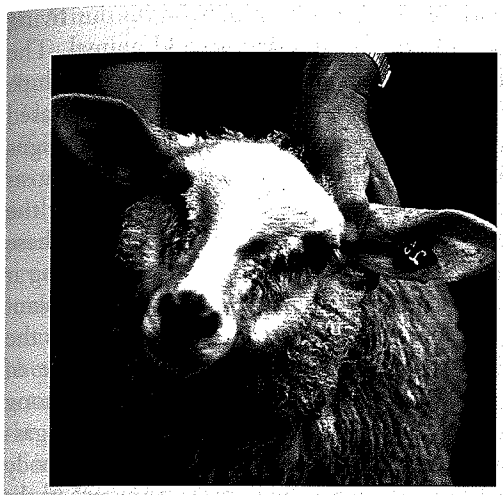

CHAPTER 20

ANIMALS AND MEDICAL GEOLOGY

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CONTENTS

I. INTRODUCTION

It has been recognized for a very long time that animals can become sick after grazing in certain areas of the world. Eventually, it was determined that local geochemical anomalies were responsible, but in some cases the exact mechanisms behind the deficiencies and intoxications have only been known for the last 50 to 70 years. Local geochemical anomalies affect both domestic and wild herbivorous animals living in an area; however, wild animals will be especially susceptible to deficiency or intoxication due to the fact that they normally are totally dependent on feeds growing in a specific area.

Problems associated with restricted access to suitable feeds are seen in domestic animals in developing countries or among animals that have been reared under less intensive conditions, and where farmers rely on locally produced feeds. Extreme weather conditions, especially drought, affect the availability of pasture and feed in areas with low groundwater tables and sensitive soils. The availability of nutrients is also affected by the seasonal development of forage plants eaten by the animals. The protein content of mature plants is often low, as is the amount of easily digestible carbohydrates and other important nutrients, but the fiber content is higher than in earlier stages of plant development. This seasonal shortage of available nutrients can be circumvented by migration between different areas and is believed to be one of the driving forces behind the seasonal migrations normally seen in many wild African herbivores. In some areas, this behavior is restricted, as some wildlife reservations are fenced to protect the animals from poachers and grazing competition from domestic animals (Maskall & Thornton, 1996). Migration between different grazing areas can also be applied to domestic animals and is a common practice for nomadic animal husbandry in Africa and continental parts of Asia. The nomadic behavior of caribou and semidomestic reindeer in the subarctic is primarily caused by climatic factors such as snow and ice, which can limit the availability of feed.

The increasing interest in organic farming in some European countries and North America exposes animals on such farms to higher risks of deficiency or dietary imbalance because of the use of feeds produced locally without conventional fertilizers. Farmers who are aware of these risks can overcome them by growing specific

feeding plants selected to accumulate or exclude particular elements known to cause nutritional imbalances.

In the intensive type of animal husbandry seen in many parts of the world today, especially in Europe and North America, the effects of local geochemical anomalies are less apparent, as the content of nutrients in the rations fed to animals is controlled, and appropriate supplements or feedstuffs are utilized to compensate for potential deficiencies or excesses.

Generally, the metabolic effects of deficient or excessive intakes of nutrients due to the local geochemistry are the same in animals as in humans; that is, a change in activity of certain important enzymes is the major effect that compromises the health of animals. The symptoms exhibited by various animal species or humans suffering from the same pathological processes will therefore be identical or similar.

A. Recognition of Problems

Pathological changes caused by mineral imbalances, deficiency, or intoxication due to local geochemical anomalies are often difficult to detect in the living animal, especially in the free-living wild animal. The diffuse and ambiguous signs of these changes include retarded growth, decreased fertility, and decreased immunological capacity. In many cases, the only signs are suboptimal growth or low reproduction. Diagnosis is further complicated by interactions among the various elements already present in the soil. These interactions affect nutrient uptake by plants, making it difficult to evaluate results obtained from soil and plant analyses with regard to the nutritional value for the grazing animal or to estimate the animal's intake of required nutrients. Interactions also occur among various elements in the animal itself, both in the gastrointestinal tract and in different tissues of the body (see Table I). The gastrointestinal interactions are probably more important in herbivores, as the longer passage time through the tract and its larger volume provide greater opportunities for chemical reactions to occur among the many different compounds present. Often, extended analyses of blood and other tissues such as liver and kidney are needed to arrive at a definite diagnosis (see Section III.J).

TABLE I. Important Interactions Between Various Elements in Animals

	F	*Na*	*Mg*	*Al*	*P*	*S*	*K*	*Ca*	*Mn*	*Fe*	*Co*	*Cu*	*Zn*	*As*	*Se*	*Mo*	*Cd*	*I*
F				+				+										+
Na							+											
Mg					+		+	+	+									
Al	+				+													
P			+	+				+	+	+		+	+			+		
S								+				+	+		+	+		
K		+	+															
Ca	+		+		+	+			+				+					
Mn			+		+			+			+							+
Fe					+				+		+	+	+					
Co									+	+								+
Cu					+	+				+			+			+	+	
Zn					+	+				+		+					+	
As															+			+
Se						+								+				
Mo					+	+						+						
Cd												+	+					
I	+								+		+			+				

Note: Interactions can occur in the gastrointestinal tract of the animal or on a cellular level in the tissues.
Source: Modified after Jacobson *et al.*, 1972.

B. Mineral and Trace Element Availability

Apart from general factors such as soil composition and pH, the plant species and stage of development will affect root uptake and hence the mineral content found in the plant. Alkaline soils will have more available molybdenum and selenium because these elements are present as anions, whereas most other metals are present as cations and their availability is favored by lower pH. The availability of minerals in soil eaten by animals is often difficult to estimate from common chemical analyses of mineral concentrations, as the actual gut absorption often is very low, depending on the chemical form of the mineral. The different types of interactions presented in Table I will also be of relatively large importance in these situations. Minerals taken up by different plants and present in plant tissues are generally more available as the root uptake requires solubility in soil water or intracellular water. Dust or other soil contaminations on plant surfaces, especially on pilose or sticky structures, will be as unavailable to absorption in the gut as pure soil eaten by an animal. Involuntary soil intake will be much higher in animals grazing hard and close to the ground, such as cattle and sheep, than goats and many wild ruminants that to a great extent feed on shrubs, bushes, and tree leaves (browse). Especially in situations of feed shortage, soil intake can be high (several kilograms per day in cattle).

C. Mineral and Trace Element Requirement and Excess

The needs for mineral and trace elements by common domestic animal species have been established in experiments using normal feeding procedures or specialized synthetic or semisynthetic feeds (see Tables II to VII). An animal's growth rate and normal development are followed in these types of experiments, as well as the health and reproductive functions of the animal. In many cases, the nutrient requirements are influenced by the selective breeding of animals to provide increased growth rates or improved milk or egg production. The complex interrelationships among minerals and trace elements and other feed components make it difficult to determine if nutrient requirements are being met or if adverse effects due to excess nutrients could be expected when unconventional or extreme feeding regimes are used. Some of the known requirements for various minerals and trace elements are discussed in Section III. The mineral and trace element requirements of wild or

TABLE II. Nutrient Requirements for Calcium and Phosphorus for Some Domestic Species

Animal	*Calcium*	*Phosphorus*	*Ref.*
Lactating dairy cows	4.8–8.5	3.1–5.3	NRC, 1989a
Growing calves	3.2–5.8	2.6–3.4	NRC, 1989a
Beef cattle	1.8–17	1.9–6.6	NRC, 1984a
Sheep	2.2–9.1	1.8–4.2	NRC, 1985b
Swine	5.6–10	4.4–7.8	NRC, 1988
Horses	2.7–7.6	1.9–4.2	NRC, 1989b
Dogs	6.6	4.9	NRC, 1985a

Note: The amounts are expressed as g/kg d.m. daily feed intake.

TABLE III. Amounts of Manganese Required for Normal Development and Health in Some Domestic Animal Species and Amounts Causing Adverse Effects

Animal	*Requirements*	*Adverse Effects*	*Ref.*
Dairy cattle	40	1000	NRC, 1989a
Beef cattle	40	1000	NRC, 1984a
Sheep	20–40	—	NRC, 1985b
Horses	40	400	NRC, 1989b
Swine	2–10	400	NRC, 1988
Chicken	30–60	2000	NRC, 1984b

Note: The amounts are expressed as mg/kg feed d.m.

TABLE IV. Nutrient Requirements for Copper and Amounts Causing Toxicity or Other Adverse Effects in Domestic Animals

Animal	*Requirements*	*Toxic or Adverse Effects*	*Ref.*
Dairy cattle	10	100	NRC, 1989a
Beef cattle	8	100	NRC, 1984a
Sheep	7–11	25	NRC, 1985b
Swine	3–6	250	NRC, 1988
Horses	10	—	NRC, 1989b
Dogs	2	—	NRC, 1985b
Chicken	6–8	500	NRC, 1984b

Note: The amounts are expressed as mg/kg feed d.m.

TABLE V. Nutrient Requirements for Zinc and Amounts Causing Adverse Effects in Domestic Animals

Animal	*Requirements*	*Adverse Effects*	*Ref.*
Dairy cattle	40	1000	NRC, 1989a
Beef cattle	30	1000	NRC, 1984a
Sheep	20–33	750	NRC, 1985a
Goats	10	—	NRC, 1979
Growing swine	50–100	1000	NRC, 1988
Breeding swine	50	—	NRC, 1988
Horses	40	—	NRC, 1989b
Chicken	35–65	1200	NRC, 1984b

Note: The amounts are expressed as mg/kg feed d.m.

TABLE VI. Nutrient Requirements for Selenium and Amounts Causing Adverse Effects in Domestic Animals

Animal	*Requirements*	*Adverse Effects*	*Ref.*
Dairy cattle	0.3	5	NRC, 1989a
Beef cattle	0.2	5	NRC, 1984a
Sheep	0.1–0.2	—	NRC, 1985b
Swine	0.1–0.3	20	NRC, 1988
Horses	0.1	5	NRC, 1989b
Dogs	0.11	—	NRC, 1985a
Chicken	0.1–0.15	—	NRC, 1984b

Note: The amounts are expressed as mg/kg feed d.m.

exotic domestic species are not well known, and neither are the amounts needed to cause deleterious effects in these animals. Extrapolations from known needs of related domestic species should be done with great caution as many wild species have evolved in specific areas and have adapted to the geochemical situations in those particular habitats.

D. Salt and Mineral Licks

Both domestic and wild animals are regularly seen eating soil or earth. Under conditions of overgrazing or a shortage of feed, soil eating is believed to correct nutritional deficiencies. In certain situations, animals are exploiting natural sources of sodium- or phosphorus-rich minerals for this purpose. Other minerals are actively sought by animals, but the mechanisms behind this behavior are not known. It is a common belief that animals, and humans, will correct deficiencies in their mineral and trace element supply by eating soil (*i.e.*, pica). This behavior is seen in many cases of nutrient deficiencies, but no known mechanism induces or regulates it. More probable in animals is that this knowledge is passed down from mother to offspring as an important factor in the utilization of special sites with favorable mineral compositions. One illustrative example of this is the utilization of minerals found in caves in Kenya that are actively mined by elephants living in the area (Bowell *et al.*, 1996). The elephants use their tusks to mine the veins of calcite–zeolite in the roofs and walls of the caves; some of the rocks are eaten by the animals, but some are left on the cave floor. The environment on the cave floor (*e.g.*, water and debris from animals) induces the formation of salts on the surfaces of the rocks. This cave salt is utilized by local tribesmen for their cattle, and it is also used by other wild animals, such as baboons (*Papio cyancephalus*) and leopards (*Pantera pardus*). Bushbucks (*Tragelphus scriptus*) also seek the formed salt deposits in the caves.

TABLE VII. Nutrient Requirements for Iodine for Some Domestic Species

Animal	*Requirements*	*Ref.*
Dairy cattle	0.5	NRC, 1984a
Beef cattle	0.5	NRC, 1989a
Sheep	0.1–0.8	NRC, 1985b
Swine	0.14	NRC, 1988
Horses	0.1	NRC, 1989b
Chicken	0.3	NRC, 1984b

Note: The amounts are expressed as mg/kg feed d.m.

II. SPECIES AND BREED DIFFERENCES

For a number of reasons, important differences can be seen between monogastric and ruminant species in the metabolic handling of several elements that cause deficiency or intoxication. One reason is the simple fact that the pH of the forestomachs of ruminant species ranges

from 6 to 7, and the pH of the abomasum, the true stomach of ruminants, is 2 to 3, which renders most metallic elements less available for absorption as compared to most monogastric species, for which the stomach pH varies from 1 to 2. Another important reason for species differences is the simple chemical reactions that can occur in the forestomachs of ruminants. The anaerobic fermentation that takes place in the forestomachs can produce valence stages and complex compounds that are not available for intestinal absorption, as most minerals and trace elements are absorbed in cationic form. For a more comprehensive description of the digestive physiology of animals see, for example, Chapter 14 in Sjaastad *et al.* (2003).

In some cases, breed differences can exist within the same domestic species due to the development of breeding animals having special properties desirable in specific situations. The very fast growth rate seen in many modern domestic animals is a breeding effect that can affect an animal's sensitivity to insufficient or excessive intakes of minerals and trace elements. Because many modern breeds have a high demand for nutrients and therefore a high feed intake, they may not necessarily meet their mineral and trace element requirements. This is especially obvious in very young animals during the suckling period if they feed on milk that is poor in iron. The available iron is insufficient to meet the requirements for normal hemoglobin formation, thus causing anemia, which, in turn, often also leads to increased susceptibility to infection.

In most cases, attributing pathological conditions to local geochemical anomalies is complicated. The clinical picture and postmortem examination are often equivocal. Support from clinical chemical analyses of blood and other tissues from the living animal as well as chemical analyses from tissues obtained during a postmortem examination are necessary to obtain a definitive diagnosis.

III. SPECIFIC ELEMENTS

This section focuses on effects seen in normal environmental situations in both wild and domestic animals and only briefly discusses effects observed in areas polluted by mining or other industrial activities. The minerals calcium and phosphorus are discussed first, followed by the trace elements in order of increasing atomic weight.

A. Phosphorus and Calcium

The metabolism of phosphorus and the metabolism of calcium are so interrelated that they are discussed together. Utilization of these two elements is profoundly affected by the amount of vitamin D present in feeds consumed by the animal. Disturbances in the metabolism of phosphorus and calcium that are seen in young growing animals can affect bone formation when cartilage is being gradually replaced by bone tissue containing hydroxyapatite, a calcium phosphate compound that makes bone hard and mineralized. If this process is disturbed, both bone growth and function are affected. A well-known pathology associated with this mineralization is rickets, a disease known in both animals and humans since antiquity. Often, rickets is caused by a vitamin D deficiency. A typical case of rickets shows enlargement of the junction between the ribs and costal cartilages (costochondral junction) as well as the growth plates (metaphyses) of the long bones. The stability of the bone is reduced, resulting in fractures or bending of the legs, thus giving the animal the tell-tale appearance of rickets. In adult animals, where bone growth is completed, a similar defect is called *osteomalacia*.

Direct toxic effects of an excessive intake of calcium are not seen as the balance between calcium and phosphorus is crucial for the biological effects. An excessive intake of calcium, however, severely affects the availability of several other minerals and trace elements, as shown in Table I. High phosphorus intake also interferes with the metabolism of many other elements, as seen in the table. Normal calcium and phosphorus requirements for common domestic species are presented in Table II; these amounts are relevant in situations where the calcium–phosphorus ratio is balanced (ideally, 1–1.2).

Endemic areas deficient in phosphorus are found in South Africa and Latin America; cattle grazing on grassland in these areas often have a very low intake of both phosphorus and calcium. Clinical signs of phosphorus and calcium deficiency are more apparent in young animals than adults. Subnormal growth, low reproduction, and pica are observed before the bone pathology (osteomalacia) becomes apparent, in both young and adult animals. Deficiencies can also be seen in pigs in the form of poor growth, gait disturbances, lameness, bone deformation, and even fractures. The fractures occur in the vertebrae, which are more prone to demineralization than the long bones of the legs.

A special situation related to excessive calcium intake is calcinosis, which is seen in areas where plants producing substances related to vitamin D are growing. In

New Guinea, the European Alps, Argentina, Brazil, and Florida, enzootic calcinosis with calcium deposits in soft tissues has been described. In the Americas solanaceous plants produce compounds that can mimic vitamin D activity in the gastrointestinal tract, thus promoting an excessively high absorption of calcium and phosphates and disturbing the normal homeostatic regulation of these elements. In Argentina and Brazil, this condition (known as *enteque seco*) is caused by ingestion of leaves from the shrub *Solanum malacoxylon*, and in Florida a large ornamental plant (*Cestrum diurnum*) is the cause. In Central Europe, calcinosis is caused by consumption of the pasture grass *Trisetum flavescens*. The increased uptake of calcium results in calcification of soft tissues in the affected animals, and the often massive deposits of calcium seen in the walls of major arteries, especially the aorta, will eventually kill the animal due to disturbed blood circulation and heart failure.

B. Aluminum

Only trace amounts of aluminum are found in most biological organisms, although this element is abundant in most soils; however, some exceptional tropical plants do accumulate aluminum, which can reach levels of >1 g/kg of plant (dry matter). Aluminum can be toxic to plants as well as fish and other aquatic biota, but direct toxic effects of aluminum on livestock are unlikely at natural environmental levels. High levels of ingested aluminum will, however, decrease the availability of nutrients such as iron, phosphorus, and, to some extent, calcium (see Table I). Most of this aluminum would be present as external contamination on the plant material eaten by the animals, especially in a dry and dusty environment. The high levels of aluminum and iron seen in some acidic soils can form insoluble phosphate complexes that produce secondary phosphorus deficiency in animals. This could result in grass tetany and osteomalacia in exposed cattle. The amounts needed to cause such problems are estimated to be 0.5 to 8 g/kg plant material (d.m.).

C. Fluorine

Some species might need fluorine as an essential trace element, but it is generally known to be toxic to both humans and animals. Small amounts of fluorine absorbed in the gastrointestinal tract will quickly form CaF, which is incorporated into bone and teeth, resulting in more stable and less reactive bone tissue. Signs of fluorine toxicity were described very early (around the year 1000) in Iceland, where cattle grazed on grass contaminated with fallen volcanic ashes. Areas with volcanic activity are particularly prone to excessive fluorine exposure due to external contamination of pasture plants. Parts of the North African coastal plain have been known for centuries to be areas of endemic fluorine toxicity. Often, drinking water is the source of excessive fluorine intake, and endemic chronic fluorosis has been described in domestic ruminants and horses in Australia, India, Turkey, and several parts of Africa due to high levels of fluorine in their drinking water (see also Chapter 12, this volume).

Ruminants are more sensitive to fluorine than monogastric species, but even ruminants can tolerate only 80 to 100 µg/g d.m. in their feed (Mertz, 1987). Poultry is more resistant to the toxic effects of fluorine, and reports suggest that poultry is able to tolerate twice as much as mammals. A high intake of aluminum or calcium (see Table I) will protect species from the toxic effects of excessive fluorine in their feed or drinking water.

Clinical signs of fluorine toxicity are evident primarily in the teeth and bone. Teeth still under development are most sensitive to high fluorine intake and become mottled and discolored. More severe indications are modifications of size and shape of developing teeth and decreased strength resulting in fractures even after limited mechanical stress. Also, bone will show changes in size and shape as a result of fluorine toxicity, especially in growing animals. Lameness can also be seen as a result of bone pathology caused by excessive fluorine intake.

Most plants have low concentrations of fluorine, but external contamination is the primary route of toxic exposures; however, in South Africa, some plants do produce fluoroacetic acid, which can poison the grazing sheep. This fluoroacetic acid is converted *in vivo* to fluorocitrate, which specifically inhibits activity of the enzyme aconitase, which is necessary for the metabolism of citrate in the energy-producing citric acid cycle (or Krebs cycle) vital to all living cells. Fluoroacetate was used earlier as a rodenticide due to its potent toxic effect.

D. Manganese

Concentrations of manganese in plant material are highly variable, and the effects of a deficiency due to low manganese intake can be seen in ruminants, swine,

and poultry fed normal feeding plants. The risk for low manganese intake is greater if the land used for feed production or grazing is excessively limed. Symptoms in affected animals are changes in lipid and carbohydrate metabolism and impaired growth and infertility, depending on the duration of the deficiency and the age of the animal. These symptoms are caused by the decreased activity of manganese-containing enzymes such as arginase, manganese–superoxide dismutase, and pyruvate carboxylase. The requirements of manganese in feeds are generally greater for poultry (see Table III), and feeds based on corn and barley could be deficient. Toxic effects of manganese are unlikely, as this element is considered one of the least toxic; however, continuous grazing on the volcanic soils of Costa Rica can result in a manganese intake of >200 mg per day and has been reported to produce reproductive changes in cattle. Adverse effects of excessive manganese intake are mainly caused by its interactions with iron and other elements (see Table I), resulting in secondary iron deficiency anemia that can be seen in both lambs and pigs.

E. Cobalt

A deficiency of cobalt *per se* is not described in carnivorous animals, but their diet should have this element incorporated into vitamin B_{12} (cyanocobalamin) for normal methionine synthesis and energy metabolism. Two different forms of vitamin B_{12} are responsible for these two metabolic pathways: methylcobalamin for methionine synthesis and adenosylcobalamin for energy metabolism. Methylcobalamin is of importance for both protein and lipid synthesis, and in humans a vitamin B_{12} deficiency typically causes a specific megaloblastic anemia (pernicious anemia) and neurological disorders due to progressive demyelination. Pernicious anemia is not seen in domestic animals in cases of vitamin B_{12} deficiency. Ruminants and other herbivorous species do not need preformed vitamin B_{12} in their feed, as the microbes present in their gastrointestinal tract, especially the rumen, can produce this complex compound if sufficient cobalt is present in the feed. The requirement in all domestic ruminant species is about 0.1 mg/kg feed (d.m.), as the uptake of the vitamin is comparatively low in ruminants and even less in monogastric animals.

Young, growing ruminants grazing cobalt-deficient pastures are most sensitive to deficient levels of the adenosylcobalamin moiety. Lambs especially will show symptoms of inanition in spite of access to grazing, but older animals can also be affected under certain circumstances. Underlying this problem is the fact that adenosylcobalamin converts methylmalonyl-CoA to succinyl-CoA, beginning with propionic acid formed in the forestomachs of ruminants. In monogastric species, this metabolic pathway is of minor significance, but the energy metabolism of ruminants is based on the volatile fatty acids (VFAs) acetate, butyrate, and propionate and not glucose, which is typical for most other species. The clinical effects of cobalt deficiency in ruminants grazing deficient pastures have been recognized for quite some time in many parts of the world. The disease, or rather the apparent symptoms, goes by various local names (*e.g.*, in New Zealand, bush sickness; in Australia, wasting disease; in the United States, salt sick or neck ail; in Brazil, *mal de colete* or *pest de secar*; in Great Britain, pining disease; in Norway, white liver disease), apart from more general terms such as muscular wasting or enzootic marasmus. Sheep grazing in deficient areas are more sensitive than cattle, and young animals are more sensitive than adults. The deficiency is often due to low levels of cobalt in peaty soils or otherwise highly organic soils. Signs of cobalt deficiency in ruminants are retarded development in lambs, slow growth rate, inappetence, emaciation, and weakness.

Eventually, animals suffering a deficiency of cobalt die of emaciation. At an early stage, the symptoms are nonspecific and other reasons for the observed pathology could be suspected. Cobalt deficiency has to be confirmed by determination of methylmalonic acid (MMA) in blood samples or determination of cobalt/vitamin B_{12} in tissue samples, preferably the liver. At autopsy, the carcass is generally pale, and the liver is also characteristically pale with a pathologic texture that gives the deficiency one of its more common names—ovine white liver disease (OWLD) (see Figures 1–3). In some situations, OWLD or cobalamin deficiency can be provoked by some additional nutritional factor suspected to be fructan or other water-soluble carbohydrate compounds present in some grasses early in the season. These carbohydrates are fermented to VFAs in the forestomachs which increases the demand for adenosylcobalamin in the energy metabolism of the animal.

Neurological symptoms due to central demyelination that have been reported in vitamin B_{12}-deficient lambs include blindness and locomotor disturbances (Ulvund & Pestalozzi, 1990). Recently, similar neurological symptoms observed for decades in Nova Scotia moose have been associated with cobalt deficiency (Frank *et al.*, 2003). Vitamin B_{12} deficiency and neurological prob-

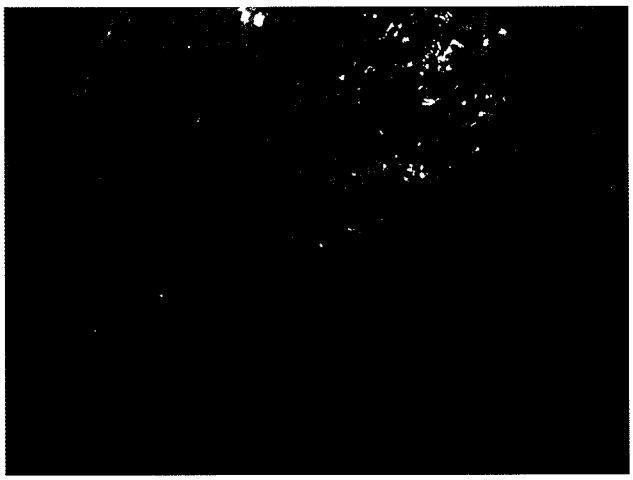

FIGURE 1 The liver from an animal euthanized due to ovine white liver disease (OWLD); note pale irregular areas protruding above the surface. (Photograph courtesy of Martha J. Ulvund, Sandnes, Norway.)

lems among elderly humans have attracted considerable interest lately.

F. Copper

The effects of copper deficiency have been extensively studied in several parts of the world, because it is a widespread problem for sheep and cattle production. Copper deficiencies due to local geochemical anomalies produce significant losses for farmers worldwide. Studies of copper metabolism in various species have shown that there are important differences between ruminants and monogastric animals due to copper–molybdenum sulfate interactions in the forestomachs and biochemical handling of copper in the body after absorption. These biochemical differences are mainly due to the specific binding properties of metallothioneins in the liver and kidneys of ruminant species which differ from those seen in nonruminants. The copper–molybdenum sulfate interactions can make it difficult to evaluate the copper status of an animal because it is necessary to know the availability of all three compounds to make a reliable estimation of biologically active copper. To avoid an imbalance between copper and molybdenum, the ratio in the feeds should be between 1 to 2 or 1 to 4 (this important interaction is further discussed in Section III.J). These differences in the binding properties of metallothionein render ruminants very sensitive to chronic copper toxicity even after slight but prolonged excessive intake of copper.

FIGURE 2 Lamb showing nonspecific signs such as serous eye discharge and small crusts on the ears, typical of OWLD. This lamb was only half the size of its healthy flockmates. (Photograph courtesy of Martha J. Ulvund, Sandnes, Norway.)

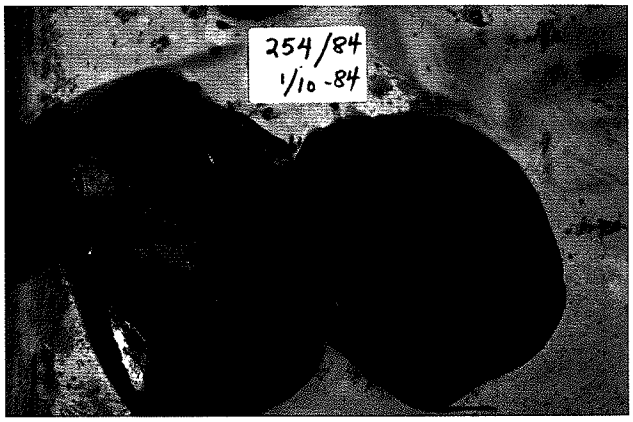

FIGURE 3 Swollen and soft liver from the animal shown in Figure 2; the color is paler than normal. (Photograph courtesy of Martha J. Ulvund, Sandnes, Norway.)

Copper deficiency has been described in cattle and sheep from many areas of the world, such as New Zealand, Australia, Northern Europe, and the United States. In Northern Europe, the problem is associated with grazing on peaty soils which often are also low in several other trace elements. The symptoms of copper deficiency are dominated by anemia and altered iron metabolism, bone disorders, diarrhea, and wasting, but also seen are infertility and depigmentation of wool and hair. In newborn lambs, dysfunctioning nerve development (swayback) can be seen when the ewe has been fed insufficient amounts of copper during the gestational period, when the central nervous system of

the fetus develops. Swayback can also be seen in goats but rarely, as goats appear to be less sensitive to this type of deficiency. Cattle can sometimes show cardiovascular disorders (falling disease) in cases of copper deficiency, with sudden death after excitement or physical activity.

1. Chronic Intoxication

Chronic copper toxicity seen in grazing ruminants is very often due to very low molybdenum and sulfate intake. A suitable ratio between the content of copper and molybdenum in the feed is 1–2 to 1–4. Sheep and calves are more sensitive to this intoxication than adult cattle and goats. The excessive copper is bound to metallothioneins and initially accumulated in the liver. Symptoms of chronic copper intoxication are seen only when the animal is stressed by pregnancy and delivery, transportation, infection, or other disease. The stress induces a massive release of copper from metallothioneins in the liver that initiates a hemolytic crisis, with erythrocyte disruption and secondary liver and kidney damage. Only at this stage is the concentration of copper in blood elevated. Often, affected animals do not show any symptoms but are suddenly found dead. If an animal survives the acute hemolytic crisis, jaundice and symptoms of liver and kidney failure will be seen. A typical postmortem picture includes a discolored carcass and kidneys. If chronic copper intoxication is suspected in a flock of sheep, supplementation with molybdenum and sulfate could be used to bind excessive copper and facilitate excretion. In areas with known high levels of copper in feeds, special boluses containing molybdenum are placed in the rumen of grazing sheep and cattle to prevent chronic copper toxicosis. Goats are less sensitive and will seldom show chronic copper toxicosis unless the copper intake is very high or the molybdenum and sulfate intake is very low.

G. Zinc

Zinc is vital to a very large number of important enzymes, and inadequate amounts of zinc in feeds will produce many different effects on animals. Apart from the interactions shown in Table I, the intestinal uptake of zinc will decrease if feed levels of phytate are high or if clay substances are ingested. Clinical apparent zinc deficiency has been reported in various parts of the world (*e.g.*, New Zealand, Australia, northwestern Europe). Early and very obvious signs are skin lesions (parakeratosis and hair loss), seen both in pigs and cattle

FIGURE 4 Severe zinc deficiency in a dairy cow causing parakeratosis and pronounced wrinkling of the neck skin.

(see Figure 4). Reduced appetite and retarded growth rate are other signs of deficiency, as are vomiting and scouring in pigs. In calves, a stiff gait and swelling of joints are seen as a result of disturbances in bone mineralization. This effect on bone metabolism is potentiated by a high calcium intake, which is often seen in young growing animals (see Table I).

In the Holstein–Friesian breed of cattle, an autosomal recessive trait has been described that interferes with intestinal absorption of zinc. In this condition, which parallels *acrodermatitis enterohepatica* in humans, affected calves show signs of zinc deficiency even though the feed intake of zinc is adequate.

H. Arsenic

Chronic arsenic poisoning is found in humans and animals in several parts of the world (*e.g.*, Bangladesh, Argentina, Mexico, and the United States). In many cases, water from deep wells with high concentrations of arsenic is responsible for the toxic effects (see also Chapter 11, this volume); however, the use of arsenic compounds in herbicides, anthelmintics, insecticides, and rodenticides presents a greater risk for accidental or inadvertent exposure of animals to toxic amounts of arsenic. The symptoms described in cattle with chronic arsenic toxicity include diarrhea with weight loss, inflammation of the eyes and upper respiratory tract, gait incoordination, and changes in hair coat. More acute cases of arsenic intoxication are rapidly lethal.

I. Selenium

Diseases caused by a high selenium intake have been recognized for several hundred years in some selenium-rich areas of the world. Diseases caused by selenium deficiency are also well known, although selenium was one of the last elements to be recognized as an essential trace element, in 1957 (see also Chapter 15, this volume).

1. Selenium Deficiency

Problems associated with a low intake of selenium were recognized much later than the toxic effects of an excess of this element; however, several areas in New Zealand, China, Finland, Sweden, and North America do have insufficient selenium levels in their native feeds. Such a deficiency seems to be related to the growth rate of animals, as young, fast-growing animals such as piglets, foals, lambs, and calves are more sensitive to a low intake of selenium. The selenium-containing enzyme glutathione peroxidase (GSH-Px) has a cytoplasmic localization and acts together with fat-soluble vitamin E, which has a membrane localization in the cell. In fresh feeds, the supply of vitamin E is high but during storage the content decreases; therefore, in situations where stored feeds are used, it is especially important to ensure that the selenium requirements are met. Normally, GSH-Px and vitamin E will detoxify the free radicals produced by the continuous oxidative metabolism present in all cells of an animal. If feeds high in polyunsaturated fatty acids or other oxidative compounds are utilized, the nutritional requirements for selenium will be higher, especially if the feed has been stored for a long time. In pigs, liver degeneration and necrosis are prominent signs, but muscular degeneration is also seen in both skeletal and cardiac muscles. Muscular pathology, often precipitated by even minor physical activity, is the dominating symptom in other species and causes paralysis and acute heart failure. In many cases, the young animals are found dead in the pasture or in their boxes. The typical postmortem picture in these cases features degeneration of muscular tissue, which looks like fish meat. Similar changes can be seen at autopsy in skeletal muscles from slaughtered paralytic animals.

2. Acute Selenium Toxicity and Blind Staggers

If large quantities of selenium are ingested, an acute form of intoxication, called *blind staggers*, can be seen for which blindness and other symptoms from the nervous system are prominent. Other symptoms include diarrhea and prostration. Affected animals often die within hours. Animals with acute intoxication also develop a garlic-like breath odor due to the formation of volatile methylated selenium compounds. This type of acute intoxication can be seen in areas throughout the world where seleniferous plants accumulate selenium from the selenium-rich soil (*e.g.*, Australia, China, North America, Russia, and Western Europe). Normally, grazing animals avoid these plants, but when a shortage of feed occurs the animals will graze on these plants and become intoxicated. If smaller amounts of selenium are ingested, the neurological symptoms are more prominent and, in addition to blindness, paralysis, respiratory problems, abdominal pain, and other signs of pain such as grinding of the teeth and salivating will be seen. Eventually the animals die due to starvation or respiratory failure. Both the blindness and the locomotor problems contribute to the inability to graze and meet the metabolic needs of the sick animal.

3. Chronic Selenium Toxicity and Alkali Disease

Around 1295, in his travels in western China, Marco Polo described what is most probably chronic selenium intoxication in horses. Animals eating certain plants that accumulated selenium showed dramatic changes, such as loss of hoofs (exungulation) and dermatological changes. Similar toxic effects were later described in North America when horses in the U.S. Cavalry were affected. It is even claimed by some that the outcome of the battle at Little Bighorn was determined by the ingestion of seleniferous plants by the horses in General Custer's squadrons which made them sick and unfit for the ensuing battle. Cattle brought by settlers who came to the Great Plains also showed signs of selenosis. These farmers associated the disease with the high salt content of the water and alkali seeps in the area and named the problem alkali disease. It appears, however, that certain seleniferous plants are necessary for the appearance of alkali disease. Such plants can accumulate selenium several hundredfold in their tissues compared to the soil concentration. Seleniferous plants are also found in limited areas of India, Israel, Central Europe, and South America, where chronic selenosis is observed. In other areas of the world, such as Hawaii and Costa Rica, the volcanic soil is rich in selenium but no seleniferous plants grow, and alkali disease is not seen.

J. Molybdenum

1. Deficiency

The biochemical roles of molybdenum-containing enzymes vary according to the different valence states

(+4, +5, or +6) attainable for this element. Deficiencies caused by low molybdenum intake are seen in experimental situations but are rare under natural conditions. The nutritional requirement in ruminants is estimated to be <0.1 mg/kg feed (Mertz, 1987). The intricate interrelationships among molybdenum, copper, and sulfate make it difficult, however, to give reliable figures for molybdenum requirements and adverse effects in various animal species (see Section III.J.2). It has been suggested, though, that a molybdenum deficiency is the cause of the high incidence of urinary xanthine calculi in New Zealand sheep grazing on pasture low in molybdenum due to the resulting low activity of the molybdenum-containing enzyme xanthine oxidase. Other situations where molybdenum deficiencies have been suspected to occur spontaneously involve poultry, but these problems have not responded to simple molybdenum supplementation because the etiology is more complex. Most probably the earlier mentioned interactions among molybdenum, copper, and sulfate are involved, but other transition elements may also be involved as contributing factors in these cases.

2. *Intoxication*

The effects of excessive molybdenum intake (known collectively as molybdenosis) are closely linked to copper deficiency, and most of the symptoms seen in molybdenosis are linked to the decreased activity of copper-containing enzymes. This is especially true in ruminants, where the balance between these two elements and sulfur in the form of sulfate or sulfur-containing amino acids is very important but often difficult to estimate from analytical data on feed composition. The chemical reason for this interaction is the formation of oxythiomolybdate and tetrathiomolybdate (TTM) in the rumen. The TTM will react with copper and other elements in the gastrointestinal tract, making these elements unavailable for absorption. TTM will also be absorbed from the gut to the blood and distributed to various tissues in the body where it binds copper in enzymes and other proteins, thus rendering them dysfunctional. Cattle are most susceptible to molybdenosis, especially dairy cows and young animals. Sheep and goats are less sensitive, and horses as well as swine appear insensitive to high intakes of molybdenum. In the young, growing foal, however, the occurrence of rickets has been reported when the mare has been kept on high-molybdenum pasture. Defective bone metabolism with osteoporosis and joint abnormalities have also been reported as a prominent symptom in molybdenotic cattle and sheep.

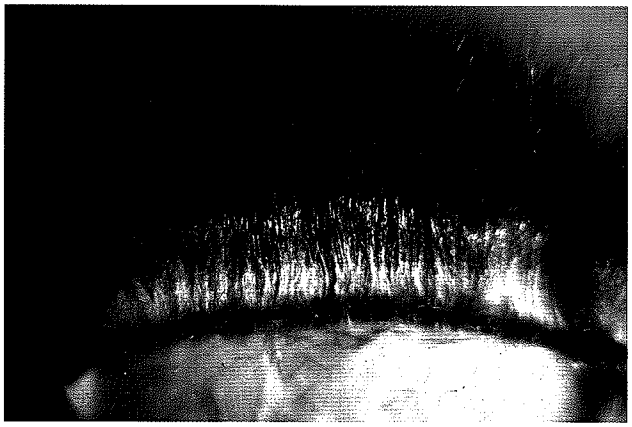

FIGURE 5 Discoloration of the black wool in a sheep suffering from molybdenosis.

Severe molybdenosis in cattle is widespread in the world. Plant uptake of molybdenum is favored by soil with a neutral or high pH. This problem has been known for a long time in England, where it is called *teart*, and in New Zealand, where the problem is known as *peat scours*. When cattle are put on pasture high in molybdenum, after only a few days they may exhibit typical signs of molybdenosis, such as profuse scouring and a harsh and discolored coat (see Figure 5). In milder cases, the diarrhea is less severe and the animals will recover rapidly if put on pasture with low molybdenum content. Less obvious effects are seen with regard to reproduction and thyroid function in cattle, for which a direct effect of molybdenum on the endocrine regulation in the hypothalamus is suspected. Anemia is also seen in cattle and sheep due to decreased hemoglobin synthesis, because the copper-containing enzyme ceruloplasmin is needed for the incorporation of iron into the heme molecule.

3. *Molybdenosis in Moose*

An example of the complexity of diagnosing trace element imbalances in animals, especially wild animals, is the occurrence of molybdenosis in moose (*Alces alces* L.) in an area in southwest Sweden (Älvsborg county) beginning around 1985 (Frank, 1998; Frank *et al.*, 2000). Affected animals that were found alive displayed a number of symptoms, including behavioral disturbances with apathy and pathological locomotion, loss of appetite, diarrhea, emaciation, discoloration and loss of hair, and opacities in the cornea and lens of one or both eyes. Postmortem examinations revealed edema, hyperemia, hemorrhage, and erosive lesions in the mucosa of the gastrointestinal tract. The heart was dilated and flabby, and myocardial lesions were seen macroscopi-

cally. Microscopic studies of different tissues showed pronounced hemosiderosis in the liver and spleen. Often, an animal showed some but not all of these symptoms or postmortem signs, making it difficult to classify a specific individual as a victim of this particular disease.

The gastrointestinal changes indicated a viral etiology of the disease, but other findings did not support this, and still no virus had been detected that could be responsible for the disease. It was suggested that starvation due to overpopulation or high age in the local moose population could account for the disease. Some of the chemical findings in samples from sick animals, however, were not compatible with starvation and lack of nutrients, energy, minerals, or trace elements. An indication of the probable etiology was found in measurements of trace elements in livers and kidneys from yearling moose sampled all over Sweden during the normal hunting periods in 1982, 1988, 1992, and 1994. These results showed that from 1982 (before the outbreak of the disease) to 1994 the hepatic concentration of selenium and especially molybdenum increased in the affected area, whereas the levels of copper, cadmium, and some other elements decreased in the livers of these young animals. These results were different from those for neighboring counties during the same period.

A plausible explanation for this discrepancy is the fact that the Älvsborg county was heavily limed to counteract the effects of acid rain, which was damaging the local forest and aquatic ecosystems. An increase in soil pH after liming increases the availability of molybdenum and selenium but decreases the availability of other metallic trace elements. The majority of symptoms and pathological signs found in the moose can be explained, then, by decreased activity of copper-containing enzymes such as tyrosinase, ceruloplasmin, superoxide dismutase, lysyloxidase, diaminoxidase, and methioninsyntase. Specific analysis of the copper enzyme cytochrome *c* oxidase in myocardial tissue showed lower activity in sick animals than in healthy controls. Determinations of the pancreatic hormone insulin in blood plasma from diseased moose showed concentrations about double those of apparently healthy animals, and still there was evidence of persistent hyperglycemia in these animals, as higher concentrations of furosine and pentosidine were found in kidney tissue compared to the levels determined in healthy animals. Furosine, pentosidine, and some other compounds are formed by nonenzymatic glucation of tissue proteins in the presence of high levels of blood glucose. The hyperinsulinemia and persistent hyperglycemia observed in the moose are similar to non-insulin-dependent diabetes (NIDD, or type 2 diabetes) often seen in humans, especially the elderly.

Some other endocrine disruptions could be suspected, because the direct effects of TTM on the hypothalamus have been demonstrated in experimental animals. Decreased reproductive capacity was suspected but difficult to detect in moose in the field; however, lowered thyroxin levels were measured in blood samples from the wild, free-living moose, which supported the idea of a central endocrine disruption. Similar pathological effects affecting central endocrine functions have recently been reported from clinical and experimental studies in sheep with chronic molybdenosis (Haywood *et al.*, 2004). Similar molybdenum-induced copper deficiency problems were suspected earlier and reported in moose (*Alces alces gigas*) in Alaska (Kubota, 1974; Flynn *et al.*, 1977) and in Grant's gazelle (*Gazelle granti*) in the Rift Valley in Kenya (Hedger *et al.*, 1964). The diagnostic biochemical investigations were, however, not complete in these earlier cases.

K. Iodine

Goiter, enlargement of the thyroid gland due to iodine deficiency, was described in ancient Egypt in humans and animals. It is still probably the most widespread trace element deficiency in world animal husbandry. Typical deficient areas are inland and mountain areas, such as the inner parts of Siberia, Africa, and South America; the slopes of the Himalayas, Alpine valleys, the Pyrenees; and the Andes, where wind and rain carry only limited amounts of iodine from the oceans. Some lowland and coastal areas also have soil in which leaching has caused iodine depletion (see also Chapter 16, this volume). The most sensitive and typical signs of iodine deficiency are enlargement of the thyroid gland and changes in the microscopic morphology (see Figure 6). Lambs and calves are often born with severe goiter when their mothers have been fed insufficient iodine during gestation. In severe cases, these newborn animals can suffocate shortly after birth due to the pressure of the enlarged thyroid gland on the trachea. If they survive the first critical period, they are often so weak that they have severe problems getting up and standing to suckle their mothers to get the antibodies and nutrients vital to the start of life.

In adult animals, iodine deficiency causes a generally depressed metabolism due to insufficient production of the thyroid hormone thyroxin. Lethargy, increased fat deposits, and impaired reproduction are other observed

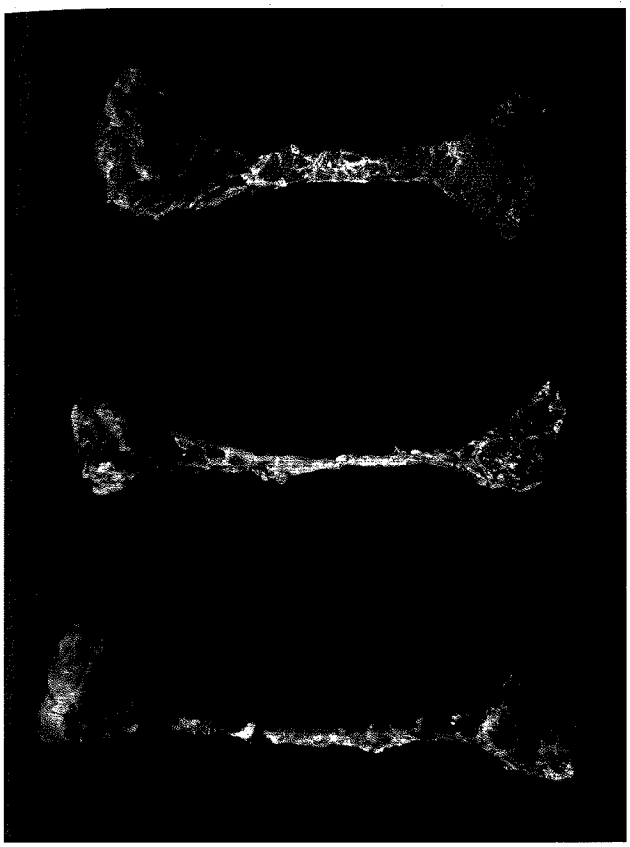

FIGURE 6 Thyroid glands from three steers fed different amounts of iodine. The gland in the middle is normal sized and comes from an animal with adequate iodine supply. The other two show different degrees of goiter. The upper gland shows a minor increase in size and the lower gland shows a moderate increase due to insufficient iodine intake.

effects. In breeding animals, irregular and suppressed estrous cycles are early signs of iodine deficiency, and the reduced fertility will have obvious effects on the economy of the farmer. If animals get pregnant, the fetus can suffer developmental problems that result in fetal death, abortion, or stillbirth.

Endemic iodine deficiency can be further aggravated by at least two factors operating in modern agriculture. First, plants containing goitrogenic substances are common in both cultivated land and growing on natural pasture. These goitrogenic substances are chemically glucosinolates (*e.g.*, isothiocyanates, thiocyanates, nitriles, and oxazolidinethiones), which block the uptake of iodine in the thyroid. Glucosinolates are present in the green parts and seeds of commonly cultivated crops of Cruciferae plants, such as various types of kale and rape. In temperate zones of the world, cultivation of these glucosinolate-containing plants is common because they contribute valuable proteins to locally produced animal feeds. A second important factor contributing to iodine deficiency is the increasing interest in organic farming, especially in North America and Western Europe, where the limited use of supplements decreases the iodine supply in deficient areas.

Both of these problems can be easily alleviated by using appropriate supplements rich in iodine. The most common remedy is the use of iodized salt (NaCl) as a salt lick or a component of mineral supplements given to the animals. An important detail regarding iodine supplementation via salt licks or otherwise is that KI, often used as an inexpensive remedy, evaporates even at ambient temperature during storage; therefore, old salt licks may not contain the necessary amount of iodine supplementation. It is particularly important to use iodine supplementation for dairy production, as milk and other diary products are a major iodine source for humans in large parts of the world, especially in areas where marine products such as kelp, fish, or shellfish are not consumed regularly.

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