

# Connecting Transition Cow Physiology, Behavior, and Nutrition

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## Introduction

In the past, efforts to improve the transition to lactation have focused largely on preventing infections and maximizing energy intake in transition cows, and these have generally been treated as independent issues. However, new models are emerging to explain the development of numerous transition disorders. A combination of insults, including social stress, negative energy balance, heat stress, endotoxin exposure, and oxidative stress may promote inflammation, suppress feed intake, and impair both metabolic and immune function during the transition period. These models suggest that transition cow management must be viewed in a holistic way, with the cow's environment, nutrition, and immune function interacting in many complex ways. Fortunately, a number of practical approaches can be used to improve the overall health of transition cows, which can decrease the cull rate in early lactation and improve both productivity and reproductive success.

## The Biology of the Transition Dairy Cow

A number of dramatic changes occur in the dairy cow during the transition period. Dairy cattle, like many other species, often consume less feed in the week prior to parturition (Grummer et al., 2004), and it can take up to a week post-calving before dry matter intake (**DMI**) exceeds what the cow was consuming in late gestation. In the final 24 hours before calving, cows typically separate themselves from other cows to the extent possible, and it is not surprising that DMI is low during this short period. However, the extended period of low DMI experienced by many cows is more difficult to explain and it is far more problematic for the cow as her nutrient requirements rise rapidly at the onset of lactation.

The drive to produce milk is given priority over nearly all other physiological processes during this time, and a number of changes occur to partition nutrients to the mammary gland. Negative energy balance and homeorhetic adaptations during the transition to lactation decrease plasma insulin concentration substantially (Doepel et al., 2002) and also decrease the responsiveness of adipose tissue to insulin (Bell and Bauman, 1997). These adaptations lead to dramatic increases in plasma non-esterified fatty acid (**NEFA**) concentration, and this also leads to greater uptake of

fatty acids by the liver. This increase in fatty acid supply to the liver often exceeds the capacity for oxidation, resulting in both ketone body production and storage of triglycerides (Drackley et al., 2001). This process can occur quite rapidly, and cows can develop moderate fatty liver and ketosis in the course of just a few days.

Increased liver glucose production is another adaptation to lactation. Meeting the increased demand for glucose during the transition period is especially challenging, because little glucose is absorbed from the ruminant gastrointestinal tract. Over the course of the first 2 months of lactation, liver glucose production increases by at least 2-fold (Schulze et al., 1991), and most of this change likely occurs within a week after calving. Several studies have found decreased capacity for gluconeogenesis in liver slices from cows with fatty liver (Mills et al., 1986, Veenhuizen et al., 1991), and others have shown that induced fatty liver results in decreased activities of several rate-determining gluconeogenic enzymes (Rukkwamsuk et al., 1999, Murondoti et al., 2004). The ability of a cow to successfully up-regulate gluconeogenesis in early lactation is critical to both avoid metabolic problems (e.g. ketosis) and to maximize peak milk production, and the negative effect of fatty liver on gluconeogenesis is one reason that this condition is of concern.

The large increase in calcium requirements also strains the regulatory mechanisms of the transition cow. Calcium requirements can increase by more than 3-fold on the very first day of lactation, and this drain continues as milk yield increases much more rapidly than DMI (Horst et al., 2005). As a result, cows selected for high milk yield will nearly always experience some decrease in available (ionized) blood calcium during the first week of lactation. Although the adoption of anionic prepartum diets has been quite successful at reducing the incidence of milk fever, subclinical hypocalcemia can occur even with careful management of dietary cation-anion difference (**DCAD**; Moore et al., 2000).

Another key component of transition cow biology is the decrease in immune function throughout the 6-week transition period. Components of both the innate and adaptive immune systems appear to be affected during this period, and have been measured as decreased function of monocytes (Nonnecke et al., 2003), lymphocytes, and neutrophils (Mallard et al., 1998). In contrast, however, monocytes response to stimulation with greater release of inflammatory cytokines such as tumor necrosis factor  $\alpha$  (**TNF $\alpha$** ) during this period (Sordillo et al., 1995). It is believed that the general decrease in immune function during the transition period contributes to the high incidence of infectious disorders at this time (i.e. mastitis, metritis), and there is growing interest in the potential effects of inflammation during this period as well.

## Physiological Interactions in the Transition Cow

Traditionally, experts on dairy cattle have focused on isolated components of dairy management: nutritionists worked on diets, veterinarians responded to disease outbreaks, and others were called upon to design facilities to maximize cow comfort. What we are learning today is how much nutrition, pathogens, and environmental challenges interact to influence the physiology of the cow.

One such interaction is the effect of energy balance on immune function. Nearly all transition cows experience at least 3 weeks of negative energy balance, a situation in which they require more energy for maintenance and milk production than is consumed from the diet. One response to this nutrient imbalance is rapid mobilization of adipose tissue triglyceride, resulting in elevation of plasma NEFA concentrations by as much as 10-fold (Ingvarsen and Andersen, 2000). Greatly elevated concentrations of NEFA often result in significant conversion of NEFA to ketones (e.g. BHBA) in the liver. Recent work has demonstrated that elevated NEFA concentrations may directly impair neutrophil viability (Scalia et al., 2006) and high BHBA concentrations can decrease neutrophil function (Grinberg et al., 2008). These relationships may help to explain at least some of the decrease in immune function during this time of negative energy balance.

Another common nutrition-related issue discussed above is the subclinical hypocalcemia that occurs in most transition cows. This issue is most commonly discussed in terms of the risk for milk fever; hypocalcemia can cause paresis because of the critical role of calcium in initiating muscle contractions and in transmission of nerve signals. However, calcium is an important signal transducer in many other cell types, including immune cells. It was demonstrated that monocytes from cows experiencing hypocalcemia had low intracellular calcium stores and did not mobilize calcium to the same extent in response to stimulation (Kimura et al., 2006). An inability of monocytes to mobilize intracellular calcium after being stimulated would be expected to dampen functional responses such as cytokine release and cell proliferation. Such findings may provide a physiological basis for the long-observed links between hypocalcemia and mastitis in transition cows (Curtis et al., 1985).

These are examples of findings that are shedding light on why nutritional deficiencies and metabolic disorders can depress immune function and promote infectious disorders in the transition period. In fact, decreased feed intake was observed before calving in cows that ended up with subclinical ketosis or metritis after calving (Huzzey et al., 2007, Goldhawk et al., 2009), suggesting that behavioral changes and nutrient imbalances can precede key transition problems by days, if not weeks. Another line of work is focusing on the other side of this relationship – why biological stressors promote metabolic problems.

## Stress, Sources of Stress, and the Consequences

Stress is a term that is widely used but rarely defined in discussions about animal agriculture. For the purposes of this discussion, I will refer to the original definition by Hans Selye in 1936 of biological stress as “the non-specific response of the body to any demand for change”. Note that this definition does not necessarily imply that stress is a negative thing; in fact, some components of the transition to lactation are certainly stressful by this definition. Furthermore, it is worth considering the “non-specific” nature of this definition. For example, the endocrinology of a cow entering lactation directs a number of specific metabolic changes that have collectively been described as an example of homeorhesis (Bauman and Currie, 1980), which are not themselves stress responses because they are programmed changes that accompany the initiation of lactation. Likewise, a cow suffering from *E. coli*-induced mastitis is expected to mount a specific response to the pathogen (i.e. antibody production and targeted phagocytosis) which is not necessarily considered stress. On the other hand, the innate immune system also responds by releasing a number of *non-specific* factors such as prostaglandins and inflammatory cytokines which make the infection a source of systemic stress for the cow. Again, this is not to imply that the stress is necessarily negative, because these non-specific factors can also play a critical role in fighting the infection.

Although stress is difficult to clearly define and impossible to measure directly, it is worth considering because it is one way in which we can understand the intricate links between behavior, nutrition, and physiology. Common stress responses include decreased feed intake and inflammation, both of which have been implicated in most transition disorders. I will discuss social stress, infection, metabolic stress, and heat stress as key sources of stress in the transition cow.

**Social Stress.** The best-studied source of social stress in transition cows is overcrowding. Competition at the feedbunk has been shown to decrease DMI of multiparous cows in the critical final week of gestation (Proudfoot et al., 2009), in spite of the fact that cows in this stage of production eat less than half as much dry matter as cows at peak lactation. Cows competing for access to feed also spent more time standing, and time spent standing during the transition period has recently been documented as a key risk factor for the diagnosis of claw horn lesions later in lactation (Proudfoot et al., 2010). Finally, feedbunk competition also results in cows consuming fewer and larger meals (Hosseinkhani et al., 2008), which could increase the risk for ruminal acidosis, at least after the transition to a lactation ration. Although few controlled studies have been conducted to evaluate the effects of re-grouping cows, anecdotal evidence suggests that repeated re-grouping of cows can induce similar stress and may likewise suppress feed intake and promote lameness.

**Infection.** Infectious disorders, as described above, cause both specific and non-specific responses. Among the most important stress responses to infection is inflammation. The host of signaling molecules released by activated immune cells includes inflammatory mediators such as nitric oxide, prostaglandins, and cytokines. While many of these molecules promote local inflammation and increased blood flow to the infected tissue, inflammatory cytokines play a key role in stimulating systemic inflammatory responses, including increased body temperature, increased heart rate, and decreased feed intake (Dantzer and Kelley, 2007). Cytokines are able to alter many physiological systems because nearly all cell types express cytokine receptors. One effect of cytokines is to activate production of acute phase proteins such as haptoglobin and serum amyloid A, primarily produced by the liver. Proteins that participate in the acute phase response are generally found in very low abundance in the bloodstream, but are greatly elevated during systemic activation of the immune system.

It is clear that mammary and uterine infections result in both local and systemic inflammation. Coliform mastitis results in release of endotoxin into the bloodstream and increased plasma concentrations of cytokines and acute phase proteins (Hoeben et al., 2000). Likewise, metritis is associated with an acute phase response in transition cows (Huzzey et al., 2009); in fact, plasma haptoglobin is elevated prior to clinical signs of metritis. These non-specific inflammatory stress responses to infection promote the development of metabolic disorders by suppressing feeding behavior, and they may also directly impair metabolic function by altering gene expression in the liver.

**Metabolic Stress.** Inflammation has been proposed as a missing link in the pathology of metabolic disorders in transition cows (Drackley, 1999), and recent findings have indeed documented relationships between inflammatory mediators and metabolic disorders. Plasma concentrations of haptoglobin and serum amyloid A were increased in cows that developed fatty liver (Ametaj et al., 2005), and Ohtsuka and colleagues (2001) observed increased serum TNF $\alpha$  activity in cows with moderate to severe fatty liver. A retrospective study of cows on 3 commercial Italian dairies suggested that liver inflammation is associated with a problematic transition to lactation (Bertoni et al., 2008). Cows were classified in quartiles for degree of liver inflammation based on plasma concentrations of acute phase proteins. Those cows with the strongest inflammatory profiles were at 8-fold greater risk for experiencing one or more transition disorders, had lower plasma calcium concentrations, took longer to re-breed, and produced less milk in the first month of lactation (Bertoni et al., 2008). These correlations have driven strong interest in potential mechanisms underlying an inflammation-based pathogenesis of transition cow disorders.

Metabolic stress can be initiated by a variety of factors, including inflammation derived from infection (discussed above), oxidative stress, and translocation of endotoxin from the gut. Oxidative stress in transition cows is likely driven by lipid peroxides, which are produced when

intracellular lipids encounter reactive oxygen species (**ROS**) such as hydrogen peroxide. Some ROS are always produced in the liver; however, events occurring in early lactation likely contribute to enhanced ROS production. One adaptation to increasing delivery of NEFA to the liver in early lactation is an increase in the capacity of peroxisomal oxidation (Grum et al., 1996), an alternative pathway for fatty acid oxidation. Enhanced peroxisomal oxidation increases total oxidative capacity of the hepatocyte, but the first step in this pathway produces hydrogen peroxide (Drackley, 1999), and therefore it contributes to ROS production to a greater extent than mitochondrial oxidation. Increased ROS production in early lactation cows, coupled with increased NEFA concentration, increases lipid peroxide formation. This is especially true for cows with excessive adipose tissue stores, likely because plasma NEFA concentrations are elevated to a greater extent in these cows. As a result, both the transition to lactation and high body condition are associated with increased plasma markers of lipid peroxidation (Bernabucci et al., 2005). Lipid peroxides are of concern because, like other ROS, they can damage cellular proteins and DNA and are potent activators of inflammatory pathways, inducing many of the same cellular responses as inflammatory cytokines (Pessayre et al., 2004).

Endotoxin is a component of the cell wall of Gram-negative bacteria, and detection of endotoxin by immune cells initiates a strong inflammatory response. It has long been debated whether acidosis promotes release and translocation of endotoxin from the rumen and into the bloodstream. Khafipour et al. (2009) nicely demonstrated that induction of sub-acute ruminal acidosis increased both ruminal and plasma endotoxin concentrations. This treatment also significantly elevated plasma concentrations of acute-phase proteins, indicating that the elevation was adequate to stimulate inflammation in the liver.

Metabolic inflammation can therefore be derived from at least 3 sources: infection, oxidative stress, and endotoxin translocated from the gut. What are the consequences of such inflammation? In 2 recent studies, inflammatory mediators directly induced metabolic problems. Trevisi and colleagues (2009) orally administered interferon- $\alpha$  (a cytokine) daily during the final 2 weeks of gestation, which caused liver inflammation and release of acute phase proteins. Compared to control cows, treated cows had significantly higher plasma ketone concentrations in the first 2 weeks after calving. Our own lab recently reported that subcutaneous injection of TNF $\alpha$  for 7 days doubled liver triglyceride content in late-lactation dairy cows (Bradford et al., 2009). We also observed changes in mRNA abundance consistent with transcriptionally-mediated increases in fatty acid uptake and esterification and decreased fatty acid oxidation. These results strongly support the hypothesis that inflammation disrupts normal metabolism, because although both of the above treatments were considered low-dose and short-term, they nevertheless promoted ketosis and fatty liver, respectively.

In addition to promoting metabolic disorders by stimulating inflammation, oxidative stress can directly suppress immune function by damaging lipids, proteins, and DNA of immune cells

(along with other cell types). Oxidative stress may, in fact, play a key role in the immunosuppression observed in transition cows, a hypothesis that is supported by numerous studies demonstrating beneficial effects of supplementing antioxidants in the transition period (Sordillo and Aitken, 2009). On the other hand, it must be cautioned that excessive supply of antioxidants can also cause oxidative stress and may actually impair immune function (Bouwstra et al., 2010).

**Heat Stress.** Another common stressor for transition cows is excessive heat load. Many operations that have become accustomed to cooling lactating animals, either because of the logic that these cows have the highest heat burden or because of the fact that the benefits of cooling lactating cows are so easy to observe in daily milk weights during heat waves. However, the stress of such environments on dry cows has not received as much attention. Recent work showed that heat stress during the dry period decreased DMI during the week of calving by nearly 50%, decreased neutrophil function after calving, and decreased peak milk production by more than 10 lbs/day (do Amaral et al., 2011). Although the exact mechanisms linking heat stress to these long-term effects remain unclear, what is clear is that there are substantial costs associated with allowing dry cows to experience sustained heat stress.

### **Cause-and-Effect?**

One frustrating aspect of transition cow biology is the continual question of which observations are causes and which are effects. For example, a cow with ketosis nearly always presents with high plasma NEFA and BHBA concentrations, low feed intake, and some degree of fatty liver. One could presume that something caused her to eat poorly, leading to mobilization of NEFA from adipose tissue, accumulation of fat in the liver, and ketone production. However, there is also evidence that NEFA (Allen et al., 2009) and/or BHBA (Rossi et al., 2000) can directly suppress feed intake, or perhaps feed intake was suppressed because of an inflammatory response associated with the liver fat accumulation. These scenarios would suggest that excessive lipolysis could be the root cause of the problem. In many such situations, all of the issues arise almost simultaneously, making it nearly impossible to use time courses to point to a single cause.

Numerous labs are investigating transition cow problems with the goal of identifying the initial insults that lead to disease. However, it is also worthwhile to remember that positive feedback loops are a hallmark of most disease states, including these conditions. For example, in a cow that moves through the transition period successfully, plasma NEFA concentration rises, but those NEFA are largely oxidized in the liver, driving glucose production, which fairly quickly provides negative feedback on lipolysis and the NEFA concentration begins to drop again. In this scenario, a state of relative homeostasis is recovered. However, in a cow that suffers from the fatty liver/ketosis complex, NEFA is elevated to a greater extent, lipids are not completely

oxidized in the liver and begin to accumulate, leading to an inhibition of glucose production. The resulting hypoglycemia further stimulates lipolysis and ketogenesis, and somewhere in this progression, feed intake begins to drop as well. This exacerbates the negative energy balance and further decreases glucose production by limiting the supply of glucose precursors, which again results in even greater stimulation of adipose tissue mobilization. This vicious cycle, or positive feedback loop, is what drives the cow into a clinical disorder. With these types of feedback loops operating, it can be quite difficult to identify a true cause of a disorder; perhaps in most cases, the problem arose because of several suboptimal conditions rather than one obvious problem. On the bright side, this reality also means that interventions do not always have to be perfectly targeted at the root cause of a problem to help resolve it.

### **Practical Implications**

These findings suggest a number of focus areas for dairy managers aiming for a holistic management scheme to accommodate the complex nutritional, environmental, and behavioral needs of the transition dairy cow.

**Housing.** The clear implication of recent findings from the group at the University of British Columbia is that it is a mistake to overcrowd dry cows. During the financial difficulties of the past several years, numerous stories have circulated about farms decreasing stocking rates of lactating cows from 120% to 100% without losing milk in the bulk tank. Perhaps this is reminder about the importance of adequate space (both in free stalls and bunk line), and if anything, the literature suggests that this is even more critical in the dry period. Behavioral responses to overstocking are expected to lead to greater lameness, more negative energy balance, and an increase in all of the transition disorders that are associated with these issues. With the recent findings from the University of Florida, similar negative effects can be expected in cows that are exposed to heat stress through the dry period. Providing adequate space and keeping cows cool should be high priorities in any dry cow management plan.

Another factor worth considering is the grouping of cows. For many years, it was recommended that dry cows be managed in separate far-off and close-up pens to allow for different diets to be fed during these periods. However, with the information now available on one-group dry cow strategies (see below), this is no longer necessary. According to some, the reduced stress of not having to move cows an extra time is reason enough to make the change to a one-group dry cow system. When considering grouping strategies for dry cows, realize that subordinate cows are the most susceptible to social stress; these are the cows who are bullied away from the feedbunk, eat less feed, and spend more time standing when overcrowded. As a result, these cows are the most susceptible to transition disorders if not properly managed. If possible, it is wise to pen close-up heifers separate from dry cows, and subordinate cows (small or simply submissive cows) can be housed with heifers if necessary. Finally, remember that pen movements do not just affect the

cow that is moving, but the entire group. As a result, even if a single pen is used to house all dry cows on a farm, the weekly influx of new cows constantly disrupts the social structure in the pen and serves as a potential source of stress. While certainly not practical on all farms, some larger operations are experimenting with “all-in, all-out” management schemes, where a group of dry cows all enter the pen together and will end up in a fresh cow pen together once all have calved. This type of system has the potential to minimize the amount of social stress for transition cows.

**Nutrition.** The primary goal in transition cow nutrition has been crystallized in the past decade: control body condition. No other factor that we can measure is a better predictor of a disastrous transition period than a BCS of 4 or greater. In fact, most academics who focus on metabolic disorders during this period would now advocate a target BCS of 3 or even less at calving, because the consequences of high BCS have proven to be far more serious than the consequences of low BCS (Garnsworthy and Topps, 1982). Cows suffering from “fat cow syndrome”, despite having more stored energy to help offset negative energy balance, experience greater decreases in DMI than healthy cows, have greater increases in plasma NEFA, and are far more likely to have clinical cases of ketosis and even infectious disorders. In my opinion, this goal is best met by feeding relatively low-energy diets throughout the dry period (Drackley and Janovick Guretzky, 2007), although a wide variety of formulations can potentially be used to accomplish this. The devil, of course, is in the details: preventing excessive sorting, promoting sufficient DMI to meet energy requirements, and balancing for DCAD.

As is the case for social stress, nutritional needs of close-up heifers can be best met by housing them separately. Because these heifers are still growing and because they are less susceptible to fat cow syndrome, it is probably logical to offer them a slightly higher-energy diet than multiparous cows. Likewise, anionic diets that benefit multiparous transition cows have been observed to dramatically decrease DMI of heifers (Moore et al., 2000). Heifers rarely experience severe hypocalcemia anyway, so it is best if they are fed diets without added sources of anions.

**Disease Prevention.** The immunosuppression that cows experience during the transition period suggests several management strategies that may help to limit disease pressure and associated stress during this time. Clearly, dairies are interested in reducing pathogen loads for all cows. However, if there is an opportunity to improve the cleanliness of certain pens, it would be wise to invest that effort in the fresh pens, since this is where the majority of mastitis and metritis cases occur. Additionally, vaccination protocols should be designed to avoid vaccinating cows during the final 3 weeks of gestation, as the decreased function of the adaptive immune system during this period would limit the effectiveness of vaccines (Mallard et al., 1998) and produce potentially harmful inflammation during a critical time.

## Conclusions

Even on farms with relatively low incidence rates of transition cow disorders, suboptimal social settings, environmental conditions, feed intake, metabolic status, or immune function may impair the ability of transition cows to reach their genetic potential for peak milk yield, resulting in significant economic losses over the lactation. While the mechanisms underlying some of these interactions remain elusive, there are some clear messages that stand out from recent research.

- Transition cows need adequate bunk and stall space, and heat stress during this period has long-term negative effects.
- Separating heifers from dry cows and minimizing group changes during the transition period allows for improved nutritional management and decreased social stress.
- Because of the numerous interactions between different physiological systems, improving feed intake after calving, improving metabolic function, or decreasing infections should all have beneficial effects on the other factors and ultimately increase health and productivity.

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