OPTIMIZING IMMUNE COMPETENCE THROUGH NUTRITION

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INTRODUCTION

The nutritional support of growth and reproduction in livestock has been realized, practiced, and improved upon over most of this past century. However, only recently researchers have begun to report on the impact of nutrition on immune competence. Efforts in this area have been focused on better understanding the direct and basic effects of nutrient deficiencies on immunity. Research efforts in this area will continue to be vital, as antibiotic and current drug therapies become more regulated and limited to livestock producers. Optimization of immune function through improved nutrition will be an essential component of our livestock management strategies. To begin to understand how nutrition may impact immunity, it is important to discuss the basic components of immune function.

Nonspecific Immunity

Components of the nonspecific immune system include physical barriers (e.g. skin), phagocytic cells (e.g. macrophages & neutrophils), and soluble proteins derived from phagocytic cells (e.g. tumor necrosis factor and interleukin 1 and 6). Components of nonspecific immunity are present both prior to and following antigen exposure and they typically are indiscriminant against most foreign substances, not "specific" for any given antigen.

Specific Immunity

Components of the specific immune system include the category of leukocytes called lymphocytes. Lymphocytes orchestrate specific immune responses within two broad categories:

1. *Humoral immunity* – mediated by circulating antibodies produced from B-lymphocytes and in response to specific antigen recognition.
2. *Cell-mediated immunity* – mediated by T lymphocytes which both recruit and stimulate phagocytic (nonspecific) activity as well as participate in direct lysis of infected cells (e.g. viral infected cells).

Several nutrients have been shown to impact immune competence, including protein, energy, vitamins, and minerals. Each of these nutrients may impact one or both of the major arms of the immune system, specific and nonspecific immunity. It is important to consider the intimate interrelationship between many nutrients. Deficiencies or toxicity in any single nutrient will often impact the functionality of another nutrient. In regards to the brevity of this review, only those nutrients that have accumulated substantial research interest will be reviewed, including 1) Energy and Protein, 2) Vitamin E and Selenium, 3) Zinc, 4) Copper, and 5) Chromium.

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ENERGY AND PROTEIN

The concentration of energy and protein in the diets of stressed receiving cattle has been shown to directly impact the incidence of morbidity and mortality (Table 1). Voluntary intake of high-energy diets is greater in stressed versus unstressed weaned calves (Lofgreen, 1983). In this study a relationship between the consumption of high-energy diets and morbidity was suggested. This relationship between high energy receiving diets and morbidity is widely accepted and has resulted in the common use of high-quality hay with protein supplement in the diets of newly received, stressed calves.

Table 1. Effect of concentrate level on health of stressed calves during 4 weeks.

Variable	Concentrate Levels		
	25 %	50 %	75 %
Percent treated for BRD	47	49	57
Treatment days per sick calf	5.3	5.5	5.7
Morbidity*	2.5	2.7	3.3

*Treatment days per calf purchased
Lofgreen, 1983

Dietary protein concentration has also been shown to influence the incidence of morbidity in receiving calves. Galyean et al. (1999) performed a regressional analysis of dietary CP concentration on the percent incidence of morbidity in newly received calves. The data were obtained from 15 separate trial means. The resulting analysis revealed an increase in percent morbidity as dietary crude protein was increased. The authors point out the similar paradox as seen with dietary energy and percent morbidity, whereas, increases in either nutrient results in both increased weight gain and calf morbidity. It appears likely that this relationship is a function of initial level of stress and disease resistance, whereas the healthier calves tend to perform better and stressed, disease prone calves worse on diets higher in energy and protein.

VITAMIN E AND SELENIUM

The antioxidant roles of vitamin E and selenium, via the metalloenzyme glutathione peroxidase, share common biological activities. The sparing of one will impact the functionality of the other. Therefore, researchers studying vitamin E and selenium take into account the dietary concentrations of each nutrient and to what degree they may impact the results of the study.

Weiss et al. (1990) reported on a survey taken on commercial dairy herds. These results showed that cattle with high serum selenium and alpha-tocopherol concentrations also had fewer incidences of clinical mastitis. This effect may be due in part to the well-observed link between vitamin E / selenium nutrition and neutrophil function. Neutrophils, nonspecific phagocytic cells, are important in the control on intramammary infections. Neutrophils isolated from the milk of selenium supplemented cows were shown to have improved killing capacity when compared to cows fed a selenium deficient diet (Grasso et al., 1990). Similarly, blood neutrophils from vitamin E supplemented cows also were shown to have improved killing ability (Table 2; Hogan et al., 1990). In cattle, neither selenium nor vitamin E appears to have a significant impact on the phagocytic abilities of neutrophils.

Table 2. Percent intracellular killing of *S. aureus* and *E.* Coli by bovine neutrophils

Bacteria	Vitamin E Supplemented	Vitamin E Unsupplemented	Selenium Supplemented	Selenium Unsupplemented
S. aureus	60.5 ± 4.1	51.7 ± 2.1	58.7 ± 3.5	53.0 ± 2.7
E. coli	60.1 ± 4.3	41.9 ± 4.4	53.0 ± 4.4	47.3 ± 4.2

Results reported as mean (± SE)

The majority of vitamin E and selenium research supports this important role on nonspecific neutrophil function. Although vitamin E and selenium may also play a part in specific immune functions, this support has been lacking.

Vitamin E, as alpha-tocopherol, does not readily cross the placenta. Newborn calves are generally born with low concentrations of vitamin E, dependent on colostrum and milk for their vitamin E intake. Maternal concentrations of alpha-tocopherol typically decline just prior to and following parturition. Injections as well as high-level supplementation of vitamin E prior to calving have been shown to maintain alpha-tocopherol concentrations during this critical period (Smith et al., 1997).

Taking these points into consideration, a focus on cow vitamin E nutrition is most important during the last few months of gestation and during early lactation. Optimized vitamin E nutrition during this period will both bolster the immune system of the cows by aiding neutrophil function and decreasing mammary infections while ensuring delivery of vitamin E nutrition to the offspring.

ZINC

Zinc is one of several trace metals essential for the functionality of a group of enzymes referred to as metalloenzymes. In particular, zinc has been shown to be important in biochemical processes involved in nucleic acid metabolism and cell division (Chesters, 1974). For this reason, zinc has long been recognized as an important nutrient for spermatogenesis and male fertility in farm animals. Recently however, the role of zinc in immune competence has received some attention.

Chirase et al. (1991) investigated the effect of an organic form of dietary zinc (zinc methionine) on feedlot steers challenged with a respiratory virus. In this study, zinc methionine supplemented steers experienced an improved rate in disease recovery. Considering the link between zinc and cell divisional processes it would appear probable that zinc may play an important role in lymphocyte functions which are dependent on a rapid cell division process called "clonal expansion" following antigen stimulation. Prasad and Kundu (1995) investigated the effect of zinc fortified milk fed to newborn calves. In this study, zinc supplementation resulted in higher immunoglobulin (antibody) responses to antigen challenge.

COPPER

The influence of copper on immune function has been widely investigated but with quite variable results. Copper is the essential element in at least two enzymes important in immune competence, copper/zinc-superoxide dismutase and ceruloplasmin (Prohaska, 1990). It is likely that that copper may exert its effect on immunity through the attenuation of one or both of these enzyme complexes.

Several groups have investigated the effect of copper on neutrophil function. Although results have been variable, it appears likely that copper has a minimal impact on specific neutrophil functions, such as killing capacity, chemotaxis, and phagocytosis (Boyne and Arthur, 1981; Boyne and Arthur, 1986; Xin et al., 1991; Arthington et al., 1995; Arthington et al., 1996a;). Although copper does not effect the direct function of neutrophils, copper deficiency does result in an increase in blood neutrophil number (neutrophilia) in cattle (Arthington et al., 1996a, Arthington et al., 1996b) and mice (Karimbakas et al., 1998). This phenomena is in contrast to that which is seen in humans, where copper deficiency results in marked neutropenia (Percival, 1995).

Research investigating the effect of copper on specific immune responses in cattle have also been variable and tend to suggest little or no effect of dietary copper on lymphocyte function (Stable et al., 1993; Arthington et al., 1995; Ward et al., 1997; Ward and Spears, 1999). In some cases lymphocyte proliferative responses to mitogen stimulation appears to be increased in response to copper deficiency (Torre et al., 1994; Arthington et al., 1996b).

Copper is transported throughout peripheral circulation complexed with its transport protein, ceruloplasmin. During instances of copper deficiency blood ceruloplasmin concentrations are decreased (Ward and Spears, 1999; Arthington 1996b). Ceruloplasmin is a sensitive acute phase protein, which increases in blood concentration following stress stimuli. Copper deficient calves are not able to mount a normal acute phase protein response following inflammatory challenge. In contrast, fibrinogen, another sensitive acute phase protein, is dramatically increased following inflammatory challenge in copper deficient calves (Figures 1a & 1b; Arthington et al., 1996b).

Figure 1a

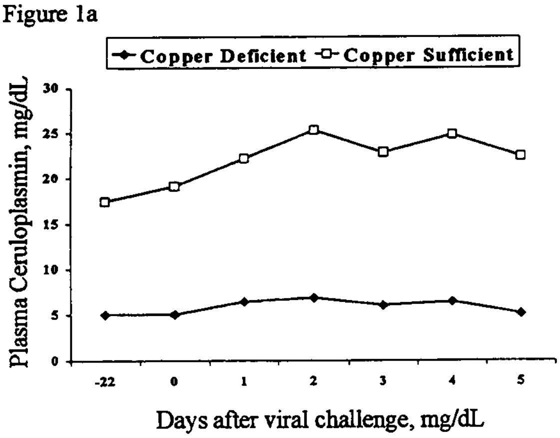
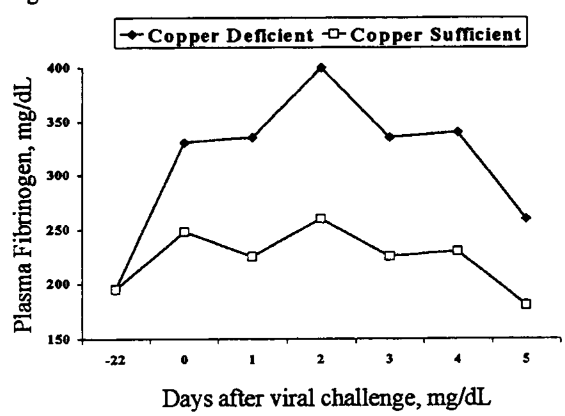


Figure 1b



It is likely that that the pathogenesis of copper deficiency in cattle manifests itself through this altered proinflammatory response. The marked neutrophilia and altered acute phase protein response in stressed, copper deficient cattle support this hypothesis.

CHROMIUM

Recently dietary chromium has received attention as a potential nutrient involved in immune competence. Studies from Canada have shown marked improvements in measures of health and stress when feeder steers where supplemented with chromium. Chang and Mowat (1992) reported a significant decrease in serum cortisol of chromium supplemented, stressed feeder calves concentrations (75.0 vs 55.6 nmol/L for control and chromium supplemented calves, respectively). Further, chromium supplemented calves fed diets with soybean meal also had increased serum immunoglobulin concentrations. Currently, this response has not been widely supported, as other laboratories have reported no effect of chromium supplementation on blood cortisol concentrations in stressed feeder steers (Kegley and Spears, 1995) or steers challenged with a respiratory virus (Arthington et al., 1997). When evaluating these results it is important to investigate the type of stress under consideration, as each of these studies utilized a differing type and intensity of stressor.

In another study, rectal temperatures of chromium supplemented stressed feeder calves, were reduced by 0.5° C (Moonsie-Shageer and Mowat, 1993). This decreased temperature response was also associated with an increase in feed intake. Other researchers have noted increases in *in vitro* lymphocyte proliferative responses to concanavalin-A (ConA) stimulation (Burton et al., 1995). In this study, lymphocytes, cultured with serum from chromium supplemented cows, experienced increased proliferation following ConA stimulation.

SUMMARY

Focusing improvements in nutrition on immune competence holds great promise in future livestock management strategies. Other nutrients, not described in this document, also have been shown to be potentially important in maintaining immune competence, these include, but are not limited to, B-vitamins, beta-carotene, vitamins A & D, manganese, cobalt, and potassium.

Many of the research results, presented in this document and in this area of science in general, are highly variable. Efforts to control the sources of variation within experimental models will result in improved results. This variation may be best explained from at least four sources of variation:

1) The level of deficiency achieved in the experiment
2) The source, concentration, and integrity of the supplemental nutrient provided
3) Influence of antagonistic factors found in the basal diet
4) Physiological state of the experimental animal (stage of pregnancy, growth, stress, etc . .)

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