STRESS EFFECTS ON IMMUNITY
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Stress, as it relates to bodily functions, has been defined as the sum of all biologic reactions to physical, emotional, or mental stimuli that disturb an individual’s homeostasis. Therefore, a stressor can be defined as any internal or external stimuli or threat that disrupts homeostasis of the body, and elicits a coordinated physiological response within the body in an attempt to reestablish homeostasis. Maintaining a state of homeostasis requires proper functioning of all physiological processes within the body including the stress and immune systems which are influenced by numerous factors including environmental conditions, pathogen exposure, genetic makeup, animal temperament, and nutrient availability or lack thereof. Throughout their production cycle, domestic livestock experience various stressors and varying magnitudes of stress that inhibit health and productivity. As researchers have continued to explore the complex interactions between stress and production parameters such as growth, reproduction, and health, multidisciplinary efforts emerged that have led to a greater understanding of homeostatic regulation. Based upon these efforts, our knowledge has extended beyond the "all or none" biological activity strictly associated with the "fight or flight" response. For instance, researchers have demonstrated that the combined immunological effects of glucocorticoids and catecholamines result in a well-orchestrated biological event designed to prevent over-stimulation of innate immunity and the production of proinflammatory cytokines while simultaneously priming the humoral immune response in an effort to provide adequate immunological protection. The perception of stress in domestic animals has evolved as well, now including indices such as environmental stress, nutritional stress, social stress, and prenatal stress. Animal stress is now identified as a unique event that elicits a specific behavioral, physiological, neuroendocrine, endocrine, and/or immune response that may be as unique as the stressful event itself. Additionally, there has been an increased effort to elucidate the interactions between stress responsiveness and immunological parameters in animals that may be either predisposed to or resistant to the detrimental effects of stress due to genetic programming and/or prior experiences. Of particular interest are animals that demonstrate differential stress and immunological responses due to previous exposure to various managerial, environmental, nutritional, or pathogenic stressors or due to varying temperaments within a genetically similar group of animals. Continued research efforts into these complex interactions may allow the implementation of alternative management practices, improved selection programs, and/or implementation of various nutritional strategies to prevent or overcome significant production losses and animal health care costs for livestock producers. Understanding the relationships that exist between stress and immune responses, and elucidating potential variations associated with various environmental conditions, the genetic makeup of the animal, and the impact of nutrition are essential steps toward developing new management strategies that will improve the overall health, productivity, and well-being of livestock.

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Immunity in the Fetal Calf By the time the fetal calf reaches 150 days of gestation all of the T cell and B cell receptor development has been completed. The concept of fetal imprinting has been developed in human immunology and its effect in cattle is not understood. The developing calf is subject to a number of immunomodulatory effects. The placenta produces progesterone, prostaglandin E2 and cytokines such as IL-4 and IL-10 that effect both the near term fetus and the dam and suppress cell mediated and memory (TH1) responses but promote TH2 antibody responses. In addition the cow produces estrogen and cortisol prior to parturition that all also have immunosuppressive effects. The cumulative effect of these hormones is to suppress the immune system and to direct the immune response away from the TH1 memory response to the short term TH2 immune response.

Innate Immunity in the Neonate While all the essential immune components are present in the neonate at birth, they do not seem fairly functional until at least 2-4 weeks of age. The humoral components of the innate system are suppressed. Interferon activity in the epithelial cells appears normal but the production by leukocytes is lower. The cellular component is also affected. Neutrophils numbers in the newborn calf are 4X higher than 3-week-old calves. The neonatal neutrophils and macrophages have reduced phagocytic ability that is increases following the ingestion of colostrum. By one week of age, neutrophils are functional and able to mount an effective response. The number of dendritic cells is lower and their ability to present antigen to the acquired immune system is also decreased. Natural killer cells are also low at one week of age (3% of total lymphocytes) and increases to 10% by 6-8 weeks of age.

Acquired immunity in the neonate The neonatal calf is agammaglobulinemic and is dependent on colostral intake for immunoglobulins. The number of B cells is greatly reduced in the neonate at 4% of the total lymphocytes at a week of age and increase gradually to 20% of total lymphocytes at 6-8 weeks of age. This low number of B cells coupled with the TH2 environment induced by the calves endogenous corticosteroids, maternal and placenta hormones results in a lack of an antibody response until at least three weeks of age. T cell subsets are at normal levels in the neonate. The total number of gamma-delta cells does not change but the percentage decreases as the percentage of B cells increase and the numbers of T cells increase. Mitogen activation of T-lymphocytes is slightly less depressed at birth and remains constant through 28 days after birth. Strong B cell responses require longer boosting intervals.

Conclusion The take home message of active immune response in young calves is that cell mediated responses to vaccines can be induced very early, however animals must be 3-4 weeks of age before vaccines will induce robust antibody responses that will develop in 10-14 days following vaccination.
Protein and Energy Nutrition Effects on Calf Immunity
Monica R. Foote

An array of management and nutritional strategies are in existence for the raising of young dairy calves. However, the effects of growth rate and/or plane of nutrition on immune function in preruminant calves are not well characterized. In order to address this issue, we performed a series of studies investigating the effects of plane of nutrition on immune responses in calves. Innate and adaptive immunity in the young calf, however, is poorly described, especially with regard to functional capacity. Despite this, the immune system of the calf has historically been considered immunodeficient and thus incapable of mounting an adult-like immune response. Therefore, our first challenge was to describe the adaptive immune response of the newborn calf and develop a model that can be used to test the effects of nutritional plane on immune responsiveness.

The newborn calf's response to vaccination is frequently characterized by marginal antibody responses whereas the cell-mediated immune response is oftentimes not assessed. In addition, the role that colostrum has in the ability of the calf to mount an adaptive response to vaccination is not well understood. Our collective studies demonstrate immune responsiveness to vaccination in neonatal calves and adult cattle is similar in some aspects. More specifically, antigen-induced T cell subset proliferation, and secretion of interferon-gamma, nitric oxide, and tumor necrosis factor-alpha by cells from vaccinated calves were similar to or greater than responses of vaccinated adults. This evidence of immune competency at an early age differs from the general assumption that the immune system of the neonatal calf is immunodeficient. In addition, we have recently shown that ingestion of colostrum inhibits the capacity of the calf to produce antibody in response to vaccination with little to no effect on cell-mediated immune responses. Although colostrum appears to block endogenous antibody production, certain functions of antibody-producing cells are retained.

We performed a series of studies to investigate the effects of nutritional plane or growth rate (no growth/malnutrition, medium growth, accelerated growth) on adaptive and innate immune responses in neonatal calves. Some studies were more controlled than others for nutrient intake and environment. Despite the variability in study design, the results collectively indicated little effect of nutrient intake on either the innate or adaptive immune responses measured. Some results suggest that calves on a high plane of nutrition may have slightly altered non-specific immune responses. Whether these findings are of physiological relevance are not known. Overall, results suggest that malnutrition in the absence of weight loss is not detrimental to adaptive immune responses and that a high growth rate does not enhance these responses. Effects of growth rate on infectious disease susceptibility need to be investigated further, as well as the effects of negative energy balance on immune responsiveness in the newborn calf.

In conclusion, the newborn calf’s immune system is capable of much more than previously assumed. In addition, growth rate or plane of nutrition, at least in the absence of weight loss, has limited effect on adaptive immune responses. However, we still do not know the effects of nutritional plane on infectious disease susceptibility.

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Vaccine Protocols for Dairy Calves – How Much is Too Much?
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The young dairy calf is a victim of economic models that cause it to be exposed to diseases at a time of life when it is vulnerable because of its immaturity. There are many techniques to reduce stress, sickness and death in this population. Management of the young dairy calf is very critical, and it involves many practices other than vaccines. Vaccines are frequently used as a means of lessening losses from sickness and death, but they are only one of many tools to be used.

Proper use of vaccines in young calves involves many factors. The historical disease load on a given farm has to be considered. Diagnostic investigation and testing are a very important first step. The eventual use and destination for the calf has to be considered to predict what disease challenges it might face. Decisions have to be made as to whether vaccines considered for use are safe and which are potentially effective against expected disease exposure the calf will face. Many of the vaccines on the market are not labeled for use in young calves. Potentially harmful interaction between vaccines has to be considered. Thorough training of managers and workers must take place to insure proper handling and management of the vaccines.

Designing vaccine protocols is a hands-on process. The veterinarian needs to know the operation and attempt to incorporate into management all the beneficial disease control measures that don’t have anything to do with medication or vaccines. He or she must constantly evaluate the disease load on the farm and be knowledgeable of what problems the calf may face as it goes through its unique life. The veterinarian must constantly re-evaluate the need for vaccination so that what is necessary is used and that too much use is avoided.

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The neonatal period is a time of high risk for enteric and respiratory infections and inadequate transfer of maternal antibody is a significant factor contributing to the increased risk of infection in newborn calves. There is a great need to optimize immune-mediated protection in newborn calves but the prevailing belief is that parenteral vaccination is not effective in the newborn. This concept has been challenged, however, by studies demonstrating that in the presence of maternal antibody it is possible to induce T cell responses but not antibody responses following parenteral vaccination of 2-5 week old calves with a modified-live viral (MLV) vaccine.

The mucosal immune system is the first defense barrier for over 90% of potential pathogens and commensal microflora rapidly colonizes the gastro-intestinal tract of the neonate after birth. Therefore, it is not surprising that the ruminant mucosal immune system is well developed in utero. The newborn lamb has a remarkable capacity to respond to mucosal vaccination of the small intestine and upper respiratory tract and mucosal vaccines are now being used in the newborn of a variety of domestic species. For example, young puppies are immunized intranasally with *Bordetella bronchiseptica* and oral vaccination of newborn chicks with *Salmonella* induces protective immunity. We, therefore, investigated whether intranasal (IN) vaccination of newborn calves with a MLV vaccine is an appropriate strategy to induce local antibody production in the presence of maternal antibody.

IgA is only 10% of maternal antibody and this IgA is transported to the mucosal surface of the upper respiratory tract and cleared in less than 5 days. Therefore, IN delivery of a multivalent MLV vaccine in calves at 3 to 8 days of age resulted in the rapid induction of local IgA production. Furthermore, it was possible to boost this local IgA production with a second IN vaccination 5 weeks later. These observations support the conclusion that IN vaccination is an effective strategy to avoid vaccine interference by maternal antibody. Furthermore, rapid IgA production following vaccination of newborn calves and a strong secondary immune response was consistent with emerging evidence that the mucosal immune system is functional in newborn animals.

Further research is required to determine the best strategies for combining mucosal and parenteral vaccines in older calves. Improvements in mucosal vaccine delivery and design will also be required to ensure sustained production of IgA beyond the neonatal period and possibly induce both mucosal and systemic immune responses.
Immunity against disease is a very complex and dynamic process, composed of innate and adaptive immunity branches that combat organisms that make us sick or even worse. Activation of the innate immune system in most instances is a required costimulatory factor for triggering adaptive immunity. Vertebrates are the only animals with a sophisticated adaptive immune system; hence, the innate immune system is limited in that it provides no immunological memory to previous disease episodes with the same pathogen. Immunological memory is the basis for vaccination programs that have helped enable eradication of many diseases. Small pox, polio and rinderpest are diseases that have been brought under control or eradicated as a result of effective vaccines. Without an adaptive immune system, these diseases would still be with us.

Today we know about the effects of various physiological stressors on functional activities of the innate and adaptive immune systems and how they contribute to disease pathogenesis. However, it is critical that we invest in research to provide a better understanding of how the innate and adaptive immune systems work so that we can design better health management programs to achieve maximal protective immunity against current and emerging diseases. Proper nutrition is needed for all aspects of performance and the immune system is a key homeostatic mechanism to keep the body healthy. Very little research has been done to define the basic nutritional requirements of cattle to support immune function—especially lacking is science defining the nutrient requirements of transition cows. Many factors like malnutrition, stress, disease and genetics can all impact innate and adaptive immunity. Someday scientists will discover immune restoratives to help compensate for a dysregulated immune system during critical phases of production such as the transition cow. We also know there are heritable aspects to immunity. Genetic differences in the duration and magnitude of immune suppression in periparturient cows have been identified and correlated to disease susceptibility. However, practical ways to include immune performance in a genetic selection index is only a distant thought. However, affordable whole genome sequencing may someday provide critical information needed to select cattle whose immune system is more resilient to the immunosuppressive effects of stress.

Although scientists around the world are investigating the role of the bovine immune system in combating disease, globally there are fewer investigators and less inflation-adjusted funding available today than 30 years ago. Given limited funds for animal health research, nations must prioritize their finite research and development resources for the most pressing diseases of their region of the world. Although commercial companies invest vast resources into product research and development, they do not invest in the type of basic research that gets to the core of animal health problems. The economic impact of mastitis and bovine respiratory disease are both extremely high and would make just about any nation’s top ten list of high priority diseases, but mastitis and bovine respiratory disease are also examples of diseases caused by many different pathogens. A multi etiology disease usually suggests an underlying impairment of immunity contributing to its development. The importance and need for basic research in these areas is abundantly clear to livestock producers, animal scientists and veterinarians who help produce the most affordable, safe and sustainable food supply in the world. Unfortunately the average consumer (a.k.a., taxpayer) may not recognize this same need.
Yeast Culture/Probiotics
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Young dairy calves are exposed to various disease microorganisms which can cause health problems and even death. Limiting exposure of calves to pathogenic organisms is the best overall management strategy. But calves will still be exposed to varying degrees, and at various times, to such organisms because conditions are not static on dairy farms.

Two dietary approaches are to include yeast cultures or probiotics in either the liquid diet of the calf or in the grain-based feed for calves. Studies published in scientific journals found a yeast culture added at 2% of the calf starter grain increased intake and daily gain particularly after weaning in one study, while in another study decreased fever, diarrhea, and death were the main benefits.

Various sources of lactobacillus, some bacilli, and other microbial sources have been isolated and cultured to determine how they might improve calf health, intake, and/or performance. Eight calf trials were reviewed with varying benefits seen in increasing populations of administered micorbials in various portions of the intestines, reducing some pathogenic bacteria, and reducing diarrhea with minor or varying effects on calf intake and daily weight gain.

Variables influencing results by calves fed yeast culture or microbial cultures include: colostrum status, males vs females, housing and bedding, stress—from calving difficulties to weaning and post weaning, dose and source of microbials, type of bacteria, and their characteristics. Calf health and performance is most problematic in their first 2 weeks of life. Other factors include: what kinds of agents do bacterial strain produce to influence calf health or performance, are those strains heat stable, how many cells are needed in a dosage, and how and when are those dosages best administered to calves?

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Genetic Contributions to Immunity
Larry Kuehn, USDA-ARS

The ultimate goal of genetic studies in disease resistance is to reduce economic losses due to disease using principals of genetic selection. For a variety of reasons, including incomplete disease exposure, misclassification of sick/healthy animals, and low disease prevalence, disease incidence is estimated to be lowly heritable. However, progress may be made through selection on indicator traits related to immune function. Several suites of immunological traits are readily measurable including immunological cell counts, cytokine levels, vaccination response, and acute phase protein levels. This presentation presents results from a variety of studies indicating selection for disease resistance through measures of immunity is possible and may improve the health and performance of livestock. Continued research in this area is required in order to establish potential antagonisms among immune functions and with resulting performance. Genomic tools may be one of the only methods to apply research results to industry populations and will require continued phenotyping efforts for estimation of genomic effects. Increased collaboration among institutions will likely be required to make a sizable improvement in this area.

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Innate Immunity: Effects of Periparturient Suppression on the Innate Immune System
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The immune system is a dynamic, robust, and complex system whose purpose is to rid a host of pathogenic organisms or cancerous cells. Cells in this system form physical barriers that prevent entry of pathogens, can secrete molecules with antimicrobial actions, and secrete signaling molecules that help to activate, direct and focus the immune response. The innate arm of the immune system has been defined as consisting of those functions that are nonspecific in nature and with which the host is born. Innate immunity provides the first line of defense against invading pathogens. However, some pathogens have developed the ability to escape detection or clearance by the innate immune system. Additionally, parturition, lactation and diet influence the effectiveness of the immune system. Better understanding of the immune system has the promise of being able to augment or direct its action when the ability of the immune system to clear an infection is compromised or insufficient.

The periparturient period is a nexus of physiological events that combine to have a profound effect on the immune system. The periparturient period has been shown to be a time of general immune suppression and leaves the animals susceptible to various diseases. Part of this immunosuppression may be due to the imbalance in calcium homeostasis during this time. Evidence has shown that more than 50% of second-lactation dairy cows are subclinically hypocalcemic (<2.0mM). However, calcium imbalance is not the only factor in periparturient immunosuppression, hormonal changes associated with parturition cause the reduction of immune cell function.

The common treatment for mastitis is antibiotics. However, the use of antibiotics is under scrutiny because of the potential of over use resulting in antibiotic-resistant strains of bacteria and the concern costumers have of any residue in the food supply. The promise of immune modulation as a means to replace or limit antibiotic use has been around for decades. One potential immune modulator is 25-hydroxyvitamin D3 (25(OH)D₃). Recent work has demonstrated that in vivo administration of 25(OH)D₃, used as a treatment, reduces the severity of an intramammary Streptococcus uberis infection. The treatment of mastitis with 25-hydroxyvitamin D₃ reduced bacterial counts, decreased the severity of the disease, and delayed loss of milk production, however, did not cure the disease.

Preventing and effectively treating diseases in dairy cattle will necessitate greater understanding of the immune system and the factors that suppress or enhance its functions. With this knowledge we can develop strategies to develop new control methods that are more effective and less reliant on use of antibiotics.

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PHYSIOLOGY OF REACTIVE OXYGEN SPECIES IN IMMUNITY
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Reactive oxygen species (ROS) is a generic term that refers to chemically reactive molecules and free radicals derived from molecular oxygen. ROS are generated within cells as a byproduct of the mitochondrial electron transport system or by oxidizing enzyme pathways. The production of low or moderate concentrations of ROS is essential for a number of normal physiological processes, especially those related to the immune response. The production of ROS by phagocytes, for example, is an essential effector response for the destruction of invading pathogens. Recent evidence suggest that ROS are involved in signal transduction pathways leading to the expression of cytokines, eicosanoids, and other immunoregulatory factors essential to host defense. ROS also can control the magnitude and duration of the inflammatory response by regulating vascular tone and the expression of cell adhesion molecules.

Although ROS have numerous beneficial effects on immune and inflammatory responses, damage to host cells can occur if free radical production becomes excessive. Several endogenous antioxidant defense mechanisms are present to tightly regulate ROS accumulation within tissues, especially during times of increased metabolism or during innate immune responses. Oxidative stress occurs when there is an imbalance between production of ROS and reduced antioxidant capabilities. Dairy cattle are especially susceptible to oxidative stress during the periparturient period due to the increased metabolic demands of lactation and the depletion of critical antioxidant capacity. Indeed, the progressive development of oxidative stress is an important contributing factor to compromised immunity and increased incidence of disease in periparturient cows. The health and performance of high producing dairy cows can be optimized to a certain extent by supplementing diets with adequate levels of micronutrients with antioxidant properties. There is a need, however, to develop innovative strategies that can better maintain oxidative balance in dairy cows during times of increased metabolic demands.

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Managing bovine respiratory disease (BRD) is a challenge for producers and veterinarians. Common approaches to managing BRD include preventing or minimizing exposure to the pathogens (disease causing agents), decreasing the challenge load of the pathogens, minimizing stresses on the animals through good management practices, and increasing immunity, primarily through vaccinations. Increasing immunity in a group of cattle produces a more optimal response if vaccinations are administered prior to anticipated pathogen exposure. Timing vaccinations just prior to anticipated pathogen exposure is frequently inconvenient with current production management in beef cow/calf operations, which creates a management challenge.

A 2 year study was conducted to evaluate preventive health protocols that were administered at common handling or processing times in the cow/calf industry. Serology (measurement of antibody titers) indicated that vaccinating calves at branding and weaning produced as effective immunological response as compared to vaccinating calves at pre-weaning and weaning. Treatment cost for BRD illness (morbidity) was not different between the group vaccinated pre-weaning/weaning and the group vaccinated at branding/weaning and was less than control calves. Additionally, starting vaccinations at branding time when routine processing occurs can improve owner compliance.

In another study, health and performance of ranch calves administered various preventive health protocols and commingling of calves of unknown health histories were evaluated. Commingling of beef calves from multiple origins with unknown health histories is common in the beef industry in North America. These commingled cattle are frequently exposed to respiratory pathogens and are considered at high-risk of developing BRD. The average daily gain (ADG) was higher in ranch origin calves than commingled cattle and market origin calves performed similar to commingled calves. The morbidity rate was highest in market origin calves, intermediate in commingled cattle and least in the ranch group. Also, weaning on the ranch of origin for 45 days resulted in the lowest health care cost.

Finally, a study was performed to compare the administration of MLV (modified live viral) respiratory vaccine once or twice on the health and performance of beef calves. Receiving health protocols for high-risk exposed beef calves developed by veterinarians frequently incorporate MLV vaccines against the common respiratory pathogens. Due to the unknown immunological response in high-risk beef calves, processing protocols may include revaccination with a MLV respiratory vaccine at 1-2 weeks following the initial processing.

Results from the study indicated that preconditioning health programs in commingled calves are beneficial by decreasing health problems in the finishing phase of production. In this study, no differences in performance were measured in the preconditioning phase of the study. Notably, in the finishing phase of the study, calves vaccinated twice had improved feed efficiency.
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BOVINE IMMUNITY TO CHRONIC INFECTION
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Chronic infections of cattle are costly to the livestock industry including regional and federal government disease control agencies. Financial hardships associated with chronic infections include costs associated with testing/vaccination, culling of infected animals, loss of trade agreements, constraints on movement, indemnity payments, maintenance of federal and regional control programs, and research to develop improved disease control strategies. Research and control efforts, however, have generally proven cost effective. For instance, it is estimated that the US bovine tuberculosis eradication program cost ~$3.5 billion from 1917 – 1962 which resulted in a net savings of ~$159 million annually, primarily due to decreased carcass condemnation, improved animal productivity, and reduced animal replacement costs. Other examples of costly chronic diseases of cattle include Johne’s disease, brucellosis, bovine viral diarrhea virus, anaplasmosis, trichomoniasis, leptospirosis, staphylococcal / streptococcal mastitis, and others. Pathogens causing chronic infections have developed complex immune evasion and interference mechanisms that co-evolved in association with the host immune response. Intensive management practices that increase transmission risks and stress the immune response via production demands alter the balance of host/pathogen co-existence – generally favoring the pathogen. Additionally, changes in wildlife population densities and habitat have resulted in ever-increasing opportunities for development and maintenance of wildlife reservoirs of chronic infections. Thus, there are continually developing challenges for the control of chronic infections in cattle.

Recent developments in our ability to understand immunity to infection have enhanced our ability to develop vaccines, immunomodulators, and diagnostic tests to assist in the control of these costly diseases. By definition, chronic infections elicit adaptive immune responses, as measured by specific antibody and cell-mediated immune responses, which fail to limit colonization and disease associated with the pathogen. Failed adaptive responses result in costly energy expenses for their host (i.e., cattle) due to continued proliferation and maintenance of ineffective immune cells. In contrast, effective adaptive responses generate a brief expansion of immune cells that clear the pathogen and provide lasting immunity. Recently, new immune networks have been described for cattle that correlate with effective (i.e., correlates of protection) versus ineffective (i.e., correlates of disease – pathology and/or colonization) responses. These responses relate to the capacity of bovine immune cells (lymphocytes directed against the pathogen) to persist for extended periods of time (long-lived memory cells), secrete multiple mediators of pathogen killing (polyfunctional T cells), and activate innate killing mechanisms. These developments will likely improve our capacity to discover and develop vaccines to decrease pathogen transmission and provide herd immunity; thereby, limiting financial hardships associated with chronic infections and improving animal health and welfare.

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DIETARY INFLUENCE ON IMMUNITY: ANTIOXIDANTS AND OTHER FUNCTION

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Any nutrient required by animals is probably required by the immune system, however immune cells have higher needs for many micronutrients than do other cells. Phagocytes produce tremendous quantities of reactive oxygen species (ROS) which are sometimes called free radicals. Production of ROS is absolutely essential for immune cells to kill invading pathogens, however the ROS are non-specific and can kill the immune cell and damage surrounding tissues. To counteract the negative effects of ROS, immune cells usually have very high concentrations of nutrients that are either antioxidants (vitamin E, B-carotene, vitamin C) or nutrients that are components of antioxidant enzymes (copper, selenium, manganese, iron, and zinc). Many, but not all, clinical studies using different livestock species have shown reduced infectious disease when those nutrients are provided in proper amounts. Numerous dietary supplementation programs have been developed with the goal of reducing ‘oxidative stress’, i.e., eliminating ROS. We now know that animals must have the proper ROS/antioxidant balance and excess antioxidant may be detrimental to immune function by preventing adequate production of ROS.

Some vitamins and trace minerals have profound effects on immune function independent of their antioxidant properties. Vitamin A, vitamin D, selenium and zinc (and likely other trace nutrients) affect immune cell differentiation, cytokine production and numerous other aspects of immune function. Many of these responses are caused by regulation of gene expression. Data on micronutrient effects on gene expression and immune cell differentiation in livestock species are generally lacking. With only a few exceptions (selenium and vitamin E; copper and zinc; vitamin A and B-carotene) we know almost nothing about interactions among micronutrients and the resulting effect on immune function. Because of both independent and overlapping functions interactions most definitely exist. The infinite number of possible combinations of micronutrients mandates that we develop better in vitro or laboratory test that relate to in vivo immune function and clinical response. A better understanding of oxidative balance and interactions among micronutrients should allow us to formulate diets that result in improved immune function and healthy animals.

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INTRODUCTION TO IMMUNOLOGY
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Cattle live in environments populated by infectious agents with the capacity to overtake their bodies and end their lives. To resist invasion, the cow has a system of immunity that recognizes and eliminates thousands of different pathogens while minimizing “collateral” damage. As in many other species, the bovine immune response has two major branches, the innate immune response and the acquired immune response. The innate immune response is immediately effective, but does not improve over time. Acquired immunity takes days to weeks to develop, but has “memory”—that is, it responds faster and more effectively to pathogens it has seen before. These two branches of the immune response work in a complementary way. Innate and acquired immune functions are mediated by soluble factors and certain cells. The early steps of the immune response are activated by a relatively small number of molecules that are common components of many infections agents called “pathogen associated molecular patterns” (PAMPs).

**Innate immunity:** Soluble factors include serum complement, lysozyme, lectins, defensins, and others; these bind to PAMPs on infectious agents, killing them or directing immune cells to destroy them. Innate immune cells include granulocytes (neutrophils and others), macrophages, natural killer cells, and gamma delta (γδ) T lymphocytes. These cells kill infectious agents by various means, and secrete chemical signals (cytokines) that activate other immune cells.

**Acquired immunity:** Antibody (aka immunoglobulin) is the soluble factor of the acquired response; it is produced by B lymphocytes (also known as B cells, [BC]) and is found in plasma, milk, and other body fluids, and on the surface of the respiratory, gastrointestinal, and urogenital tracts. Antibody molecules bind to pathogens and prevent them from infecting the host (neutralizing antibody), or target them for destruction by immune cells (opsonizing antibody). Different types of antibody molecules produced by BC include IgM, IgG, IgA, and IgE. These different molecules have different functions and exist in variable concentrations in different parts of the body. Other cells of the acquired immune response include T lymphocytes (or T cells), which are subdivided into T “helper” (TH) cells and T “cytotoxic” (TC) cells (TC). TC cells kill infected cells and are thus important in defense against viruses. TH cells help other cells respond to infection by producing cytokines and expressing costimulatory molecules. Different types of TH cells include TH1, TH2, TH0, and TH17 cells, which drive different types of immune responses appropriate for different types of infection. TH cells receive their first stimulus to respond from “antigen presenting cells” (APC). APC live in many tissues and constantly sample the environment, looking for infectious agents. When they identify infectious agents, APC pick them up and break them into pieces called “antigens”, which they “present” to young TH cells.

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