Nutrition and Disease

Robert W. Phillips, *D.V.M.*
Department of Physiology and Biophysics
Colorado State University
Fort Collins, CO 80523

Introduction

Multiple interactions exist between nutrition and disease. Nutritional input, as well as a variety of environmental stresses, may modify an animal's ability to withstand an infectious process or other disease. A recent listing of such stresses as they relate to animal protein production includes many factors which will have a direct interplay with nutrition (6). Environmental heat stress can increase susceptibility to some infectious diseases, as well as depress appetite. Conversely, the growth of certain bacteria and viruses may be inhibited at higher temperature such as during a febrile response. Calves have been shown to have a reduced cellular immune response during heat stress of 35°C (6). Cold stress particularly associated with damp conditions can also increase the incidence of disease and mortality in young calves. Low environmental temperatures will increase metabolic rate and nutrient requirements. In young calves with minimal energy reserves, anorexia under conditions such as cold environmental stress can be rapidly fatal.

Social upheaval, transport, crowding and mixing with resultant requirements to re-establish a social order may decrease nutrient intake and render animals more susceptible to infection. Subordinate animals have been shown to be less resistant to parasite infections. Whether this is due to decreased food intake is not clear. Bovine shipping fever with its attendant stresses remains a significant problem in intensive agriculture.

Weaning, which reduces and alters nutrient input and limit feeding both decrease immunocompetence. The post weaning increase in glucocorticoids may be influential in the former case while limit feeding of protein presumably acts by a different mechanism.

From a broad perspective, two interactions between nutrition and disease will be considered here. First, how various diseases may modify nutrition, and second how nutritional imbalances can cause disease. The former represents a surprisingly ignored facet of our attempts to reduce the impact of disease. This topic too may be subdivided, and I have chosen arbitrarily to consider how disease modifies (a) nutrient intake, (b) nutrient absorption, and (c) nutrient utilization. Conversely, inappropriate nutritional input can result in disease. Our scientific literature is replete with explicit examples of both nutritional deficiency and excess. These problems are particularly troublesome in areas where intensive agriculture occurs. As producers strive for maximum growth and production, a more careful balancing of nutrient inputs is required. A diet that is adequate for maintenance of minimal rates of growth or production may be quite inadequate for high production situations. This type of generalization is well accepted. Unfortunately, in most cases, the hard data necessary to substantiate specific nutrient requirements which might prevent or ameliorate a given disease are not known. Diseases such as parturient paresis, hypomagnesemia, and lactation ketosis continue to be significant problems.

Effects of Disease on Nutrition

Nutrient Intake

Anorexia! The most common sign of general disease—a sick animal won't eat. An occurrence which develops at a time when adequate caloric and micronutrient availability may be critical. Anorexia is pervasively prevalent during disease. Is this bad, or is it of benefit to the animal to decrease food intake when ill? Certainly in some of the production diseases such as lactation ketosis or grain ingestion acidosis, the decrease in production following onset of anorexia will reduce the seriousness of the disease, but decreased production is not an economically feasible goal for livestock producers. Since anorexia is such a general or basic phenomenon associated with disease, is their a single mechanism which will explain its occurrence?

In a normal animal the desire for food—hunger—is controlled by a variety of inputs to the hunger and satiety centers in the hypothalamus. Major factors reducing the hunger drive following a meal include the hormone cholecystokinin (CCK), core body temperature, circulating substrate levels, and automatic nervous system input. The hormone CCK is found not only in the small intestine but also in the central nervous system and is increasingly implicated as a prime factor controlling food intake (1). Current concepts are that it is released following a meal and interacts with the hunger and/or satiety centers following which the feeling of hunger disappears. Core body temperature is also important. A postprandial increase in temperature occurs due to enhanced splanchnic metabolism which has the effect of decreasing food intake. Other factors which may raise body temperature such as exercise, high environmental temperature or fever will also decrease food intake.

How then does disease cause inappetance? Several mechanisms have been delineated. In parasitism due to trichostrongylus the parasite interacts in some fashion with the intestinal cells which produce CCK causing an increased rate of hormonal release and, subsequently, a decrease in food intake (16). This is a curious occurrence, almost a case of bungling parasitism. Intuitively, from the standpoint of a gastrointestinal parasite, it would appear more logical to stimulate food intake and the parasites nutrient supply. Perhaps the decrease in appetite is a host response to decrease potential nutrient supply and thus limit the parasitic burden. Although the host benefit would seem minimal unless it were associated with other strategies, perhaps immunologic to remove the parasites. Changes in CCK release may occur in other disease situations, but such a response is not well documented.

An increase in core body temperature such as a febrile response to an infectious process, will decrease food intake. When leukocytes are stimulated to phagocytose foreign material, they subsequently release a protein product known as endogenous pyrogen (EP) also more broadly called leukocyte endogenous mediator (LEM) which, in addition to its other functions, acts on the hypothalamus to increase body temperature. One result of which is anorexia. It has been clearly shown in many species that fever per se enhances survival. The extent to which the inappetance associated with fever is beneficial is not as clear. Possible beneficial aspects may relate to protein, energy, and trace mineral metabolism. During the acute phase of infectious disease and disease associated with many gastrointestinal parasites, there is a decrease in food intake with significant changes in body protein metabolism. A decrease occurs in muscle protein synthesis with increased degradation. At this time, most evidence indicates that the changes in skeletal muscle protein metabolism are principally due to innutrition itself, not specific effects of the pathogens. Changes in hepatic protein synthesis may include an increase or decrease in albumin synthesis. As immunologic defenses are activated, globulin synthesis is increased. These changes in plasma protein metabolism are not always recognized in the vascular system as many diarrheal and parasitic diseases modify intestinal permeability so that both albumins and globulins are increasingly lost to the gastrointestinal tract (12). For example, in trichostrongylus infestation the turnover of plasma proteins is twice as rapid due to their intestinal loss. This may be a host defense and the mechanism for ensuring that newly synthesized antihelminth globulins come in contact with the parasite. The decrease in total nutrient intake and increased muscle protein breakdown results in a considerable decrement in productive capability. Not only due to inappetence but to a decreased efficiency of utilization of the food that is consumed (3, 10). Deworming parasitized dairy cows at parturition will signicantly increase milk production.

Animals which are suffering from bacteremia and/or endotoxemia are inappetent, have a decrease in the set-point of plasma glucose, and a relative hypoglycemia. The apparent basis for the hypoglycemia is an increased sensitivity of all cells of the body, including pancreated beta cells to glucose. The response is in many ways analogous to the development of fever via LEM. The first metabolic component following the development of endotoxemia is an increase in insulin secretion which brings about a rapid metabolism of glucose and a hypoglycemia. The second phase is steady state hypoglycemia which is "apparently" recognized by the body as euglycemia (4). The host benefit of decreased food intake and hypoglycemia is not apparent at this time.

A clearer case can be made for the decreased availability of iron. Iron is required particularly by pathogenic bacteria for their multiplication. When a bacterial infection develops, several processes occur which limit the availability of iron to the bacteria. First, anorexia decreases iron intake and the provision of oral iron to animals suffering from a gastrointestinal or bacterial disease will enhance the severity of that disease by providing additional iron for bacterial growth. Within the body, LEM released by neutrophils causes an increase in hepatic iron uptake and a decrease in plasma transferrin levels. The resultant hypoferremia limits the potential for bacterial growth.

There are two other generalized host responses in trace element metabolism to infectious disease. First, there is an increase in zinc absorption from the intestines and an increase in hepatic zinc sequestration. Both actions are associated with an increase in metallothionein synthesis in the liver. Whether the increase in metallothionein production precedes or is a sequela to the increased hepatic zinc uptake is not clear (9).

There are a number of acute-phase globulins which are synthesized in increased quantities under the influence of LEM. The one designated as α_2-macroglobulin is the principle zinc metalloprotein and inhibits protease activity by forming complexes with circulating proteases which causes them to be removed from circulation. In disease conditions, these proteins are believed to stimulate granulocyte formation and to act as carriers for macrophage activating factor (9). Zinc availability to host cells may also be important in the recovey from disease as zinc is required for nucleic acid and protein synthesis and therefore necessary for tissue repair. Zinc deficiency has been shown to result in significant decrements in cellular immunity.

Major changes are also seen in copper metabolism during infection. Copper deficiency reduces the ability of leukocytes to destroy pathogens, although it does not apparently restrict their phagocytic capacity (5). The decreased ability to destroy microbial pathogens has been linked to a decrease in the activity of host cellular superoxide dismutase (SOD). This enzyme is a major copper-containing enzyme in the body and has a basic function of scavenging oxygen radicals during metabolism.

Nutrient Malabsorption

The malabsorption of nutrients can result in impaired nutrition in several ways. In the normal bovine, significant absorption of volatile fatty acids (VFA) occurs in the rumen. Most other nutrients are absorbed in the small intestine, particularly the more proximal segments. Normal absorption is based on the integrated functioning of the absorptive-secretory epithelial cells on the intestinal villi and the integrity and function of the villus including its counter-current vascular loop. A number of disease situations may modify the functional capacity of the small intestine. Most block absorption and create a diarrhea, although in some conditions increased secretory activity may also result in diarrheal states. Viruses, chlamydia bacteria, coccidia and helminth parasites may all modify intestinal function blunting decreases of the effective surface area of intestinal villi. Epithelial cells are modified both morphologically and functionally resulting in impaired absorptive capacity. There are conflicting reports concerning the effects of helminth parasites on intestinal absorptive function. Both inhibition and no change have been reported (15). It is possible that decreased transit time may be a more important factor than limitations in transepithelial transport although during trichostrongylus infection epithelial cells become cuboidal. In the bovine, *Ostertagia* infection results in dedifferentiation of the gastric mucosa with a significant decrease in acid production which may secondarily inhibit the activation of pepsinogen and subsequent intestinal protein digestion (8). Endocrine cells are also decreased in numbers during acute parasitic infections and their loss may further modify gastrointestinal function. Impaired skeletal development is often seen apparently due to decreased bone mineralization because of a phosphorus deficiency. Osteo-dystrophy develops and may have long-term detrimental effects on growth and productivity.

Functional and morthologic changes in the small intestine are common in the viral diarrheas. The resultant malabsorption syndrome has been associated with a deficit in the active transport of glucose and amino acids across the epithelial barrier. Following transport inhibition, the increased quantities of luminal nutrients, provide a medium for enhanced bacterial growth and an increase in bacterial numbers in the intestine (14). A combination of increased bacterial numbers and damage to the epithelial barrier increases the occurrence of bacteremia and endotoxemia as a sequela to viral gastrointestinal damage.

Bacterial diarrheal disease is more often associated with an entertoxin induced increase in secretory activity with normal electrolyte absorptive capacity. An increase in the rate of passage may secondarily decrease absorptive function. The overall result is anorexia, increased electrolyte and water loss and decreased nutrient acquisition by the animal. Some changes in digestive-absorptive capacity, such as inhibition of intestinal lactase activity, are frequently seen in diarrheic young animals.

Both coccida and *Fasciola hepatica* cause a deficiency of iron due to hemorrhage. In these cases, iron supplementation is of benefit in stimulating the animals erythropoietic capacity (12).

As a final example, iatrogenic malabsorption can be induced in calves by the provision of therapeutic doses of oral antibiotics, particularly those that block protein synthesis. The resulting diarrheal syndrome includes both morphologic and biochemical damage.

Nutrient Utilization

As previously discussed, the impact of disease has significant effects on the manner in which nutrients are utilized within the body. It is difficult to separate anorexia and decreased nutrient intake from some of the other specific sequela to disease. Generalizations include the fact that fever increases metabolism and nutrient oxidation. Due to altered requirements for acute-phase globulin synthesis, decreased muscle protein synthesis, and altered hepatic protein synthesis, there is often a decrease in the circulating amino acid pool. Plasma levels of insulin are reduced while glucagon and glucocorticoids are increased. The resultant shift in metabolism and metabolite utilization includes a decrease in carbohydrate oxidation, an increase in gluconeogenesis from amino acid precursors, negative nitrogen balance, and an increase in the mobilization and utilization of free fatty acids from lipid depots with a varying degree of ketosis. The latter phenomena cannot be separated from the decrease in nutrient intake, as fasting under any condition will enhance lipid mobilization and oxidation as well as hepatic ketogenesis.

Feeding Sick Animals

Overall, diseases significantly modify nutrient intake, absorption and utilization yet our appropriate response as animal health care providers is not clear. In order to reduce the loss of production due to disease, we need to have a better basic understanding of the benefits and detriments of anorexia. Should we force feed sick cattle or attempt to develop and use antianorectic drugs which could increase nutrient intake (1)? Would such an approach be of equal value in young calves with minimum nutrient reserves and adult cattle that may be able to successfully survive longer periods of inanition? If it appears beneficial to provide nutrients, are there particular general diets that would be most beneficial for a sick preruminant or adult ruminant animal? It appears that iron intake should be reduced in many infectious diseases. Should zinc and copper be increased? What changes in protein intake would be beneficial? Clearly much remains to be done.

Effects of Nutrition on Disease

The methods used to produce edible animal protein, meat and milk, continue to evolve. Changing agricultural practice leads to increasingly intensive plant and animal husbandry as cattle raisers develop new techniques for increasing rates of growth, milk production or numbers of animals supported per unit of ground. These practices, as they are successful, uncover latent metabolic limits or subclinical deficiencies. We now recognize a host of "production diseases" that become evident when feed intake is increased or crop production stimulated by introducing new plant species, fertilization or irrigation. The limiting or initiating factor in producing a clinical disease may be an animal function due to an inability to metabolize or balance nutrient input and output. Conversely, it may be a dietary function in that the diet has a relative deficiency or excess of some nutrient or element.

Production Disease—Animal Limited

Some examples of the more prevalent animal limited production diseases are lactation ketosis, and parturient paresis. Lactation ketosis has become a more common entity as animal breeders expand the dairy cow's lactation potential. In early lactation, high producing cows are in negative energy balance in spite of extremely high rates of food intake. Most animals are able to adapt and partition their energy expenditures within the limits of health (2). In other cases, as energy output, predominately in the form of milk constituents exceeds dietary energy input, reserve energy stores must be utilized. Lipolysis is stimulated by a combination of hypoglycemia with attendant hypoinsulinemia and increases in circulating levels of the counter-regulatory hormones, glucagon, growth hormone, and glucocorticoids. Free fatty acids are metabolized, in part to ketones, in the liver and released into the vascular system. The basic problem appears to be one of excessive mobilization of the requisite energy source. Once that has occurred, rapid metabolism of a portion of the free fatty acids to ketones is assured. Appropriate prophylactic steps might include hormonal modification of the peak lactation response, changing dietary input to decrease the negative energy balance or reduction of the rate of lipolysis by hormonal or drug action on the adipocytes.

Parturient paresis also effects dairy cows in early lactation. It is characterized as a hypocalcemia and hypophosphatemia. Mechanisms that bring about parturient paresis are not completely elucidated. A current concept is that the freshly parturient cow cannot mobilize sufficient bone calcium in spite of increased intestinal absorption. Since mammary drain exceeds intestinal and renal absorption and limited bone resorption, hypocalcemia occurs. The factors limiting bone resorption are subject to controversy. Some data indicate that the parathyroid gland is suppressed on high calcium intake during the preparturient period. However, the preponderance of data indicates that the problem is not at the level of the parathyroid gland. The basic defect is related to the 1-25 $(OH)_2D$ calcium mobilization system and a lag in homeostatic control develops (7). The hypocalcemic cow develops motor paralysis and may become unconscious. Hypophosphatemia, although present, is not considered the prime defect.

An effective prophylactic approach is to place animals on low calcium intake during the last 2 weeks of gestation so that their calcium mobilizing and absorbing system is activated prior to initiation of mammary drain. Low intake will enhance efficiency of calcium absorption and bone mobilization. Following parturition, dietary calcium levels should be increased. Legume hays should be avoided in the prepartum period because of their high calcium content. It has been suggested that low calcium diets prepartum may suppress both food intake and milk production following parturition.

Production Disease—Diet Limited

Many nutrients can become limiting as we provide cattle with diets that will allow them to express their maximum productive capacity. Most commonly deficiency or excess of trace elements is seen.

Changing agricultural practice has led to increasingly intensive plant and animal husbandry that may alter availability of trace elements and their requirements by animals; e.g., increased fertilization and irrigation lead to greater plant growth and leaching of well-drained soils. The former may cause direct changes in plant composition and the latter may deplete some microelements from the soil (17). Many other factors can modify the trace element composition of diets (13). Replacement of natural forage with new plant species or the use of single food sources may create nutritional imbalance. These and other production techniques will alter availability of trace elements to the animal and may result in deficiency syndromes in areas where they did not previously exist. Animals acquire trace elements naturally from water and plant ingestion and from soil contamination of herbage.

Trace element interrelationships are very complex. One of the best defined is that between copper and molybdenum. Both elements may be deficient or present in toxic quantities, and each reduces absorption and utilization of the other. On molybdenum-marginal soils, copper can cause a molybdenum deficiency, whereas copper is a therapeutic choice for animals having molybdenum toxicosis. Zinc, iron, calcium and SO_4 can also reduce the availability of dietary copper. Copper is required for a variety of body functions which include hematopoiesis, myelin formation, pigmentation, connective tissue metabolism, and bone formation. It is a component of many enzymes including cytochrome oxidase and several concerned with aromatic amino acid metabolism.

Magnesium is an essential intracellular ion and a co-factor for many enzymes, particularly those involved in high energy transfer. When deficient neuromuscular hyperirritability is seen. Hypomagnesemia, grass tetany, is a common occurrence in temperate climates, particularly in cattle grazed on lush, cool-season grass pastures or grain stubble fields that have been liberally fertilized. Beef cattle that are producing milk are particularly susceptible, since milk represents a significant additional drain of magnesium during critical periods. Rapid growth of grass occurs during early spring when lactation is also heavy. Dairy cows are less likely to be afflicted because they routinely receive concentrate or concentrate-mineral supplements during lactation. Factors that result in grass tetany are complex and incompletely understood (11). Many are closely related; e.g., high potassium fertilization causes a high potassium content in plants that results in high potassium intake. As potassium and nitrogen content of young grass increases the availability of magnesium, which is poorly absorbed under the best conditions, is decreased. Dietary calcium is also important and the ratio of K/(Ca+Mg) can be used to assess potassium availability.

Production Disease—Animal and Diet Limited

Frothy bloat, as seen in cattle feeding on leguminous forages is due to a combination of factors which include both plant and animal constituents. Saponins and soluble protein are associated with young leafy growth, and the formation of a stable froth within the rumen. From the animal's side, salivary quantity and constituents are important as well as rumen microbial population and activity. All of the specific factors that cause clinical bloating have not been agreed upon but it is clear that fertilization and irrigation, of N_2 fixing, leguminous pasture is a prelude to increased incidence of this disease.

The preceeding examples of bovine production disease were not intended to serve as a complete listing of the many mechanisms by which intensive management practices cause disease. Rather, to represent diet and animal interactions where normal homeostasis breaks down. Certainly, a number of important clearly identified nutrition-related diseases of cattle have not been presented.

References

1. Baile, C.A. and C.L. McLaughlin: 1984 in Agric. Chem. of the Future, Ed. J.L. Hilton. Rowman and Allanheld Pub. Chapt. 11. 2. Bauman, D.E. and W.B. Currie: 1980 J. Dairy Sci., 63:1514. 3. Coop, R.L., A.R. Sykes and K.W. Angus: 1976 Res. Vet. Sci., 21:253. 4. Hand, M.S., M.J. Fettman, L.G. Chandrasena, J.L. Cleek, R.A. Mason and R.W. Phillips: 1983 Circ. Shock, 11:287. 5. Jones, D.G. and N.F. Suttle: 1981 Res. Vet. Sci., 31:151. 6. Kelly, K.W.: 1980 Ann. Rech. Vet., 11:445. 7. Littledyke, E.T.: 1977 J. Dairy Sci., 60:1947. 8. Myers, G.D.: 1984 Anim. Nutr. Health, 39:#2, 34. 9. Powanda, M.C.: 1980 Am. J. Vet. Res., 41:1905. 10. Randall, R.W. and H.C. Gibbs: 1981 Am. J. Vet. Res., 42:1730. 11. Rendig, V.V. and D.L. Grunes: 1978 Grass Tetany, Crop Sci. Soc. Am., Madison, Wisconsin. 12. Soulsby, E.J.L.: 1982 Helminths, Arthropods and Protozoa of Domesticated Animals, Lea and Febiger. 13. Smart, M.E., J. Gudmundson and D.A. Christensen: 1981 Can. Vet. J., 22:372. 14. Storz, J., J.R. Collier, A.K. Eugster and K.P. Altera: 1981 Ann. N.Y. Acad. Sci., 1976:162. 15. Symons, L.E.A.: 1976 in Pathophysiology of Parasitic Infections, Ed. E. Soulsby Acad. Press, 11. 16. Symons, L.E.A. and D.R. Hennessy: 1981 Int. J. Parasit., 11:55. 17. Underwood, E.J.: 1977 Trace Elements in Human and Animal Nutrition, 4th Ed., Academic Press.

Paper presented at the XIIIth World Congress on Cattle Diseases, Durban, S. Africa, Sept. 17-21, 1984.