The study of mastitis has a very long history that has contributed seminal observations to some of our most basic understandings of immunology. Elie Metchnikoff was a Russian Zoologist who first proposed a cellular theory of immunity in 1892. For this work he was awarded the Nobel Prize in 1908. During his Nobel Lecture, Metchnikoff described disease "a battle between a morbid agent, the external microorganism, and the mobile cells of the organism itself. A cure would represent the victory of the cells, and immunity would be the sign of an activity on their part sufficiently great to prevent an invasion of microorganisms". In his lecture, Metchnikoff cited the work of a Swiss veterinary expert named Zschokke, who found that plentiful phagocytosis of streptococci in the battle against infectious mastitis in cows was a good sign. When phagocytosis was insignificant or not present, the cows were written off as no longer capable of producing good milk. This was later extended to include the idea that not only must phagocytes engulf the microorganisms, but that these devouring cells must utterly destroy the microorganisms. In some cases, the streptococci of mastitis were found to "destroy the phagocytes after being engulfed by them thus liberating themselves to carry on their deadly work." In the mid-1800's, Zschokke had isolated what is known today as *Streptococcus agalactiae* in 297 out of 444 cases of abnormal milk. Today we know cellular immunity is extremely important in defense of the bovine mammary gland and it should not be surprising that minimal protection against invading mastitis pathogens is afforded to the mammary gland by antibodies in milk. This is largely due to the fact that levels of milk antibodies are diluted to only a fraction of serum and colostrum levels. However, vaccines that protect against endotoxemia (e.g., J-5 vaccines) are effective in reducing clinical severity of coliform mastitis because serum antibodies neutralize endotoxins released by coliform pathogens. These points are mentioned here to emphasize two points: 1) there has been over a century of research into the causes of mastitis and the host defense mechanisms that help cows combat mastitis, and 2) while mastitis remains the major cause of economic loss to dairy producers, considerable progress in mastitis control has been made when you consider 150 years ago, over two-thirds of clinical mastitis was attributed to *Streptococcus agalactiae* whereas today it is an extremely rare pathogen on modern U.S. dairies.

**What are the Consequences of Mastitis and its Contributing Factors?**

With a $35.7 billion Gross Domestic Value for milk produced in the U.S. during 2007, the dairy industry was the single largest component of the 2007 U.S. animal agriculture economic engine after dairy beef is added. The value of milk produced in 2007 represented 30.2% of the total value of animal agriculture production. This figure has grown from $21-23 billion/year a decade ago. The 2007 NAHMS Dairy Study reported that during 2006, 23.6% of cows were culled from operations, 26.3% and 23% were removed for reproductive and udder health problems respectively. In addition, 16.5% of cow mortalities were due to mastitis. Clearly, the economic value of controlling mastitis pathogens is immense. Most economic analyses of the cost of
mastitis cite a 10% production loss as only one part of the overall cost of the disease. A majority (65 to 70%) of losses are associated with decreased milk yield resulting in a lower production efficiency, the remainder of the costs are attributed to treatment. In addition to these direct losses, mastitis causes significant problems in milk quality control, dairy manufacturing practices, quality and yield of cheese, nutritional quality of milk, antibiotic residue problems in milk, meat and the environment, and genetic losses due to premature culling. These additional costs are very significant and are not always included in economic analyses of mastitis costs. This paper is not an economic analysis of the cost of mastitis, but it is important to understand that although mastitis is very difficult if not impossible to completely eliminate, there are strong economic reasons for us to remain vigilant in our efforts to devise new, science-based strategies for more effective control. The majority of dairy farmers underestimate the cost of mastitis in their herds. All economically viable industries depend on continuous investment into research and development to ensure they have the best tools available to deliver the highest quality products to their customers or consumers. Ongoing investment into research on mastitis specifically and animal health in general will pay future dividends back to producers in the form of healthier, more profitable cattle. Here we review the association between immune suppression and infectious disease, highlight several factors that contribute to immune suppression in cattle and point out which of them you might be able to control better to beneficially affect your bottom line.

What is Immune Suppression and What are Some Contributors in Cattle?

A literal definition of immune suppression is diminished immune responsiveness. This simplistic definition impacts a highly diverse system that affords protection against disease. Immunity against infectious diseases is mediated by diverse and often interdependent cellular and humoral mechanisms. Many environmental and genetic factors influence the ability of cattle to mount effective host defense strategies against the various pathogens and normal flora that cattle are exposed to throughout their lifetime. Immune suppression may occur as a consequence of several possible factors: 1) natural physiological conditions (e.g., pregnancy, parturition and neonatal immaturity); 2) primary infectious disease episodes can predispose cattle to secondary disease events; 3) exposure to various types of stress (both natural and management-induced), environmental factors (nutritional deficits, toxicity, shipping/transport stress, commingling, etc.) or it may be deliberately induced by drugs such as glucocorticoids and other anti-inflammatory products. Much is known about the various causes of immune suppression but much remains to be resolved with regards to mechanisms of immune suppression and how we might better manage our animals to overcome it.

Periparturient Immune Suppression and Link to Postpartum Infectious Disease

Much research has been driven by the observation that most clinical mastitis occurs in dairy cows in early lactation. Because bovine mastitis is caused by opportunistic pathogens we hypothesize that these cows must be immune suppressed. Today there is an abundance of scientific evidence supporting the three following concepts: 1) the prepartum mammary gland is highly susceptible to new infections; 2) the postpartum dairy cow is highly susceptible to clinical disease; 3) the degree and duration of immune suppression is correlated with
the increased incidence and severity of clinical mastitis, metritis and retained placental membranes in postpartum cows. Several scientific reviews of this topic have been published.

Many organisms that cause bovine mastitis are opportunistic pathogens. Opportunistic bacterial infections occur when the integrity of native host defenses is breached and often are indicative of predisposing immunosuppression in the host animal. Mastitis, metritis, retained placenta, pneumonia and diarrhea are all diseases that occur with elevated frequency in dairy cattle during the periparturient transition period. Over the past 30 years much research to improve mastitis control has focused on the immunophysiological status of the periparturient dairy cow. During that time, researchers around the world have revealed considerable evidence that immune suppression at calving time is prevalent among dairy cattle, that some cattle experience more immune suppression than others, that many factors such as genetics, nutrition and management practices affect the degree and duration of immune suppression experienced by periparturient cows. Today it is well recognized the bovine immune system is less capable of battling pathogens during the periparturient period. The periparturient cow has suppressed immune competence, manifest as reduced capacity for nearly all types of immune cells. This immunosuppression is most evident in the Th1 branch of the immune system and may be essential in preventing unwanted immune reactions against self and paternal antigens exposed to the mother's immune system as a result of normal tissue damage in the reproductive tract during parturition. However, an unfortunate and perhaps unintended consequence of this suppression of the Th1 branch of the immune system is that many of the cytokines normally produced by these cells are critical to fully activate neutrophils that are absolutely critical to the defense of the mammary gland. Without a fully functional cellular immunity both adaptive and innate branches of the cellular immune system operate at diminished capacity for immune surveillance and pathogen clearance. This is the very circumstance that periparturient cows find themselves in and why it is so critical to manage transition cows to minimize their exposure to pathogens in the environment and to avoid metabolic disorders that might further stress their immune system.

Viral Infections Can Cause Immune Suppression

There is an abundance of evidence that selected pathogens can induce immune suppression. These suppressive effects may be sufficiently severe so as to directly result in an increase in secondary infections or they may add to the degree and duration of immune suppression experience in transition cows or during shipping, commingling and weaning stress. Several viruses of cattle have known suppressive effects on the immune system that contribute to productivity losses and higher culling rates. Two of the more important viruses to U.S. dairy producers are bovine viral diarrhea virus (BVDV) and bovine leukemia virus (BLV). Exposure to BVDV may result in acute or persistent infections. BVDV exists as one of two biotypes, cytopathic and non-cytopathic. While both biotypes may cause acute infections only the non-cytopathic biotype can establish persistent infections. Establishment of a persistent infection occurs when a fetus is exposed between 30 and 125 of gestation. Such fetuses develop an immune tolerance to the infecting virus, never clear it and shed virus to their environment for the rest of their life. A predisposition to infections with other pathogens has been noted in both acutely and persistently infected animals. The non-cytopathic biotype predominates in nature and economic losses experienced by producers are primarily due to infection with non-cytopathic
strains. Cytopathic BVDV are only isolated from cases of mucosal disease, a highly fatal and rare clinical presentation resulting from the super-infection of an animal persistently infected with a non-cytopathic BVDV strain with a cytopathic BVDV strain. The ability of non-cytopathic BVDV to establish persistent infections illustrates their ability to evade and subvert the immune system. However, even acute infections result in transient immunosuppression that leads to increases in frequency and severity of secondary infections. Acute BVDV infections with non-cytopathic BVDV suppress both innate and acquired immune responses. It is known BVDV has a tropism for lymphoid cells and the virus spreads throughout the body via the lymphatic system. Immunosuppressive effects of BVDV extend beyond their lymphotrophic nature, in that the effects of viral infection can impair several functions of neutrophils (decreased microbicidal activity, chemotaxis and antibody-dependent cell-mediated cytotoxicity),\textsuperscript{46,49,50} A marked impairment or inhibition of degranulation in neutrophils from infected cattle was consistently observed after infection with either a cytopathic or a non-cytopathic strain of BVD virus.\textsuperscript{50} The impaired activity of the neutrophil’s myeloperoxidase, hydrogen peroxide, halide system has significance in that this system has potent bactericidal, fungicidal, and virucidal effects. Moreover, deficits in neutrophil degranulation after BVDV infection are compounded by a decrease in the number of circulating PMN. This impairment of neutrophil function may partially explain the increased susceptibility of cattle to secondary bacterial infection during infection with BVDV. The dual effects of BVDV on both lymphocyte and PMN function does not bode well for the dairy cow. BVDV infection affects the innate immune system by depressing the function of neutrophils (decreases microbicidal activity, chemotaxis and antibody-dependent cell-mediated cytotoxicity),\textsuperscript{46,49,50} macrophages (depressed phagocytosis, decreased Fc receptor levels, complement receptor expression, microbicidal activity, chemotactic factors, decreases antigen uptake and ability to stimulate T cell responses)\textsuperscript{4,12,37,43,60} and cells of the airway epithelium.\textsuperscript{2} BVDV infection decreases numbers of circulating T-lymphocytes\textsuperscript{3} as well as T-lymphocytes in the spleen and thymus.\textsuperscript{5,6,20,33-36} Down regulation of IFN-γ production by T-cells as a result of non-cytopathic BVDV infection may also inhibit cell-mediated responses.\textsuperscript{11} Recent studies in our lab (Neill, J.D., et al, unpublished) have found that in addition to inhibition of the type I interferon response that is critical to fight viral infections, BVDV appears to inhibit intracellular signaling through toll-like receptors and the TNF-α receptor. These receptors are very important components of the host immune response against a wide array of bacterial pathogens, including many that cause mastitis. Cells infected with BVDV show lower levels of activation of NF-κB following treatment with factors that trigger host defenses (e.g., dsRNA, bacterial lipopolysaccharide or TNF-α). The mechanism behind the disruption of the intracellular signaling is unknown.

Bovine leukemia virus (BLV) is a lymphotropic retrovirus that is present in cattle worldwide. It belongs to a small subfamily of exogenous retroviruses that includes the human retroviruses HTLV-1, HTLV-II and the simian virus, STLV-1. Like other retroviruses, infection with BLV results in deregulation of the host immune system at both humoral and cellular levels. Advancing stages of BLV infection have been correlated with decreased T-cell competence.\textsuperscript{40} Part of the immune impairment associated with BLV infection may in fact relate to a reduction in the capacity of the immune system to produce selected cytokines critical for host protection against disease. Cytokines such as interleukin-2 (IL-2), IL-12 and interferon-γ are initially increased in peripheral blood mononuclear cells (PBMCs) from animals with early disease but then are decreased in PBMCs from animals with late disease stages of bovine leukemia virus.
(BLV) infection. Although the effects of some of these viral infections may be more insidious, reducing the capacity for production of these cytokines is not in the long term best interest of a cow to stay in a herd. Most studies have found that BLV-infected cows are culled prematurely compared with uninfected cows. Differences between these studies may simply reflect confounding effects of genetic susceptibility of cattle to BLV infection being linked to unrelated desirable production traits in certain lineages.

Genetic Variation in Immune Suppression

Although not a major topic of this review, as with most production traits, there is significant genetic influence on the immune system the degree of immune suppression experienced in periparturient cows and the incidence of infectious disease. There is clear evidence that stressed cattle fail to elicit typical responses to vaccines. In spite of its well documented efficacy, J-5 vaccine studies affirm that the booster given around calving affords little if any detectable anamnestic response as evidenced by increased antigen-specific (J-5) serum or whey IgG titers. Although genetic progress is being made by incorporating somatic cell scores into selection indices, the heritability of the ability of cattle to resist immunosuppressive effects of various forms of stress might someday afford even greater genetic improvements in resistance to disease.

Conclusions

As noted above, there are many contributing factors to immune suppression in dairy cattle. The consequences of immune suppression are increases in infectious disease and premature loss from the herd both of which add significantly to the cost of production and decrease the profitability of dairy farming. Simple solutions will not likely be found for something as complex as immune suppression, however, without additional significant research into this topic we can be assured that no progress will be made.
References


