J. Dairy Sci. 104:8380–8410
https://doi.org/10.3168/jds.2021-20330

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

E. A. Horst, S. K. Kvidera, and L. H. Baumgard*
Department of Animal Science, Iowa State University, Ames 50011

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 nonesterified 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 homeorhetic 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

Received February 19, 2021.
Accepted April 15, 2021.
*Corresponding author: baumgard@iastate.edu

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 carbohydrate 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 (Thilsing-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; Sjollema 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 classify 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.,

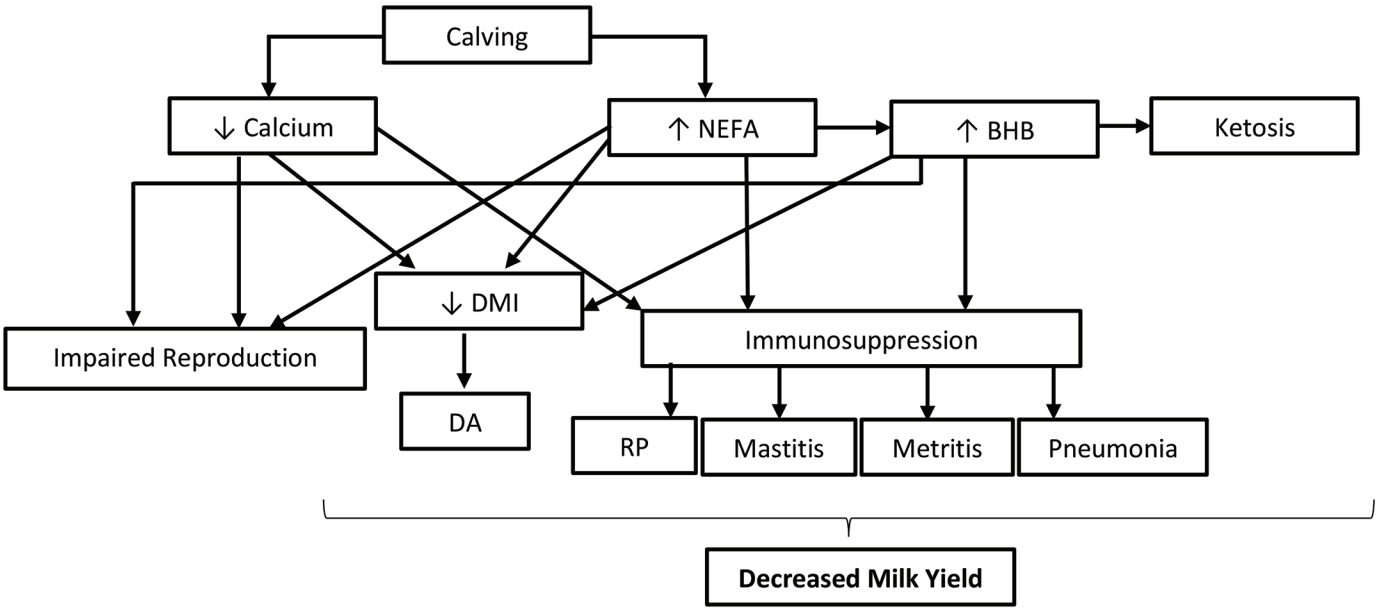

Figure 1. Traditional mechanisms by which hypocalcemia and increased nonesterified fatty acids (NEFA) and hyperketonemia are thought to cause poor transition cow health and performance. DA = displaced abomasum; RP = retained placenta.

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 $\geq$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 ~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 (Ingvartsen 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; Ingvartsen and Andersen, 2000; Hayirli et al., 2002; Ingvartsen, 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. Prepartum 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, suboptimal 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-

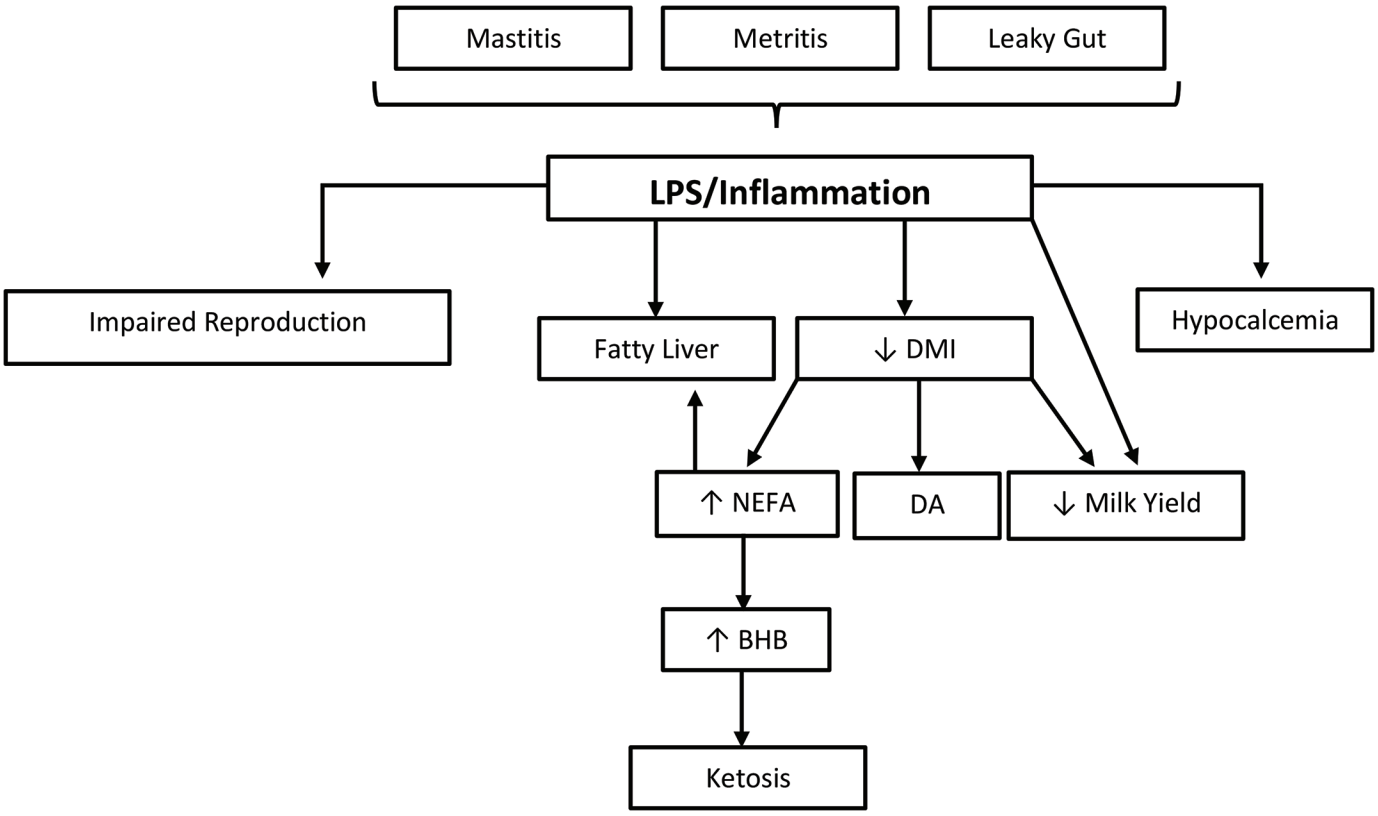

Figure 2. Potential downstream consequences of immune activation. In this model, decreased feed intake, hypocalcemia, excessive nonesterified fatty acids (NEFA), hyperketonemia, and hepatic lipidosis are not causative of poor transition cow performance and health but rather reflect prior immune stimulation.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

tion can be experimentally modeled via administrating 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 semipermeable 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 m^2 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 adrenocorticotropin 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 immune 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 (Griel 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). Administrating 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-κβ, 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 diary 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

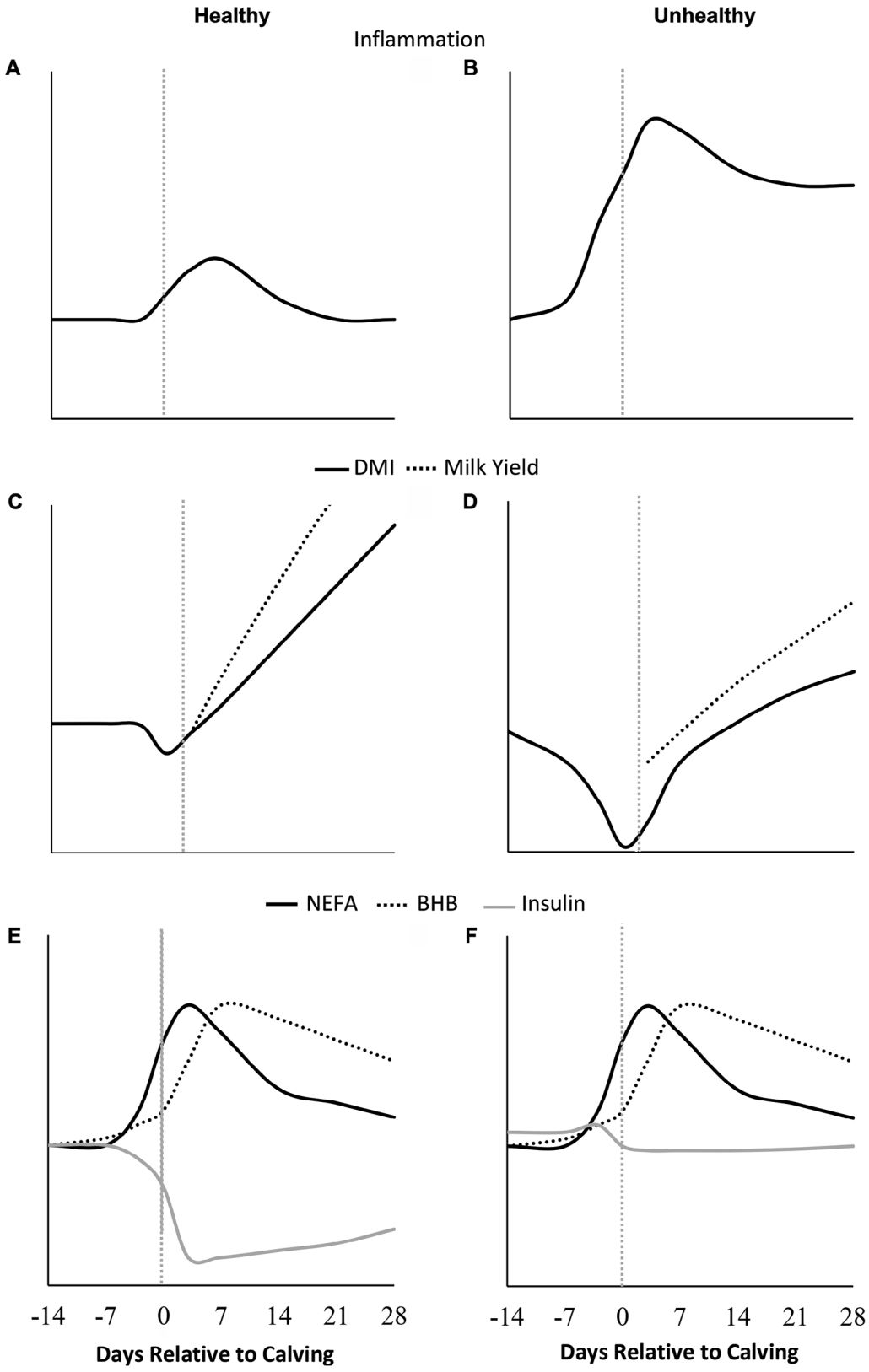

Figure 3. Examples of the temporal patterm of inflammation (A and B), feed intake and milk yield (C and D), and metabolism (E and F) in healthy and unhealthy (immune-activated) cows. The vertical dashed line represents parturition, and the x-axis represents time. NEFA = nonesterified fatty acids.

(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 pariparturient 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 postcalving 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, INFγ, 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 decrease 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 homeorhetic 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.

ACKNOWLEDGMENTS

The authors are grateful to the Norman Jacobson Endowment (Iowa State University, Ames) and input (festive debates and befuddled arguments) from Mike Allen, Dale Bauman, Don Beitz, Stephen Butler, Bob Collier, Brian Crooker, Jesse Goff, Pat Gorden, Ron Horst, Jane Kay, Mark Kehrli, Mark McGuire, Chel Moore, Luis Rodriguez, Robert Rhoads, Victoria Sanz Fernandez, and Matt Waldron. The authors have not stated any conflicts of interest.

REFERENCES

Abdelli, A., D. Raboisson, R. Kaidi, B. Ibrahim, A. Kalem, and M. Iguer-Ouada. 2017. Elevated non-esterified fatty acid and β-hydroxybutyrate in transition dairy cows and their association with reproductive performance and disorders: A meta-analysis. Theriogenology 93:99–104. https://doi.org/10.1016/j.theriogenology.2017.01.030.

Abuajamieh, M., S. K. Kvidera, M. V. S. Fernandez, A. Nayeri, N. C. Upah, E. A. Nolan, S. M. Lei, J. M. DeFrain, H. B. Green, K. M. Schoenberg, W. E. Trout, and L. H. Baumgard. 2016. Inflammatory biomarkers are associated with ketosis in periparturient Holstein cows. Res. Vet. Sci. 109:81–85. https://doi.org/10.1016/j.rvsc.2016.09.015.

Adamo, S. A. 2005. Parasitic suppression of feeding in the tobacco hornworm, *Manduca sexta*: Parallels with feeding depression after an immune challenge. Arch. Insect Biochem. Physiol. 60:185–197. https://doi.org/10.1002/arch.20068.

Adrover, J. M., J. A. Nicolas-Avila, and A. Hidalgo. 2016. Aging: A temporal dimension for neutrophils. Trends Immunol. 37:334–345. https://doi.org/10.1016/j.it.2016.03.005.

Ahmed, K., S. Tunaru, C. Tang, M. Muller, A. Gille, A. Sassmann, J. Hanson, and S. Offermanns. 2010. An autocrine lactate loop mediates insulin-dependent inhibition of lipolysis through GPR81. Cell Metab. 11:311–319. https://doi.org/10.1016/j.cmet.2010.02.012.

Aiumlamai, S., G. Fredriksson, H. Kindahl, and L. E. Edqvist. 1992. A possible role of endotoxins in spontaneous paretic cows around parturition. Zentralbl. Veterinärmed. A 39:57–68. https://doi.org/10.1111/j.1439-0442.1992.tb00156.x.

Al-Qaisi, M., S. K. Kvidera, E. A. Horst, C. S. McCarthy, E. J. Mayorga, M. A. Abeyta, B. M. Goetz, N. C. Upah, D. M. McKilligan, H. A. Ramirez-Ramirez, L. L. Timms, and L. H. Baumgard. 2020. Effects of an oral supplement containing calcium and live yeast on post-absorptive metabolism, inflammation and production following intravenous lipopolysaccharide infusion in dairy cows. Res. Vet. Sci. 129:74–81. https://doi.org/10.1016/j.rvsc.2020.01.007.

Albert-Bayo, M., I. Paracuellos, A. M. González-Castro, A. Rodríguez-Urrutia, M. J. Rodríguez-Lagunas, C. Alonso-Cotoner, J. Santos, and M. Vicario. 2019. Intestinal mucosal mast cells: Key modulators of barrier function and homeostasis. Cells 8:135. https://doi.org/10.3390/cells8020135.

Aleri, J. W., B. C. Hine, M. F. Pyman, P. D. Mansell, W. J. Wales, B. Mallard, and A. D. Fisher. 2016. Periparturient immunosuppression and strategies to improve dairy cow health during the periparturient period. Res. Vet. Sci. 108:8–17. https://doi.org/10.1016/j.rvsc.2016.07.007.

Allen, M. S. 2020. Review: Control of feed intake by hepatic oxidation in ruminant animals: Integration of homeostasis and homeorhesis. Animal 14(Suppl. 1):s55–s64. https://doi.org/10.1017/S1751731119003215.

Allen, M. S., B. J. Bradford, and M. Oba. 2009. Board invited review: The hepatic oxidation theory of the control of feed intake and its application to ruminants. J. Anim. Sci. 87:3317–3334. https://doi.org/10.2527/jas.2009-1779.

Ametaj, B. N. 2017. Retained placenta: A systems veterinary approach. Pages 121–137 in Periparturient Diseases of Dairy Cows: A Systems Biology Approach. B. N. Ametaj, ed. Springer International Publishing AG.

Ametaj, B. N., B. J. Bradford, G. Bobe, R. A. Nafikov, Y. Lu, J. W. Young, and D. C. Beitz. 2005. Strong relationships between mediators of the acute phase response and fatty liver in dairy cows. Can. J. Anim. Sci. 85:165–175. https://doi.org/10.4141/A04-043.

Ametaj, B. N., Q. Zebeli, and S. Iqbal. 2010. Nutrition, microbiota, and endotoxin-related diseases in dairy cows. Rev. Bras. Zootec. 39(Suppl.):433–444. https://doi.org/10.1590/S1516-35982010001300048.

Arredouani, M. S., A. Kasran, J. A. Vanoirbeek, F. G. Berger, H. Baumann, and J. L. Ceuppens. 2005. Haptoglobin dampens endotoxin-induced inflammatory effects both in vitro and in vivo. Immunology 114:263–271. https://doi.org/10.1111/j.1365-2567.2004.02071.x.

Asaf, S., G. Leitner, O. Furman, Y. Lavon, D. Kalo, D. Wolfenson, and Z. Roth. 2013. Effects of *Escherichia coli*- and *Staphylococcus aureus*- induced mastitis in lactating cows on oocyte developmental competence. Reproduction 147:33–43. https://doi.org/10.1530/REP-13-0383.

Atabai, K., D. Sheppard, and Z. Werb. 2007. Roles of the innate immune system in mammary gland remodeling during involution. J. Mammary Gland Biol. Neoplasia 12:37–45. https://doi.org/10.1007/s10911-007-9036-6.

Aubert, A., G. Goodall, R. Dantzer, and G. Gheusi. 1997. Differential effects of lipopolysaccharide on pup retrieving and nest building in lactating mice. Brain Behav. Immun. 11:107–118. https://doi.org/10.1006/brbi.1997.0485.

Bach, K. D., D. M. Barbano, and J. A. A. McArt. 2019. Association of mid-infrared-predicted milk and blood constituents with early-lactation disease, removal, and production outcomes in Holstein cows. J. Dairy Sci. 102:10129–10139. https://doi.org/10.3168/jds.2019-16926.

Bagby, G. J., and J. A. Spitzer. 1980. Lipoprotein lipase activity in rat heart and adipose tissue during endotoxin shock. Am. J. Physiol. 238:H325–H330.

Baird, G. D. 1982. Primary ketosis in the high-producing dairy cow: Clinical and subclinical disorders, treatment, prevention and outlook. J. Dairy Sci. 65:1–10. https://doi.org/10.3168/jds.S0022-0302(82)82146-2.

Ballou, M. A. 2012. Inflammation: Role in the etiology and pathophysiology of clinical mastitis in dairy cows. J. Anim. Sci. 90:1466–1478. https://doi.org/10.2527/jas.2011-4663.

Ballou, M. A., G. D. Cruz, W. Pittroff, D. H. Keisler, and E. J. DePeters. 2008. Modifying the acute phase response of Jersey calves by supplementing milk replacer with omega-3 fatty acids from fish oil. J. Dairy Sci. 91:3478–3487. https://doi.org/10.3168/jds.2008-1016.

Barker, A. R., F. N. Schrick, M. J. Lewis, H. H. Dowlen, and S. P. Oliver. 1998. Influence of clinical mastitis during early lactation on reproductive performance of Jersey cows. J. Dairy Sci. 81:1285–1290. https://doi.org/10.3168/jds.S0022-0302(98)75690-5.

Barnes, M. A., G. W. Kazmer, R. M. Akers, and R. E. Pearson. 1985. Influence of secretion for milk yield on endogenous hormones and metabolites in Holstein heifers and cows. J. Anim. Sci. 60:271–284. https://doi.org/10.2527/jas1985.601271x.

Barragan, A. A., J. M. Piñeiro, G. M. Schuenemann, P. J. Rajala-Schultz, D. E. Sanders, J. Lakritz, and S. Bas. 2018. Assessment of daily activity patterns and biomarkers of pain, inflammation, and stress in lactating dairy cows diagnosed with clinical metritis. J. Dairy Sci. 101:8248–8258. https://doi.org/10.3168/jds.2018-14510.

Battaglia, D. F., H. B. Krasa, V. Padmanabhan, C. Viguie, and F. J. Karsch. 2000. Endocrine alterations that underlie endotoxin-induced disruption of the follicular phase in ewes. Biol. Reprod. 62:45–53. https://doi.org/10.1095/biolreprod62.1.45.

Bauman, D. E., and W. B. Currie. 1980. Partitioning of nutrients during pregnancy and lactation: A review of mechanisms involving homeostasis and homeorhesis. J. Dairy Sci. 63:1514–1529. https://doi.org/10.3168/jds.S0022-0302(80)83111-0.

Bauman, D. E., and R. G. Vernon. 1993. Effects of exogenous bovine somatotropin on lactation. Annu. Rev. Nutr. 13:437–461. https://doi.org/10.1146/annurev.nu.13.070193.002253.

Baumgard, L. H., R. J. Collier, and D. E. Bauman. 2017. A 100-year review: Regulation of nutrient partitioning to support lactation. J. Dairy Sci. 100:10353–10366. https://doi.org/10.3168/jds.2017-13242.

Baumgard, L. H., and R. P. Rhoads Jr.. 2013. Effects of heat stress on postabsorptive metabolism and energetics. Annu. Rev. Anim. Biosci. 1:311–337. https://doi.org/10.1146/annurev-animal-031412-103644.

Belay, T. K., M. Svendsen, Z. M. Kowalski, and T. Ådnøy. 2017. Genetic parameters of blood β- hydroxybutyrate predicted from milk infrared spectra and clinical ketosis, and their associations with milk production traits in Norwegian Red cows. J. Dairy Sci. 100:6298–6311. https://doi.org/10.3168/jds.2016-12458.

Bell, A. W. 1995. Regulation of organic nutrient metabolism during transition from late pregnancy to early lactation. J. Anim. Sci. 73:2804–2819. https://doi.org/10.2527/1995.7392804x.

Bell, A. W., and D. E. Bauman. 1997. Adaptations of glucose metabolism during pregnancy and lactation. J. Mammary Gland Biol. Neoplasia 2:265–278. https://doi.org/10.1023/A:1026336505343.

Berg, J., J. Tymoczko, and L. Stryer. 2002. Biochemistry. 5th ed. Freeman.

Berge, A. C., and G. Vertenten. 2014. A field study to determine the prevalence, dairy herd management systems, and fresh cow clinical conditions associated with ketosis in western European dairy herds. J. Dairy Sci. 97:2145–2154. https://doi.org/10.3168/jds.2013-7163.

Bertoni, G., E. Trevisi, X. Han, and M. Bionaz. 2008. Effects of inflammatory conditions on liver activity in puerperium period and consequences for performance in dairy cows. J. Dairy Sci. 91:3300–3310. https://doi.org/10.3168/jds.2008-0995.

Bicalho, M. L. S., F. S. Lima, E. K. Ganda, C. Foditsch, E. B. S. Meira Jr., V. S. Machado, A. G. V. Teixeira, G. Oikonomou, R. O. Gilbert, and R. C. Bicalho. 2014. Effect of trace mineral supplementation on selected minerals, energy metabolites, oxidative stress, and immune parameters and its association with uterine diseases in dairy cattle. J. Dairy Sci. 97:4281–4295. https://doi.org/10.3168/jds.2013-7832.

Bicalho, M. L. S., E. C. Marques, R. O. Gilbert, and R. C. Bicalho. 2017. The association of plasma glucose, BHBA, and NEFA with postpartum uterine diseases, fertility, and milk production of Holstein dairy cows. Theriogenology 88:270–282. https://doi.org/10.1016/j.theriogenology.2016.09.036.

Bionaz, M., E. Trevisi, L. Calamari, L. Librandi, A. Ferrari, and G. Bertoni. 2007. Plasma paraoxonase, health, inflammatory conditions, and liver function in transition dairy cows. J. Dairy Sci. 90:1740–1750. https://doi.org/10.3168/jds.2006-445.

Björntorp, B. 1966. Effect of ketone bodies on lipolysis in adipose tissue in vitro. J. Lipid Res. 7:621–626. https://doi.org/10.1016/S0022-2275(20)39242-7.

Blackard, W. G., J. H. Anderson Jr., and J. J. Spitzer. 1976. Hyperinsulinism in endotoxin shock dogs. Metabolism 25:675–684. https://doi.org/10.1016/0026-0495(76)90065-2.

Blander, J. M., and L. E. Sander. 2012. Beyond pattern recognition: Five immune checkpoints for scaling the microbial threat. Nat. Rev. Immunol. 12:215–225. https://doi.org/10.1038/nri3167.

Blum, J. W., T. Reding, F. Jans, M. Wanner, M. Zemp, and K. Bachmann. 1985. Variations of 3-methylhistidine in blood of dairy cows. J. Dairy Sci. 68:2580–2587. https://doi.org/10.3168/jds.S0022-0302(85)81140-1.

Borregaard, N., and T. Herlin. 1982. Energy metabolism of human neutrophils during phagocytosis. J. Clin. Invest. 70:550–557. https://doi.org/10.1172/JCI110647.

Bors, S. I., G. Solcan, and A. Vlad-Sabie. 2014. Effects of propylene glycol supplementation on blood indicators of hepatic function, body condition score, milk fat-protein concentration and reproductive performance of dairy cows. Acta Vet. Brno 83:27–32.

Bradford, B. J., L. K. Mamedova, J. E. Minton, J. S. Drouillard, and B. J. Johnson. 2009. Daily injection of tumor necrosis factor-α increases hepatic triglycerdies and alters transcript abundance of metabolic genes in lactating dairy cattle. J. Nutr. 139:1451–1456. https://doi.org/10.3945/jn.109.108233.

Bradley, A. J., and M. J. Green. 2004. The importance of the nonlactating period in the epidemiology of intramammary infection and strategies for prevention. Vet. Clin. North Am. Food Anim. Pract. 20:547–568. https://doi.org/10.1016/j.cvfa.2004.06.010.

Brockman, R. P. 1979. Roles for insulin and glucagon in the development of ruminant ketosis—A review. Can. Vet. J. 20:121–126.

Buehler, P. W., B. Abraham, F. Vallelian, C. Linnemayr, C. P. Pereira, J. F. Cipollo, Y. Jia, M. Mikolajczyk, F. S. Boretti, G. Schoedon, A. I. Alayash, and D. J. Schaer. 2009. Haptoglobin preserves the CD163 hemoglobin scavenger pathway by shielding hemoglobin from peroxidative modification. Blood 113:2578–2586. https://doi.org/10.1182/blood-2008-08-174466.

Burke, C. R., S. Meier, S. McDougall, C. Compton, M. Mitchell, and J. R. Roche. 2010. Relationships between endometritis and metabolic state during the transition period in pasture-grazed dairy cows. J. Dairy Sci. 93:5363–5373. https://doi.org/10.3168/jds.2010-3356.

Burton, J. L., and R. J. Erskine. 2003. Immunity and mastitis. Some new ideas for an old disease. Vet. Clin. North Am. Food Anim. Pract. 19:1–45. https://doi.org/10.1016/S0749-0720(02)00073-7.

Caixeta, L. S., S. L. Giesy, C. S. Krumm, J. W. Perfield II, A. Butterfield, K. M. Schoenberg, D. C. Beitz, and Y. R. Boisclair. 2017. Effects of circulating glucagon and free fatty acids on hepatic FGF21 production in dairy cows. Am. J. Physiol. Regul. Integr. Comp. Physiol. 313:R526–R534. https://doi.org/10.1152/ajpregu.00197.2017.

Calder, P. C., G. Dimitriadis, and P. Newsholme. 2007. Glucose metabolism in lymphoid and inflammatory cells and tissues. Curr. Opin. Clin. Nutr. Metab. Care 10:531–540. https://doi.org/10.1097/MCO.0b013e3281e72ad4.

Cameron, R. E. B., P. B. Dyk, T. H. Herdt, J. B. Kaneene, R. Miller, H. F. Bucholtz, J. S. Liesman, M. J. Vandehaar, and R. S. Emery. 1998. Dry cow diet, management, and energy balance as risk factors for displaced abomasum in high producing dairy herds. J. Dairy Sci. 81:132–139. https://doi.org/10.3168/jds.S0022-0302(98)75560-2.

Capel, M. B., K. D. Bach, S. Mann, and J. A. A. McArt. 2021. A randomized controlled trial to evaluate propylene glycol alone or in combination with dextrose as a treatment for hyperketonemia in dairy cows. J. Dairy Sci. 104:2185–2194. https://doi.org/10.3168/jds.2020-19111.

Cardenas-Rivero, N., B. Chernow, M. A. Stoiko, S. R. Nussbaum, and I. D. Todres. 1989. Hypocalcemia in critically ill children. J. Pediatr. 114:946–951. https://doi.org/10.1016/S0022-3476(89)80435-4.

Carlstedt, F., M. Eriksson, R. Kiiski, A. Larsson, and L. Lind. 2000. Hypocalcemia during porcine endotoxemic shock: Effects of cal-

cium administration. Crit. Care Med. 28:2909–2914. https://doi.org/10.1097/00003246-200008000-00037.
Carneiro, L., S. Geller, X. Fioramonti, A. Hébert, C. Repond, C. Leloup, and L. Pellerin. 2016a. Evidence for hypothalamic ketone body sensing: Impact on food intake and peripheral metabolic responses in mice. Am. J. Physiol. Endocrinol. Metab. 310:E103–E115. https://doi.org/10.1152/ajpendo.00282.2015.
Carneiro, L., S. Geller, A. Hébert, C. Repond, X. Fioramonti, C. Leloup, and L. Pellerin. 2016b. Hypothalamic sensing of ketone bodies after prolonged cerebral exposure leads to metabolic control dysregulation. Sci. Rep. 6:34909. https://doi.org/10.1038/srep34909.
Carpenter, A. J., C. F. Vargas Rodriguez, J. A. B. Jantz, and B. J. Bradford. 2017. Short communication: Sodium salicylate negatively affects rumen fermentation in vitro and in situ. J. Dairy Sci. 100:1935–1939. https://doi.org/10.3168/jds.2016-11832.
Carpenter, A. J., C. F. V. Rodriguez, J. A. B. Jantz, and B. J. Bradford. 2016. Hot topic: Early postpartum treatment of commercial dairy cows with nonsteroidal antiinflammatory drugs increases whole-lactation milk yield. J. Dairy Sci. 99:672–679. https://doi.org/10.3168/jds.2015-10048.
Ceciliani, F., J. J. Ceron, P. D. Eckersall, and H. Sauerwein. 2012. Acute phase proteins in ruminants. J. Proteomics 75:4207–4231. https://doi.org/10.1016/j.jprot.2012.04.004.
Challis, J. R., C. J. Lockwood, L. Myatt, J. E. Norman, J. F. Strauss III, and F. Petraglia. 2009. Inflammation and pregnancy. Reprod. Sci. 16:206–215. https://doi.org/10.1177/1933719108329095.
Chang, C. J., and S. H. Young. 1992. Changes of mammary vein concentrations of glucose and free fatty acids induced by exogenous insulin and glucose, and relation to mammary gland function in Saanen goats. Small Rumin. Res. 7:123–133. https://doi.org/10.1016/0921-4488(92)90202-F.
Chapinal, N., M. Carson, T. F. Duffield, M. Capel, S. Godden, M. Overton, J. E. P. Santos, and S. J. LeBlanc. 2011. The association of serum metabolites with clinical disease during the transition period. J. Dairy Sci. 94:4897–4903. https://doi.org/10.3168/jds.2010-4075.
Chapinal, N., S. J. Leblanc, M. E. Carson, K. E. Leslie, S. Godden, M. Capel, J. E. Santos, M. W. Overton, and T. F. Duffield. 2012. Herd-level association of serum metabolites in the transition period with disease, milk production, and early lactation reproductive performance. J. Dairy Sci. 95:5676–5682. https://doi.org/10.3168/jds.2011-5132.
Charbonneau, E., D. Pellerin, and G. R. Oetzel. 2006. Impact of lowering dietary cation-anion difference in nonlactating dairy cows: A meta-analysis. J. Dairy Sci. 89:537–548. https://doi.org/10.3168/jds.S0022-0302(06)72116-6.
Charmandari, E., C. Tsigos, and G. Chrousos. 2005. Endocrinology of the stress response. Annu. Rev. Physiol. 67:259–284. https://doi.org/10.1146/annurev.physiol.67.040403.120816.
Chelikani, P. K., D. H. Keisler, and J. J. Kennelly. 2003. Response of plasma leptin concentration to jugular infusion of glucose or lipid is dependent on the stage of lactation of Holstein cows. J. Nutr. 133:4163–4171. https://doi.org/10.1093/jn/133.12.4163.
Clutter, A. D., W. E. Clutter, P. E. Cryer, J. A. Collins, and D. M. Bier. 1981. Epinephrine plasma thresholds for lipolytic effects in man: Measurements of fatty acid transport with [1–13C] palmitic acid. J. Clin. Invest. 67:1729–1738.
Coetzee, G. A., A. F. Strachan, D. R. van der Westhuyzen, H. C. Hoppe, M. S. Jeenah, and F. C. De Beer. 1986. Serum amyloid A-containing human high density lipoprotein 3. Density, size, and apolipoprotein composition. J. Biol. Chem. 261:9644–9651. https://doi.org/10.1016/S0021-9258(18)67562-3.
Coffey, M. P., G. Simm, and S. Brotherstone. 2002. Energy balance profiles for the first three lactations of dairy cows estimated using random regression. J. Dairy Sci. 85:2669–2678. https://doi.org/10.3168/jds.S0022-0302(02)74352-X.
Coleman, E. S., T. H. Elsasser, R. J. Kemppainen, D. A. Coleman, and J. L. Sartin. 1993. Effect of endotoxin on pituitary hormone secretion in sheep. Neuroendocrinology 58:111–122. https://doi.org/10.1159/000126520.
Collage, R. D., G. M. Howell, X. Zhang, J. L. Stripay, J. S. Lee, D. C. Angus, and M. R. Rosengart. 2013. Calcium supplementation during sepsis exacerbates organ failure and mortality via calcium/calmodulin-dependent protein kinase kinase (CaMKK) signaling. Crit. Care Med. 41:e352–e360. https://doi.org/10.1097/CCM.0b013e31828cf436.
Collier, R. J., L. H. Baumgard, A. L. Lock, and D. E. Bauman. 2005. Physiological limitations, nutrient partitioning. Pages 351–377 in Yield of Farmed Species: Constrains and Opportunities in the 21st Century. Proc. 61st Easter School, Nottingham, England. J. Wiseman and R. Bradley, ed. Nottingham University Press.
Collier, R. J., J. P. McNamara, C. R. Wallace, and M. H. Dehoff. 1984. A review of endocrine regulation of metabolism during lactation. J. Anim. Sci. 59:498–510. https://doi.org/10.2527/jas1984.592498x.
Conrad, H. R., A. D. Pratt, and J. W. Hibbs. 1964. Regulation of feed intake in dairy cows. 1. Change in importance of physical and physiological factors with increasing digestibility. J. Dairy Sci. 47:54–62. https://doi.org/10.3168/jds.S0022-0302(64)88581-7.
Cooke, R. F., and D. W. Bohnert. 2011. Technical note: Bovine acute-phase response after corticotrophin-release hormone challenge. J. Anim. Sci. 89:252–257. https://doi.org/10.2527/jas.2010-3131.
Cooke, R. F., J. A. Carroll, J. Dailey, B. I. Cappellozza, and D. W. Bohnert. 2012. Bovine acute-phase response after different doses of corticotropin-releasing hormone challenge. J. Anim. Sci. 90:2337–2344. https://doi.org/10.2527/jas.2011-4608.
Crocker, D. E., J. D. Williams, D. P. Costa, and B. J. Le Boeuf. 2001. Maternal traits and reproductive effort in northern elephant seals. Ecology 82:3541–3555. https://doi.org/10.1890/0012-9658(2001)082[3541:MTAREI]2.0.CO;2.
Csak, T., M. Ganz, J. Pespisa, K. Kodys, A. Dolganiuc, and G. Szabo. 2011. Fatty acid and endotoxin activate inflammasomes in mouse hepatocytes that release danger signals to stimulate immune cells. Hepatology 54:133–144. https://doi.org/10.1002/hep.24341.
Curtis, C. R., H. N. Erb, C. J. Sniffen, and R. D. Smith. 1984. Epidemiology of parturient paresis: Predisposing factors with emphasis on dry cow feeding and management. J. Dairy Sci. 67:817–825. https://doi.org/10.3168/jds.S0022-0302(84)81372-7.
Curtis, C. R., H. N. Erb, C. J. Sniffern, R. D. Smith, P. A. Powers, M. C. Smith, M. E. White, R. B. Hillman, and E. J. Pearson. 1983. Association of parturient hypocalcemia with eight periparturient disorders in Holstein cows. J. Am. Vet. Med. Assoc. 183:559.
Davies, H. T. O., I. K. Crombie, and M. Tavakoli. 1998. When can odds ratios mislead? BMJ 316:989–991. https://doi.org/10.1136/bmj.316.7136.989.
Davies, D., K. G. Meade, S. Herath, P. D. Eckersall, D. Gonzalez, J. O. White, R. S. Conlan, C. O'Farrelly, and I. M. Sheldon. 2008. Toll-like receptor and antimicrobial peptide expression in the bovine endometrium. Reprod. Biol. Endocrinol. 6:53.
Davis, J., D. Wirtshafter, K. Asin, and D. Brief. 1981. Sustained intracerebroventricular infusion of brain fuels reduces body weight and food intake in rats. Science 212:81–83.
Day, C. P., and O. F. James. 1998. Steatohepatitis: A tale of two "hits"? Gastroenterology 114:842–845. https://doi.org/10.1016/S0016-5085(98)70599-2.
De Buck, M., M. Gouwy, J. M. Wang, J. Van Snick, P. Proost, S. Struyf, and J. Van Damme. 2016. The cytokine-serum amyloid A-chemokine network. Cytokine Growth Factor Rev. 30:55–69. https://doi.org/10.1016/j.cytogfr.2015.12.010.
DeGaris, P. J., and I. J. Lean. 2008. Milk fever in dairy cows: A review of pathophysiology and control principles. Vet. J. 176:58–69. https://doi.org/10.1016/j.tvjl.2007.12.029.
Dervishi, E., G. Zhang, D. Hailemariam, S. M. Dunn, and B. N. Ametaj. 2015. Innate immunity and carbohydrate metabolism alterations precede occurrence of subclinical mastitis in transition dairy cows. J. Anim. Sci. Technol. 57:46–65. https://doi.org/10.1186/s40781-015-0079-8.
Dervishi, E., G. Zhang, D. Hailemariam, S. M. Dunn, and B. N. Ametaj. 2016a. Occurrence of retained placenta is preceded by an inflammatory state and alterations of energy metabolism in tran-

sition dairy cows. J. Anim. Sci. Biotechnol. 7:26–39. https://doi.org/10.1186/s40104-016-0085-9.

Dervishi, E., G. Zhang, D. Hailemariam, S. Goldansaz, Q. Deng, S. M. Dunn, and B. N. Ametaj. 2016b. Alterations in innate immunity reactants and carbohydrate and lipid metabolism precede occurrence of metritis in transition dairy cows. Res. Vet. Sci. 104:30–39. https://doi.org/10.1016/j.rvsc.2015.11.004.

Dias, C. R. B., H. P. Leite, P. C. K. Nogueira, and W. Brunow de Carvalho. 2013. Ionized hypocalcemia is an early event and is associated with organ dysfunction in children admitted to the intensive care unit. J. Crit. Care 28:810–815. https://doi.org/10.1016/j.jcrc.2013.03.019.

Dohoo, I. R., and S. W. Martin. 1984. Subclinical ketosis: Prevalence and associations with production and disease. Can. J. Comp. Med. 48:1–5.

Drackley, J. K. 1999. Biology of dairy cows during the transition period: The final frontier? J. Dairy Sci. 82:2259–2273. https://doi.org/10.3168/jds.S0022-0302(99)75474-3.

Drackley, J. K., T. R. Overton, and G. N. Douglas. 2001. Adaptations of glucose and long-chain fatty acid metabolism in liver of dairy cows during the periparturient period. J. Dairy Sci. 84(E.-Suppl.):E100–E112.

Dryerre, H., and J. R. Greig. 1925. Milk fever: Its possible association with derangements in the internal secretions. Vet. Rec. 5:225–231.

Ducusin, R. J., T. Sarashina, Y. Uzuka, S. Tanabe, and M. Ohtani. 2001. Phagocytic response of bovine polymorphonuclear leukocytes to different incubation conditions and following exposure to some effectors of phagocytosis and different anticoagulants in vitro. Can. J. Vet. Res. 65:38–44.

Ducusin, R. J., Y. Uzuka, E. Satoh, M. Otani, M. Nishimura, S. Tanabe, and T. Sarashina. 2003. Effects of extracellular Ca^{2+} on phagocytosis and intracellular Ca^{2+} concentrations in polymorphonuclear leukocytes of postpartum dairy cows. Res. Vet. Sci. 75:27–32. https://doi.org/10.1016/S0034-5288(03)00038-9.

Duffield, T. 2000. Subclinical ketosis in lactating dairy cattle. Vet. Clin. North Am. Food Anim. Pract. 16:231–253. https://doi.org/10.1016/s0749-0720(15)30103-1.

Duffield, T. F., K. D. Lissemore, B. W. McBride, and K. E. Leslie. 2009. Impact of hyperketonemia in early lactation dairy cows on health and production. J. Dairy Sci. 92:571–580. https://doi.org/10.3168/jds.2008-1507.

Eaton, J. W., P. Brandt, J. R. Mahoney, and J. T. Lee. 1982. Haptoglobin—A natural bacteriostat. Science 215:691–693. https://doi.org/10.1126/science.7036344.

Eckel, E. F., and B. N. Ametaj. 2016. Invited review: Role of bacterial endotoxins in the etiopathogenesis of periparturient diseases of transition dairy cows. J. Dairy Sci. 99:5967–5990. https://doi.org/10.3168/jds.2015-10727.

Elsasser, T. H., M. Richards, R. Collier, and G. F. Hartnell. 1996. Physiological responses to repeated endotoxin challenge are selectively affected by recombinant bovine somatotropin administration to calves. Domest. Anim. Endocrinol. 13:91–103. https://doi.org/10.1016/0739-7240(95)00048-8.

Emery, R. S., N. Burg, L. D. Brown, and G. N. Blank. 1964. Detection, occurrence and prophylactic treatment of borderline ketosis with propylene glycol feeding. J. Dairy Sci. 47:1074–1079. https://doi.org/10.3168/jds.S0022-0302(64)88848-2.

Emmanuel, D. G., K. L. Madsen, T. A. Churchill, S. M. Dunn, and B. N. Ametaj. 2007. Acidosis and lipopolysaccharide from *Escherichia coli* B:055 cause hyperpermeability of rumen and colon tissues. J. Dairy Sci. 90:5552–5557. https://doi.org/10.3168/jds.2007-0257.

Endo, M., T. Masaki, M. Seike, and H. Yoshimatsu. 2007. TNF-α induces hepatic steatosis in mice by enhancing gene expression of sterol regulatory element binding protein-1c (SREBP-1c). Exp. Biol. Med. (Maywood) 232:614–621.

Erridge, C., T. Attina, C. M. Spickett, and D. J. Webb. 2007. A high-fat meal induces low-grade endotoxemia: Evidence of a novel mechanism of postprandial inflammation. Am. J. Clin. Nutr. 86:1286–1292. https://doi.org/10.1093/ajcn/86.5.1286.

Estrada, D. E., E. Elliott, B. Zinman, I. Poon, Z. Liu, A. Klip, and D. Daneman. 1994. Regulation of glucose transport and expression of GLUT3 transporters in human circulating mononuclear cells: Studies in cells from insulin-dependent diabetic and nondiabetic individuals. Metabolism 43:591–598. https://doi.org/10.1016/0026-0495(94)90201-1.

Farney, J. K., L. K. Mamedova, and J. F. Coetzee. 2013a. Anti-inflammatory salicylate treatment alters the metabolic adaptations to lactation in dairy cattle. Am. J. Physiol. Regul. Integr. Comp. Physiol. 305:R110–R117. https://doi.org/10.1152/ajpregu.00152.2013.

Farney, J. K., L. K. Mamedova, and J. F. Coetzee., BKuKanich, L. M., S. K. Sordillo, J. E. Stoakes, L. C. Minton, Hollis, and B. J. Bradford. 2013b. Sodium salicylate treatment in early lactation increases whole-lactation milk and milk fat yield in mature dairy cows. J. Dairy Sci. 96:7709–7718. https://doi.org/10.3168/jds.2013-7088.

Feingold, K. R., J. L. Funk, A. H. Moser, J. K. Shigenaga, J. H. Rapp, and C. Grunfeld. 1995. Role for circulating lipoproteins in protection from endotoxin toxicity. Infect. Immun. 63:2041–2046. https://doi.org/10.1128/IAI.63.5.2041-2046.1995.

Fowler, M., C. Champagne, and D. Crocker. 2018. Adiposity and fat metabolism during combined fasting and lactation in elephant seals. J. Exp. Biol. 221(Suppl. 1):jeb161554. https://doi.org/10.1242/jeb.161554.

Fowler, M. A., C. Debier, C. D. Champagne, D. E. Crocker, and D. P. Costa. 2016. The demands of lactation promote differential regulation of lipid stores in fasting elephant seals. Gen. Comp. Endocrinol. 225:125–132. https://doi.org/10.1016/j.ygcen.2015.09.024.

Frost, R. A., and C. H. Lang. 2005. Skeletal muscle cytokines: Regulation by pathogen associated molecules and catabolic hormones. Curr. Opin. Clin. Nutr. Metab. Care 8:255–263. https://doi.org/10.1097/01.mco.0000165003.16578.2d.

Furken, C., T. Nakao, and M. Hoedemaker. 2015. Energy balance in transition cows and its association with health, reproduction and milk production. Tierarztl. Prax. Ausg. G Grosstiere Nutztiere 43:341–349. https://doi.org/10.15653/TPG-150371.

Garcia, M., T. H. Elsasser, Y. Qu, X. Zhu, and K. M. Moyes. 2015. Glucose supplementation has minimal effects on blood neutrophil function and gene expression in vitro. J. Dairy Sci. 98:6139–6150. https://doi.org/10.3168/jds.2014-9183.

Galyean, M. L., R. W. Lee, and M. E. Hubbert. 1981. Influence of fasting and transit on ruminal and blood metabolites in beef steers. J. Anim. Sci. 53:7–18. https://doi.org/10.2527/jas1981.5317.

Geishauser, T., K. Leslie, T. Duffield, and V. Edge. 1997. An evaluation of milk ketone tests for the prediction of left displaced abomasum in dairy cows. J. Dairy Sci. 80:3188–3192. https://doi.org/10.3168/jds.S0022-0302(97)76291-X.

Giri, S. N., P. Emau, J. S. Cullor, G. H. Stabenfeldt, M. L. Bruss, R. H. Bondurant, and B. I. Osburn. 1990. Effects of endotoxin infusion on circulating levels of eicosanoids, progesterone, cortisol, glucose, lactic acid, and abortion in pregnant cows. Vet. Microbiol. 21:211–231. https://doi.org/10.1016/0378-1135(90)90033-R.

Goff, J. P. 2008. The monitoring, prevention, and treatment of milk fever and subclinical hypocalcemia in dairy cows. Vet. J. 176:50–57. https://doi.org/10.1016/j.tvjl.2007.12.020.

Goff, J. P., and R. L. Horst. 1997. Physiological changes at parturition and their relationship to metabolic disorders. J. Dairy Sci. 80:1260–1268. https://doi.org/10.3168/jds.S0022-0302(97)76055-7.

Goff, J. P., R. L. Horst, F. J. Mueller, J. K. Miller, G. A. Kiess, and H. H. Dowlen. 1991. Addition of chloride to prepartal diet high in cations increases 1,25-dihydroxyvitamin D response to hypocalcemia preventing milk fever. J. Dairy Sci. 74:3863–3871. https://doi.org/10.3168/jds.S0022-0302(91)78579-2.

Goff, J. P., A. Liesegang, and R. L. Horst. 2014. Diet-induced pseudohypoparathyroidism: A hypocalcemia and milk fever risk factor. J. Dairy Sci. 97:1520–1528. https://doi.org/10.3168/jds.2013-7467.

Graugnard, D. E., K. M. Moyes, E. Trevisi, M. J. Khan, D. Keisler, J. K. Drackley, G. Bertoni, and J. J. Loor. 2013. Liver lipid content and inflammometabolic indices in peripartal dairy cows are altered

in response to prepartal energy intake and postpartal intramammary inflammatory challenge. J. Dairy Sci. 96:918–935. https://doi.org/10.3168/jds.2012-5676.

Griel, L. C., A. Zarkower, and R. J. Eberhart. 1975. Clinical and clinic-pathological effects of *Escherichia coli* endotoxin in mature cattle. Can. J. Comp. Med. 39:1–6.

Grinberg, N., S. Elazar, I. Rosenshine, and N. Y. Shpigel. 2008. β-Hydroxybutyrate abrogates formation of bovine neutrophil extracellular traps and bactericidal activity against mammary pathogenic *Escherichia coli*. Infect. Immun. 76:2802–2807. https://doi.org/10.1128/IAI.00051-08.

Gröhn, Y. T., H. N. Erb, C. E. McCulloch, and H. S. Saloniemi. 1989. Epidemiology of metabolic disorders in dairy cattle: Association among host characteristics, disease, and production. J. Dairy Sci. 72:1876–1885. https://doi.org/10.3168/jds.S0022-0302(89)79306-1.

Groschwitz, K. R., D. Wu, H. Osterfeld, R. Ahrens, and S. P. Hogan. 2013. Chymase-mediated intestinal epithelial permeability is regulated by a protease-activating receptor/matrix metalloproteinase-2-dependent mechanism. Am. J. Physiol. Gastrointest. Liver Physiol. 304:G479–G489. https://doi.org/10.1152/ajpgi.00186.2012.

Gurr, J. A., and T. A. Ruh. 1980. Desensitization of primary cultures of adult rat liver parenchymal cells to stimulation of adenosine 3′,5′-monophosphate production by glucagon and epinephrine. Endocrinology 107:1309–1319. https://doi.org/10.1210/endo-107-5-1309.

Hamarneh, S. R., B.-M. Kim, K. Kaliannan, S. A. Morrison, T. J. Tantillo, Q. Tao, M. M. R. Mohamed, J. M. Ramirez, A. Karas, W. Liu, D. Hu, A. Teshager, S. S. Gul, K. P. Economopoulos, A. K. Bhan, M. S. Malo, M. Y. Choi, and R. A. Hodin. 2017. Intestinal alkaline phosphatase attenuates alcohol-induced hepaticsteatosis in mice. Dig. Dis. Sci. 62:2021–2034. https://doi.org/10.1007/s10620-017-4576-0.

Hammon, D. S., I. M. Evjen, T. R. Dhiman, J. P. Goff, and J. L. Walters. 2006. Neutrophil function and energy status in Holstein cows with uterine health disorders. Vet. Immunol. Immunopathol. 113:21–29. https://doi.org/10.1016/j.vetimm.2006.03.022.

Hammon, H. M., G. Sturmer, F. Schneider, A. Tuchscherer, H. Blum, T. Engelhard, A. Genzel, R. Staufenbiel, and W. Kanitz. 2009. Performance and metabolic and endocrine changes with emphasis on glucose metabolism in high-yielding dairy cows with high and low fat content in liver after calving. J. Dairy Sci. 92:1554–1566. https://doi.org/10.3168/jds.2008-1634.

Hand, M. S., M. J. Fettman, L. G. Chandrasena, J. L. Cleek, R. A. Mason, and R. W. Phillips. 1983. Increased glucose uptake precedes hyperinsulinemia in awake endotoxemic minipigs. Circ. Shock 11:287–295.

Hargrove, D. M., C. H. Lang, G. J. Bagby, and J. J. Spitzer. 1989. Epinephrine-induced increase in glucose turnover is diminished during sepsis. Metabolism 38:1070–1076. https://doi.org/10.1016/0026-0495(89)90042-5.

Hart, I. C., J. A. Bines, C. C. Balch, and A. T. Cowie. 1975. Hormone and metabolite differences between lactating beef and dairy cattle. Life Sci. 16:1285–1291. https://doi.org/10.1016/0024-3205(75)90313-6.

Hart, I. C., J. A. Bines, and S. V. Morant. 1979. Endocrine control of energy metabolism in the cow: Correlations of hormones and metabolites in high and low yielding cows for stages of lactation. J. Dairy Sci. 62:270–277. https://doi.org/10.3168/jds.S0022-0302(79)83235-X.

Hart, I. C., J. A. Bines, S. V. Morant, and J. L. Ridley. 1978. Endocrine control of energy metabolism in the cow: Comparison of the levels of hormones (prolactin, growth hormone, insulin, and thyroxine) and metabolites in the plasma of high- and low-yielding cattle at various stages of lactation. J. Endocrinol. 77:333–345. https://doi.org/10.1677/joe.0.0770333.

Hayden, C. E., and L. B. Scholl. 1923. The Blood and Urine in Milk Fever. Report of New York State Veterinary College. Cornell University.

Hayirli, A., R. R. Grummer, E. V. Nordheim, and P. M. Crump. 2002. Animal and dietary factors affecting feed intake during the prefresh transition period in Holsteins. J. Dairy Sci. 85:3430–3443. https://doi.org/10.3168/jds.S0022-0302(02)74431-7.

Herdt, T. H. 1988. Fatty liver in dairy cows. Vet. Clin. North Am. Food Anim. Pract. 4:269–287. https://doi.org/10.1016/S0749-0720(15)31048-3.

Herdt, T. H. 2000. Ruminant adaptation to negative energy balance. Influences on the etiology of ketosis and fatty liver. Vet. Clin. North Am. Food Anim. Pract. 16:215–230. https://doi.org/10.1016/S0749-0720(15)30102-X.

Hibbs, J. W. 1950. Milk fever (parturient paresis) in dairy cows—A review. J. Dairy Sci. 33:758–789. https://doi.org/10.3168/jds.S0022-0302(50)91966-7.

Hoeben, D., R. Heyneman, and C. Burvenich. 1997. Elevated levels of beta-hydroxybutyric acid in periparturient cows and in vitro effect on respiratory burst activity of bovine neutrophils. Vet. Immunol. Immunopathol. 58:165–170. https://doi.org/10.1016/S0165-2427(97)00031-7.

Hoedemaker, M., D. Prange, H. Zerbe, J. Frank, A. Daxenberger, and H. H. D. Meyer. 2004. Peripartal propylene glycol supplementation and metabolism, animal health, fertility, and production in dairy cows. J. Dairy Sci. 87:2136–2145. https://doi.org/10.3168/jds.S0022-0302(04)70033-8.

Holowaychuk, M. K., A. J. Birkenheuer, J. Li, H. Marr, A. Boll, and S. K. Nordone. 2012. Hypocalcemia and hypovitaminosis D in dogs with induced endotoxemia. J. Vet. Intern. Med. 26:244–251. https://doi.org/10.1111/j.1939-1676.2012.00886.x.

Holtenius, P., and K. Holtenius. 1996. New aspects of ketone bodies in energy metabolism of dairy cows: A review. Zentralbl. Veterinarmed. A. 43:579–587. https://doi.org/10.1111/j.1439-0442.1996.tb00491.x.

Hooper, L. V., and A. J. Macpherson. 2010. Immune adaptations that maintain homeostasis with the intestinal microbiota. Nat. Rev. Immunol. 10:159–169. https://doi.org/10.1038/nri2710.

Horst, E. A., S. K. Kvidera, E. J. Mayorga, C. S. Shouse, M. Al-Qaisi, M. J. Dickson, J. Ydstie, H. A. Ramirez-Ramirez, A. F. Keating, D. J. Dickson, K. E. Griswold, and L. H. Baumgard. 2018. Effect of chromium on bioenergetics and leukocyte dynamics following immunoactivation in lactating Holstein cows. J. Dairy Sci. 101:5515–5530. https://doi.org/10.3168/jds.2017-13899.

Horst, E. A., E. J. Mayorga, M. Al-Qaisi, M. A. Abeyta, B. M. Goetz, H. A. Ramirez-Ramirez, D. H. Kleinschmit, and L. H. Baumgard. 2019. Effects of dietary zinc source on the metabolic and immunological response to lipopolysaccharide in lactating Holstein dairy cows. J. Dairy Sci. 102:11681–11700. https://doi.org/10.3168/jds.2019-17037.

Horst, E. A., E. J. Mayorga, M. Al-Qaisi, M. A. Abeyta, S. L. Portner, C. S. McCarthy, B. M. Goetz, S. K. Kvidera, and L. H. Baumgard. 2020a. Effects of maintaining eucalcemia following immunoactivation in lactating Holstein dairy cows. J. Dairy Sci. 103:7472–7486. https://doi.org/10.3168/jds.2020-18268.

Horst, E. A., E. J. Mayorga, M. Al-Qaisi, S. Rodriguez-Jimenez, B. M. Goetz, M. A. Abeyta, P. J. Gorden, S. K. Kvidera, and L. H. Baumgard. 2020b. Evaluating effects of zinc hydroxychloride on biomarkers of inflammation and intestinal integrity during feed restriction. J. Dairy Sci. 103:11911–11929. https://doi.org/10.3168/jds.2020-18860.

Horst, R. L., J. P. Goff, and T. A. Reinhardt. 2005. Adapting to the transition between gestation and lactation: Differences between rat, human and dairy cow. J. Mammary Gland Biol. Neoplasia 10:141–156. https://doi.org/10.1007/s10911-005-5397-x.

Horst, R. L., J. P. Goff, T. A. Reinhardt, and D. R. Buxton. 1997. Strategies for preventing milk fever in dairy cattle. J. Dairy Sci. 80:1269–1280. https://doi.org/10.3168/jds.S0022-0302(97)76056-9.

Hove, K. 1974. Nocturnal plasma insulin levels in cows with varying levels of plasma ketone bodies; Relations to plasma sugar and acetoacetate. Acta Endocrinol. (Copenh.) 76:513–524. https://doi.org/10.1530/acta.0.0760513.

Hove, K. 1978. Insulin secretion in lactating cows: Responses to glucose infused intravenously in normal, ketonemic, and starved animals. J. Dairy Sci. 61:1407–1413. https://doi.org/10.3168/jds.S0022-0302(78)83742-4.

Humblet, M. F., H. Guyot, B. Boudry, F. Mbayahi, C. Hanzen, F. Rollin, and J. M. Godeau. 2006. Relationship between haptoglobin, serum amyloid A, and clinical status in a survey of dairy herds during a 6-month period. Vet. Clin. Pathol. 35:188–193. https://doi.org/10.1111/j.1939-165X.2006.tb00112.x.

Huszenicza, G., M. Fodor, M. Gacs, M. Kulcsar, M. J. W. Dohmen, M. Vamos, L. Porkolab, T. Kegl, J. Bartyik, J. A. C. M. Lohuis, S. Janosi, and G. Szita. 1999. Uterine bacteriology, resumption of cyclic ovarian activity and fertility in postpartum cows kept in large-scale dairy herds. Reprod. Domest. Anim. 34:237–245. https://doi.org/10.1111/j.1439-0531.1999.tb01246.x.

Huzzey, J. M., T. F. Duffield, S. J. LeBlanc, D. M. Veira, D. M. Weary, and M. A. G. von Keyserlingk. 2009. Short communication: Haptoglobin as an early indicator of metritis. J. Dairy Sci. 92:621–625. https://doi.org/10.3168/jds.2008-1526.

Huzzey, J. M., D. V. Nydam, R. J. Grant, and T. R. Overton. 2011. Associations of prepartum plasma cortisol, haptoglobin, fecal cortisol metabolites, and nonesterified fatty acids with postpartum health status in Holstein dairy cows. J. Dairy Sci. 94:5878–5889. https://doi.org/10.3168/jds.2010-3391.

Ibeagha-Awemu, E. M., J.-W. Lee, A. E. Ibeagha, D. D. Bannerman, M. J. Paape, and X. Zhao. 2008. Bacterial lipopolysaccharide induces increased expression of toll-like receptor (TLR) 4 and downstream TLR signaling molecules in bovine mammary epithelial cells. Vet. Res. 39:11. https://doi.org/10.1051/vetres:2007047.

Ilan, Y. 2012. Leaky gut and the liver: A role for bacterial translocation in nonalcoholic steatohepatitis. World J. Gastroenterol. 18:2609–2618. https://doi.org/10.3748/wjg.v18.i21.2609.

Ingvartsen, K. L. 2006. Feeding- and management related diseases in the transition cow: Physiological adaptations around calving and strategies to reduce feeding related diseases. Anim. Feed Sci. Technol. 126:175–213. https://doi.org/10.1016/j.anifeedsci.2005.08.003.

Ingvartsen, K. L., and J. B. Andersen. 2000. Integration of metabolism and intake regulation: A review focusing on periparturient animals. J. Dairy Sci. 83:1573–1597. https://doi.org/10.3168/jds.S0022-0302(00)75029-6.

Iseri, V. J., and K. C. Klasing. 2013. Dynamics of the systemic components of the chicken (*Gallus gallus domesticus*) immune system following activation by *Escherichia coli*; Implications for the cost of immunity. Dev. Comp. Immunol. 40:248–257. https://doi.org/10.1016/j.dci.2013.02.005.

Iseri, V. J., and K. C. Klasing. 2014. Changes in the amount of lysing in protective proteins and immune cells after a systemic response to dead *Escherichia coli:* Implications for nutritional costs of immunity. Integr. Comp. Biol. 54:922–930. https://doi.org/10.1093/icb/icu111.

Janovick, N. A., and J. K. Drackley. 2010. Prepartum dietary management of energy intake affects postpartum intake and lactation performance by primiparous and multiparous Holstein cows. J. Dairy Sci. 93:3086–3102. https://doi.org/10.3168/jds.2009-2656.

Jarrett, I. G., O. H. Filsell, and F. J. Ballard. 1974. Metabolic and endocrine interrelationships in normal and diabetic sheep. Horm. Metab. Res. 4(Suppl.):111–116.

Jebb, D., and M. Hiller. 2018. Recurrent loss of HMGCS2 shows that ketogenesis is not essential for the evolution of large mammalian brains. eLife 7:e38906. https://doi.org/10.7554/eLife.38906.

Jepson, M. M., J. M. Pell, P. C. Bates, and D. J. Millward. 1986. The effects of endotoxemia on protein metabolism in skeletal muscle and liver of fed and fasted rats. Biochem. J. 235:329–336. https://doi.org/10.1042/bj2350329.

Jia, L., X. Chang, S. Qian, C. Liu, C. C. Lord, N. Ahmed, C. E. Lee, S. Lee, L. Gautron, M. C. Mitchell, J. D. Horton, P. E. Scherer, and J. K. Elmquist. 2018. Hepatocyte toll-like receptor 4 deficiency protects against alcohol-induced fatty liver disease. Mol. Metab. 14:121–129. https://doi.org/10.1016/j.molmet.2018.05.015.

Jin, C. J., A. J. Engstler, D. Ziegenhardt, S. C. Bischoff, C. Trautwein, and I. Bergheim. 2017. Loss of lipopolysaccharide-binding protein attenuates the development of diet-induced non-alcoholic fatty liver disease in mice. J. Gastroenterol. Hepatol. 32:708–715. https://doi.org/10.1111/jgh.13488.

Jordan, D. L., R. E. Erb, P. V. Malven, C. J. Callahan, and E. L. Veenhuizen. 1981. Artificial induction of lactation in cattle: Effect of modified treatments on milk yield, fertility, and hormones in blood plasma and milk. Theriogenology 16:315–329. https://doi.org/10.1016/0093-691X(81)90016-9.

Kaneene, J. B., R. Miller, T. H. Herdt, and J. C. Gardiner. 1997. The association of serum nonesterified fatty acids and cholesterol, management and feeding practices with peripartum disease in dairy cows. Prev. Vet. Med. 31:59–72. https://doi.org/10.1016/S0167-5877(96)01141-5.

Karstrup, C. C., K. Klitgaard, T. K. Jensen, J. S. Agerholm, and H. G. Pedersen. 2017. Presence of bacteria in the endometrium and placentomes of pregnant cows. Theriogenology 99:41–47. https://doi.org/10.1016/j.theriogenology.2017.05.013.

Kehrli, M. E., B. J. Nonnecke, and J. A. Roth. 1989. Alterations in bovine neutrophil function during the periparturient period. Am. J. Vet. Res. 50:207–214.

Khafipour, E., D. O. Krause, and J. C. Plaizier. 2009. A grain-based subacute ruminal acidosis challenge causes translocation of lipopolysaccharide and triggers inflammation. J. Dairy Sci. 92:1060–1070. https://doi.org/10.3168/jds.2008-1389.

Kimura, K., J. P. Goff, M. E. Kehrli Jr., J. A. Harp, and B. J. Nonnecke. 2002. Effects of mastectomy on composition of peripheral blood mononuclear cell populations in periparturient dairy cows. J. Dairy Sci. 85:1437–1444. https://doi.org/10.3168/jds.S0022-0302(02)74211-2.

Kimura, K., T. A. Reinhardt, and J. P. Goff. 2006. Parturition and hypocalcemia blunts calcium signals in immune cells of dairy cattle. J. Dairy Sci. 89:2588–2595. https://doi.org/10.3168/jds.S0022-0302(06)72335-9.

Kleppe, B. B., R. J. Aiello, R. R. Grummer, and L. E. Armentano. 1988. Triglyceride accumulation and very low density lipoprotein secretion by rat and goat hepatocytes in vitro. J. Dairy Sci. 71:1813–1822. https://doi.org/10.3168/jds.S0022-0302(88)79750-7.

Koch, F., U. Thom, E. Albrecht, R. Weikard, W. Nolte, B. Kuhla, and C. Kuehn. 2019. Heat stress directly impairs gut integrity and recruits distinct immune cell populations into the bovine intestine. Proc. Natl. Acad. Sci. USA 116:10333–10338. https://doi.org/10.1073/pnas.1820130116.

Koprowski, J. A., and H. A. Tucker. 1973. Bovine serum growth hormone, corticoids and insulin during lactation. Endocrinology 93:645–651. https://doi.org/10.1210/endo-93-3-645.

Kosteli, A., E. Sugaru, G. Haemmerle, J. F. Martin, J. Lei, R. Zechner, and A. W. Ferrante Jr.. 2010. Weight loss and lipolysis promote a dynamic immune response in murine adipose tissue. J. Clin. Invest. 120:3466–3479. https://doi.org/10.1172/JCI42845.

Krebs, H. A. 1966. Bovine ketosis. Vet. Rec. 78:187–192. https://doi.org/10.1136/vr.78.6.187.

Kronfeld, D. S. 1971. Hypoglycemia in ketotic cows. J. Dairy Sci. 54:949–961. https://doi.org/10.3168/jds.S0022-0302(71)85951-9.

Kronfeld, D. S. 1982. Major metabolic determinants of milk volume, mammary efficiency, and spontaneous ketosis in dairy cows. J. Dairy Sci. 65:2204–2212. https://doi.org/10.3168/jds.S0022-0302(82)82483-1.

Kronfeld, D. S., G. P. Mayer, J. McD. Robertson, and F. Raggi. 1963. Depression of milk secretion during insulin administration. J. Dairy Sci. 46:559–563. https://doi.org/10.3168/jds.S0022-0302(63)89095-5.

Kuhla, B. 2020. Review: Pro-inflammatory cytokines and hypothalamic inflammation: Implications for insufficient feed intake of transition dairy cows. Animal 14(Suppl. 1):s65–s77. https://doi.org/10.1017/S1751731119003124.

Kuhla, B., C. C. Metges, and H. M. Hammon. 2016. Endogenous and dietary lipids influencing feed intake and energy metabolism of

peripartuirent dairy cows. Domest. Anim. Endocrinol. 56:S2–S10. https://doi.org/10.1016/j.domaniend.2015.12.002.

Kumar, H., T. Kawai, and S. Akira. 2011. Pathogen recognition by the innate immune system. Int. Rev. Immunol. 30:16–34. https://doi.org/10.3109/08830185.2010.529976.

Kushibiki, S., K. Hodate, H. Shingu, Y. Obara, E. Touno, M. Shinoda, and Y. Yokomizo. 2003. Metabolic and lactational responses during recombinant bovine tumor necrosis factor-α treatment in lactating cows. J. Dairy Sci. 86:819–827. https://doi.org/10.3168/jds.S0022-0302(03)73664-9.

Kushner, I., and A. Mackiewicz. 1987. Acute phase proteins as disease markers. Dis. Markers 5:1–11.

Kvidera, S. K., M. J. Dickson, M. Abuajamieh, D. B. Snider, M. V. Sanz Fernandez, J. S. Johnson, A. F. Keating, P. J. Gorden, H. B. Green, K. M. Schoenberg, and L. H. Baumgard. 2017a. Intentionally induced intestinal barrier dysfunction causes inflammation, affects metabolism, and reduces productivity in lactating Holstein cows. J. Dairy Sci. 100:4113–4127. https://doi.org/10.3168/jds.2016-12349.

Kvidera, S. K., E. A. Horst, M. Abuajamieh, E. J. Mayorga, M. V. Sanz Fernandez, and L. H. Baumgard. 2016. Technical note: A procedure to estimate glucose requirements of an activated immune system in steers. J. Anim. Sci. 94:4591–4599. https://doi.org/10.2527/jas.2016-0765.

Kvidera, S. K., E. A. Horst, M. Abuajamieh, E. J. Mayorga, M. V. Sanz Fernandez, and L. H. Baumgard. 2017b. Glucose requirements of an activated immune system in lactating Holstein cows. J. Dairy Sci. 100:2360–2374. https://doi.org/10.3168/jds.2016-12001.

Kvidera, S. K., E. A. Horst, E. J. Mayorga, M. V. Sanz-Fernandez, M. Abuajamieh, and L. H. Baumgard. 2017c. Estimating glucose requirements of an activated immune system in growing pigs. J. Anim. Sci. 95:5020–5029. https://doi.org/10.2527/jas2017.1830.

Kvidera, S. K., E. A. Horst, M. V. Sanz Fernandez, M. Abuajamieh, S. Ganesan, P. J. Gorden, H. B. Green, K. M. Schoenberg, W. E. Trout, A. F. Keating, and L. H. Baumgard. 2017d. Characterizing effects of feed restriction and glucagon-like peptide 2 administration on biomarkers of inflammation and intestinal morphology. J. Dairy Sci. 100:9402–9417. https://doi.org/10.3168/jds.2017-13229.

Lacetera, N., D. Scalia, U. Bernabucci, B. Ronchi, D. Pirazzi, and A. Nardone. 2005. Lymphocyte fuctions in overconditioned cows around parturition. J. Dairy Sci. 88:2010–2016. https://doi.org/10.3168/jds.S0022-0302(05)72877-0.

Lacetera, N., D. Scalia, O. Franci, U. Bernabucci, B. Ronchi, and A. Nardone. 2004. Short communication: Effects of nonesterified fatty acids on lymphocyte function in dairy heifers. J. Dairy Sci. 87:1012–1014. https://doi.org/10.3168/jds.S0022-0302(04)73246-4.

Lamping, N., R. Dettmer, N. W. Schröder, D. Pfeil, W. Hallatschek, R. Burger, and R. R. Schumann. 1998. LPS-binding protein protects mice from septic shock caused by LPS or gram-negative bacteria. J. Clin. Invest. 101:2065–2071. https://doi.org/10.1172/JCI2338.

Lang, C. H., G. J. Bagby, C. Dobrescu, A. Ottlakan, and J. J. Spitzer. 1992. Sepsis- and endotoxin-induced increase in organ glucose uptake in leukocyte-depleted rats. Am. J. Physiol. 263:R1324–R1332. https://doi.org/10.1152/ajpregu.1992.263.6.R1324.

Lang, C. H., G. J. Bagby, and J. J. Spitzer. 1985. Glucose kinetics and body temperature after lethal and nonlethal doses of endotoxin. Am. J. Physiol. 248:R471–R478. https://doi.org/10.1152/ajpregu.1985.248.4.R471.

Lang, C. H., C. Dobrescu, and K. Mészáros. 1990. Insulin-mediated glucose uptake by individual tissues during sepsis. Metabolism 39:1096–1107. https://doi.org/10.1016/0026-0495(90)90172-9.

Lang, C. H., Z. Spolarics, A. Ottlakan, and J. J. Spitzer. 1993. Effect of high-dose endotoxin on glucose production and utilization. Metabolism 42:1351–1358. https://doi.org/10.1016/0026-0495(93)90137-D.

Lanza-Jacoby, S., and A. Tabares. 1990. Triglyceride kinetics, tissue lipoprotein lipase, and liver lipogenesis in septic rats. Am. J. Physiol. 258:E678–E685. https://doi.org/10.1152/ajpendo.1990.258.4.E678.

Larauche, M., C. Kiank, and Y. Tache. 2009. Corticotropin releasing factor signaling in colon and ileum: Regulation by stress and pathophysiological implications. J. Physiol. Pharmacol. 60(Suppl. 7):33–46.

Lavon, Y., G. Leitner, U. Moallem, E. Klipper, H. Voet, S. Jacoby, G. Glick, R. Meidan, and D. Wolfenson. 2011. Immediate and carryover effects of gram-negative and gram-positive toxin-induced mastitis on follicular function in dairy cows. Theriogenology 76:942–953. https://doi.org/10.1016/j.theriogenology.2011.05.001.

Lean, I. J., M. L. Bruss, H. F. Troutt, J. C. Galland, T. B. Farver, R. Rostami, C. A. Holmberg, and L. D. Weaver. 1994. Bovine ketosis and somatotrophin: Risk factors for ketosis and effects of ketosis on health and production. Res. Vet. Sci. 57:200–209. https://doi.org/10.1016/0034-5288(94)90058-2.

LeBlanc, S. 2010. Monitoring metabolic health of dairy cattle in the transition period. J. Reprod. Dev. 56(Suppl.):S29–S35. https://doi.org/10.1262/jrd.1056S29.

LeBlanc, S. J. 2008. Postpartum uterine disease and dairy herd reproductive performance. A review. Vet. J. 176:102–114. https://doi.org/10.1016/j.tvjl.2007.12.019.

LeBlanc, S. J. 2020. Review: Relationships between metabolism and neutrophil function in dairy cows in the peripartum period. Animal 14(Suppl. 1):s44–s54. https://doi.org/10.1017/S1751731119003227.

LeBlanc, S. J., K. E. Leslie, and T. F. Duffield. 2005. Metabolic predictors of displaced abomasum in dairy cattle. J. Dairy Sci. 88:159–170. https://doi.org/10.3168/jds.S0022-0302(05)72674-6.

LeBlanc, S. J., K. D. Lissemore, D. F. Kelton, T. F. Duffield, and K. E. Leslie. 2006. Major advances in disease prevention in dairy cattle. J. Dairy Sci. 89:1267–1279. https://doi.org/10.3168/jds.S0022-0302(06)72195-6.

Lecchi, C., F. Dilda, P. Sartorelli, and F. Ceciliani. 2012. Widespread expression of SAA and Hp RNA in bovine tissues after evaluation of suitable reference genes. Vet. Immunol. Immunopathol. 145:556–562. https://doi.org/10.1016/j.vetimm.2011.12.017.

Leliefeld, P. H. C., C. M. Wessels, L. P. H. Leenen, L. Koenderman, and J. Pillay. 2016. The role of neutrophils in immune dysfunction during severe inflammation. Crit. Care 20:73. https://doi.org/10.1186/s13054-016-1250-4.

Lewis, R. S. 2001. Calcium signaling mechanisms in T lymphocytes. Annu. Rev. Immunol. 19:497–521. https://doi.org/10.1146/annurev.immunol.19.1.497.

Li, Y., Z. Song, K. A. Kerr, and A. J. Moeser. 2017. Chronic social stress in pigs impairs intestinal barrier and nutrient transporter function, and alters neuro-immune mediator and receptor expression. PLoS One 12:e0171617. https://doi.org/10.1371/journal.pone.0171617.

Liu, Q., C. Wang, W. Z. Yang, W. W. Zhang, X. M. Yang, D. C. He, K. H. Dong, and Y. X. Huang. 2009. Effects of feeding propylene glycol on dry matter intake, lactation performance, energy balance and blood metabolites in early lactation dairy cows. Animal 3:1420–1427. https://doi.org/10.1017/S175173110999036X.

Lomander, H., J. Frössling, K. L. Ingvartsen, H. Gustafsson, and C. Svensson. 2012. Supplemental feeding with glycerol or propylene glybol of dairy cows in early lactation—Effects on metabolic status, body condition, and milk yield. J. Dairy Sci. 95:2397–2408. https://doi.org/10.3168/jds.2011-4535.

Lu, Y. C., W. Yeh, and P. S. Ohashi. 2008. LPS/TLR4 signal transduction pathway. Cytokine 42:145–151. https://doi.org/10.1016/j.cyto.2008.01.006.

Maitra, U., S. Chang, N. Singh, and L. Li. 2009. Molecular mechanism underlying the suppression of lipid oxidation during endotoxemia. Mol. Immunol. 47:420–425. https://doi.org/10.1016/j.molimm.2009.08.023.

Malcolm, D. S., G. P. Zaloga, and J. W. Holadav. 1989. Calcium administration increases the mortality of endotoxic shock in rats. Crit. Care Med. 17:900–903. https://doi.org/10.1097/00003246-198909000-00012.

Mallard, B. A., J. C. Dekkers, M. J. Ireland, K. E. Leslie, S. Sharif, C. L. Vankampen, L. Wagter, and B. N. Wilkie. 1998. Alteration in immune responsiveness during the peripartum period and its rami-

fication on dairy cow and calf health. J. Dairy Sci. 81:585–595. https://doi.org/10.3168/jds.S0022-0302(98)75612-7.

Malmuthuge, N., M. Li, P. Fries, P. J. Griebel, and L. L. Guan. 2012. Regional and age dependent changes in gene expression of Toll-like receptors and key antimicrobial defence molecules throughout the gastrointestinal tract of dairy calves. Vet. Immunol. Immunopathol. 146:18–26. https://doi.org/10.1016/j.vetimm.2012.01.010.

Mani, V., T. E. Weber, L. H. Baumgard, and N. K. Gabler. 2012. Growth and Development Symposium: Endotoxin, inflammation, and intestinal function in livestock. J. Anim. Sci. 90:1452–1465. https://doi.org/10.2527/jas.2011-4627.

Mann, S., A. S. Sipka, and J. K. Grenier. 2019. The degree of postpartum metabolic challenge in dairy cows is associated with peripheral blood mononuclear cell transcriptome changes of the innate immune system. Dev. Comp. Immunol. 93:28–36. https://doi.org/10.1016/j.dci.2018.11.021.

Maratou, E., G. Dimitriadis, A. Kollias, E. Boutati, V. Lambadiari, P. Mitrou, and S. A. Raptis. 2007. Glucose transporter expression on the plasma membrane of resting and activated white blood cells. Eur. J. Clin. Invest. 37:282–290. https://doi.org/10.1111/j.1365-2362.2007.01786.x.

Markusfeld, O. 1986. The association of displaced abomasum with various periparturient factors in dairy cows. A retrospective study. Prev. Vet. Med. 4:173–183. https://doi.org/10.1016/0167-5877(86)90021-8.

Markusfeld, O. 1987. Periparturient traits in seven high dairy herds. Incidence rates, association with parity, and interrelationships among traits. J. Dairy Sci. 70:158–166. https://doi.org/10.3168/jds.S0022-0302(87)79990-1.

Martel, C. A., L. K. Mamedova, J. E. Minton, M. L. Jones, J. A. Carroll, and B. J. Bradford. 2014. Continuous low-dose infusion of tumor necrosis factor alpha in adipose tissue elevates adipose tissue interleukin 10 abundance and fails to alter metabolism in lactating dairy cows. J. Dairy Sci. 97:4897–4906. https://doi.org/10.3168/jds.2013-7777.

Martin, T. R., J. C. Mathison, P. S. Tobias, D. J. Letúrcq, A. M. Moriarty, R. J. Maunder, and R. J. Ulevitch. 1992. Lipopolysaccharide binding protein enhances the responsiveness of alveolar macrophages to bacterial lipopolysaccharide. Implications for cytokine production in normal and injured lungs. J. Clin. Invest. 90:2209–2219. https://doi.org/10.1172/JCI116106.

Martín-Tereso, J., and H. Martens. 2014. Calcium and magnesium physiology and nutrition in relation to the prevention of milk fever and tetany (dietary management of macrominerals in preventing disease). Vet. Clin. North Am. Food Anim. Pract. 30:643–670. https://doi.org/10.1016/j.cvfa.2014.07.007.

Martinez, N., C. A. Risco, F. S. Lima, R. S. Bisinotto, L. F. Greco, E. S. Ribeiro, F. Maunsell, K. Galvão, and J. E. P. Santos. 2012. Evaluation of peripartal calcium status, energetic profile, and neutrophil function in dairy cows at low or high risk of developing uterine disease. J. Dairy Sci. 95:7158–7172. https://doi.org/10.3168/jds.2012-5812.

Martinez, N., L. D. P. Sinedino, R. S. Bisinotto, E. S. Ribeiro, G. C. Gomes, F. S. Lima, L. F. Greco, C. A. Risco, K. N. Galvão, D. Taylor-Rodriguez, J. P. Driver, W. W. Thatcher, and J. E. P. Santos. 2014. Effect of induced subclinical hypocalcemia on physiological responses and neutrophil function in dairy cows. J. Dairy Sci. 97:874–887. https://doi.org/10.3168/jds.2013-7408.

Mateus, L., L. Lopes da Costa, P. Diniz, and A. J. Ziecik. 2003. Relationship between endotoxin and prostaglandin (PGE2 and PGFM) concentrations and ovarian function in dairy cows with puerperal endometritis. Anim. Reprod. Sci. 76:143–154. https://doi.org/10.1016/S0378-4320(02)00248-8.

McArt, J. A. A., and R. C. Neves. 2020. Association of transient, persistent, or delayed subclinical hypocalcemia with early lactation disease, removal, and milk yield in Holstein cows. J. Dairy Sci. 103:690–701. https://doi.org/10.3168/jds.2019-17191.

McArt, J. A. A., D. V. Nydam, G. R. Oetzel, T. R. Overton, and P. A. Ospina. 2013. Elevated non-esterified fatty acids and β-hydroxybutyrate and their association with transition dairy cow performance. Vet. J. 198:560–570. https://doi.org/10.1016/j.tvjl.2013.08.011.

McArt, J. A. A., D. V. Nydam, P. A. Ospina, and G. R. Oetzel. 2011. A field trial on the effect of propylene glycol on milk yield and resolution of ketosis in fresh cows diagnosed with subclinical ketosis. J. Dairy Sci. 94:6011–6020. https://doi.org/10.3168/jds.2011-4463.

McNamara, J. P. 1997. Adipose tissue metabolism during lactation: Where do we go from here? Proc. Nutr. Soc. 56(1A):149–167. https://doi.org/10.1079/PNS19970018.

Memon, R. A., K. R. Feingold, A. H. Moser, W. Doerrler, S. Adi, C. A. Dinarello, and C. Grunfeld. 1992. Differential effects of interleukin-1 and tumor necrosis factor on ketogenesis. Am. J. Physiol. 263:E301–E309. https://doi.org/10.1152/ajpendo.1992.263.2.E301.

Mészáros, K., K. Bojta, A. P. Bautista, C. H. Lang, and J. J. Spitzer. 1991. Glucose utilization by Kupffer cells, endothelial cells, and granulocytes in endotoxemic rat liver. Am. J. Physiol. 260:G7–G12. https://doi.org/10.1152/ajpgi.1991.260.1.G7.

Mészáros, K., C. H. Lang, G. J. Bagby, and J. J. Spitzer. 1987. Contribution of different organs to increased glucose consumption after endotoxin administration. J. Biol. Chem. 262:10965–10970. https://doi.org/10.1016/S0021-9258(18)60912-3.

Mezzetti, M., A. Minuti, F. Piccioli-Cappelli, M. Amadori, M. Bionaz, and E. Trevisi. 2019. The role of altered immune function during the dry period in promoting the development of subclinical ketosis in early lactation. J. Dairy Sci. 102:9241–9258. https://doi.org/10.3168/jds.2019-16497.

Minuti, A., S. Ahmed, E. Trevisi, F. Piccioli-Cappelli, G. Bertoni, N. Jahan, and P. Bani. 2014. Experimental acute rumen acidosis in sheep: Consequences on clinical, rumen, and gastrointestinal permeability conditions and blood chemistry. J. Anim. Sci. 92:3966–3977. https://doi.org/10.2527/jas.2014-7594.

Minuti, A., N. Jahan, V. Lopreiato, F. Piccioli-Cappelli, L. Bomba, S. Capomaccio, J. J. Loor, P. Ajmone-Marsan, and E. Trevisi. 2020. Evaluation of circulating leukocyte transcriptome and its relationship with immune function and blood markers in dairy cows during the transition period. Funct. Integr. Genomics 20:293–305. https://doi.org/10.1007/s10142-019-00720-0.

Moallem, U., Y. Folman, and D. Sklan. 2000. Effects of somatotropin and dietary calcium soaps of fatty acids in early lactation on milk production, dry matter intake, and energy balance of high-yielding dairy cows. J. Dairy Sci. 83:2085–2094. https://doi.org/10.3168/jds.S0022-0302(00)75090-9.

Moeser, A. J., K. A. Ryan, P. K. Nighot, and A. T. Blikslager. 2007. Gastrointestinal dysfunction induced by early weaning is attenuated by delayed weaning and mast cell blockage in pigs. Am. J. Physiol. Gastrointest. Liver Physiol. 293:G413–G421. https://doi.org/10.1152/ajpgi.00304.2006.

Monks, J., F. J. Geske, L. Lehman, and V. A. Fadok. 2002. Do inflammatory cells participate in mammary gland involution? J. Mammary Gland Biol. Neoplasia 7:163–176. https://doi.org/10.1023/A:1020351919634.

Moore, S. G., A. C. Ericsson, S. E. Poock, P. Melendez, and M. C. Lucy. 2017. Hot topic: 16S rRNA gene sequencing reveals the microbiome of the virgin and pregnant bovine uterus. J. Dairy Sci. 100:4953–4960. https://doi.org/10.3168/jds.2017-12592.

Mor, G., and I. Cardenas. 2010. The immune system in pregnancy: A unique complexity. Am. J. Reprod. Immunol. 63:425–433. https://doi.org/10.1111/j.1600-0897.2010.00836.x.

Mullins, C. R., L. K. Mamedova, M. J. Brouk, C. E. Moore, H. B. Green, K. L. Perfield, J. F. Smith, J. P. Harner, and B. J. Bradford. 2012. Effects of monensin on metabolic parameters, feeding behavior, and productivity of transition dairy cows. J. Dairy Sci. 95:1323–1336. https://doi.org/10.3168/jds.2011-4744.

Murphy, K. 2012. The mucosal immune system. Pages 465–507 in Janeway's Immunobiology. 8th ed. Garland Science.

Naylor, J. M., and D. S. Kronfeld. 1986. Relationships between metabolic changes and clinical signs in pregnant sheep given endotoxin. Can. J. Vet. Res. 50:402–409.

Neves, R. C., B. M. Leno, K. D. Bach, and J. A. A. McArt. 2018a. Epidemiology of subclinical hypocalcemia in early-lactation Holstein dairy cows: The temporal associations of plasma calcium concentration in the first 4 days in milk with disease and milk production. J. Dairy Sci. 101:9321–9331. https://doi.org/10.3168/jds.2018-14587.

Neves, R. C., B. M. Leno, M. D. Curler, M. J. Thomas, T. R. Overton, and J. A. A. McArt. 2018b. Association of immediate postpartum plasma calcium concentration with early-lactation clinical diseases, culling, reproduction, and milk production in Holstein cows. J. Dairy Sci. 101:547–555. https://doi.org/10.3168/jds.2017-13313.

Neville, M. C. 1990. The physiological basis of milk secretion. Ann. N. Y. Acad. Sci. 586:1–11. https://doi.org/10.1111/j.1749-6632.1990.tb17783.x.

Newby, N. C., K. E. Leslie, H. D. Putnam Dingwell, D. F. Kelton, D. M. Weary, L. Neuder, S. T. Millman, and T. F. Duffield. 2017. The effects of periparturient administration of flunixin meglumine on the health and production of dairy cattle. J. Dairy Sci. 100:582–587. https://doi.org/10.3168/jds.2016-11747.

Newby, N. C., D. L. Pearl, S. J. LeBlanc, K. E. Leslie, M. A. G. von Keyserlingk, and T. F. Duffield. 2013. Effects of meloxicam on milk production, behavior, and feed intake in dairy cows following assisted calving. J. Dairy Sci. 96:3682–3688. https://doi.org/10.3168/jds.2012-6214.

Newsholme, P., R. Curi, T. C. Pithon Curi, C. J. Murphy, C. Garcia, and M. Pires de Melo. 1999. Glutamine metabolism by lymphocytes, macrophages, and neutrophils: Its importance in health and disease. J. Nutr. Biochem. 10:316–324. https://doi.org/10.1016/S0955-2863(99)00022-4.

Newsholme, P., and E. A. Newsholme. 1989. Rates of utilization of glucose, glutamine and oleate and formation of end-products by mouse peritoneal macrophages in culture. Biochem. J. 261:211–218. https://doi.org/10.1042/bj2610211.

Nguyen, A. T., S. Mandard, C. Dray, V. Deckert, P. Valet, P. Besnard, D. J. Drucker, L. Lagrost, and J. Grober. 2014. Lipopolysaccharides-mediated increase in glucose-stimulated insulin secretion: Involvement of the GLP-1 pathway. Diabetes 63:471–482. https://doi.org/10.2337/db13-0903.

Nielsen, L., C. M. Røntved, M. O. Nielsen, L. R. Norup, and K. L. Ingvartsen. 2003. Leukocytes from heifers at different ages express insulin and insulin-like growth factor-1 (IGF-1) receptors. Domest. Anim. Endocrinol. 25:231–238. https://doi.org/10.1016/S0739-7240(03)00065-1.

Nielsen, P. K., A. K. Rasmussen, R. Butters, U. Feldt-Rasmussen, K. Bendtzen, R. Diaz, E. M. Brown, and K. Olgaard. 1997. Inhibition of PTH secretion by interleukin-1β in bovine parathyroid glands in vitro is associated with an upregulation of the calcium-sensing receptor mRNA. Biochem. Biophys. Res. Commun. 238:880–885. https://doi.org/10.1006/bbrc.1997.7207.

Nunn, W. D. 1986. A molecular view of fatty acid catabolism in *Escherichia coli*. Microbiol. Rev. 50:179–192. https://doi.org/10.1128/MR.50.2.179-192.1986.

O'Boyle, N. J., G. A. Contreras, S. A. Mattmiller, and L. M. Sordillo. 2012. Changes in glucose transporter expression in monocytes of periparturient dairy cows. J. Dairy Sci. 95:5709–5719. https://doi.org/10.3168/jds.2012-5327.

O'Neill, L. A. J., and E. J. Pearce. 2016. Immunometabolism governs dendritic cell and macrophage function. J. Exp. Med. 213:15–23. https://doi.org/10.1084/jem.20151570.

Oftedal, O. T. 2000. Use of maternal reserves as a lactation strategy in large mammals. Proc. Nutr. Soc. 59:99–106. https://doi.org/10.1017/S0029665100000124.

Oh, S. K., N. Pavlotsky, and A. I. Tauber. 1990. Specific binding of haptoglobin to human neutrophils and its functional consequences. J. Leukoc. Biol. 47:142–148. https://doi.org/10.1002/jlb.47.2.142.

Ohtsuka, H., M. Koiwa, A. Hatsugaya, K. Kudo, F. Hoshi, N. Itoh, H. Yokota, H. Okada, and S. Kawamura. 2001. Relationship between serum TNF activity and insulin resistance in dairy cows affected with naturally occurring fatty liver. J. Vet. Med. Sci. 63:1021–1025. https://doi.org/10.1292/jvms.63.1021.

Oikawa, S., H. K. Elsayed, C. Shibata, K. Chisato, and K. Nakada. 2019. Peripartum metabolic profiles in a Holstein dairy herd with alarm level prevalence of subclinical ketosis detected in early lactation. Can. J. Vet. Res. 83:50–56.

Ospina, P. A., D. V. Nydam, T. Stokol, and T. R. Overton. 2010a. Evaluation of nonesterified fatty acids and β-hydroxybutyrate in transition dairy cattle in the northeastern United States: Critical thresholds for prediction of clinical diseases. J. Dairy Sci. 93:546–554. https://doi.org/10.3168/jds.2009-2277.

Ospina, P. A., D. V. Nydam, T. Stokol, and T. R. Overton. 2010b. Associations of elevated nonesterified fatty acids and β-hydroxybutyrate concentrations with early lactation reproductive performance and milk production in transition dairy cattle in the northeastern United States. J. Dairy Sci. 93:1596–1603. https://doi.org/10.3168/jds.2009-2852.

Østergaard, S., M. A. Krogh, V. H. S. Oliveira, T. LarsenGplusE Consortium, and N. D. Otten. 2020. Only few benefits from propylene glycol drench in early lactation for cows identified as physiologically imbalanced based on milk spectra analyses. J. Dairy Sci. 103:1831–1842. https://doi.org/10.3168/jds.2019-17205.

Overman, E. L., J. E. Rivier, and A. J. Moeser. 2012. CRF induces intestinal epithelial barrier injury via the release of mast cell proteases and TNF-α. PLoS One 7:e39935. https://doi.org/10.1371/journal.pone.0039935.

Overton, T. R., J. A. A. McArt, and D. V. Nydam. 2017. A 100-year review: Metabolic health indicators and management of dairy cattle. J. Dairy Sci. 100:10398–10417. https://doi.org/10.3168/jds.2017-13054.

Palsson-McDermott, E. M., and L. A. O'Neill. 2013. The Warburg effect then and now: From cancer to inflammatory diseases. BioEssays 35:965–973. https://doi.org/10.1002/bies.201300084.

Parés, S., F. Fàbregas, À. Bach, E. Garcia-Fruitós, A. de Prado, and A. Arís. 2020. Short communication: Recombinant mammary serum amyloid A3 as a potential strategy for preventing intramammary infections in dairy cows at dryoff. J. Dairy Sci. 103:3615–3621. https://doi.org/10.3168/jds.2019-17276.

Pennington, R. J. 1952. The metabolism of short-chain fatty acids in the sheep. I. Fatty acid utilization and ketone body production by rumen epithelium and other tissues. Biochem. J. 51:251–258. https://doi.org/10.1042/bj0510251.

Peter, A. T., and W. T. Bosu. 1988. Relationship of uterine infections and folliculogenesis in dairy cows during early puerperium. Theriogenology 30:1045–1051. https://doi.org/10.1016/0093-691X(88)90278-6.

Pfeiffer, T., S. Schuster, and S. Bonhoeffer. 2001. Cooperation and competition in the evolution of ATP-producing pathways. Science 292:504–507. https://doi.org/10.1126/science.1058079.

Pohl, C. S., J. E. Medland, E. Mackey, L. L. Edwards, K. D. Bagley, M. P. DeWilde, K. J. Williams, and A. J. Moeser. 2017. Early weaning stress induces chronic functional diarrhea, intestinal barrier defects, and increased mast cell activity in a porcine model of early life adversity. Neurogastroenterol. Motil. 29:e13118. https://doi.org/10.1111/nmo.13118.

Proudfoot, K. L., D. M. Weary, S. J. LeBlanc, L. K. Mamedova, and M. A. G. von Keyserlingk. 2018. Exposure to an unpredictable and competitive social environment affects behavior and health of transition dairy cows. J. Dairy Sci. 101:9309–9320. https://doi.org/10.3168/jds.2017-14115.

Quiroz-Rocha, G. F., S. K. LeBlanc, T. Duffield, D. Wood, K. Leslie, and R. M. Jacobs. 2009. Evaluation of prepartum serum cholesterol and fatty acid concentrations as predictors of postpartum retention of the placenta in dairy cows. J. Am. Vet. Med. Assoc. 234:790–793. https://doi.org/10.2460/javma.234.6.790.

Radloff, H. D., and L. H. Schultz. 1967. Blood and rumen changes in cows in early stages of ketosis. J. Dairy Sci. 50:68–72. https://doi.org/10.3168/jds.S0022-0302(67)87355-7.

Radloff, H. D., L. H. Schultz, and W. G. Hoekstra. 1966. Relationship of plasma free fatty acids to other blood components in ruminants under various physiological conditions. J. Dairy Sci. 49:179–182. https://doi.org/10.3168/jds.S0022-0302(66)87821-9.

Rahman, M. M., C. Lecchi, G. Avallone, P. Roccabianca, P. Sartorelli, and F. Ceciliani. 2010. Lipopolysaccharide-binding protein: Local expression in bovine extrahepatic tissues. Vet. Immunol. Immunopathol. 137:28–35. https://doi.org/10.1016/j.vetimm.2010.04.006.

Rahman, M. M., C. Lecchi, H. Sauerwein, M. Mielenz, S. Häußler, L. Restelli, C. Giudice, and F. Ceciliani. 2015. Expression of α1-acid glycoprotein and lipopolysaccharide binding protein in visceral and subcutaneous adipose tissue of dairy cattle. Vet. J. 203:223–227. https://doi.org/10.1016/j.tvjl.2014.12.001.

Raju, S. M., A. P. Kumar, A. N. Yadav, K. Rajkumar, S. Mvs, and S. Burgula. 2019. Haptoglobin improves acute phase response and endotoxin tolerance in response to bacterial LPS. Immunol. Lett. 207:17–27. https://doi.org/10.1016/j.imlet.2019.01.002.

Randle, P. J. 1998. Regulatory interactions between lipid and carbohydrates: The glucose fatty acid cycle after 35 years. Diabetes Metab. Rev. 14:263–283. https://doi.org/10.1002/(SICI)1099-0895(199812)14:4<263::AID-DMR233>3.0.CO;2-C.

Rathbun, F. M., R. S. Pralle, S. J. Bertics, L. E. Armentano, K. Cho, C. Do, K. A. Weigel, and H. M. White. 2017. Relationships between body condition score change, prior mid-lactation phenotypic residual feed intake, and hyperketonemia onset in transition dairy cows. J. Dairy Sci. 100:3685–3696. https://doi.org/10.3168/jds.2016-12085.

Ratter, J. M., J. I. P. van Heck, H. M. M. Rooijackers, H. J. Jansen, P. C. M. van Poppel, C. J. Tack, and R. Stienstra. 2021. Insulin acutely activates metabolism of primary human monocytes and promotes a proinflammatory phenotype. J. Leukoc. Biol. JLB.3AB0120-019RR. https://doi.org/10.1002/JLB.3AB0120-019RR.

Reeds, P. J., C. R. Fjeld, and F. Jahoor. 1994. Do the differences between the amino acid compositions of acute-phase and muscle proteins have a bearing on nitrogen loss in traumatic states? J. Nutr. 124:906–910. https://doi.org/10.1093/jn/124.6.906.

Reinhardt, T. A., J. D. Lippolis, B. J. McCluskey, J. P. Goff, and R. L. Horst. 2011. Prevalence of subclinical hypocalcemia in dairy herds. Vet. J. 188:122–124. https://doi.org/10.1016/j.tvjl.2010.03.025.

Rhoads, R. P., J. W. Kim, B. J. Leury, L. H. Baumgard, N. Segoale, S. J. Frank, D. E. Bauman, and Y. R. Boisclair. 2004. Insulin increases the abundance of the growth hormone receptor in liver and adipose tissue of periparturient cows. J. Nutr. 134:1020–1027. https://doi.org/10.1093/jn/134.5.1020.

Ribeiro, E. S., F. S. Lima, L. F. Greco, R. S. Bisinotto, A. P. A. Monteiro, M. Favoreto, H. Ayres, R. S. Marsola, N. Martinez, W. W. Thatcher, and J. E. P. Santos. 2013. Prevalence of periparturient diseases and effects on fertility of seasonally calving grazing dairy cows supplemented with concentrates. J. Dairy Sci. 96:5682–5697. https://doi.org/10.3168/jds.2012-6335.

Rodriguez-Jimenez, S., K. J. Haerr, E. Trevisi, J. J. Loor, F. C. Cardoso, and J. S. Osorio. 2018. Prepartal standing behavior as a parameter for early detection of postpartal subclinical ketosis associated with inflammation and liver function biomarkers in peripartal dairy cows. J. Dairy Sci. 101:8224–8235. https://doi.org/10.3168/jds.2017-14254.

Rodriguez-Jimenez, S., E. A. Horst, E. J. Mayorga, M. A. Abeyta, B. M. Goetz, S. Carta, and L. H. Baumgard. 2020. Effects of LPS administration and subsequent nutrient restriction on metabolism in lactating dairy cows. J. Dairy Sci. 103(Suppl. 1):155.

Rosales, C. 2018. Neutrophil: A cell with many roles in inflammation or several cell types? Front. Physiol. 9:113. https://doi.org/10.3389/fphys.2018.00113.

Rukkwamsuk, T., T. Wensing, and M. J. Geelen. 1998. Effect of overfeeding during the dry period on regulation of adipose tissue metabolism in dairy cows during the periparturient period. J. Dairy Sci. 81:2904–2911. https://doi.org/10.3168/jds.S0022-0302(98)75851-5.

Rukkwamsuk, T., T. Wensing, and M. J. Geelen. 1999. Effect of overfeeding during the dry period on the rate of esterification in adipose tissue of dairy cows during the periparturient period. J. Dairy Sci. 82:1164–1169. https://doi.org/10.3168/jds.S0022-0302(99)75339-7.

Sadleir, R. M. F. S. 1982. Energy consumption and subsequent partitioning in lactating black-tailed deer. Can. J. Zool. 60:382–386. https://doi.org/10.1139/z82-051.

Sampson, J., A. C. Gonzaga, and C. E. Hayden. 1933. The ketones of the blood and urine of the cow and ewe in health and disease. Cornell Vet. 23:184–207.

Sato, K., Y. Kashiwaya, C. A. Keon, N. Tsuchiya, M. T. King, G. K. Radda, B. Chance, K. Clarke, and R. L. Veech. 1995. Insulin, ketone bodies, and mitochondrial energy transduction. FASEB J. 9:651–658.

Sato, M., R. Ohkawa, A. Yoshimoto, K. Yano, N. Ichimura, M. Nishimori, S. Okubo, Y. Yatomi, and M. Tozuka. 2016. Effects of serum amyloid A on the structure and antioxidant ability of high-density lipoprotein. Biosci. Rep. 36:e00369. https://doi.org/10.1042/BSR20160075.

Scalia, D., N. Lacetera, U. Bernabucci, K. Demeyere, L. Duchateau, and C. Burvenich. 2006. In vitro effects of nonesterified fatty acids on bovine neutrophils oxidative burst and viability. J. Dairy Sci. 89:147–154. https://doi.org/10.3168/jds.S0022-0302(06)72078-1.

Schmidt, G. H. 1966. Effect of insulin on yield and composition of milk of dairy cows. J. Dairy Sci. 49:381–385. https://doi.org/10.3168/jds.S0022-0302(66)87878-5.

Schröder, N. W., S. Morath, C. Alexander, L. Hamann, T. Hartung, U. Zahringer, U. B. Gobel, J. R. Weber, and R. R. Schumann. 2003. Lipotheicoic acid (LTA) of *Streptococcus pneumoniae* and *Staphylococcus aureus* activates immune cells via Toll-like receptor (TLR-2), lipopolysaccharide-binding protein (LBP), and CD14, whereas TLR-4 and MD-2 are not involved. J. Biol. Chem. 278:15587–15594. https://doi.org/10.1074/jbc.M212829200.

Sheldon, I. M., and M. H. Roberts. 2010. Toll-like receptor 4 mediates the response of epithelial and stromal cells to lipopolysaccharide in endometrium. PLoS One 5:e12906.

Shen, T., X. Li, J. J. Loor, Y. Zhu, X. Du, X. Wang, D. Xing, Z. Shi, Z. Fang, X. Li, and G. Liu. 2019. Hepatic nuclear factor kappa B signaling pathway and NLR family pyrin domain containing 3 inflammasome is over-activated in ketotic dairy cows. J. Dairy Sci. 102:10554–10563.

Shwartz, G., K. L. Hill, M. J. VanBaale, and L. H. Baumgard. 2009. Effects of flunixin meglumine on pyrexia and bioenergetics variables in postparturient dairy cows. J. Dairy Sci. 92:1963–1970. https://doi.org/10.3168/jds.2008-1581.

Shah, C., R. Hari-Dass, and J. G. Raynes. 2006. Serum amyloid A is an innate immune opsonin for Gram-negative bacteria. Blood 108:1751–1757. https://doi.org/10.1182/blood-2005-11-011932.

Shakhar, K., and G. Shakhar. 2015. Why do we feel sick when infected—Can altruism play a role? PLoS Biol. 13:e1002276. https://doi.org/10.1371/journal.pbio.1002276.

Shaw, J. C. 1956. Ketosis in dairy cattle. A review. J. Dairy Sci. 39:402–434. https://doi.org/10.3168/jds.S0022-0302(56)94765-8.

Sheldon, I. M., J. G. Cronin, and J. J. Bromfield. 2019. Tolerance and innate immunity shape the development of postpartum uterine disease and the impact of endometritis in dairy cattle. Annu. Rev. Anim. Biosci. 7:361–384. https://doi.org/10.1146/annurev-animal-020518-115227.

Sheldon, I. M., G. S. Lewis, S. LeBlanc, and R. O. Gilbert. 2006. Defining postpartum uterine disease in cattle. Theriogenology 65:1516–1530. https://doi.org/10.1016/j.theriogenology.2005.08.021.

Sheldon, I. M., S. B. Price, J. Cronin, R. O. Gilbert, and J. E. Gadsby. 2009. Mechanisms of infertility associated with clinical and subclinical endometritis in high producing dairy cattle. Reprod. Domest. Anim. 44(Suppl. 3):1–9. https://doi.org/10.1111/j.1439-0531.2009.01465.x.

Sherwin, R. S., R. G. Hendler, and P. Felig. 1975. Effect of ketone infusions on amino acid and nitrogen metabolism in man. J. Clin. Invest. 55:1382–1390. https://doi.org/10.1172/JCI108057.

Silva-del-Río, N., P. M. Fricke, and R. R. Grummer. 2010. Effects of twin pregnancy and dry period feeding strategy on milk production, energy balance, and metabolic profiles in dairy cows. J. Anim. Sci. 88:1048–1060. https://doi.org/10.2527/jas.2009-2206.

Sjollema, B., and J. E. Van Der Zande. 1923. Metabolism in acetonemia in milch cows. J. Metab. Res. 4:525.

Skarnes, R. C., and L. C. Chedid. 1964. Biological degraduation and inactivation of endotoxin (chromate-labeled). Pages 575–587 in Bacterial Endotoxins. M. Landy and W. Braun, ed. Rutgers University Press.

Smith, K. L., D. A. Todhunter, and P. S. Schoenberger. 1985. Environmental mastitis: Cause, prevalence, and prevention. J. Dairy Sci. 68:1531–1553. https://doi.org/10.3168/jds.S0022-0302(85)80993-0.

Spencer, J. A., D. Konetchy, and A. Ahmadzadeh. 2020. Influences of non-steroidal anti-inflammatory drugs on dairy cattle reproductive performance. Appl. Anim. Sci. 36:397–406. https://doi.org/10.15232/aas.2019-01969.

Spitzer, J. A., G. J. Leach, and M. A. Palmer. 1980. Some metabolic and hormonal alterations in adipocytes isolated from septic dogs. Adv. Shock Res. 4:55–62.

Spitzer, J. A., K. M. Nelson, and R. E. Fish. 1985. Time course of changes in gluconeogenesis from various precursors in chronically endotoxemic rats. Metabolism 34:842–849. https://doi.org/10.1016/0026-0495(85)90109-X.

Spruss, A., G. Kanuri, S. Wagnerberger, S. Haub, S. C. Bischoff, and I. Bergheim. 2009. Toll-like receptor 4 is involved in the development of fracture-induced hepatic steatosis in mice. Hepatology 50:1094–1104. https://doi.org/10.1002/hep.23122.

Steele, M. A., G. B. Penner, F. Chaucheyras-Durand, and L. L. Guan. 2016. Development and physiology of the rumen and the lower gut: Targets for improving gut health. J. Dairy Sci. 99:4955–4966. https://doi.org/10.3168/jds.2015-10351.

Stefanska, B., W. Człapa, E. Pruszynska-Oszmałek, D. Szczepankiewicz, V. Fievez, J. Komisarek, K. Stajek, and W. Nowak. 2018. Subacute ruminal acidosis affects fermentation and endotoxin concentration in the rumen and relative expression of the CD14/TLR4/MD2 genes involved in lipopolysaccharide systemic immune response in dairy cows. J. Dairy Sci. 101:1297–1310. https://doi.org/10.3168/jds.2017-12896.

Ster, C., M. C. Loiselle, and P. Lacasse. 2012. Effect of postcalving serum nonesterified fatty acids concentration on the functionality of bovine immune cells. J. Dairy Sci. 95:708–717. https://doi.org/10.3168/jds.2011-4695.

Stienstra, R., F. Saudale, C. Duval, S. Keshtkar, J. E. M. Groener, N. van Rooijen, B. Staels, S. Kersten, and M. Müller. 2010. Kupffer cells promote hepatic steatosis via interleukin–1β-dependent suppression of peroxisome proliferator-activated receptor α activity. Hepatology 51:511–522. https://doi.org/10.1002/hep.23337.

Stinson, O. 1928. Observations on twenty cases of acetonemia. Vet. Rec. 8:880–881.

Stocks, S. E., and M. S. Allen. 2014. Effects of lipid and propionic acid infusions on feed intake of lactating dairy cows. J. Dairy Sci. 97:2297–2304. https://doi.org/10.3168/jds.2013-7066.

Strnad, P., F. Tacke, A. Koch, and C. Trautwein. 2017. Liver—Guardian, modifier and target of sepsis. Nat. Rev. Gastroenterol. Hepatol. 14:55–66. https://doi.org/10.1038/nrgastro.2016.168.

Stumpf, M. T., V. Fischer, C. M. McManus, G. J. Kolling, M. B. Zanela, C. S. Santos, A. S. Abreu, and P. Montagner. 2013. Severe feed restriction increases permeability of mammary gland cell tight junctions and reduces ethanol stability of milk. Animal 7:1137–1142. https://doi.org/10.1017/S1751731113000128.

Sun, Y., L. Li, J. Wu, P. Yu, C. Li, J. Tang, X. Li, S. Huang, and G. Wang. 2015. Bovine recombinant lipopolysaccharide binding protein (BRLBP) regulated apoptosis and inflammation response in lipopolysaccharide-challenge bovine mammary epithelial cells (BMEC). Mol. Immunol. 65:205–214. https://doi.org/10.1016/j.molimm.2015.01.026.

Suriyasathaporn, W., A. J. J. M. Daemen, E. N. Noordhuizen-Stassen, S. J. Dieleman, M. Nielen, and Y. H. Schukken. 1999. β-Hydroxybutyrate levels in peripheral blood and ketone bodies supplemented in culture media affect the in vitro chemotaxis of bovine leukocytes. Vet. Immunol. Immunopathol. 68:177–186. https://doi.org/10.1016/S0165-2427(99)00017-3.

Takeyama, N., Y. Itoh, Y. Kitazawa, and T. Tanaka. 1990. Altered hepatic mitochondrial fatty acid oxidation and ketogenesis in endotoxic rats. Am. J. Physiol. 259:E498–E505. https://doi.org/10.1152/ajpendo.1990.259.4.E498.

Takiya, C. S., S. R. Montgomery, L. K. Mamedova, G. Kra, N. Nemes-Navon, Y. Levin, S. D. Fleming, B. J. Bradford, and M. Zachut. 2019. Proteomic analysis reveals greater abundance of complement and inflammatory proteins in subcutaneous adipose tissue from postpartum cows treated with sodium salicylate. J. Proteomics 204:103399. https://doi.org/10.1016/j.jprot.2019.103399.

Taubes, G. 2001. Nutrition. The soft science of dietary fat. Science 291:2536–2545. https://doi.org/10.1126/science.291.5513.2536.

Teitelbaum, A. A., M. G. Gareau, J. Jury, P. C. Yang, and M. H. Perdue. 2008. Chronic peripheral administration of corticotropin-releasing factor causes colonic barrier dysfunction similar to psychological stress. Am. J. Physiol. Gastrointest. Liver Physiol. 295:G452–G459. https://doi.org/10.1152/ajpgi.90210.2008.

Tennant, B., M. Reina-Guerra, and D. Harrold. 1973. Metabolic response of calves following acute experimental endotoxemia. Ann. Rech. Vet. 4:135–147.

Thilsing-Hansen, T., R. J. Jorgensen, and S. Østergaard. 2002. Milk fever control principles: A review. Acta Vet. Scand. 43:1–19. https://doi.org/10.1186/1751-0147-43-1.

Thomas, A. H. 1889. Parturient apoplexy in cows—A form of septicaemia. Vet. J. Ann. Comp. Pathol. 28:1–4. https://doi.org/10.1016/S2543-3377(17)37660-4.

Thompson, G. N., B. Y. L. Hsu, J. J. Pitt, E. Treacy, and C. A. Stanley. 1997. Fasting hypoketotic coma in a child with deficiency of mitochondrial 3-hydroxy-3-methylglutaryl-CoA synthase. N. Engl. J. Med. 337:1203–1207. https://doi.org/10.1056/NEJM199710233371704.

Toribio, R. E., C. W. Kohn, J. Hardy, and T. J. Rosol. 2005. Alterations in serum parathyroid hormone and electrolyte concentrations and urinary excretion of electrolytes in horses with induced endotoxemia. J. Vet. Intern. Med. 19:223–231. https://doi.org/10.1111/j.1939-1676.2005.tb02686.x.

Trevisi, E., M. Amadori, S. Cogrossi, E. Razzuoli, and G. Bertoni. 2012. Metabolic stress and inflammatory response in high-yielding, periparturient dairy cows. Res. Vet. Sci. 93:695–704. https://doi.org/10.1016/j.rvsc.2011.11.008.

Trevisi, E., A. Ferrari, F. Piccioli-Cappelli, P. Grossi, and G. Bertoni. 2010. An additional study on the relationship between the inflammatory condition at calving time and net energy efficiency in dairy cows. Pages 489–490 in Energy and Protein Metabolism and Nutrition. EAAP publication no. 127. European Federation of Animal Science.

Trevisi, E., X.-T. Han, F. Piccioli-Cappelli, and G. Bertoni. 2002. Dry matter intake reduction before calving in dairy cows: Relationship with immune system and metabolism conditions. Page 54 in Proc. 53rd Annual Meet. EAAP, Cairo, Egypt. European Federation of Animal Science.

Trevisi, E., and A. Minuti. 2018. Assessment of the innate immune response in the periparturient cow. Res. Vet. Sci. 116:47–54. https://doi.org/10.1016/j.rvsc.2017.12.001.

Tucker, C. B., S. J. Lacy-Hulbert, and R. J. Webster. 2009. Effect of milking frequency and feeding level before and after dry off on dairy cattle behavior and udder characteristics. J. Dairy Sci. 92:3194–3203. https://doi.org/10.3168/jds.2008-1930.

Utzeri, E., and P. Usai. 2017. Role of non-steroidal anti-inflammatory drugs on intestinal permeability and nonalcoholic fatty liver disease. World J. Gastroenterol. 23:3954–3963. https://doi.org/10.3748/wjg.v23.i22.3954.

Vailati Riboni, M., S. Meier, V. Priest, C. R. Burke, J. K. Kay, S. McDougall, M. D. Mitchell, C. G. Walker, M. Crookenden, A. Heiser, J. R. Roche, and J. J. Loor. 2015. Adipose and liver gene expression profiles in response to treatment with a nonsteroidal anti-inflammatory drug after calving in grazing dairy cows. J. Dairy Sci. 98:3079–3085. https://doi.org/10.3168/jds.2014-8579.

van der Heijden, P. J., W. Stok, and A. T. J. Bianchi. 1987. Contribution of immunoglobulin-secreting cells in the murine small

intestine to the total "background" immunoglobulin production. Immunology 62:551–555.
van Miert, A. S., and J. Frens. 1968. The reaction of different animal species to bacterial pyrogens. Zentralbl. Veterinärmed. A 15:532–543. https://doi.org/10.1111/j.1439-0442.1968.tb00456.x.
Vander Heiden, M. G., L. C. Cantley, and C. B. Thompson. 2009. Understanding the Warburg effect: The metabolic requirements of cell proliferation. Science 324:1029–1033. https://doi.org/10.1126/science.1160809.
Vanholder, T., J. Papen, R. Bemers, G. Vertenten, and A. C. B. Berge. 2015. Risk factors for subclinical and clinical ketosis and association with production parameters in dairy cows in the Netherlands. J. Dairy Sci. 98:880–888. https://doi.org/10.3168/jds.2014-8362.
Vernay, M. C., O. Wellnitz, L. Kreipe, H. A. van Dorland, and R. M. Bruckmaier. 2012. Local and systemic response to intramammary lipopolysaccharide challenge during long-term manipulated plasma glucose and insulin concentrations in dairy cows. J. Dairy Sci. 95:2540–2549. https://doi.org/10.3168/jds.2011-5188.
Vernon, R. G. 1992. Effect of diet on lipolysis and its regulation. Proc. Nutr. Soc. 51:397–408. https://doi.org/10.1079/PNS19920053.
Vives-Pi, M., N. Somoza, J. Fernández-Alvarez, F. Vargas, P. Caro, A. Alba, R. Gomis, M. O. Labeta, and R. Pujol-Borrell. 2003. Evidence of expression of endotoxin receptors CD14, toll-like receptors TLR4 and TLR2 and associated molecule MD-2 and of sensitivity to endotoxin (LPS) in islet beta cells. Clin. Exp. Immunol. 133:208–218. https://doi.org/10.1046/j.1365-2249.2003.02211.x.
Waldron, M. R., A. E. Kulick, A. W. Bell, and T. R. Overton. 2006. Acute experimental mastitis is not causal toward the development of energy-related metabolic disorders in early postpartum dairy cows. J. Dairy Sci. 89:596–610. https://doi.org/10.3168/jds.S0022-0302(06)72123-3.
Waldron, M. R., T. Nishida, B. J. Nonnecke, and T. R. Overton. 2003a. Effect of lipopolysaccharide on indices of peripheral and hepatic metabolism in lactating cows. J. Dairy Sci. 86:3447–3459. https://doi.org/10.3168/jds.S0022-0302(03)73949-6.
Waldron, M. R., B. J. Nonnecke, T. Nishida, R. L. Horst, and T. R. Overton. 2003b. Effect of lipopolysaccharide infusion on serum macromineral and vitamin D concentrations in dairy cows. J. Dairy Sci. 86:3440–3446. https://doi.org/10.3168/jds.S0022-0302(03)73948-4.
Walrand, S., C. Guillet, Y. Boirie, and M.-P. Vasson. 2004. In vivo evidence that insulin regulates human polymorphonuclear neutrophil functions. J. Leukoc. Biol. 76:1104–1110. https://doi.org/10.1189/jlb.0104050.
Walrand, S., C. Guillet, Y. Boirie, and M.-P. Vasson. 2006. Insulin differentially regulates monocyte and polymorphonuclear neutrophil functions in healthy young and elderly humans. J. Clin. Endocrinol. Metab. 91:2738–2748. https://doi.org/10.1210/jc.2005-1619.
Wang, A., S. C. Huen, H. H. Luan, S. Yu, C. Zhang, J.-D. Gallezot, C. J. Booth, and R. Medzhitov. 2016. Opposing effects of fasting metabolism on tissue tolerance in bacterial and viral inflammation. Cell 166:1512–1525. https://doi.org/10.1016/j.cell.2016.07.026.
Wang, L. F., S. D. Jia, G. Q. Yang, R. Y. Liu, G. Y. Yang, M. Li, H. S. Zhu, Y. Y. Wang, and L. Q. Han. 2017. The effects of acute lipopolysaccharide challenge on dairy goat liver metabolism assessed with (1) HNMR metabolomics. J. Anim. Physiol. Anim. Nutr. (Berl.) 101:180–189. https://doi.org/10.1111/jpn.12439.
Wang, S. P., H. Yang, J. W. Wu, N. Gauthier, T. Fukao, and G. A. Mitchell. 2014. Metabolism as a tool for understanding human brain evolution: Lipid energy metabolism as an example. J. Hum. Evol. 77:41–49. https://doi.org/10.1016/j.jhevol.2014.06.013.
Wannemacher, R. W. Jr., F. A. Beall, P. G. Canonico, R. E. Dinterman, C. L. Hadick, and H. A. Neufeld. 1980. Glucose and alanine metabolism during bacterial infections in rats and rhesus monkeys. Metabolism 29:201–212. https://doi.org/10.1016/0026-0495(80)90061-X.
Warburg, O. 1923. Metabolism of tumors. Biochem. Z. 142:317–333.
Warburg, O., K. Gawehn, and A. W. Geissler. 1958. Metabolism of leukocytes. Z. Naturforsch. B 13B:515–516. https://doi.org/10.1515/znb-1958-0806.
Weisberg, S. P., D. McCann, M. Desai, M. Rosenbaum, R. L. Leibel, and A. W. Ferrante Jr.. 2003. Obesity is assocated with macrophage accumulation in adipose tissue. J. Clin. Invest. 112:1796–1808. https://doi.org/10.1172/JCI200319246.
Wellnitz, O., C. Zbinden, X. Huang, and R. M. Bruckmaier. 2016. Short communication: Differential loss of bovine mammary epithelial barrier integrity in response to lipopolysaccharide and lipoteichoic acid. J. Dairy Sci. 99:4851–4856.
Wenz, J. R., G. M. Barrington, F. B. Garry, K. D. McSweeney, R. P. Dinsmore, G. Goodell, and R. J. Callan. 2001. Bacteremia associated with naturally occurring acute coliform mastitis in dairy cows. J. Am. Vet. Med. Assoc. 219:976–981. https://doi.org/10.2460/javma.2001.219.976.
Williams, E. J., S. Herath, G. C. England, H. Dobson, C. E. Bryant, and I. M. Sheldon. 2008. Effect of *Escherichia coli* infection of the bovine uterus from the whole animal to the cell. Animal 2:1153–1157. https://doi.org/10.1017/S1751731108002413.
Wilms, J., G. Wang, J. Doelman, M. Jacobs, and J. Martín-Tereso. 2019. Intravenous calcium infusion in a calving protocol disturbs calcium homeostasis compared with an oral calcium supplement. J. Dairy Sci. 102:6056–6064. https://doi.org/10.3168/jds.2018-15754.
Xu, T., F. C. Cardoso, A. Pineda, E. Trevisi, X. Shen, F. Rosa, J. S. Osorio, and J. J. Loor. 2017. Grain challenge affects systemic and hepatic molecular biomarkers of inflammation, stress, and metabolic responses to a greater extent in Holstein than Jersey cows. J. Dairy Sci. 100:9153–9162. https://doi.org/10.3168/jds.2017-13321.
Xu, T., Z. Dong, X. Wang, S. Qi, X. Li, R. Cheng, X. Liu, Y. Zhang, and M.-Q. Gao. 2018. IL-1β induces increased tight junction permeability in bovine mammary epithelial cells via the IL-1β-ERK1/2-MLCK axis upon blood-milk barrier damage. J. Cell. Biochem. 119:9028–9041. https://doi.org/10.1002/jcb.27160.
Yan, J., S. Li, and S. Li. 2014. The role of the liver in sepsis. Int. Rev. Immunol. 33:498–510. https://doi.org/10.3109/08830185.2014.889129.
Yousefi, A. R., H. Kohram, A. Zare Shahneh, M. J. Zamiri, and A. A. Fouladi-Nashta. 2016. Effects of dietary supplementation of pioglitazone on metabolism, milk yield, and reproductive performance in transition dairy cows. Theriogenology 85:1540–1548. https://doi.org/10.1016/j.theriogenology.2016.01.015.
Yuan, K., J. K. Farney, L. K. Mamedova, L. M. Sordillo, and B. J. Bradford. 2013. TNF-α altered inflammatory responses, impaired health and productivity, but did not affect glucose or lipid metabolism in early-lactation dairy cows. PLoS One 8:e80316. https://doi.org/10.1371/journal.pone.0080316.
Zaloga, G. P. 1992. Hypocalcemia in critically ill patients. Crit. Care Med. 20:251–262. https://doi.org/10.1097/00003246-199202000-00014.
Zarrin, M., L. De Matteis, M. C. M. B. Vernay, O. Wellnitz, H. A. van Dorland, and R. M. Bruckmaier. 2013. Long-term elevation of β-hydroxybutyrate in dairy cows through infusion: Effects on feed intake, milk production, and metabolism. J. Dairy Sci. 96:2960–2972. https://doi.org/10.3168/jds.2012-6224.
Zarrin, M., O. Wellnitz, H. A. van Dorland, and R. M. Bruckmaier. 2014a. Induced hyperketonemia affects the mammary immune response during lipopolysaccharide challenge in dairy cows. J. Dairy Sci. 97:330–339. https://doi.org/10.3168/jds.2013-7222.
Zarrin, M., O. Wellnitz, H. A. van Dorland, J. J. Gross, and R. M. Bruckmaier. 2014b. Hyperketonemia during lipopolysaccharide-induced mastitis affects systemic and local intramammary metabolism in dairy cows. J. Dairy Sci. 97:3531–3541. https://doi.org/10.3168/jds.2013-7480.
Zebeli, Q., S. Sivaraman, S. M. Dunn, and B. N. Ametaj. 2011. Intermittent parenteral administration of endotoxin triggers metatabolic and immunological alterations typically associated with displaced abomasume and retained placenta in periparturient dairy cows. J. Dairy Sci. 94:4968–4983. https://doi.org/10.3168/jds.2011-4194.
Zhang, G., D. Hailemariam, E. Dervishi, Q. Deng, S. A. Goldansaz, S. M. Dunn, and B. N. Ametaj. 2015. Alterations of innate immunity

reactants in transition dairy cows before clinical signs of lameness. Animals (Basel) 5:717–747. https://doi.org/10.3390/ani5030381.

Zhang, G., D. Hailemariam, E. Dervishi, S. A. Goldansaz, Q. Deng, S. M. Dunn, and B. M. Ametaj. 2016. Dairy cows affected by ketosis show alterations in innate immunity and lipid and carbohydrate metabolism during the dry off period and postpartum. Res. Vet. Sci. 107:246–256. https://doi.org/10.1016/j.rvsc.2016.06.012.

Zhang, S., R. I. Albornoz, J. R. Aschenbach, D. R. Barreda, and G. B. Penner. 2013. Short-term feed restriction impairs the absorptive function of the reticulo-rumen and total tract barrier function in beef cattle. J. Anim. Sci. 91:1685–1695. https://doi.org/10.2527/jas.2012-5669.

Zhao, F. Q., and A. F. Keating. 2007. Expression and regulation of glucose transporters in the bovine mammary gland. J. Dairy Sci. 90:E76–E86. https://doi.org/10.3168/jds.2006-470.

Zhou, Z., J. J. Loor, F. Piccioli-Cappelli, F. Librandi, G. E. Lobley, and E. Trevisi. 2016. Circulating amino acids in blood plasma during the peripartal period in dairy cows with different liver functionality index. J. Dairy Sci. 99:2257–2267. https://doi.org/10.3168/jds.2015-9805.

Zhou, Z., E. Trevisi, D. N. Luchini, and J. J. Loor. 2017. Differences in liver functionality indexes in peripartal dairy cows fed rumen-protected methionine or choline are associated with performance, oxidative stress status, and plasma amino acid profiles. J. Dairy Sci. 100:6720–6732. https://doi.org/10.3168/jds.2016-12299.

Zinicola, M., and R. C. Bicalho. 2019. Association of peripartum plasma insulin concentration with milk production, colostrum insulin levels, and plasma metabolites of Holstein cows. J. Dairy Sci. 102:1473–1482. https://doi.org/10.3168/jds.2017-14029.

Zonneveld, R., G. Molema, and F. B. Plötz. 2016. Measurement of functional and morphodynamic neutrophil phenotypes in systemic inflammation and sepsis. Crit. Care 20:235. https://doi.org/10.1186/s13054-016-1391-5.

Zweigner, J., H. J. Gramm, O. C. Singer, K. Wegscheider, and R. R. Schumann. 2001. High concentrations of lipopolysaccharide-binding protein in serum of patients with severe sepsis or septic shock inhibit the lipopolysaccharide response in human monocytes. Blood 98:3800–3808. https://doi.org/10.1182/blood.V98.13.3800.

ORCIDS

L. H. Baumgard https://orcid.org/0000-0002-3077-5996