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IF IMMUNITY FAILS, DON'T PICK ON YOUR DRUG SALESMAN -- IT MAY BE NUTRITIONAL

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INTRODUCTION

"But I vaccinated those calves for enterotoxemia, they couldn't have died from *Clostridium perfringens*. That vaccine must not be any good! Just wait until I get hold of that drug company salesperson." Does this scenario or a similar experience seem familiar to you? I'm not saying that there aren't times when vaccines fail to cause the animal to produce the desired immune response, because that does occur. However, we sometimes forget that a vaccine itself has no protective power but it causes the animal to produce its own protective response by stimulating the immune system. A substance foreign to the body that induces the immune system to respond is called an antigen, as found in vaccines or organisms such as bacteria or viruses. An animal's immunological response to a vaccine is acquired. The immune system is composed of humoral and cellular portions both of which respond to an antigen (Table 1).

Table 1. Cell Types of the Immune System Which React with Antigens

Bone Marrow origin of precursor lymphocytes	T lymphocytes	T cells	Cellular immunity
	B lymphocytes	B cells	Humoral immunity (antibodies, immunoglobulins)

Phagocytes - macrophages and neutrophils physically engulf and destroy antigens

The humoral component has antibodies which are proteins that circulate in the blood. These antibodies are formed in lymphoid cells termed B cells, in direct response to a specific antigen. The antibody combines specifically with that antigen to cause the antigen's inactivation. If an animal has never had previous contact with a specific antigen, it takes several days before antibodies appear. Antibody numbers increase, reaching maximal levels in 10 to 14 days, then rapidly decline and disappear within a few weeks. This first antibody response is termed the primary response and is small, giving minimal protection against a specific antigen. If in a few weeks after the first time an antigen is given, the same antigenis given a second time, a much faster increase in antibody level is attained in the blood. This response is the secondary immune response, is greater and remains for a longer period of time. Sometimes several inoculations (boosters) with the same antigen over a period of time (months) may be required to elicit a rapid

production of antibodies in order to give a high level of protection to that antigen. The level of antibody in the blood is called a titer and the greater the titer the higher the antibody numbers. Antibodies are called immunoglobulins (Ig) which circulate in the blood. These Ig are a group or class of antibodies produced by an individual in response to many different antigens. Of the 5 different classes of Ig, IgG and IgM are the primary ones present in mammalian serum.

Cellular immunity is important in protecting against abnormal cells within the body as when the animal's own cells contain bacteria or viruses. This cellular immune system involves the production of lymphocyte cells in different lymphoid tissues. Some lymph tissues primarily produce lymphocytes, whereas other lymphoid tissues process them, producing T cells. T cells are responsive to specific antigens and destroy only them. The ability of T cells to replicate is determined by the blastogenesis test. In this test, lymphocytes obtained from blood are stimulated with a naturally occurring substance called a mitogen which causes the T cells to divide. This is one *in vitro* test for measuring cell mediated immunity.

In order for a maximal immune response to an antigen to occur, both the humoral and cellular components must work together. It must be remembered that the production of antibodies and cells requires a large expenditure of energy, increases protein needs (Table 2) and has a possible lag time of several days before maximal response occurs to an antigen.

Table 2. Nutrient Requirements of the Immune System - a Partial List and Function

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1. Energy - needed for rapid proliferation of immune cells

2. Protein - needed for cell replication, synthesis of antibodies, cytokines, complement etc.

3. Minerals (Cu, Zn, Mn, Se, Fe, S)
    a. Antioxidant systems
    b. Energy production
    c. Protein synthesis
    d. Membrane integrity - physical barrier to pathogen

4. Vitamins (Vitamins A, D, E, C, B complex)
    a. Antioxidant systems
    b. Cellular differentiation
    c. Energy production
    d. Protein synthesis
    e. Membrane integrity

Obviously, the animal needs an immediate nonspecific defense system when a pathogen enters the body. Cells called phagocytes migrate to the site of infection, adhere to the organism, ingest it and kill it in a process called phagocytosis (Table 1). One of these phagocytic cell types is the neutrophil which when activated may destroy foreign material by producing free radicals.

These free radicals are powerful oxidants which can lead to cell destruction. Examples of free radicals are the hydroxyl radical (HO^-) and superoxide radical (O_2^-). In addition, other oxidants called peroxides, can be damaging and if they remain for a time, as they can be converted to the hydroxyl radical. Free radicals produced by neutrophils and most other cells in the body must be detoxified (reduced) as they can destroy the neutrophil and surrounding cells. Antioxidants such as vitamin E and carotenoids, may come from the diet, and reduce the free radicals so they are no longer oxidants (Table 2). Cells in the body and neutrophils also produce enzymes to get rid of free radicals and peroxides. These enzymes require specific trace elements for their activity such as copper and zinc in the enzyme superoxide dismutase, and selenium in the enzyme glutathione peroxidase. A deficiency of vitamin antioxidants and trace elements would therefore jeopardize neutrophil function and survival. All immune tissues may be benefitted by these free radical and peroxide reducing systems since these tissues are also producing these oxidants during the course of their functioning. Furthermore these trace elements are also essential to energy production, protein synthesis and cell replication needed in the immune response.

Specific Nutrients Affecting Ruminant Immunity

Nutrients which have been shown to impact cattle disease resistance are the carotenoids and vitamin A (Chew, 1987), vitamin D (Reinhart and Hustmyer, 1987), vitamin E (Nockels, 1991b), vitamin C (Itze, 1984) and the elements selenium (Sc), copper (Cu) and zinc (Zn). The importance of these trace minerals and vitamin E to ruminant health will be addressed. Preceding the presentation of more detailed and technical information regarding each nutrient will be a brief summary of what is known about that nutrient's impact on immune function.

Copper (Cu). Copper is required for energy production and maintaining iron utilization which also is needed by the immune system. Neutrophil production requires Cu as well as the enzyme Cu, Zn superoxide dismutase (SOD) which rids cells of the damaging oxidant, superoxide. Immunological defects arising in Cu deficient ruminants are decreased neutrophil numbers, the inability of neutrophils to phagocytize and kill organisms due to poor oxidant formation and decreased SOD formation with fewer surviving neutrophils. Other Cu induced immune disfunctions were decreased IgM concentrations after disease exposure, reduced antibody titer development to vaccination and reduced lymphocyte replication.

Neutrophils from Cu deficient sheep, had less SOD activity, decreased killing of *Candida albicans*, poorer generation of O_2^- but no difference in phagocytosis of the yeast (Jones and Suttle, 1981). Neutrophils from Cu deficient cattle did not have a depression in phagocytosis but killing of ingested *C. albicans* was compromised relative to controls (Boyne and Arthur, 1981; Arthur and Boyne, 1985). Since the previous studies utilized tetrathiomolybdate to enhance the effects of low dietary Cu, the intent of the next research was to determine if Cu deficiency produced by feeding iron (Fe), would cause similar changes in cattle neutrophil activity as that produced when using molybdenum (Mo). A group of cattle were also fed at 80% of ad libitum intake of controls to simulate the influence of decreased feed intake during Cu deficiency (Boyne and Arthur, 1986). Regardless of whether Mo or Fe was used to produce Cu deficiency neutrophil candidacidal activity was decreased. To a lesser extent this activity was also reduced in the neutrophils from restricted-fed cattle. Phagocytosis of the neutrophils was also decreased

by Cu deficiency but not by dietary restriction.

In a recently completed study conducted in our department (unpublished data) both Cu deficiency as well as Cu source were investigated in calves relative to titer development to IBRV following stress. Thirteen steer calves weighing approximately 239 kg were allotted to each of five treatments: 1) control, no Cu supplement; 2) 5 ppm Cu from copper sulfate; 3) 5 ppm Cu from copper proteinate; 4)10 ppm Cu from copper sulfate and 5)10 ppm Cu from copper proteinate. The calves were individually fed. The basal diet (corn silage, corn, protein, vitamin and mineral supplement) contained approximately 3.5 ppm Cu. Molybdenum from sodium molybdate was added to each treatment to maintain a 1:3 Cu to Mo ratio. The cattle were weighed and bled each 28 days for 84 days. Then the cattle were stressed by transporting, handling, mingling with unfamiliar steers and fasted for 48 hours. The calves were then vaccinated with IBRV. Blood serum for antibody titers to IBR were obtained prior to stress and at 14 and 28 days postinoculation. Neither feed efficiency or weight gain were affected by treatment pre- or poststress. Serum Cu in the controls (deficients) dropped ($P<.05$) during the first 84 days with no change in hematocrits. Twenty-eight days after stress, hematocrits were less ($P<.05$) in the controls and 5 ppm copper sulfate supplemented steers than those fed 10 ppm Cu. Titers to IBR were better ($P<.05$) in those steers receiving 10 ppm copper proteinate relative to controls and those given 10 ppm copper sulfate 2 weeks after inoculation. This difference ($P<.05$) included those supplemented with 5 ppm copper sulfate at 4 weeks. These data are evidence that the level and source of copper fed to cattle that were stressed does affect their ability to produce antibody titers to a virus.

Zinc (Zn). Enzymes initiating energy production need zinc and there would be no protein synthesis without it. Zinc helps stabilize membranes against bacterial endotoxins and protects many portions of the cell from destruction by the free radical superoxide as it's a constituent of the enzyme Cu, Zn SOD. Zinc is also very necessary in maintaining the thymus gland which produces mature T-cells needed in cellular immunity. Zinc also aids disease resistance by maintaining the epithelium which is a protective barrier against pathogen entry. In a zinc deficiency feed intake is depressed, which reduces other nutrients needed by the immune system and also increases production of the hormone, cortisol, which itself inhibits immune function. While there have yet been no studies conducted on immune function in zinc deficient cattle, cattle following stress have been benefitted by supplemental zinc by showing increased antibody response to vaccines and increasing certain types and numbers of lymphocytes.

Stressed steer calves were weighed, bled, vaccinated for bovine herpes virus-1 (BHV-1) and PI_3 and randomly assigned to treatments after arrival at the feedlot (Spears et al., 1991). The control treatment 1) ration contained 26 mg Zn/kg; treatments 2) and 3) had 25 mg of Zn added from zinc methionine or zinc oxide, respectively to the control diet. Weight gains for the 28-day study were not different among treatments but steers fed zinc methionine and zinc oxide consumed 5.2 and 4.4% more feed, respectively, than controls. Antibody titers to BHV-1 14 days after inoculation tended to be higher ($P<.16$) in steers fed zinc. Steers fed zinc methionine had greater ($P<.07$) antibody titers of 4-8 to BHV-1 than controls with antibody titers of 0-2. Only 10% of the zinc methionine fed steers were seronegative, whereas controls were 33% and zinc oxide were 23% at 14 days. No differences in PI_3 titers were found among treatment steers,

however, most had titers on arrival.

Selenium (Se). Selenium occurs in the enzyme GSH-Px which converts peroxides, destructive oxidants to water. Its most recently defined role is in the deiodinase enzyme which converts thyroxine to the active triiodothyronine hormone. This hormone is needed for increasing energy production and protein synthesis. When cattle were Se deficient, neutrophil killing as well as several of its other functions were reduced. Humoral immunity was reduced by Se deficiency as indicated by decreased antibody and IgM and IgG levels. Glutathione peroxidase activity has been investigated in immunity as peroxide could be detrimental to neutrophil function.

Both the primary and secondary immune response were studied in Se adequate and deficient calves infected with IBRV (Reffett et al., 1988b). Whole blood and plasma GSH-Px were increased after IBRV inoculation in Se adequate but not Se deficient calves. Serum IgM was higher in the Se fortified calves during challenge. Antibody titers to IBR were higher in Se supplemented calves compared to controls. Calves marginally deficient or adequate in Se were stressed by weaning and transporting followed in three days by infection with *Pasteurella haemolytica* (Stabel et al., 1989). Blood and plasma GSH-Px concentrations were higher in the Se adequate calves. Plasma GSH-Px was increased in response to infection. Se supplemented calves had higher IgM levels but no change in IgG concentrations and lower anti-*P. haemolytica* titers than calves not getting Se.

In order to test the effect of Se on the primary and secondary humoral immune response, calves were allotted to six treatments (Swecker et al., 1989). Calves were fed a Se deficient ration supplemented with 1)10 mg Se/kg mineral mixture ad libitum, 2) same as 1), and injected with 0.1 mg Se and 0.22 IU vitamin E/kg body weight, or fed 3) 80 mg, 4) 120 mg, 5) 160 mg or 6) 200 mg of Se/kg of mineral. The calves were weighed, vaccinated twice with hen egg lysozyme, a noninfectious antigen, and bled periodically to measure IgG antibody titers and Se levels. Selenium supplemented at 120 mg/kg or more of mineral increased blood Se values. Calves getting 200 mg Se/kg mineral ate less mineral than any other group and no adverse effects were noted. Humoral antibody responses over time were lowest in treatment 1 calves, intermediate in treatments 2, 5 and 6 and highest in treatments 3 and 4. No differences in weight gains were found among the calves at any time. These data give further evidence that the amount of nutrient necessary for an optimal immune response is greater than that needed for growth.

Vitamin E (Vit E). Vitamin E reduces free radicals and thereby prevents free radical initiated lipoperoxidation which leads to membrane destruction in cells and the production of peroxide. The destruction to membranes may be extensive so that enzymes which leak into the blood are used as indicators of damage. In addition, membrane damage also results in decreased energy utilization and poorer growth which impairs immunity. Vitamin E has also been found to reduce the prostaglandin, PGE_2, and cortisol both of which suppress lymphocyte function. Vitamin E deficiency decreases humoral antibody production and IgM and IgG serum levels. Cellular immunity is also decreased in a Vit E deficiency as noted by depressed lymphocyte replication. Also decreased by inadequate Vit E intake are phagocytosis and neutrophil function.

When 1400 IU of Vit E was administered weekly to Holstein calves, their IgM level

(P<.01) and lymphocyte blastogenesis (P<.05) were enhanced (P<.01) (Reddy et al., 1986). Yearling heifers given a single injection of 2000 IU of Vit. E also demonstrated increased lymphocyte replication upon stimulation. Feeding 500 IU of Vit E daily to calves resulted in enhanced (P<.05) secondary antibody response to bovine herpes virus (Reddy et al., 1987). Feeding as little as 125 IU of the vitamin daily to a calf also increased (P<.05) mitogen stimulated lymphocyte replication. Neutrophil killing of bacteria was improved (P<.05) if the cattle had been fed Vit E (Hogan et al., 1990).

Se-Vitamin E. Since S2 and Vit E are quite mutually beneficial on both the utilization of each other and in regards to their antioxidant capacity to reduce free radicals (McDowell, 1989), then the administration of the two together might increase immunocompetence. In one study there was an additive affect of antibody increase when the two nutrients were fed together, however no further improvement was found in 1gM or IgG or antibody concentration, phagocytosis or killing by phagocytes in other studies.

The primary and secondary immune response in sheep to parainfluenza virus (PI_3) was studied relative to Se and Vit E administration (Reffett et al., 1988a). The four treatments were combinations of no or added Se (.2 mg/kg diet) and no or added vitamin E (20 mg/kg diet). Se supplementation increased 1gM but not IgG concentrations and were unaffected by the Vit E. Selenium and Vit E were found to each independently increase antibody titers to $_{PI3.}$

The effect of injecting 25 mg Se and/or 340 IU Vit E or 50 mg Se plus 680 IU Vit E into steers either before or after transport to the feedlot and vaccinated with P. haemolytica was investigated in five trials (Droke and Loerch, 1989). Serum antibody response to P. haemolytica was enhanced with the combination of Se and Vit E which was better than if either nutrient alone was given.

Cattle Nutrient Deficiencies

Now that you know the importance of a few of the nutrients relative to cattle health some questions have probably arisen.

Are my cattle getting enough of these nutrients?
What are the signs of a deficiency?
How do I test for their adequacy?
Who should I talk to about possible deficiencies?
What chemical forms of the minerals should I supplement?

Begin by talking to your area extension person to find out what is known about these nutrients in your area. Also contact your veterinarian and possibly your feed dealer who may be making special supplements for people with similar problems.

Generally feed, water and animal tissue samples are analyzed by a laboratory. After adequately getting a good representative sample(s) of the feeds available the laboratory will analyze them for minerals. Recent research has found, however, that many minerals while

adequate in amounts according to chemical analyses are not very available to the ruminant and may produce a deficiency. If you are borderline in what is needed, then supply a supplement and discuss this and the chemical form (inorganic vs organically bound minerals) with a nutritionist.

Blood and liver samples may also be taken to help define the cattle's nutrient status. These samples may only be helpful if taken from healthy, nonstressed cattle. Some very important considerations in taking and handling the samples should first be obtained from a reputable laboratory that analyzes for these nutrients. Very erroneous information may be obtained if sampling and handling of samples is improper. Blood values of nutrients may not always be good indicators of a deficiency so blood enzymes using these nutrients may be better diagnostic tests of adequacy. Borderline deficiencies don't give overt deficiency signs but reduce animal gains, feed efficiency, health and reduce your profit. After making these general comments let's proceed to some specifics about each nutrient.

Zinc. Much of the western U.S. is zinc deficient where soils are alkaline. This together with feeding plants or supplements high in calcium will further reduce zinc utilization. Zinc deficiency will produce a loss of appetite, dermatitis, hair loss, decreased growth, reproduction and vitamin A deficiency. Zinc deficiency may be diagnosed by blood serum levels less than 0.6 ppm and a depression in alkaline phosphatase.

Copper. Much of the western and midwestern portions of the U.S. have copper deficiency problems in cattle. The cause of the deficiency may be primary, low plant levels, or secondary due to excessive levels of molybdenum, sulfur or iron which makes the copper unavailable. The levels of copper in the plant is even less available to cattle when the plant is growing. Copper deficiency may cause cattle with red hair to lighten and black hair to gray. Calves may scour and do poorly with cows having poor reproduction and all may be anemic. Serum levels less than 0.6 ppm or liver levels less than .5-10 ppm may indicate deficiency. Blood enzyme assays are currently being assessed as better indicators of status.

Selenium. Selenium in plants is frequently deficient where soils are more acid and may reach toxic levels when the soil is alkaline. Because there is such a small margin between deficient and toxic levels never supplement until you are sure there is a problem. A classic deficiency sign is white muscle disease in which the muscle has deteriorated and the white appearance is the remaining connective tissue. If calves are born alive and able to get up, their tongue muscles may not function so nursing does not occur. Other deficiency signs are the heart which may fail, paralysis, retained placenta and decreased reproduction. A deficiency may be present if blood serum is less than 0.06 ppm, whole blood glutathione peroxidase is below 250 μmol/ml/min and liver has less than .1-.15 ppm.

Vitamin E. Little is known about the requirement for this vitamin in beef cattle. The useable form is d-α-tocopherol which may be very low in certain plants, declines rapidly as plants mature and may be undetectable in hay three months after harvest. A deficiency most likely would develop in late winter to early spring when fetal development is maximal or in young calves. Stress decreases body levels and disease intensifies the need. Vitamin E deficiency gives muscle degenerative signs similar to that of selenium as they both have similar but not the

same antioxidant functions. Blood plasma levels of a-tocopherol less than 0.2 mg/dl is indicative of a deficiency as well as increasing levels of enzymes coming from deteriorating tissues.

SUMMARY

In order to maintain health in animals challenged with increased stresses from production and management, the nutrient demands of the immune system must be met. These nutrient levels are not static as the animal is required to continually produce more product. As more of the nutrients are partitioned into product, less is available for immune defense mechanisms. It is far better to maintain health and prevent infection than to incur the costs of medication, labor, decreased productivity and antibiotic residue problems. This presentation has briefly addressed animal deficiencies, and deficiency signs and testing for the nutrients needed by the immune system. An ounce (nutrient) of prevention is worth a pound (antibiotic) of cure (Ye Olde Cliché, 1776).

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