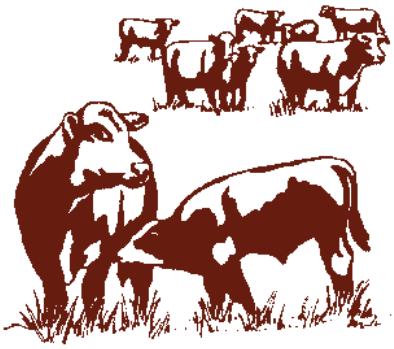
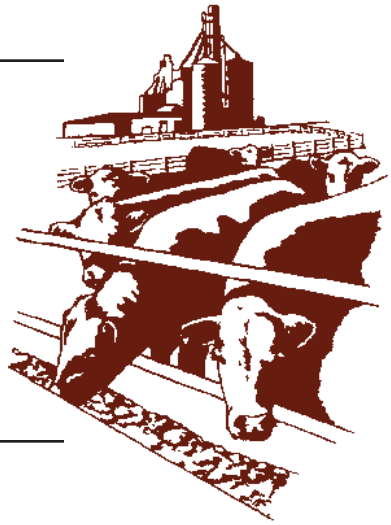


Beef Cattle Handbook



BCH-5454

Product of Extension Beef Cattle Resource Committee
Adapted from the Cattle Producer's Library

Trace Minerals and Immunology

Richard C. Bull, Professor of Animal Sciences, University of Idaho

In many areas of the world, trace mineral deficiencies are known to limit livestock production through dysfunctions in animal metabolism. Many of these deficiencies are marginal, resulting in unrecognized disorders that reduce animal performance and profitability. Several trace minerals, along with other essential nutrients, have been identified as important factors in a properly functioning immune system.

Vaccination of animals does not always induce an effective immune response. This can occur if the vaccine is improper or if the immune response is (1) too limited in active agents, or (2) is not protective in character because of the general health of the animal. Appropriate cells must be stimulated to induce immunity that effectively renders the animal resistant to natural infection by a particular microorganism. When vaccination is contemplated, several factors must be considered, including: (a) the nature of the disease process, (b) the type of immunity required, (c) the status of the animal, (d) the vaccine, and (e) the vaccination protocol.

Trace Mineral x Disease (Immunology) Interactions

The immune response depends on good nutritional status of the animal before the vaccination process. The literature on nutritional status and the ability of an animal to resist an infectious organism is well established, but only recently have trace minerals been investigated in their role in the proper functioning of the immune system. In this recent research, deficiencies of zinc, iron, copper, and selenium have been shown to lower resistance to disease either through an impaired immune response or faulty leukocyte function (Table 1).

Manganese may be added to the list of trace minerals enhancing (Smialowicz et al. 1985) or, if present in high levels, reducing the immune response (Krisuchart et al. 1987).

Zinc

The relationships between zinc and the immune function are reviewed in a symposium summary by Fraker et al. (1986). A zinc deficiency results in atrophy of the thymus (Fraker et al. 1977) and an increase in leukocyte count (evidence of infectious disease) with a reduced number of lymphocytes.

Immature (band) neutrophils are also elevated in zinc-deficient animals. Because the thymus is important in T-cell formation, the effect of zinc on this phase of the immune system has received considerable research attention in recent years (Cossack 1989). A zinc deficiency induces the following effects on the immune system:

a. Induces lymphoid atrophy and decreases in vivo response to many T-dependent antigens (Fraker et al. 1977, Chandra 1985).
b. Reduces the number of IgM and IgG plaque-forming cells per spleen in response to immunization with sheep red blood cells. The zinc deficiency apparently interferes with T-cell helper function, which causes substantial losses in humoral immune capacity (Ferandes et al. 1979, Moulder and Steward 1989).
c. Drastically reduces the concentration of thymic hormone and thymus weight (Golden et al. 1977).

Table 1. Thymic Factor Activity (mean reciprocal titer[1]) of Animals Deficient in Certain Trace Minerals and of Control Animals.[2]

Nutrient	Deficient Animals	Pair-fed Controls
Copper	16	64
Zinc	8	64
Selenium	16	32
Ad libitum control	64	64

[1] *Estimated by rosetting, in the appearance of azathioprine, of splenocytes obtained from thymectomized mice.*

[2] *From Chandra (1985).*

Newborn animals might be affected to a greater degree than mature ones since the young will exhibit the nutritional effects of a nutritional stress earlier, and will not have the ability to prevent diseases from past immune activity while the nutrition was adequate (Beach et al. 1980, 1982a, 1982b). Most newborn animals have an extensive thymus gland development, which again points to the possible importance of this gland to the health of the young during their early development.

Iron

Considerable research information has been reported on the effects of iron deficiency and its relationship to microbial growth and infections in animals (Kadis et al. 1984, Brock and Mainou-Fowler 1986, Dallman 1987, Dhur et al. 1989, Lepper et al. 1989a). Some reports suggest low transferrin saturation (a blood-iron transport protein) may be a primary defense mechanism against infection. All bacteria require trace amounts of iron for their nutritional needs (Neilands 1981), but transport proteins of the transferrin class (serum transferrin, lactoferrin, and ovotransferrin) have been found to inhibit microbial growth (Brock and Mainou-Fowler 1986, Desousa et al. 1988). Many species of bacteria multiply more rapidly if the serum is saturated with sufficient parenteral iron and the animal is challenge-dosed with certain bacterial infections (Klasing et al. 1980, Knight et al. 1983, Kadis et al. 1984, Desousa 1989, Lepper et al. 1989b).

Other researchers have reported impaired cell-mediated immune response and bacterial activity of leukocytes in children when hemoglobin levels fell to 10 g/dl or less. Low iron transferrin levels would eventually result in anemia and low hemoglobin levels within blood (Kuvibidila and Sarpong 1990, Kuvibidila et al. 1990). A deficiency of iron appears primarily to effect the antibody formation associated with B-cell lymphocytes, although studies with T cells show a slight reduction in rosette-forming cells. Antibody production in animals immunized with a toxoid was more sensitive to decreases in dietary iron than were hemoglobin, serum iron, serum proteins, liver iron, or body weight. Iron-deficient pigs were more susceptible to the lethal action of bacterial endotoxin (E. coli) than their non-deficient littermates. The true status of iron as single agent in immunity is difficult to ascertain. Its role in the disease-preventing system will be clarified in the future with new research and techniques that are not now available to investigators.

Selenium

Kiremidjian-Schumacher and Stotzky (1987) have an extensive review on selenium and the immune response. Briefly, selenium deficiency reduces T-cell-dependent antibody responses, an effect that is magnified with a vitamin E deficiency. Numerous studies have linked selenium status to immunocompetence. Studies with small animals supplemented with 0.7 or 2.8 ppm selenium resulted in a 7 or 30-fold increase in antibody titers (sheep red blood cell antigen), respectively, over the non-supplemented group (Spallholz et al. 1973a, 1973b, 1975). Both vitamin E and selenium independently enhanced the immune response of calves and together had an additive effect in increasing hemagglutinin titers (Reffett et al. 1988a, 1988b; Swecker et al. 1989).

Smith et al. (1985) found evidence of selenium acting to reduce the incidence and duration of clinical mastitis in dairy cattle. This action may be observed in a reduction of somatic cell counts in milk, thus increasing milk quality when selenium is adequate in the diet of the dairy cow. Some of this activity may be associated with the action of vitamin E. However, selenium alone reduced the duration of clinical symptoms of mastitis by 46 percent and vitamin E alone reduced duration of the symptoms by 44 percent. In combination, selenium and vitamin E reduced the duration of symptoms by 62 percent.

The principal biochemical role of selenium is a selenium-containing enzyme (glutathione peroxidase) that serves to destroy certain toxic peroxides within the body cells. The mechanism by which selenium enhances immunocompetence is unknown, but several researchers suggest that the lipid peroxide-destroying activity of glutathione peroxidase may be involved because vitamin E and synthetic antioxidants also stimulate the immune response (Kiremidjian-Schumacher and Stotzky 1987, Stabel et al. 1989).

Copper

Suttle and Jones (1986, 1989) have reviewed some of the recent work on the relationships of copper and other trace minerals to the metabolism of disease resistance and their effects on immune responsiveness in ruminants. Copper-deficient animals exhibit several symptoms of immune system dysfunctions. These include an absolute decrease in the number of T cells and especially T-helper cells (Lukasewycz et al. 1985), and a marked decrease in the T and B-cell mitogens on splenic lymphocytes (Lukasewycz et al. 1983, 1985; Flynn 1984). Copper-deficient animals show a decrease in antibody-cell response with increased susceptibility to infection (Prohaska and Lukasewycz 1981, Vyas and Chandra 1983, Suttle and Jones 1986).

Marginal copper deficiency in the ewe's diet caused a marked increase in lamb mortality, particularly associated with infectious disease. Rats fed diets containing

copper at 0, 2, or 6 ppm did not differ significantly in body weights but had a significant increase in organ weights expressed as percentage of body weight. Copper-deficient rats had a higher percentage of weight for liver and heart and lower percentage of thymus (Koller et al. 1987). Antibody titers and natural killer-cell cytotoxicity were markedly suppressed in animals fed a diet with no copper. A severe or marginal deficiency in copper caused a gradual reduction in the immune status of mice (Mulhern and Koller 1988).

Acute and chronic infections in humans, sheep, and chicks due to viral or bacterial organisms usually result in an increase in serum copper and ceruloplasmin (a copper-containing enzyme). Chicks and other animals infected with Salmonella gallinarum or other pathogenic bacteria had a 6-fold increase in ceruloplasmin activity (Hill 1979, Koller et al. 1987). Furthermore, intravenous injection of certain endotoxin preparations of three strains of E. coli into pathogen-free fowls resulted in a two to five-fold increase in ceruloplasmin levels. The function of ceruloplasmin in this immune process may only be its role in the transport of copper to target tissue sites where copper may be functioning.

Copper has been identified as a dominant component of intermediary metabolism, which serves as a mediator of many physiological and pathological processes (Richards 1989). Lymphocyte plasma membrane is an important key to functions of an immune system, which may include capping, cell-to-cell contact, and antigen binding. Copper deficiency appears to alter the plasma membrane, thus altering immune responses to infections. Through these activities, copper has been hypothesized as playing an important role in the defense of the organism against metabolic, neoplastic, infectious, inflammatory, and other forms of stress.

Summary

A well-coordinated nutrition, health care, and management program is required to maximize efficiency and productivity. A proper nutrition program can be fully effective only if the animals have adequate health care. The converse is also true. The higher the productivity level in a herd, the higher are the nutritional, health, and management requirements for the animals.

Animals fed properly are more resistant to many bacterial and parasitic infections. This is due to better body tissue integrity, more antibody production, more immunity to diseases, greater detoxifying ability, increased blood regeneration, and other factors. When proper nutritional programs are implemented, greater animal productivity can be attained, with the potential of increased profits. Proper nutrition should mean nutrient levels adjusted for metabolic needs for maintenance, growth, reproduction, and lactation. It should not mean to "over supplement" with certain minerals. Mineral balance and interrelations are important to the proper functions of the immune system. Toxic levels of trace minerals can reduce the ability of the immune system to function just as much as a deficiency.

The future challenge is to develop more adequate nutritional, health care, and management programs for the highly productive herds and flocks.

References

1. Beach, R. S., M. E. Gershwin, and L. S. Hurley. 1980. "Growth and Development of Postnatally Zinc-Deprived Mice." *J. Nutr.* 110:201.
2. _____ 1982a. "Gestational Zinc Deprivation in Mice: Persistence of Immunodeficiency for Three Generations." *Science* 218:469.
3. _____. 1982b. "The Reversibility of Developmental Retardation Following Murine Fetal Zinc Deprivation." *J. Nutr.* 112:1,169.
4. Brock, J. H., and T. Mainou-Fowler. 1986. "Iron and Immunity." *Proc. Nutr. Soc.* 45:303.
5. Chandra, R. K. 1985. "Effect of Macro- and Micronutrient Deficiencies and Excesses on Immune Response." *Food Tech.* 39:91.
6. Cossack, Z. T. 1989. "T-lymphocyte Dysfunction in the Elderly Associated with Zinc-deficiency and Subnormal Nucleoside Phosphorylase-activity — Effect of Zinc Supplementation." *Eur. J. Canc. Clin. Oncol.* 25:973.
7. Dallman, Peter R. 1987. "Iron Deficiency and the Immune Response." *Am. J. Clin. Nutr.* 46:329.
8. Desousa, M. 1989. "Immune Cell Functions in Iron Overload." *Clin. Exp. Immunol.* 75:1.
9. Desousa, M., F. Breedvelt, R. Dynesiustrentham, D. Trentham, and J. Lum. 1988. "Iron, Iron-binding Proteins, and Immune-system Cells." *Ann. N. Y. Acad. Sci.* 526:310.
10. Dhur, A., P. Galan, and S. Hercberg. 1989. "Iron Status, Immune Capacity, and Resistance to Infections." *Comp. Biochem. Phys. A-Comp. Phys.* 94:11.
11. Fernandes, G., A. Nair, K. Onoe, R. Tanaka, R. Floyd, and R. A. Good. 1979. "Impairment of Cell-mediated Immunity Functions by Dietary Zinc Deficiency in Mice." *Proc. Natl. Acad. Sci. USA* 76:457.
12. Flynn, A. 1984. "Control of *in vitro* Lymphocyte Proliferation by Copper, Magnesium, and Zinc Deficiency." *J. Nutr.* 114:2034.
13. Fraker, Pamela J., M. Eric Gershwin, Robert A. Good, and Ananda Prasad. 1986. "Interrelationships between Zinc and Immune Function." *Fed. Proc.* 45:1474.
14. Fraker, P. J., S. Haas, and R. W. Lueke. 1977. "Effect of Zinc Deficiency on the Immune Response of Young Adult A/J Mouse." *J. Nutr.* 107:1889.
15. Golden, M. H. N., A. A. Jackson, and B. E. Golden. 1977. "Effect of Zinc on Thymus of Recently Malnourished Children." *Lancet* 2:1,057.
16. Hill, C. H. 1979. "Dietary Influences on Resistance to Salmonella Infection in Chicks." *Fed. Proc.* 38:2,129.
17. Kadis, S., F. A. Udeze, J. Polanco, and D. W. Dreesen. 1984. "Relationship of Iron Administration to Susceptibility of Newborn Pigs to Enterotoxic Colibacillosis." Amer. J. Vet. Res. 45:225.
18. Kiremidjian-Schumacher, L., and G. Stotzky. 1987.

"Review: Selenium and Immune Responses." *Environ. Res.* 42:277.
19. Klasing, K. C., C. D. Knight, and D. M. Forsyth. 1980. "Effects of Iron on the Anti-coli Capacity of Sow's Milk *in vitro* and in Ligated Intestinal Segments." *J. Nutr.* 110:1,914.
20. Knight, C. D., K. C. Klasing, and D. M. Forsyth. 1983. "E. Coli Growth in Serum of Iron Dextran-supplemented Pigs." *J. Anim. Sci.* 57:387.
21. Koller, L. D., S. A. Mulhern, N. C. Frankel, M. G. Steven, and J. R. Williams. 1987. "Immune Dysfunction in Rats Fed a Diet Deficient in Copper." *Amer. J. Clin. Nutr.* 45:997.
22. Kuvibidila, S., and D. Sarpong. 1990. "Mitogenic Response of Lymph-nodes and Spleen Lymphocytes from Mice with Moderate and Severe Iron-deficiency Anemia." *Nutr. Res.* 10:195.
23. Kuvibidila, S., M. Dardenne, W. Savino, and F. Lepault. 1990. "Influence of Iron-deficiency Anemia on Selected Thymus Functions in Mice — Thymulin Biological-activity, T-cell Subsets, and Thymocyte Proliferation." *Amer. J. Clin. Nutr.* 51:228.
24. Lepper, A. W. D., D. H. Embury, D. A. Anderson, and V. M. Lewis. 1989a. "Effects of Altered Dietary Iron Intake in Mycobacterium-paratuberculosis Infected Dairy-cattle — Sequential Observations on Growth, Iron and Copper-metabolism, and Development of Paratuberculosis." *Res. Vet. Sci.* 46:289.
25. Lepper, A., C. R. Wilks, M. Kotiw, J. T. Whitehead, and K. S. Swart. 1989b. "Sequential Bacteriological Observations in Relation to Cell-mediated and Humoral Antibody-responses of Cattle Infected with Mycobacterium-paratuberculosis and Maintained on Normal or High Iron Intake." *Australian Vet. J.* 66:50.
26. Lukasewycz, O. A., and J. R. Prohaska. 1983. "Lymphocytes from Copper-deficient Mice Exhibit Decreased Mitogen Reactivity." *Nutr. Res.* 3:335.
27. Lukasewycz, O. A., J. R. Prohaska, G. S. Meyer, J. R. Schmidt, S. M. Hatfield, and P. Marder. 1985. "Alterations in Lymphocyte Subpopulations in Copper-deficient Mice." *Infect. Immun.* 48:644.
28. Moulder, K., and M. W. Steward. 1989. "Experimental Zinc-deficiency — Effects on Cellular-responses and the Affinity of Humoral Antibody." *Clin. Exp. Immunol.* 77:269.
29. Mulhern, S. A., and L. D. Koller. 1988. "Severe or Marginal Copper Deficiency Results in a Graded Reduction in Immune Status in Mice." *J. Nutr.* 118:1,041.
30. Neilands, J. 1981. "Microbial Iron Compounds." *Ann. Rev. Biochem.* 50:715.
31. Prohaska, J. R., and O. A. Lukasewycz. 1981. "Copper Deficiency Suppresses the Immune Response of Mice." *Science* 213:559.
32. Reffett, J. K., J. W. Spears, and T. T. Brown, Jr. 1988a. "Effects of Dietary Selenium on the Primary and Secondary Immune Response in Calves Challenged with Infectious Bovine Rhinotrachetris Virus." *J. Nutr.* 118:229.
33. _____. 1988b. "Effects of Dietary Selenium and Vitamin E on the Primary and Secondary Immune Response in Lambs Challenged with Parainfluenza3 Virus." *J. Anim. Sci.* 66:1,520.
34. Richards, Mark P. 1989. "Recent Developments in Trace Element Metabolism and Function: Role of Metallothionein in Copper and Zinc Metabolism." *J. Nutr.* 119:1,062.
35. Smialowicz, R. J., R. W. Luebke, R. R. Rogers, M. M. Riddle, and D. G. Rowe. 1985. "Manganese Chloride Enhances Natural Cell-mediated Immune Effector cell Function: Effects on Macrophages." *J. Immunopharmacology* 9:1.
36. Smith, K. L., H. R. Conrad, B. A. Amiet, P. S. Schoenberger, and D. A. Todhunter. 1985. "Effect of Vitamin E and Selenium Dietary Supplementation on Mastitis in First Lactation Cows." *J. Dairy Sci.* 86(Suppl. 1):190(Abstract).
37. Spallholz, J. R., J. L. Martin, M. L. Gerlach, and R. H. Heinzerling. 1975. "Injectable Selenium: Effect on the Primary Immune Response of Mice." *Proc. Soc. Exp. Biol. Med.* 148:37.
38. _____. 1973a. "Immunologic Responses of Mice Fed Diets Supplemented with Selenite Selenium." *Proc. Soc. Exp. Biol. Med.* 143:685.
39. _____. 1973b. "Enhanced Immunoglobulin M and Immunoglobulin G Antibody Titers in Mice Fed Selenium." *Infect. Immun.* 8:841.
40. Stabel, J. Reffert, J. W. Spears, T. T. Brown, Jr., and J. Brake. 1989. "Selenium Effects on Glutathione Peroxidase and the Immune Response of Stressed Calves Challenged with Pasteurella Hemolytica." *J. Anim. Sci.* 67:557.
41. Suttle, N. F., and D. G. Jones. 1986. "Copper and Disease Resistance in Sheep: A Rare Natural Confirmation of Interaction Between a Specific Nutrient and Infection." *Proc. Nutr. Soc.* 45:317.
42. _____. 1989. "Recent Developments in Trace Element Metabolism and Function: Trace Elements, Disease Resistance, and Immune Responsiveness in Ruminants." *J. Nutr.* 119:1,055.
43. Swecker, W. S., D. E. Eversole, C. D. Thatcher, D. J. Blodgett, G. G. Schurig, and J. B. Meldrum. 1989. "Influence of Supplemental Selenium on Humoral Immune-responses in Weaned Beef-calves." *Amer. J. Vet.* Res. 50:1,760.
44. Vyas, D., and R. K. Chandra. 1983. "Thymic Factor activity, Lymphocyte Stimulation Response, and Antibody-producing Cell in Copper Deficiency." *Nutr. Res.* 3:343.

Author:
Richard C. Bull, Professor of Animal Sciences, University of Idaho
Adapted from the Cattle Producer's Library

This publication was prepared in cooperation with the Extension Beef Cattle Resource Committee and its member states and produced in an electronic format by the University of Wisconsin-Extension, Cooperative Extension. Issued in furtherance of Cooperative Extension work, ACTS of May 8 and June 30, 1914.

BCH-5454 Trace Minerals and Immunology