hindered productivity) was observed in cows experiencing either persistent or delayed SCH. The distinguishing feature between these different SCH types may be immune activation.

As previously mentioned (see “Calcium Homeostasis”), hypocalcemia is a well-characterized response to LPS, which presumably reflects a nonleukocyte strategy of LPS detoxification via lipoprotein sequestration. Impressively, early investigators hypothesized that immune activation caused milk fever (Thomas, 1889; Hibbs, 1950), but until recently (Aiumlamai et al., 1992; Eckel and Ametaj, 2016) it has rarely been considered a contributing factor. It is of interest to elucidate whether inflammation can explain the manifestation of the different hypocalcemia types, especially considering their associations with poor performance. Akin to increased NEFA and hyperketonemia, strong evidence suggests that some hypocalcemia is a consequence of immune activation and is not itself causative of transition disorders.

Immunosuppression

More than 30 yr ago, dairy science pioneers described impairments in leukocyte cellular functions during the

periparturient period (Kehrli et al., 1989); this immunosuppressive state has continued to be a topic of intensive investigation (Goff and Horst, 1997; Kimura et al., 2002; Lacetera et al., 2004, 2005; LeBlanc, 2020). Cellular leukocyte functions such as neutrophil phagocytosis, the ability of lymphocytes to respond to mitogens and produce antibodies, peripheral blood mononuclear cell DNA synthesis, immunoglobulin concentration, $\text{INF}\gamma$, complement, and lysozyme are often depressed prepartum (Kehrli et al., 1989; Goff and Horst, 1997; Mallard et al., 1998; Lacetera et al., 2005; Trevisi and Minuti, 2018). In large part, changes in cellular function are most evident in the immediate postpartum period (Goff and Horst, 1997; Trevisi and Minuti, 2018). In contrast to past literature, recent transcriptome analysis reports have demonstrated that many leukocyte cellular functions are actually upregulated postpartum (Mann et al., 2019; Minuti et al., 2020). Interestingly, Mann et al. (2019) demonstrated that leukocyte inflammatory pathways were upregulated to a larger extent in cows with a greater energy deficit (as determined by NEFA, BHB, and glucose concentrations). Although the exact sequence of events cannot be confirmed, it could be suggested that cows with an exacerbated inflammatory response have a subsequent greater magnitude of nutrient deficit and metabolic disease, as suggested above. Generalizing that an animal's entire immune system is suppressed based on the *ex vivo* function of one cell type can lead to oversimplification. Recently, it has been suggested that the immune system is not necessarily suppressed but rather is in an altered and dynamic state around parturition (Mor and Cardenas, 2010; Trevisi and Minuti, 2018; Minuti et al., 2020). This involves a disparity between systemic inflammation and the leukocyte cell function where systemic inflammation intensifies simultaneously with decreasing leukocyte function. Although this may hamper the ability of some leukocytes to clear pathogens, it also may be keeping leukocyte-mediated inflammation in check to prevent collateral tissue damage. The immune system is extremely complex and requires a coordinated effort of hundreds of different cell types to ensure that the insult is neutralized without exerting overinflammation. This often involves reduced function of one cell type and increased function of another. An increase in synthesis and secretion of APP simultaneous with a decrease in function in circulating neutrophils may be representative of this survival strategy.

RP and Reproductive Performance

Expulsion of fetal membranes necessitates an immune response as leukocytes facilitate the degradation of the cotyledon-caruncle attachment that separates

the placental membrane from maternal tissue (LeBlanc, 2008). The importance of inflammation in this response is evident by the fact that blocking inflammation (via administering nonsteroidal anti-inflammatory drugs, **NSAID**) increases the incidence of RP (Newby et al., 2017). Interestingly, intermittent endotoxin administration during the periparturient period also increases the incidence of RP (Zebeli et al., 2011). Results of this repeated insult model are consistent with decreased leukocyte function that may occur as a result of an amplified inflammatory response. Retained placenta increases the risk of uterine infections, and this appears to be at least partially mediated by its effects on the elimination of lochia, which contains high concentrations of LPS (Ametaj, 2017).

Both localized and systemic inflammation can negatively affect reproductive performance (Peter and Bosu, 1988; Williams et al., 2008; Sheldon et al., 2009; Lavon et al., 2011; Asaf et al., 2013). For example, uterine infection prolongs the luteal phase (Peter and Bosu, 1988; Williams et al., 2008; Sheldon et al., 2009), disrupts steroidogenesis (Sheldon et al., 2009), and has deleterious effects on postpartum folliculogenesis (Huszenicza et al., 1999). In addition, distal inflammation (e.g., mastitis) affects follicular steroid concentrations and impedes oocyte maturation (Lavon et al., 2011; Asaf et al., 2013). Early-lactation mastitic cows have delayed breeding and increased days open (Barker et al., 1998). Endotoxin administration significantly disrupts hypothalamic and pituitary hormone release and ovarian responsiveness (Coleman et al., 1993; Battaglia et al., 2000) and causes abortion (Giri et al., 1990). Thus, regardless of the origin, immune activation and the resulting inflammation negatively influence immediate and future reproduction. The direct effects of LPS and the ensuing inflammatory milieu on reproduction likely explain the modest correlations that NEFA, ketones, and Ca have with fertility (because immune activation also directly affects these metabolites).

NSAID

Considering the deleterious effects of excessive inflammation and transition cow health, NSAID have become an attractive strategy to negate postpartum diseases. In fact, administering NSAID to transitioning dairy cows increased both immediate and long-term milk yield (Farney et al., 2013b; Carpenter et al., 2016). However, moderate inflammation is still observed in cows that successfully navigate the transition period, suggesting that some level of inflammation is tolerable and even required. In fact, inhibiting inflammation can actually increase the incidence of unfavorable health outcomes (i.e., fever, stillbirth, RP, metritis) and de-

crease milk yield (Shwartz et al., 2009; Newby et al., 2013, 2017). Furthermore, side effects of NSAID may include interference with fiber digestion, reduced feed intake, hypoglycemia, reduced energy balance, intestinal hyperpermeability, and increased inflammatory activity in adipose tissue (Farney et al., 2013a; Carpenter et al., 2016, 2017; Utzeri and Usai, 2017; Takiya et al., 2019). Additionally, inconsistencies exist as NSAID can have negative or positive effects on milk yield depending on parity (Farney et al., 2013b), and fertility outcomes are dependent on timing (Spencer et al., 2020). Some of the variation in the aforementioned studies may be due to the different NSAID used (e.g., salicylate, flunixin, meloxicam) and the complexities that may exist within each class. Current knowledge regarding NSAID effects on cow health and productivity suggests that inflammation is a double-edged sword in which a moderate amount is needed to ensure a successful transition and that benefits may favor a particular parity or administration timing. Therefore, although modulating periparturient inflammation to improve cow health and performance holds promise, the concept remains in its infancy and requires further refinement. As of now, management, nutritional, and veterinary efforts should be focused on preventing immune activation and thus the ensuing inflammatory sequelae.

CONCLUSIONS

Marked adjustments in energetic and mineral metabolism that are necessary for lactogenesis and galactopoiesis occur during the periparturient period. The homeorhetic changes are characterized by increased circulating NEFA, hyperketonemia, and SCH. The magnitude of changes in these 3 are mildly correlated with suboptimal feed intake and productivity, health problems and culling, and poor reproduction. The observed association between negative transition cow outcomes and high NEFA, hyperketonemia, and hypocalcemia has errantly evolved into a causal relationship. Despite a lack of supportive evidence from controlled and intervening experiments, the global dogma is that efforts should be made to prevent the increase in NEFA and ketones and decrease in circulating Ca. Immune activation is accompanied by large changes in whole-body energetic and mineral metabolism to support the nutrient requirements of leukocytes. Incidentally, many of these adjustments are similar to those observed in a poorly transitioning dairy cow. Of particular importance is immune-induced hypophagia and the metabolic consequences of this during rapid rates of increased milk yield. In transition dairy cows, immune activation likely stems from a compromised epithelial barrier at the uterus, mammary gland, intes-

tine, or any combination thereof. Consequently, almost all periparturient dairy cows, even overtly healthy ones, experience periparturient inflammation. The severity of the inflammation dictates the phenotypic outcomes and precedes clinical diagnosis of a disorder or disease. It is time to re-evaluate the traditional paradigm of the periparturient dairy cow. The body of evidence linking changes in increased circulating NEFA, hyperketonemia, and hypocalcemia with negative outcomes has never been overly strong. Further, the doctrine lacks biological plausibility as these are natural homeostatic adaptations that healthy cows use to synthesize milk, an integral component of the mammalian reproductive cycle. A more likely reason for the observed correlation is that they are merely signs of immune activation.

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