Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

General Systemic States

4

Several systemic states contribute to the effects of many diseases. Because these systemic states are common to many diseases they are considered here as a group to avoid unnecessary repetition. Hyperthermia, fever, septicemia, toxemia, and the acute phase response are closely related in their effects, and an appreciation of them is necessary if they are not to be overlooked in the efforts to eliminate the causative agent. Likewise, hypovolemic, hemorrhagic, maldistributive, and obstructive shock are best examined together. Anaphylactic shock is covered in Chapter 11. This chapter will also briefly introduce pain and stress as it relates to disease. Syndromes of poor performance, decreased appetite, and sudden and unexpected death are also covered.

Hypothermia, Hyperthermia, and Fever

Hypothermia, hyperthermia, and fever—characterized by physiologically significant changes in core body temperature—are presented here together, along with an introduction to thermoregulation mechanisms of the body.

BODY TEMPERATURE

Farm animals maintain a relatively constant body core temperature (**homeothermy**) during extreme ranges of thermal environments. This **homeothermic** state is achieved by physiologic and behavioral mechanisms that modify either rates of heat loss from the body or the rate at which heat is produced by the metabolism of feed or body energy reserves. For the body temperature to remain constant in changing thermal environments, the rate of heat loss must equal the rate of heat gain. The body temperature is a reflection of the balance between **heat gain** from the environment (radiation, conduction, and convection) or caused by metabolic activity (maintenance, exercise, growth, lactation, gestation, and feeding) and **heat loss** to the environment (radiation, conduction, convection, and evaporation) or caused by metabolic activity (milk removal, fecal elimination, and urinary elimination). Absorption of heat from the environment occurs when the external temperature rises above that of the body.

HEAT PRODUCTION

Heat production occurs as a result of metabolic activity and the digestion of feed, muscular movement, and the maintenance of muscle tone. **Shivering thermogenesis** is a response to sudden exposure to cold and is a major contributor to enhanced heat production. **Nonshivering thermogenesis** is also induced by exposure to cold and is the mechanism by which heat is produced by the calorigenic effect of epinephrine and norepinephrine. In the neonate, heat is produced by the metabolism of brown adipose tissue, which is present in newborn farm animals and is a particularly important mechanism of heat production to prevent neonatal hypothermia.

HEAT LOSS

Heat is transferred to or from an animal by the four standard physical phenomena of **convection**, **conduction, radiation,** and **evaporation**. Convection is a transfer of heat between two media at different temperatures such as the coat surface and the air. As such, convective heat transfer depends on the temperature gradient between the coat surface and air, the surface area, and the air speed over the surface. Conduction is the transfer of heat between two media that are in direct contact such as the skin and water. Radiation is the absorption or emission of electromagnetic radiation at the body surface and depends on the skin surface temperature and area. Evaporative heat transfer is a process by which heat is lost by the evaporation of water

and is dependent on the water vapor pressure gradient between the epithelial surface and the environment and the air speed over the surface.

Evaporation occurs by sweating, salivation, and respiration, with the relative importance of each varying between species. Losses by evaporation of moisture vary between species depending on the development of the sweat gland system and are less important in animals than in humans, beginning only at relatively high body temperatures. Horses sweat profusely, but in pigs, sheep, goats, New World camelids, and European cattle sweating cannot be considered to be an effective mechanism of evaporative heat loss. In zebu cattle the increased density of cutaneous sweat glands suggests that sweating may be more important. Profuse salivation and exaggerated respiration, including mouth breathing, are important mechanisms in the dissipation of excess body heat in animals. The tidal volume is decreased and the respiratory rate is increased at high body temperatures so that heat is lost but alkalemia caused by respiratory alkalosis is avoided.

BALANCE BETWEEN HEAT LOSS AND GAIN

The balance between heat gain and heat loss is controlled by the heat-regulating functions of the hypothalamus. The afferent impulses derive from peripheral hot and cold receptors and the temperature of the blood flowing through the hypothalamus. The efferent impulses control respiratory center activity, the caliber of skin blood vessels, sweat gland activity, and muscle tone. Heat storage occurs and the body temperature rises when there is a decrease in rate and depth of respiration, constriction of skin blood vessels, cessation of perspiration, and increased muscle tone. Heat loss occurs when these functions are reversed. These physiologic changes occur in, and are the basis of, the increment and decrement stages of fever.

BREED DIFFERENCES

Differences exist between breeds and races of cattle in coat and skin characters that affect heat absorption from solar radiation and heat loss by evaporative cooling; differences also exist in the metabolic rate, which influences the basic heat load. Interest in this subject has been aroused by the demands for classes of animal capable of high production in the developing countries of the tropical zone. Detailed information on the physiologic effects of, and the mechanisms of adaptation to, high environmental temperatures are therefore available elsewhere but are not dealt with in this book because they appear to be minimally related to the development of clinical illness.

Hypothermia, caused by exposure to low environmental temperatures, and **hyperthermia** (**heat stroke** or **heat exhaustion**), caused by exposure to high environmental temperatures, are the major abnormalities of body temperature associated with extremes of environmental temperatures. **Anhidrosis**, occurring primarily in horses in hot humid climates and associated with the inability to sweat, is described in Chapter 16.

HYPOTHERMIA

Hypothermia is a lower than normal body temperature, which occurs when **excess heat is lost** or **insufficient heat is produced**. Neonatal hypothermia is a major cause of morbidity and mortality in newborn farm animals within the first few days of life. Cold injury and frostbite are presented under that heading in Chapter 4.

ETIOLOGY

Excessive Loss of Heat

Exposure to excessively cold air temperatures causes heat loss if increased metabolic activity, shivering and sustained muscular contraction, and peripheral vasoconstriction are unable to compensate.

Insufficient Heat Production

Insufficient body reserves of energy and insufficient feed intake result in insufficient heat production. Hypothermia also occurs secondary to many diseases in which there may be a decrease in the ability to shiver and skeletal muscle contraction associated with decreased cardiac output, decreased peripheral perfusion, and shock. Examples include parturient paresis, acute ruminal acidosis (grain overload), during anesthesia and sedation, and the reduction of metabolic activity that occurs in the terminal stages of many diseases. A sudden fall in body temperature in a previously febrile animal, the so-called premortal fall, is an unfavorable prognostic sign.

Combination of Excessive Heat Loss and Insufficient Heat Production

A combination of excessive heat loss and insufficient heat production is often the cause of hypothermia. Insufficient energy intake or starvation of newborn farm animals in a cold environment can be a major cause of hypothermia. This may not occur under the same environmental conditions if the animals receive an adequate energy intake. Fatal hypothermia may also occur in other circumstances such as in certain breeds of pig (pot-bellied) following general anesthesia or sedation with higher doses of azaperone. Mature pot-bellied pigs deprived of feed and kept outdoors during cooler months of the year may develop hypothermia, which would not normally occur in these conditions if the pigs were receiving adequate food.

EPIDEMIOLOGY

Neonatal Hypothermia

Newborn farm animals are prone to hypothermia in cool environments, and hypothermia is a major cause of neonatal mortality. Neonates cannot maintain their core body temperatures at normal values during the first few hours after birth under cold environmental conditions. Hypothermia and environmental thermoregulatory interactions are of particular importance in piglets and lambs because of their surface to volume ratio but are also relevant in calves and sick foals.

At birth, the neonatal ruminant moves from a very stable thermal environment, of similar temperature to its core body temperature, to a variable and unstable thermal environment that is 10 to 50°C colder than its core temperature. The coat is wet with placental fluids, and energy loss is increased by evaporation and the low insulative value of a wet coat. The newborn calf becomes hypothermic in the first 6 hours after birth and only limited tissue substrates are available as energy sources. Neonates also are exposed to a variety of environmental pathogens against which they have little specific immunity. Thus the neonatal period is one of the most critical to the survival of an animal, and during this period the morbidity and mortality can be high under adverse environmental conditions.

The continued emphasis in modern agriculture on the production of neonates throughout the year, including times of inclement weather and limited feed (late winter and early spring calving in beef herds in northern climates); the emphasis on short calving seasons; the use of high stocking densities; and the production of animals with high muscle growth potential, which may be associated with an increased incidence of dystocia resulting in decreased vitality of newborn animals at birth; all appear to combine to increase the incidence of mortality caused by hypothermia and related diseases of the neonate.

In lambs, more than 30% of deaths occur in the first few days of life, and mortalities may be greater than 10%, with more than half of the losses caused by hypothermia from either exposure or starvation. In calves, approximately 50% of deaths occur within 48 hours of birth, and most losses are either directly caused by, or follow, dystocial parturitions in which stillbirths and early postnatal mortality rates are about 20% compared with less than 5% in calves born without dystocia (eutocial).

Thermoregulation in Neonatal Farm Animals

Response to Cold Stress

Neonatal ruminants, compared with many **altricial** neonatal mammals, are **precocial** in their development, with well-developed thermoregulatory mechanisms that allow them to maintain homeothermy in many environments. Prolonged exposure to heat or cold induces hormonal and metabolic changes specific to each stress. This involves

secretion of glucocorticoid hormones and increased activity of the sympathetic nervous system augmented by increased secretion of catecholamines. The principal metabolic effect of these increases is greater availability and utilization of substrates (fat, glycogen, and protein) for catabolism, with increased production of heat.

Cold-Induced Thermogenesis

This is achieved by shivering thermogenesis in skeletal muscle tissue and nonshivering thermogenesis in brown adipose tissue. **Shivering thermogenesis** consists of involuntary, periodic contractions of skeletal muscle. Heat is produced during contraction of muscle bundles in skeletal muscle tissue that has increased in tone as well as in skeletal muscle contracting in overt tremors. Increased heat production in neonatal calves in the first several hours after birth can be significant when the animals first stand for 10 minutes; this effect is reproduced later when the calves are stronger and stand for longer periods. The principal site of cold-induced nonshivering thermogenesis in animals is brown adipose tissue, which is present in neonatal lambs, kids, and calves but not in piglets. In neonatal lambs, approximately 40% of the thermogenic response during summit metabolism is attributed to **nonshivering thermogenesis**, with the balance of about 60% attributed to shivering thermogenesis.

Control of Heat Loss

The insulative nature of the external hair coat and cutaneous tissues to resist nonevaporative heat loss during cold exposure is critical in maintaining homeothermy. Total thermal insulation is the sum of tissue insulation and external insulation.

Tissue Insulation. This is the resistance of cutaneous tissue to conductive heat loss from the body core to the skin surface. Tissue insulation is influenced by subcutaneous fat depth, which is minimal in neonates, and by vasoconstriction. Tissue insulation increases with age.

External Insulation. This is the thermal resistance of the hair coat and air interface to radiative, convective, and conductive heat losses from the skin surface to the environment. External insulation is a function of length and type of hair coat and the air interface. When exposed to dry, cold still air environmental conditions, external insulation as a proportion of total thermal insulation in neonatal calves ranges from 65% to 75%. Moisture and mud in the coat decrease the value of external insulation; wind and rain can also decrease external insulation.

The neonate's total thermal resistance to heat loss is a function of the physical properties of the skin and hair coat and the ability to induce vasoconstriction of cutaneous blood vessels and piloerection of the hair coat. Neonatal calves are remarkably cold tolerant in a dry, still air environment. The thermal demand of an outdoor cold environment is a function of **wind** and **precipitation** as well as **ambient temperature**.

Conductive heat loss is controlled by sympathetic regulation of blood vessels that supply cutaneous tissues, especially the ears and lower extremities. In response to cold, vessels constrict, peripheral blood flow diminishes, and heat transfer is limited. Vasoconstriction of cutaneous vessels during cold exposure occurs first in the ears, followed by the lower extremities, and then the skin surrounding the trunk. **Phasic vasodilation** in the skin of the ears and distal extremities at a point near freezing occurs by the sudden opening of arteriovenous anastomoses to permit **intermittent warming** (called the **hunting reaction**). Phasic vasodilation does not occur on the skin of the trunk.

Thermoregulating Mechanisms

Heat exchange between any homeotherm and the environment is the result of the following:

- Heat production by metabolism
- Insensible heat loss by evaporation of moisture from the respiratory tract and skin
- Sensible heat transfer by conduction, convection, and radiation

There is a range in the effective thermal environment, called the **thermoneutral zone**, over which an animal maintains body temperature with minimal metabolic effort. Within this zone, body temperature is maintained primarily by varying blood flow to the body surface, piloerection of the hair coat, and behavioral and postural changes. These responses adjust the physical processes of heat transfer to balance the body's heat production. The lower limit of the thermoneutral zone (the **lower critical temperature)** is the minimum temperature that an animal can tolerate without actually increasing its rate of metabolic heat production to maintain thermal balance (Fig. 4-1). The lower critical temperature of an animal is determined by the animal's ability to resist heat loss (thermal insulation) and the animal's resting, thermoneutral heat production through metabolism. An increase in thermal insulation or an increase in thermoneutral metabolic rate decreases the lower critical temperature, improving cold tolerance.

Estimates of lower critical temperatures of calves during the first day of life are not available, but some estimates for older calves include 13°C for 2-day-old Ayrshire calves and 8 to 10°C for dairy and crossbred calves at 1 to 8 weeks of age. In lambs, estimates are 37 and 32°C for light (2-kg) and heavy (5-kg) birth weights immediately after birth while still wet with amniotic fluid, and 31 and 22°C when these lambs are more than 1 day old.

The thermoneutral zone for lactating dairy cows is 5 to 25°C. Adult cattle are very cold tolerant, with lower critical temperatures of 0°C for 1-month-old calves, −16 to −37°C for lactating dairy cows depending on their level of milk production, and −36°C for finishing feedlot cattle. At the lower border of the cold zone is the **cold lethal limit,** the ambient temperature below which the calf is unable to generate sufficient heat to offset heat losses required to maintain thermal balance, and at which hypothermia begins. Prolonged periods of exposure below the cold lethal limit will result in death. The cold lethal limit also can be defined as the ambient temperature below which heat loss exceeds the animal's summit or maximal metabolism. Because published values for lower critical temperatures assume **still air**, **dry clean coats**, **standard radiation,** and a **standing animal given a maintenance level of feeding**, there continue to be limitations to their use. Insulation of extremities decreases, and heat loss increases, at temperatures below freezing. Thus some lower critical temperatures for cattle are too low, which means that neonates may be affected by cold temperatures not normally considered harmful. External insulation can change because of changes in air velocity and long-wave radiation. Behavioral changes of animals may occur to minimize heat loss. For example, animals may orient toward the wind to decrease their profile, and they may seek shelter, huddle, and change their posture. Solar radiation varies throughout the daylight hours depending on the quantity of cloud. Generally, radiation balance is positive in the day, whereas at night, when the skies are clear, the radiation balance is usually negative. Heat production varies with the time of day and time since the last meal and physical activity. Rain will often depress intake of feed and illness, hypothermia severely depresses feed intake, and cold stimulates intake.

Heat Production

Heat produced by metabolism varies directly with the level of feed intake, particularly in adult ruminants in which the heat increment produced by forestomach fermentation is considerable. The more an animal eats, the greater the heat increment of feeding, and this results in an increase in core temperature of up to 0.3°C in lactating dairy cows, compared with dry cows. Animals subjected to cold environmental temperatures will increase their feed intake if given the opportunity, with proportionate dry matter increases of up to 35% being typical. Heat is also generated from physical activity. When newborn calves stand for the first time and are able to stand for 10 minutes, the energy expenditure is increased proportionately 30 to 100%. As calves become stronger and are able to stand for more than 30 minutes, heat production increases by 40%.

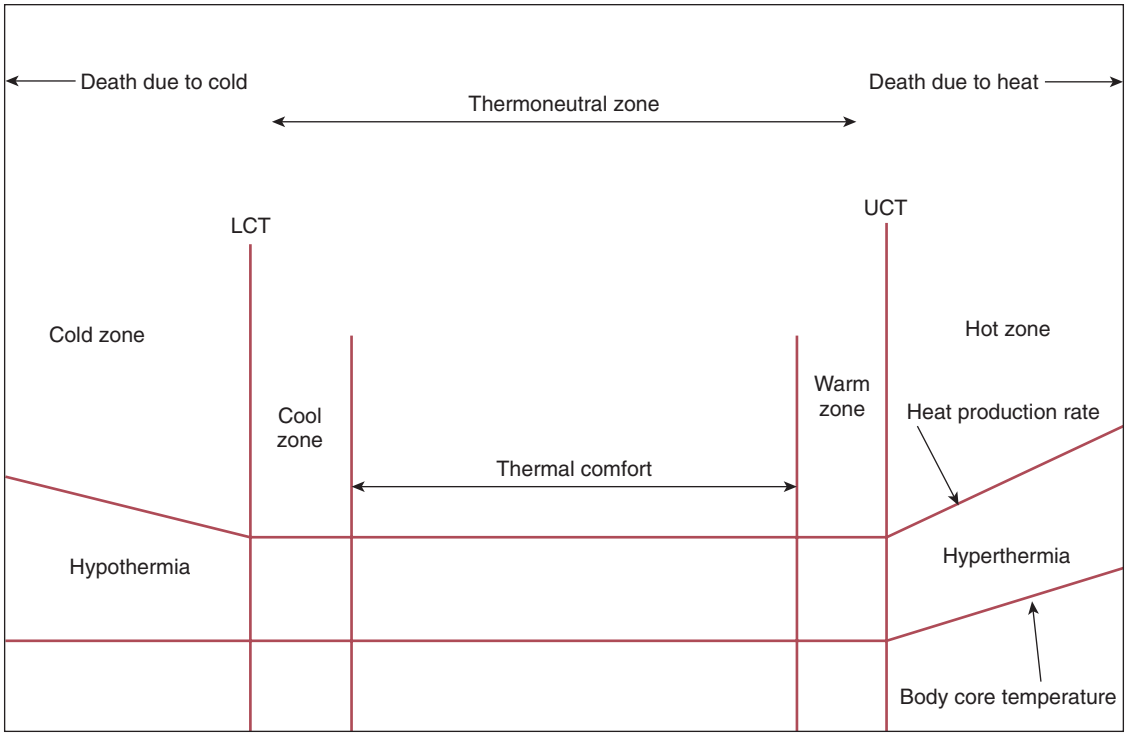

Fig. 4-1 Relationship between environmental temperature, heat production rate, and body core temperature in agricultural animals. *LCT,* lower critical temperature; *UCT,* upper critical temperature. (Adapted from Kadzere et al. *Livestock Prod Sci*, 2002; 77:59-91.)

Cold Thermogenesis

The major source of heat in cold thermogenesis, whether it is induced by either shivering thermogenesis or by nonshivering thermogenesis, is lipid. Glycogen is also important for maximum metabolic rates and for lipid metabolism. For the neonate, in the first 24 hours there is little digestion of colostral proteins and little catabolism of amino acids.

Shivering Thermogenesis. This is the most obvious sign of increased heat production of cold thermogenesis.

Nonshivering Thermogenesis. Functional brown adipose tissue is present in newborn calves, lambs, and kids, and its primary function is to generate heat by nonshivering thermogenesis. The release of norepinephrine during cold exposure in neonatal ruminants stimulates increased blood flow to brown adipose tissue. Thyroid hormones also have an essential role in regulating cold thermogenesis. Glucocorticoids are essential for cold thermogenesis through the mobilization of lipid and glycogen to supply energy substrates. Large deposits of brown adipose tissue are present in the abdominal cavity (perirenal), around large blood vessels, and in the inguinal and prescapular areas. In calves, brown fat may represent 20 g/kg body weight (BW) and in lambs from well-fed ewes, brown fat may represent 6g/kg BW. At parturition, marked changes occur in both the neonate's supply and demand for nutrients. In utero the fetal ruminant is provided with high levels of carbohydrate and low levels of fat, whereas after birth it is provided with colostrum high in fat and low in carbohydrate. Before colostrum is fed, the neonatal ruminant depends on mobilization of tissue glycogen and lipids to provide energy substrates for basal metabolism as well as thermogenesis in shivering muscle tissue and in brown adipose tissue. The major sources of energy substrates for thermogenesis in neonatal ruminants include glycogen and lipid in liver and muscle because protein catabolism is minimal during the early postnatal period.

Summit Metabolism. This is the maximal rate of metabolism that occurs in response to cold without a decline in body temperature. The time for which summit metabolism can be maintained is usually short, e.g., a few minutes in neonatal lambs. Summit metabolism is approximately five times the resting metabolic rate and is associated with increased sympathetic activity, development of metabolic acidosis, and increased plasma concentrations of glucose, glycerol, free fatty acids, and L-lactate. Prepartum hypoxia is likely associated with postpartum depression of sympathetic nervous activity and of thermogenic responses to cold.

Birth Weight and Summit Metabolism. The principal factor that determines an animal's resting, thermoneutral metabolism is body size. In newborn animals, thermoneutral metabolic rates and summit metabolic rates are proportional to their weight (W^1) rather than $W^{0.75}$, which means that summit metabolism per unit of W is similar for all neonates regardless of size, but lightweight animals have more surface area per unit of W than heavyweight neonates. Therefore lightweight neonates have a lower summit metabolic rate per unit of surface area and, consequently, lightweight neonates will be less cold tolerant than heavyweight neonates. Lightweight neonates therefore have a more difficult time maintaining thermal balance during cold stress because of a lower cold-induced thermogenic rate per unit of skin surface area than heavier animals. This, in part, explains the higher incidence of neonatal mortality in smaller piglets and lambs, and in smaller calves born to first-calf heifers, and even to mature cows.

Factors Affecting Cold Thermogenesis

Several factors affect the ability of the newborn calf to avoid hypothermia. Prompt activation of thermogenic mechanisms must occur immediately after birth when the demand for heat production is usually highest. The development of functional brown adipose tissue must occur in fetal life to enable calves to have maximal nonshivering thermogenesis during the early postnatal period. Most of the functional brown adipose tissue is deposited in late gestation in lambs and calves.

Ambient temperature and nutrition during pregnancy can affect cold thermogenesis of lambs. Maternal cold exposure by winter shearing of sheep increases lamb birth weight and the amount of perirenal adipose tissue independent of changes in prepartum feed intake. Thus newborn lambs from cold-exposed ewes are more cold tolerant. Acute cold exposure during late gestation increases glucose supply to the fetus, which stimulates insulin secretion, which in turn promotes fetal growth; recruitment and proliferation of brown adipose tissue occurs to enhance cold tolerance of the newborn lamb. There is some evidence that prepartum exposure of pregnant cows to a cold environment may result in heavier calf weights.

Malnutrition of the Dam During Late Gestation. This can adversely affect neonatal calf survival. Prepartum energy restriction beginning at day 90 of gestation of ewes can also reduce the proportional weight of perirenal adipose tissue and reduce the nonshivering ability of newborn lambs. The influence of prepartum nutritional restriction on cold thermogenesis in newborn calves is unknown, but prepartum protein restriction during the last trimester reduced thermoneutral thermogenic rates by 12% without affecting birth weights, resulting in an estimated increase in the lower critical temperature. Maternal malnutrition also adversely affects the availability of energy substrates required by the neonate for cold thermogenesis. Nutritional restriction of pregnant ewes reduces total body lipid in fetal lambs but not muscle or liver glycogen. Thus nutritional restriction of the fetus impairs cold tolerance of the neonate by reducing body substrate reserves available for cold thermogenesis and reduces nonshivering thermogenic capabilities.

European or British breeds of cattle are also more cold tolerant and more adaptable to temperate climates, whereas zebu cattle are more adaptable to subtropical climates because of greater heat tolerance. The lack of cold tolerance of the newborn *Bos indicus* calf is associated with a higher mortality rate in purebred Brahman herds in the United States. These calves are less cold tolerant and more susceptible to the weak calf syndrome.

Postnatal Changes in Cold Thermogenesis

As calves and lambs grow during the early postnatal period, heat loss per unit of body weight declines because of improved thermal insulation and a decrease in the ratio of skin surface area to body weight. Nonshivering thermogenesis decreases during the first month of age in lambs and calves, which is associated with a decrease in summit metabolism. This coincides with the conversion of brown adipose tissue to white adipose tissue by about 10 days after birth. Postnatal exposure to cold delays the disappearance of brown adipose tissue, which enhances cold tolerance of the lamb and calf by delaying the normal decline in nonshivering thermogenesis.

Risk Factors for Neonatal Hypothermia

Calves

Beef calves born outdoors during cold weather are susceptible to hypothermia. Wind, rain, and snow decrease the level of insulation and increase the lower critical temperature. Dairy calves born indoors are not usually exposed to cold environments that cause hypothermia; however, hypothermia has been recognized in dairy calves reared outdoors in cold climates and in some calves affected with enteritis.

Dystocia can affect cold thermogenesis. During a normal delivery, fetal hypoxemia may occur, causing anaerobic glycolysis, the production of lactic acid, and a mixed respiratory–metabolic acidosis that the calf can usually compensate for within hours after birth. In prolonged dystocia, a metabolic acidosis may occur, which will inhibit nonshivering thermogenesis and impair cold tolerance immediately after birth. Dystocia may result in a weak calf that has weak teat-seeking activity, a poor suck reflex, and a poor appetite for colostrum, resulting in colostrum deprivation and hypogammaglobulinemia.

Colostrum supplies **passive immunity** to the calf and the **nutrients** to meet energy demands during the immediate postpartum period. For the calf to maintain thermal balance during cold exposure, it is critical that the calf ingests colostrum early to provide enough energy reserves to sustain cold thermogenesis. Thus it is vitally important that newborn calves consume adequate colostrum to ensure adequate passive immunity and to aid in the maintenance of thermal stability during the early postnatal period when rates of heat loss are greatest. The limited availability of energy substrates from body reserves also requires that adequate quantities of colostrum are ingested during long periods of cold exposure, especially in neonatal calves at higher risk for developing hypothermia. The thermoneutral maintenance requirements of a 40-kg calf can be met with about 2.4 L of cow colostrum; an additional 125 mL of colostrum is required to supply the energy requirements for every 1°C decrease in effective environmental temperature below the lower critical temperature.

Young calves to be reared for veal are usually transported for 1 to 2 days during the first 2 weeks of life. These calves are prone to cold stress because they are very young and are being fed at a low level directly after transport. Veal calves arriving in a veal calf unit are dependent on body reserves to meet their energy requirement because of limited feed allowances, and ambient temperatures should not be below 14°C immediately after arrival to prevent extra mobilization of energy reserves. The thermal requirements of these calves are higher during standing than during lying, and the provision of bedding that stimulates lying will have a positive effect on thermal requirements.

Lambs

Cold exposure resulting in hypothermia is a primary cause of lamb mortality, as seen when large numbers of lambs die during or soon after periods of a few hours of low temperatures (<5°C) with wind and rain, or after prolonged rain. Deaths in "bad" weather cannot necessarily be attributed with certainty to exposure as a primary cause, because lambs debilitated for other reasons, such as starvation, are highly susceptible to chilling and conditions such as low birth weight, birth injury, and sparse hair coat, which all predispose lambs to cold exposure. Under less harsh conditions such lambs may survive.

Colostrum intake is also critical in lambs. Under field conditions in the United Kingdom it is estimated that lambs require 180 to 210 mL colostrum per kilogram BW in the first 18 hours after birth to provide sufficient energy substrate for heat production. This colostral requirement exceeds that for adequate transfer of colostral immunoglobulins. The thermoneutral and summit metabolic rates are much higher in lambs fed colostrum compared with unfed lambs at 4 to 5 hours of age. The increased metabolic rates are attributed to increased availability of energy substrates from colostrum: plasma concentrations of glucose and nonesterified free fatty acids are doubled from birth to 4 hours of age in colostrum-fed lambs but remain unchanged in colostrum-deprived lambs.

The heaviest losses in Australian sheep flocks, which occur in the form of *outbreaks* when the weather is very bad, are caused by hypothermia. The high mortality rates in newborn lambs caused by the effects of cold exposure and starvation occur because many of these lambs are born during the late winter and early spring, when adverse conditions are most likely to occur. This is also true in the northern United States and Canada. The lambs are often born outdoors in unprotected pens designed to accommodate a large number of ewes. Under these circumstances, the lambs may be severely cold stressed because the ambient air temperatures outside and within the lambing sheds are often 15°C or less, which is considerably lower than the critical temperatures described for heavyweight (32°C) and lightweight (37°C) lambs. Cold-stressed lambs often become hypothermic because of excessive heat loss from exposure to inclement weather and because of heat production caused by severe hypoxia at birth or to starvation. Factors that further increase the susceptibility of lambs to hypothermia include the following:

- Lambs from ewes in poor condition
- Lambs from young or aged ewes
- Lambs from multiple births
- Lambs from dystocias
- Lambs with a low birth weight or born prematurely
- Breed differences in susceptibility to cold, and genetic differences within a breed
- Length of the birth coat
- Wetting of the birth coat
- Exposure to wind

The effects of experimental cold stress (0°C and −10°C) on pregnant ewes during the last weeks of gestation and their lambs of up to 3 days of age have been examined. Generally, ewes were unaffected by treatment. Cold-induced changes in lambs included physical weakness, depression, and poor nursing response. Serum concentrations of glucose and insulin decreased and cortisol increased. The mortality rate was 40% in stressed lambs and 10% in lambs kept at the warmer temperatures. Cold-exposed lambs had reduced amounts of adipose tissue in perirenal areas and extensive subcutaneous hemorrhages and edema in the distal portions of the thoracic and pelvic limbs.

Wetness of the fleece is a major factor in determining whether or not lambs become hypothermic. Wet lambs suffer a reduction in coat insulation, primarily as a result of reduced coat depths, but this effect is small compared with the increase in the evaporative heat loss that occurs as a result of wetting. Lambs exposed to experimental air movement from a fan produce more body heat than those in still air, and differences in resistance to cold stress between single and twin lambs are largely caused by the corresponding differences in body weight and coat depth.

The relative importance of environmental and maternal factors is not easy to determine. Lamb mortality is typically related to birth weight by a U-shaped curve, with an optimal birth weight for survival between 4.5 and 5.5 kg. Inclement weather kills many lambs, probably more than would otherwise die, but principally those that are at risk because of reduced vigor (dependent on poor preceding nutrition) or because of poor mothering (itself as dependent on poor nutrition of the ewe as on her inherited lack of mothering ability). The vigor of the lamb, principally manifested as *sucking drive*, is reduced by lack of reward, so that a vicious cycle is created if the ewe will not stand. Vigor is also greatly reduced by cold discomfort, giving inclement weather two points at which it influences lamb survival rates. The lamb dies of hypothermia and inanition.

Piglets

At birth, the newborn piglet experiences a sudden and dramatic 15 to 20°C decrease in its thermal environment. Because the newborn pig is poorly insulated, maintenance of homeothermia depends almost exclusively on its capacity to produce heat. Unlike most other mammals the newborn pig does not possess brown adipose tissue. Consequently, neonatal pigs are assumed to rely essentially on muscular thermogenesis for thermoregulatory purposes. Newborn pigs shiver vigorously from birth because it is the main heat-producing mechanism and the thermogenic efficiency of shivering increases during the first 5 days of life.

Thermoregulation in the newborn piglet is important in the first 2 days. Metabolic heat production and rectal temperature increase and the development of adequate thermal insulation helps to withstand the effects of a cold environment. Body reserves are important for the piglet to survive in the first few hours, and glycogen and fat reserves are used as major energy substrates for heat production within the first 12 to 24 hours. Thus ingestion of colostrum and a high ambient temperature in the first several days of life are crucial. Application of 0.5 to 1 kg of chopped straw on a daily basis combined with 2 kg for nest building when the sow was about to farrow decreased the percentage of stillbirths by 27% but increased the number of piglets that were crushed.[1] Coldness impairs the development of thermostability and induces hypothermia, which diminishes the vigor of the piglet and reduces colostrum intake and immunoglobulins.

Foals

Newborn foals that are premature, dysmature, or affected with neonatal maladjustment syndrome cannot maintain their rectal temperatures at normal values during the first few hours after birth under the environmental conditions usually encountered within foaling boxes in the United Kingdom. Their overall mean metabolic rate is about 25% below the mean value for recumbent healthy foals.

This difference in resting metabolic rate affects the lower critical temperature or the air temperature below which heat loss exceeds resting heat production. The lower critical temperature for healthy foals is estimated to be about 10°C and for sick foals is about 24°C. When wet with amniotic fluid, the lower critical temperature probably will be much higher. Covering these foals with rugs and providing thermal radiation using radiant heaters would increase the lower critical temperature.

Premature foals are the most compromised compared with dysmature and those with neonatal maladjustment syndrome. They have small body masses, the lowest rates of metabolism, and the lowest rectal temperature. Premature foals are also likely to be deficient in energy reserves and thermal insulation, in addition to immaturity of organ systems, which could limit further energy availability. **Colostrum intake** is also crucial to their survival.

Postshearing Hypothermia in Sheep

Cold, wet, and windy weather can cause high mortality caused by hypothermia in newly shorn sheep; a fall in body weight in the period immediately preceding shearing is a major risk factor for mortality. In outbreaks in Australia in January the mean temperature can be 10°C, with a high rainfall and high wind velocity, accounting for a **wind chill factor** (a function of temperatures, rain, and wind velocity). Other factors that increase heat loss include sunshine versus cloud and the depth of the wool cover. The speed of the wind at the location of the animals varies greatly depending on the presence of protective windbreaks such as trees.

Cold Environments and Animal Production

Farm animals maintain a relatively constant body core temperature during exposure to the extreme range of thermal environments experienced in countries such as Canada. The severity of the winter is particularly challenging. Homeothermy is achieved by physiologic and behavioral mechanisms that modify either rates of heat loss from the body or the rate at which heat is produced by metabolism of feed or body energy reserves. Despite the extremely cold temperatures that occur in most of the agricultural regions of Canada, the effective severity of extremely cold temperatures is reduced because of the dryness of the frozen environment and the effective external insulation of the animal's hair coat. The influence of wind can add to cold stress, and the provision of shelter from wind by natural tree shelter belts or manmade structures such as porosity fences is required.

Prolonged exposure to cold results in subtle adaptation of hormonal and metabolic responses. Acclimatization to cold and winter conditions generally has little long-term effect on energy metabolism but increases thermal insulation and appetite. During prolonged exposure of cattle and sheep to cold environments down to −10 to −20°C there is a reduction in the apparent digestibility of the diet. To offset the lowered digestibility, the animals would accordingly need to consume more feed to achieve a similar digestible energy intake when kept outdoors during winter than if they were kept in a heated barn.

PATHOGENESIS

Sudden exposure of neonatal animals at birth and during the first few days of life to cold ambient temperature results in subnormal body temperature and shivering as well as decreased cardiac output, heart rate, and blood pressure. This results in muscular weakness and mental depression, respiratory failure, recumbency, and a state of collapse and, eventually, coma and death. The entire body, especially the extremities, becomes cold and the rectal temperature is below

37°C and may drop to 30°C or lower in neonates. Cold injury or frostbite of the extremities may occur in extremely cold conditions. Nonshivering-induced thermogenesis may occur, resulting in depletion of brown adipose tissue deposits. The neurologic signs of convulsions seen in some cases of hypothermia have not been adequately explained. The nervous signs observed in piglets with an inadequate intake of milk and exposed to cold environmental temperatures are probably caused by a marked hypoglycemia rather than hypothermia.

In newborn lambs carbohydrate and lipid are the major energy substrates for heat production because protein catabolism is minimal during the first day after birth. Liver glycogen concentrations increase markedly during the last few days before normal parturition. The amount of liver and skeletal muscle glycogen available in the newborn lamb at birth determines how long it can avoid hypoglycemia and hypothermia if not fed. The amount of lipid present in the newborn lamb can also affect the duration of the glycogen reserves. In growth-retarded lambs, lipid availability is decreased and glycogen exhaustion occurs earlier than normal. Such lambs are highly susceptible to hypothermia but this can be minimized by the early ingestion of colostrum, which is rich in lipid and extends the availability of glycogen.

Death results from excessive body cooling caused by low temperature, driving winds, and starvation. Wetness may or may not be involved. The starvation results indirectly from poor mothering by the ewe, either because she is a poor mother, because the weather interferes with mothering, or because the lamb is weak from poor antepartum nutrition. These lambs often walk after birth but at postmortem examination there is little to see. They may have sucked but there is little digestion and the intestine on the recumbent side is flaccid. There are also subcutaneous hemorrhages of the limbs and depletion of brown fat stores.

Hypothermia secondary to other diseases is caused by failure of the thermoregulation mechanism and is usually accompanied by varying degrees of shock and the inability to invoke shivering thermogenesis.

CLINICAL FINDINGS

A decrease in body temperature to below 37°C represents hypothermia for most farm animal species. Weakness, decreased activity, cold extremities, and varying degrees of shock are common. Bradycardia, weak arterial pulse, and collapse of the major veins are characteristic. The mucous membranes of the oral cavity are cool and there is a lack of saliva.

Neonatal Hypothermia

Body temperatures may be as low as 35°C in neonatal calves, piglets, lambs, and foals exposed to a cold environment within hours after birth or following 12 to 24 hours of profuse diarrhea accompanied by marked dehydration and acidemia. However, acute dehydration in a thermoneutral environment is accompanied by a mild increase in rectal temperature. In the early stage of hypothermia, affected animals may be shivering and trembling and the skin of their extremities and ears feels cool to touch. Hypothermic piglets will attempt to huddle together, are lethargic, do not suck, and eventually become recumbent and die. Hypothermic calves exposed to a cold environment will assume sternal recumbency, lie quietly, will have a weak suck reflex, and will die in a few hours. In later stages further weakness leading to coma is common. The mucous membranes of the oral cavity are cool and may be dry. The heart rate is slower than normal and the intensity of the heart sounds decreased. Death is common when the body temperature falls below 35°C, but field observations indicate that the temperature may fall below 30°C and animals still survive if treated intensively.

Shorn Sheep Hypothermia

Sheep with hypothermia associated with recent shearing and inclement weather have a range of body temperatures from 35 to 38°C. They huddle in tight groups and the animals that cannot maintain sufficient heat will become weak, recumbent, and die within a few hours. They may be found in lateral or sternal recumbency with their heads back over their shoulders. Palpebral reflexes are decreased, skin and extremities are cold, mucous membranes are pale to white, and generalized weakness similar to circulatory collapse is common.

Hypothermia Secondary to Other Diseases

Hypothermia secondary to other diseases is usually not marked, and there are clinical findings related to the underlying illness. Hypothermia is common in diseases, such as milk fever in cattle, but returns to normal within a few hours after successful treatment with calcium salts. Successful treatment of the primary disease will usually return the temperature to within the normal range.

CLINICAL PATHOLOGY

Clinical pathologic examinations are usually not done because the diagnosis is frequently obvious and the variability in biochemical changes makes them of limited value in reaching a diagnosis of hypothermia. The serum concentrations of glucose, nonesterified fatty acids, and immunoglobulins are commonly reduced, and hypoglycemia may be profound. However, the glucose concentration depends on the level of starvation that coexisted with the hypothermia. In starvation-induced depletion of body lipid and glycogen reserves, there is a depression in cold thermogenesis and subsequent hypothermia. In neonatal calves and lambs with hypothermia caused by excessive heat loss during short cold exposure, the serum concentrations of glucose, nonesterified fatty acids, and immunoglobulins may be at adequate levels. Hemoconcentration, azotemia, and metabolic acidosis may occur.

Necropsy Findings

Lesions associated with hypothermia depend on the duration and severity of the hypothermia. Fatal hypothermia in lambs and calves is characterized by an absence of lesions. A relative absence of milk in the abomasum is common. Experimental cold stress may result in subcutaneous edema of the ventral body wall and subcutaneous edema and hemorrhages of the extremities. Marked reductions in the amount of perirenal adipose tissue may be obvious. However, intense cold exposure of short duration may cause death of calves with no significant changes in the visual appearance of perirenal and pericardial adipose tissue depots.

TREATMENT

Hypothermic Newborn Lambs

A standardized approach for the detection and treatment of hypothermia in newborn lambs can improve the survival rate. Most lambs become hypothermic within 5 hours or at more than 12 hours after birth. Hypothermia in the first 5 hours of life is most commonly caused by a high rate of heat loss from the wet newborn lamb, whereas a depressed rate of heat production consequent to starvation is the most common cause in the older lamb. Twin and triplet lambs are more susceptible to hypothermia than singles because of lower body energy reserves; the ewe takes longer to lick dry two or three lambs, and the milk requirement of two or three lambs is higher than that of a single lamb and starvation is more likely.

Using an electronic thermometer, the body temperature of any weak or suspect lamb is taken. Lambs of any age with mild hypothermia (37–39°C) are dried off if necessary to reduce heat loss, given ewe or cow colostrum by stomach tube, and placed in a sheltered pen with the ewe. Lambs less than 5 hours of age with severe hypothermia (<37°C) are dried off and given an intraperitoneal injection of 20% glucose at a temperature of 39°C. A large lamb (>4.5 kg) is given 50 mL, a medium lamb (3.0–4.5 kg) 35 mL, and a small lamb (<3.0 kg) 25 mL. Hypothermic lambs are then placed in warming pens, measuring 2 × 2 m and made of horizontally laid straw bales, two bales high. The pen is divided horizontally into two chambers by a sheet of weld mesh upon which the lambs lie. Warm air, at 38 to 40°C, is blown into the lower chamber from a domestic heater, and a sheet of polythene fitted over the entire pen retains the heat. When the lamb's temperature reaches 37°C, it is

removed from the warmer and immediately fed ewe or cow colostrum by stomach tube at a rate of 50 mL/kg BW. Any lamb that is vigorous and able to suck is returned to its ewe in a sheltered pen and monitored over the next several hours. Colostrum can be hand milked from the ewe after administration of oxytocin.

The immersion of hypothermic lambs in water at 38°C can result in the recovery to a euthermic state in about 28 minutes at a reduced expense in metabolic effort by lambs. However, this requires extra labor and lambs must be quickly dried, otherwise the heat loss is exaggerated after removal from water because of the wet fleece.

Hypothermic Newborn Calves

Clinical management of hypothermic newborn calves is similar to that of lambs. Supplemental heat must be provided immediately. Rewarming can be done in small, enclosed boxes bedded with blankets and heat provided by infrared heat lamps. Colostrum or milk should be warmed to 40°C and intubated using an esophageal feeder. Fluids given intravenously must be warmed but their temperature usually decreases to the ambient environmental temperature before entering the jugular vein. Submersion of the intravenous line in a sustained source of hot water and ensuring an appropriate environmental temperature can mitigate the cooling of intravenously administered fluids before they reach the calf. Intravenous dextrose (1 mL of 50% dextrose per kilogram BW) should be routinely administered to all hypothermic calves because most have moderate to severe hypoglycemia. This dosage rate of 50% dextrose will increase the serum glucose concentration of the calf by approximately 100 mg/dL, assuming that the extracellular fluid space is 50% of the calf's body weight. The rectal temperature should be taken every 30 minutes during rewarming to assess progress.

A more aggressive rewarming technique involves the repeated administration of warm (40°C) 0.9% NaCl enemas via a flexible soft tube; a 20 to 30 Fr Foley catheter works well in this regard when it is advanced through the anus and the bulb inflated to maintain the catheter in the rectum. Rectally administered fluid should be aspirated before infusing additional fluid volumes via the Foley catheter to maximize the warming ability of enema fluids. Use of enema fluids as part of the rewarming protocol makes it more difficult to monitor the increase in body temperature. Whether immersion of hypothermic calves in water at 38 to 40°C is beneficial has not been determined, but immersion presents practical difficulties.

Hypothermic Newborn Foals

The clinical management of sick foals that are prone to hypothermia is presented in the section Control.

Hypothermic Newborn Piglets

Hypothermic piglets must be placed in a warming box with a heat lamp and treated with intraperitoneal administration of glucose for the hypoglycemia (see Chapter 19).

CONTROL

Control and prevention of hypothermia is dependent on providing the necessary surveillance at the time of parturition in animals being born in cold environments. Early recognition and treatment of animals with diseases leading to hypothermia is also necessary.

Lambs and Calves

Prevention of hypothermia in calves depends on the planning and implementation of effective management strategies that will limit the risk factors known to predispose newborn calves to hypothermia and starvation. Management strategies to prevent hypothermia from excessive heat loss are most important in the first 24 hours after birth. These include changing the calving season to a warmer time of the year to minimize exposure to severe weather. Measures to minimize excessive heat loss include providing a dry, draft-free environment for calving and lambing. Providing a protective shelter for beef cow/calf pairs for calving and during the first week after birth can reduce mortality from hypothermia. In extensive beef cow/calf herds, calf huts large enough for 8 to 10 calves provide excellent shelter from wind, rain, and snow.

The provision of adequate surveillance and assistance at the time of lambing or calving is necessary to minimize the incidence of dystocia and its consequences for the neonate. The ingestion of adequate quantities of colostrum, beginning as soon after birth as possible, is important to provide immunoglobulin and energy sources for the neonate.

Piglets

The newborn piglet requires an adequate intake of colostrum within a few hours after birth, continued intake of milk after the colostral period, a warm external environment of 30 to 34°C for at least the first 3 days of life (with heat lamps), and protection from traumatic injuries such as crushing by the sow. Sows do not instinctively remove the amniotic fluid from the surface of piglets; it is removed by contact with other surfaces or by evaporation. Smaller than normal piglets and weak piglets should be dried manually after birth to minimize excessive heat loss. Cross-fostering is used when gilts or sows have large litters that they cannot nurse adequately.

Sick Foals

Sick foals are prone to hypothermia, but cold stress can be reduced by good management procedures, including the following:

- The foal should be housed in an environment with minimal drafts, in which the air temperature is controlled at a steady value and set according to the foal's needs. Air temperature should be at, or a few degrees above, the lower critical temperature. This temperature may exceed 24°C for a sick, uncovered recumbent foal. Radiant heaters are useful but should not be placed too close to the foal.
- Excessive moisture should be removed from the foal's hair coat immediately after birth. A sick foal that cannot increase its metabolic rate is particularly susceptible to cold stress when wet with amniotic fluid.
- Additional insulation with foal rugs and leg bandages will reduce heat loss from the dry body surface. The dry sick foal needs an additional 10 mm of insulation for each 10°C decline in air temperature below 24°C. Because sick foals are recumbent, they should lie on a heated pad or on thick bedding material to minimize heat loss by conduction to the floor.
- Energy intake should be sufficient to sustain resting metabolism and can be given by the oral or parenteral route.
- Frequent monitoring of both rectal and air temperature, as well as energy intake, will assist in the diagnosis of thermal stress, so that appropriate action can be taken. A lack of shivering does not indicate an absence of cold stress.

FURTHER READING

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COLD INJURY (FROSTBITE AND CHILBLAINS)

SYNOPSIS

Etiology Exposure of extremities to cold temperatures, usually below freezing, without adequate protection.

Epidemiology Cooler seasons of the year, primarily in young animals, especially beef calves, debilitated from other disease. Teats of lactating dairy cows also susceptible.

Clinical findings Lesions can occur on extremities of limbs, especially hindfeet, ears, and tail. Demarcated lesions with initial swelling with edema followed by necrosis and sloughing. Teats and udder of adult cows can be affected.

Clinical pathology None specific.

Necropsy findings Subcutaneous edema and hemorrhage in affected areas.
Diagnostic confirmation Clinical findings and history of exposure to cold.
Treatment Warm, dry environment. Improve peripheral circulation.
Control Remove debilitated calves from cold environments. Adequate and dry bedding.

ETIOLOGY AND EPIDEMIOLOGY

Injury occurs during cold weather in the winter or spring months and is most common in **calves** that are weak or in which the peripheral circulation of the limbs is impaired, usually because of diarrhea and dehydration. In a retrospective study of frostbite in calves, 80% of cases were associated with a concurrent disease such as pneumonia, diarrhea, omphalitis, septicemia, and ocular disease. Hypothermia (<37.5°C) was present in about 50% of the calves. The disease in calves appears more common in beef breeds, possibly because of management risk factors.

In **dairy herds** with loose housing, access to outdoor exercise yards without adequate bedding can be a risk factor. There can be a high incidence of teat lesions in drylot-housed herds in temperate areas when freak cold weather fronts invade the region. Regional differences in teat chapping in winter are associated with regional differences in winter temperature.

PATHOGENESIS

Physiologically, body heat is lost from the skin surface by radiation and convection and by conduction and evaporation when the skin and hair coat are wet. **Newborn calves** are particularly susceptible to cold because of their inadequate insulation and high ratio of body surface area (through which heat is lost) to body volume (in which heat is generated). The core and trunk body temperature is preferentially conserved during cold stress at the expense of the peripheral tissues, which are most susceptible to cold injury.

Peripheral tissues are also most susceptible because of their contact with the ambient temperature and wet environments. When cattle are in sternal recumbency, the uppermost pelvic limb is fully exposed and the distal aspect of the opposite limb from the hoof to above the fetlock joint is exposed to the environment. The distal extremities of the thoracic limbs are usually covered by the thorax. Thus any situation that results in prolonged sternal recumbency will allow the distal extremities of the pelvic limbs to cool excessively, and if there is impairment of circulation because of preexisting dehydration, varying degrees of cold injury can occur. Field observations suggest that if a weak calf does not move from a sternally recumbent position for several hours then the cold injury can progress to the stage of severe irreversible frostbite before the clinical signs are recognized by the owner.

The **teats of dairy cows** are also exposed when standing and lying. Residual teat dip after milking predisposes to cold injury.

Cold injuries of extremities vary from mild to severe. Exposure to cold results in vasoconstriction and coolness of the affected part. Most dry–cold injury is superficial and the skin may become gangrenous resulting in a hard shell or carapace over healthier tissue. Deeper cold injury causes inflammation, redness or cyanosis, local swelling, and pain or loss of sensation.

CLINICAL FINDINGS

Frostbite of the **feet** of calves is not readily obvious, even to the experienced observer. The normal hair covering and pigmentation of the skin often mask the early changes of frostbite. Commonly, cases are identified during the treatment with fluids of scouring, recumbent calves, when further clinical examination reveals that the hindfeet are cool and clammy.

In the **early stages** of frostbite of the distal parts of the limbs, the tissues are swollen, edematous, and may have well-demarcated limits. After several hours of warming indoors, the feet remain cool and close examination reveals some moistness and dark red to bluish coloration of the skin. There may be a line of demarcation between normal and affected tissue at about the level of the fetlock joints. If the injury is not severe, complete recovery can occur in a few days.

In more **severe cases**, within 24 to 48 hours, necrosis and sloughing of the skin occur and the hooves become detached several days later. There is pain on palpation of affected tissues, especially at the line of demarcation.

When there is avascular necrosis of the affected part, the skin will be hard like a shell (known as a carapace) and moderate palpation will elicit pain.

Freezing of the **ears** results in loss of pliability of the ears, gangrene, and loss of the affected parts and curling of the affected skin adjacent to the affected parts. Some sloughing of affected parts will occur, and after several days the ears appear shortened.

Freezing of the **tail** occurs most commonly at the distal end, resulting in stiffness and loss of flexibility because of a carapace. Varying portions of the tail may be affected, but usually 5 to 10 cm of the distal end is involved. The distal parts of the tail of adult cattle may freeze in very cold weather.

In adult cattle, freezing of the **teats** and **base of the udder** can occur in lactating cattle that have inadequate bedding and shelter from wind and snow. Affected teats are swollen and cold and the skin begins to vesiculate and peel. Freezing of the teats of cows may result in permanent injury, chronic thelitis, and the possibility of mastitis with gangrene. Less severe lesions predispose to mastitis.

Freezing of the **scrotum** occurs in yearling beef bulls kept outdoors during the cold winter months, but the lesions are not commonly recognized until the spring of the year.

NECROPSY FINDINGS

Necrosis of the skin of the affected area with severe diffuse hemorrhagic subcutaneous edema is typical of frostbite.

TREATMENT

Affected calves should be moved to a warm, well-bedded **dry environment** and circulation should be improved by providing **fluid therapy** as necessary. In early cases, affected calves will recover in a few days and the swelling and pain will regress. Field observations suggest that superficial freezing of the skin between the fetlock and coronets will heal over a period of several weeks providing the lesion does not extend into the coronary bands and the laminae of the feet, which commonly results in sloughing of the hoof.

In severe cases with extensive necrosis, the skin will begin to slough. Such open wounds should be treated with suitable antibiotic ointments and bandaged for several days. Calves with extensive freezing of the hindlimbs extending from the feet up to hock joints are incurable and should be euthanized.

There is no specific treatment for freezing of the ears and tails of calves or the teats of cows.

CONTROL

The prevention of cold injury in newborn **calves** requires daily surveillance of calves to ensure that any animal that is inactive for any reason is examined for evidence of illness and treated immediately and placed in a protected environment.

When an exceptional cold period is forecast for **dairy cows** at risk, teat dipping should be temporarily suspended during the cold period. Additional bedding should be provided for loose-housed cows, and bedding with some manure can be piled in the center of drylot yards to provide composting heat upon which the cows can bed.

HYPERTHERMIA (HEAT STROKE OR HEAT EXHAUSTION)

Hyperthermia is the elevation of core body temperature caused by excessive heat production or absorption, or to deficient heat loss, when the causes of these abnormalities are purely physical. Heat stroke (heat exhaustion) is the most commonly encountered clinical entity.

ETIOLOGY

The major causes of hyperthermia are the physical ones of high environmental

temperature and prolonged, severe muscular exertion, especially when the humidity is high, the animals are fat, have a heavy hair coat, or are confined with inadequate ventilation such as on board ship or during road transportation. Fat cattle, especially British beef breeds, can be overcome by the heat in feedlots. Brahman cattle in the same pen may be unaffected. Angora goats are much more sensitive to high environmental temperatures than sheep, especially when they are young.

High Environmental Temperature

The upper border of the thermoneutral zone (the **upper critical temperature)** is the effective ambient temperature above which an animal must increase heat loss to maintain thermal balance (see Fig. 4-1). The upper critical limit for dairy cows is 25 to 26°C. The upper critical temperature in sheep with a light wool coat on board ship appears to be 35°C (95°F) at a humidity of 33 to 39 mm Hg (4.4–5.2 kPa) vapor pressure. Differences between breeds of animal in their tolerance to environmental high temperatures, exposure to sunlight, and exercise are important in animal management and production. Holstein cows carrying the *slick hair* gene (phenotypically having a short, sleek and sometimes glossy hair coat) are better able to regulate body temperature during heat stress than wild-type Holsteins, with slick-haired animals having an increased sweating rate.[1] Water buffalo have been shown to be less heat tolerant than Shorthorn steers, which were less tolerant than Javanese Banteng and Brahman crossbreeds (the last two appear to be equally tolerant). The differences appear to be at least partly caused by the capacity to increase cutaneous evaporation under heat stress.

There are similar differences in heat tolerance between lactating and nonlactating cows; lactating animals show significantly greater increases in rectal temperature and heart and respiratory rates when the environmental temperature is raised. This is primarily a result of the greater dry matter intake and heat of fermentation in dairy cattle that must be dissipated. Heat stress is therefore an important production-limiting disease when dairy cattle are kept in conditions of high heat and humidity.

Rested, hydrated horses are well able to maintain homeothermy in the hottest environmental conditions. Their most efficient mechanism in ensuring that body temperature is kept low is their capacity for heavy sweating.

Other Causes of Hyperthermia

- Neurogenic hyperthermia: Damage to hypothalamus, e.g., spontaneous hemorrhage, may cause hyperthermia or poikilothermia
- Dehydration: Caused by insufficient tissue fluids to accommodate heat loss by evaporation
- Excessive muscular activity: For example, strychnine poisoning
- Miscellaneous poisonings, including levamisole and dinitrophenols
- Malignant hyperthermia in the porcine stress syndrome
- Malignant hyperthermia in Quarter Horses[2,3]
- Hyperkalemic periodic paresis in horses
- Fescue toxicity in ruminants and horses
- Cattle with hereditary bovine syndactyly
- Administration of tranquilizing drugs to sheep in hot weather
- Specific mycotoxins, e.g., *Claviceps purpurea* and *Acremonium coenophialum,* are causes of epidemic hyperthermia; bovine idiopathic hyperthermia in cattle in Australia may be caused by *Claviceps purpurea*
- Iodism
- Sylade (possibly) poisoning

PATHOGENESIS

The means by which hyperthermia is induced have already been described. The physiologic effects of hyperthermia are important and are outlined briefly here.

Unless the body temperature reaches a critical point, a short period of hyperthermia is advantageous in an infectious disease because phagocytosis and immune body production are facilitated and the viability of most invading organisms is impaired. These changes provide justification for the use of artificial fever to control bacterial disease. However, the metabolic rate may be increased by as much as 40 to 50%, liver glycogen stores are rapidly depleted, and extra energy is derived from increased endogenous metabolism of protein. Feed intake is decreased and there is a change in postabsorptive carbohydrate metabolism in cattle, characterized by increased plasma insulin concentration and insulin release to a glucose tolerance test. If anorexia occurs because of respiratory embarrassment and dryness of the mouth, there will be considerable loss of body weight and lack of muscle strength accompanied by hypoglycemia and an increase in plasma urea nitrogen concentration caused by the use of skeletal muscle for energy.

There is increased thirst caused in part by dryness of the mouth. An increase in heart rate occurs directly because of the rise in blood temperature and indirectly to the fall in blood pressure resulting from peripheral vasodilatation. An increased respiratory rate cools by increasing salivary secretion and the rate of air flow across respiratory epithelial surfaces, increasing the rate of evaporative cooling. Urine secretion is decreased because of the reduced renal blood flow resulting from peripheral vasodilatation and because of physicochemical changes in body cells that result in retention of water and chloride ions.

When the critical temperature is exceeded, there is depression of nervous system activity and depression of the respiratory center usually causes death by respiratory failure. Circulatory failure also occurs caused by myocardial weakness and the heart rate becoming fast and irregular. If the period of hyperthermia is unduly prolonged, rather than excessive in degree, the deleterious effects are those of increased endogenous metabolism and deficient food intake. There is often an extensive degenerative change in most body tissues, but this is more likely to be caused by metabolic changes than by the direct effects of elevation of the body temperature.

Malignant hyperthermia is an autosomal dominant trait in Quarter Horse lineages caused by a single missense point mutation in the ryanodine receptor 1 (*RyR1*) gene. Dysfunction of the *RyR1* gene leads to excessive release of calcium into the cytosol and a hypermetabolic state of the skeletal muscle cells, which in severe cases can result in rectal temperatures exceeding 43°C. Malignant hyperthermia is potentially fatal in horses carrying the genetic defect, with an estimated mortality rate of 34%.[2,3]

CLINICAL FINDINGS

An elevation of body temperature is the primary requisite for a diagnosis of hyperthermia, and in most species the first observable clinical reaction to hyperthermia occurs when the rectal temperature is increased by 3 to 4°C (4–7°F) above normal. In most instances the temperature exceeds 42°C (107°F) and may reach 43.5°C (110°F). An increase in heart and respiratory rates with a weak pulse of large amplitude, sweating, and salivation occur initially, followed by a marked absence of sweating. The animal may be restless but soon becomes dull, stumbles while walking, and tends to lie down.

In the early stages there is increased thirst and the animal seeks cool places, often lying in water or attempting to splash itself. Additional increases in rectal temperature lead to labored respiration and general distress is evident. Beyond this point the respirations become shallow and irregular, the pulse becomes very rapid and weak, and these signs are usually accompanied by collapse, convulsions, and terminal coma. Death occurs in most species when the core temperature exceeds the normal value by approximately 5 to 7°C (8–10°F). Abortion may occur if the period of hyperthermia is prolonged, and a high incidence of embryonic mortality has been recorded in sheep that were 3 to 6 weeks pregnant. In cattle, breeding efficiency is adversely affected by prolonged heat stress and in intensively housed swine a syndrome known as summer infertility, manifested by a decrease in conception rate and litter size and an increase in anestrus, occurs during and following the hot summer months in most countries. A

case series of 4- to 6-month-old lambs examined in summer with clinical signs of high rectal temperature, tachypnea, and neurologic disease has been reported in Texas.[4] Neurologic signs included postural kyphosis and limb hyperextension to sternal recumbency and was attributed to hyperthermia-induced spinal cord injury.

Respiratory rate at the lower end of the thermoneutral zone is 20 breaths per minute in cattle and 25 to 30 breaths per minute in sheep and goats. An increase in respiratory rate above 40 breaths per minute in adult ruminants represents panting, which has the homeostatic goal of facilitating cooling by respiratory evaporation. The respiratory rate is therefore the most practical indicator of heat stress in adult ruminants, with respiratory rates of 40 to 60, 60 to 80, and 80 to 120 breaths per minute representing low, moderate, and severe heat stress, respectively. It is not uncommon in hot humid climates to see cattle open-mouth breathing with respiratory rates exceeding 80 breaths per minute during periods of heat stress. In summary, the progression of changes in cattle with heat stress is increased respiratory rate, rectal temperature, and heart rate; followed by decreased urine concentration (caused by increased water intake); and finally decreased appetite and milk production.

Heat stress in horses and donkeys is associated with increased respiratory rate and depth, flared nostrils, nodding of the head, and apathy.[5] Hyperthermic horses are fatigued and have profound fluid and electrolyte losses, characterized by hypotonic dehydration caused by excessive sweating. The resultant clinical signs include decreased performance, depression, weakness, increased heart and respiratory rates, and marked increases in rectal temperature (usually exceeding 42°C). Because of the hyponatremia, affected horses may lose the stimulus to drink, exacerbating their dehydration. In advanced cases, the skin is dry and hot because sweating is impaired. Hyperthermic horses that have been participating in an endurance event may have synchronous diaphragmatic flutter as a result of hypocalcemia and metabolic alkalosis. Coma and death can occur in extreme cases of hyperthermia that are not identified and treated until the condition is advanced.

CLINICAL PATHOLOGY

No important clinicopathologic change is observed in simple hyperthermia. However, horses with advanced hyperthermia typically have hyponatremic dehydration and azotemia. Horses with synchronous diaphragmatic flutter are typically hypocalcemic.

Necropsy Findings

At necropsy there are only poorly defined gross changes. Peripheral vasodilatation may be evident, clotting of the blood is slow and incomplete, and rigor mortis and putrefaction occur early. There are no constant or specific histopathologic changes.

TREATMENT

The presence of adequate drinking water is essential and, together with shade and air movement, is of considerable assistance when multiple animals are exposed to high air temperature.

If treatment of individual animals is necessary because of the severity or duration of the hyperthermia, affected animals should be immediately placed in the shade and hosed on the midline of the back with cold water so that their coats are saturated. Fans should be immediately placed in front of the animal to promote evaporative cooling, and cooled water, with and without added electrolytes, should be made available for the animal to drink. In severe cases of hyperthermia in which large volumes of water are not available, very cold water (2–8°C) should be applied and immediately scraped off because the water becomes warm almost immediately. The application of very cold water does not induce a clinically relevant degree of peripheral vasoconstriction and has not been associated with clinically relevant side effects. Water applied by hose does not need to be scraped off because heat is conducted to the applied water stream. Placement of wet sheets or towels over the head or neck is not recommended because they provide unneeded insulation.

The rectal temperature should be monitored frequently during cooling, and water application should be stopped when the rectal temperature has returned to normal. Because affected animals may not be interested in or capable of drinking, the intravenous administration of fluids such as 0.9% NaCl is indicated in animals that are weak, recumbent, or dehydrated. Horses often need 20 to 40 L of intravenous fluids over the first few hours of treatment. Horses with synchronous diaphragmatic flutter should be treated with intravenous calcium after verifying the presence of hypocalcemia.

Fluids can also be administered orally to horses, but care should be taken to ensure that gastrointestinal motility is not impaired. A practical oral electrolyte solution is obtained by dissolving 20 g of table salt (NaCl) and 20 g of Litesalt (NaCl and KCl) in 5 L of water; this provides 107, 28, and 132 mmol/L of sodium, potassium, and chloride, respectively. Five liters of this fluid can be administered to an adult horse each hour by nasogastric tube.

CONTROL

Shade alone is the most important factor in maintaining the comfort of livestock and preventing heat stress. Shade reduces the heat gain from solar radiation and can be provided by trees or artificially by roofs or shades made from cloth or artificial material. Shades should be placed over feed and where the producer wants the animals to spend their time. The efficiency of metal shades can be increased by painting metal shades white on the topside and black on the underside. A north–south orientation will permit drying under the shades as the shaded area moves throughout the day; this may be helpful in decreasing the incidence of coliform mastitis if sprinklers are used under the shades and cattle prefer to lie under the shades than in freestalls.

In dairy and feedlot cattle, the following measures should be taken to manage heat stress:

- Provide cool clean water and plenty of trough space for drinking.
- Use shades and intermittent sprinkler systems (wet time of 1–2 min with an adequate dry off time of 20–30 min); continuous application of water increases the local humidity and decreases the effectiveness of evaporative cooling.
- Enhance airflow by fans or by providing mounds for cattle to stand on.
- Adjust rations and feed a larger percentage of the ration in the evening when it is cooler.
- Minimize handling during periods of greatest heat stress.
- Select cattle based on breed and coat characteristics, and house the most susceptible cattle (heavy, black) on east-sloping lots with the most shade; genetic studies have identified genes associated with resistance to heat stress in dairy cattle.[1,6]

In exercising horses, periodic rests in the shade with fans and water sprinklers and maintaining a normal hydration status can be very helpful in preventing heat stress. Monitoring the heart rate is a useful and practical method of assessing the degree of heat stress in horses, because heart rates remain elevated for a longer period of time in horses undergoing heat stress.

If animals have to be confined under conditions of high temperatures and humidity, the use of tranquilizing drugs has been recommended to reduce unnecessary activity. However, care is needed because blood pressure falls and the animals may have difficulty losing heat if the environment is very hot and in some cases may gain heat. Chlorpromazine, for example, has been shown to increase significantly the survival rate of pigs exposed to heat and humidity stress.

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FEVER (PYREXIA)

Fever is an elevation of core body temperature above that normally maintained by an animal and is independent of the effects of ambient conditions on body temperature. It is important to realize that fever is a combination of hyperthermia and infection or inflammation that results from an elevated set point for temperature regulation.

ETIOLOGY

Fevers may be septic, the more common type, or aseptic, depending on whether or not infection is present.

Septic Fevers

These include infection with bacteria, viruses, protozoa, or fungi as

- Localized infection such as abscess, cellulitis, and empyema
- Intermittently systemic, as in bacteremia and endocarditis
- Consistently systemic, as in septicemia

Aseptic Fevers

- Chemical fevers, caused by injection of foreign protein and intake of dinitrophenols
- Surgical fever, caused by breakdown of tissue and blood
- Fever from tissue necrosis, e.g., breakdown of muscle after injection of necrotizing material
- Severe hemolytic crises (hemoglobinemia)
- Extensive infarction
- Extensive necrosis in rapidly growing neoplasms such as multicentric lymphosarcoma in cattle
- Immune reactions such as anaphylaxis and angioneurotic edema

PATHOGENESIS

Most fevers are mediated through the action of endogenous pyrogens produced by granulocytes, monocytes, and macrophages. The most important and best known **endogenous pyrogen** is interleukin-1 (IL-1), produced by monocytes and macrophages. The febrile response is initiated by the introduction of an **exogenous pyrogen** into the body. Exogenous pyrogens include pathogens such as bacteria, viruses, bacterial endotoxins, antigen–antibody complexes, hemoglobinemia in a hemolytic crisis, and many inorganic substances. In hypersensitivity states, soluble antigen–antibody complexes may act as mediators. One of the most potent exogenous pyrogens is the lipopolysaccharide of gram-negative bacteria.

Endogenous Pyrogens

Endogenous pyrogens are proteins released from monocytes and, to a lesser extent, lymphocytes. These proteins were originally designated as **monokines** and **lymphokines,** respectively, but are now more commonly referred to under the more general term of **cytokines**. One of the pyrogenic cytokines is IL-1, formerly known as lymphocyte activating factor. **IL-1** stimulates T-lymphocyte proliferation in the presence of antigen, enhancing the immune response. The mediators between endogenous pyrogen and the hypothalamus appear to be prostaglandins, and the level of calcium in the hypothalamus appears to regulate its activity.

Interleukin-1 initiates fever by inducing an abrupt increase in the synthesis of **prostaglandins**, particularly prostaglandin E_2, in the anterior hypothalamus. The elevated prostaglandin levels in the hypothalamus raise the thermostatic set point and induce the mechanisms of heat conservation (vasoconstriction) and heat production (shivering thermogenesis) until the blood and core temperature are elevated to match the hypothalamic set point.

Prostaglandin precursors are thought to be the chemical mediators of fever according to the following sequence:

1. Endogenous pyrogens cause the release of arachidonic acid, with subsequent synthesis of prostaglandins.
2. Arachidonic acid breakdown products modulate the hypothalamic thermoregulatory mechanism, resulting in an increase in the set point value.
3. Prostaglandin synthetase-inhibitor antipyretics lower fever by blocking the synthesis of prostaglandins or prostaglandin precursors from arachidonic acid.

A cytokine known as **tumor necrosis factor-α (TNF-α)** reproduces many of the physiologic derangements observed in septic shock and mediates many of the deleterious effects of gram-negative bacterial infection, including fever.

In addition to their pyrogenic activity, cytokines mediate the acute phase response, which is a term now being used to describe the reaction of animals to pathogen invasion, tissue injury, immunologic reactions, and inflammatory processes. The physiologic mechanisms involved in the production of fever after stimulation by pyrogens must be matured or sensitized by previous exposure to pyrogen. Injection of pyrogens into newborn lambs does not cause fever but subsequent injections do.

Effect of Pyrogens on the Hypothalamus

The effect of bacterial and tissue pyrogens is exerted on the thermoregulatory center of the hypothalamus so that the thermostatic level of the body is raised. The immediate response on the part of organs involved in heat regulation is the prevention of heat loss and the increased production of heat. This is the period of **increment**, or chill, which is manifested by cutaneous vasoconstriction, resulting coldness and dryness of the skin, and an absence of sweating. Respiration is reduced and muscular shivering occurs, and urine formation is minimal. The extremities are cold to the touch, the rectal temperature is elevated, and the pulse rate increased. When the period of heat increment has raised the body temperature to a new thermostatic level the second period of fever, the **fastigium**, or period of constant temperature, follows. In this stage the mechanisms of heat dissipation and production return to normal. Cutaneous vasodilatation causes flushing of the skin and mucosa, sweating occurs and may be severe, and diuresis develops. During this period there is decreased forestomach motility in ruminants, metabolism is increased considerably to maintain the body temperature, and tissue wasting may occur. There is also an inability to maintain a constant temperature when environmental temperatures vary.

When the effect of the pyrogenic substances is removed, the stage of **decrement**, or fever defervescence, appears and the excess stored heat is dissipated. Vasodilatation, sweating, and muscle flaccidity are marked and the body temperature falls. The fall in body temperature after the initial rise is accompanied by a decline in plasma zinc and plasma total iron concentrations. If the toxemia accompanying the hyperthermia is sufficiently severe, the ability of tissues to respond to heat production or conservation needs may be lost and as death approaches there is a precipitate fall in body temperature.

Febrile Response

The febrile response, and the altered behavior that accompanies it, are thought to be part of a total mechanism generated to conserve the resources of energy and tissue being wasted by the causative infection. The febrile response has major effects on immune mechanisms. Endogenous pyrogens stimulate T-cell proliferation. The increased body temperature causes increases in leukocyte mobility, leukocyte bactericidal and phagocytic activities, and lymphocyte transformation as well as enhances the effects of interferon and IL-1.

Some possible adverse effects of fever include anorexia, which can lead to excessive catabolism if prolonged. Rarely, extremely high fevers can result in disseminated intravascular coagulation and effects on the central nervous system (CNS) that may lead to convulsions.

CLINICAL FINDINGS

The effects of fever are the combined effects of hyperthermia and infection or inflammation. There is elevation of body temperature, an increase in heart rate with a diminution of amplitude and strength of the arterial pulse, hyperpnea, wasting, oliguria often with albuminuria, increased thirst, anorexia, scant feces, depression, and muscle weakness. The temperature elevation is always moderate and rarely goes above 42°C (107°F).

The **form of the fever may vary.** Thus the temperature rise may be

- Transient
- Sustained, without significant diurnal variation
- Remittent, when the diurnal variation is exaggerated
- Intermittent, when fever peaks last for 2 to 3 days and are interspersed with normal periods
- Atypical, when temperature variations are irregular

A biphasic fever, consisting of an initial rise, a fall to normal, and a secondary rise, occurs in some diseases, e.g., in strangles in the horse and in erysipelas in swine. The outstanding example of intermittent fever in animal disease is equine infectious anemia.

In farm-animal practice the most common cause of a fever is the presence of an inflammatory process such as pneumonia, peritonitis, mastitis, encephalitis, septicemia, viremia, etc. The clinical abnormalities that are typical of the particular disease must be detected and differentiated in the process of making a diagnosis. In the absence of physical causes of hyperthermia, the presence of a fever indicates the presence of inflammation, which is not always readily apparent. A **fever of unknown origin** occurs commonly in farm animals and requires repeated clinical and laboratory examinations to elucidate the location and nature of the lesion.

In **horses**, a **fever of unknown origin** is characterized by prolonged, unexplained fever associated with nonspecific findings such as lethargy, inappetence, and weight loss. In a series of horses with fever of unknown origin, the cause was found to be infection in 43%, neoplasia in 22%, immune mediated in 7%, and miscellaneous diseases in 19%. The cause remained undetermined in 10%.

The **magnitude of the fever** will vary with the disease process present, and it is often difficult to decide at what point the elevated temperature is significant and represents the presence of a lesion that requires specific treatment. This is especially true when examining groups of animals with nonspecific clinical findings including an elevated temperature. The typical example is a group of feedlot cattle affected with depression, inappetence, dyspnea, and fever ranging from 39.5 to 40.5°C. The suspected disease may be pneumonic pasteurellosis but it may be impossible to make that diagnosis based on auscultation of the lungs of all the affected animals. Some of the animals may have a fever of unknown origin from which they will recover in a few days and specific therapy is not required. Under these circumstances and based on clinical experience, the tendency is to make a diagnosis of **acute undifferentiated bovine respiratory disease** or **undifferentiated fever** in animals with a temperature ≥40.5°C for 2 days in succession. This emphasizes the need to select an upper threshold value that indicates a clinically and physiologically significant fever. Infrared thermography offers great promise as a noninvasive method of identifying pyrexic individuals in group housing, particularly pigs raised in confinement housing and feedlot cattle.

CLINICAL PATHOLOGY

There are no clinicopathologic findings that are specific for fever. The hemogram will reflect the changes associated with the cause of the fever. Inflammation is characterized by marked changes in the total and differential leukocyte count characteristic for each disease. A wide variety of tests can be performed to identify the location and nature of the lesion causing the fever. The most common tests include the following:

- Microbiologic testing of blood samples
- Analysis of serous fluids from body cavities
- Cerebrospinal fluid analysis
- Milk sample analysis
- Reproductive tract secretion analysis
- Joint fluid analysis
- Biopsies
- Exploratory laparotomy

Medical imaging may be necessary to detect deep abscesses.

Necropsy Findings

The necropsy findings will be characteristic of the individual disease process and are commonly characterized by varying degrees of peracute, acute, and chronic inflammation depending on the severity of the disease, the length of illness, and whether or not treatment had been given. In the case of longstanding fevers, these findings are still characteristic but they may fluctuate in severity daily or over longer periods.

Fever must be differentiated from hyperthermia caused by a physical cause such as **heat stroke** or **exhaustion** or **malignant hyperthermia** of pigs and Quarter Horses. In **fever of unknown origin**, the history, physical examination, laboratory findings, and epidemiologic setting should be reviewed. Localizing clinical findings may provide a clue to the body system or organ involved. Common inflammatory processes include the following:

- Abscesses of the peritoneum, pleura, and lungs
- Septic metritis
- Endocarditis
- Polyarthritis
- Pyelonephritis

Many animals are placed in the category of fever of unknown origin because the veterinarian overlooks, disregards, or rejects an obvious clue. No algorithms or computer-assisted diagnostic programs are likely to solve this diagnostic challenge. To improve the diagnostic accuracy veterinarians will have to work harder. This requires obtaining a detailed history, repeated physical examinations, reconsideration of the epidemiologic characteristics of the affected animal, requesting consultations from colleagues, and the investment of time to consider the diagnosis and the circumstances.

TREATMENT

Antimicrobial Agents

The most important aspects of the clinical management of fever should be directed at its cause. The main objective is to identify and treat the primary disease. Antimicrobial agents are indicated for the treatment of bacterial infections. The selection of antimicrobial, the route of administration, and the duration of treatment depend on the cause of the infection, its severity, and the accessibility of the lesion to the drug. The use of antimicrobial agents to prevent secondary bacterial infections in animals with viral diseases (e.g., viral interstitial pneumonia) is controversial and of doubtful benefit.

In animals with a **fever of unknown origin**, broad-spectrum antimicrobial agents seem rational. However, blind therapy is not recommended because it may lead to drug toxicity, superinfection caused by resistant bacteria, and interference with subsequent accurate diagnosis by cultural methods. In addition, the fall of the temperature following treatment may be interpreted as a response to therapy, with the conclusion that an infectious disease is present. If such a trial is begun the response should be monitored daily to determine effectiveness, and continued efforts should be made to determine the cause of the fever. In some cases it may be necessary to surgically remove by drainage techniques the source of the infection located in abscesses or body cavities such as the pleural cavity.

Antipyretics

Because fever ordinarily does little harm and usually benefits the animal's defense mechanism, antipyretic agents are rarely essential and may actually obscure the effect of a specific therapeutic agent or of the natural

course of the disease. If the fever is high enough to cause discomfort or inappetence, or is so high that death from hyperthermia is possible, then nonsteroidal antiinflammatory drugs (NSAIDs) should be administered. Most NSAIDs, such as flunixin meglumine, are inhibitors of prostaglandin synthesis and act centrally to lower the thermoregulatory set point. Rectal temperatures start to decline within 30 minutes of parenteral NSAID administration but usually do not completely return to within the normal physiologic range.

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Acute Phase Response

Acute phase proteins are plasma proteins that change their concentration when animals are subjected to external stressors, such as transportation, or internal stimuli, such as inflammation, bacterial infection, neoplasia, and surgical trauma.[1] Acute phase proteins have been categorized as positive or negative dependent on whether their concentration increases (positive) or decreases (negative) in response to an external or internal stimulus. There has been increased interest in measuring the serum concentration of acute phase reactants to monitor the severity of an infectious disease, assist in making a diagnosis, and to verify that an animal produced for food is healthy and fit for slaughter. During the hepatic acute phase response, the liver increases the synthesis of specific proteins (**positive acute phase proteins**) in response to release of IL-1β, IL-6, and TNF-α (proinflammatory cytokines) from macrophages and monocytes, whereas albumin synthesis is reduced (negative acute phase protein). Interleukin-1β induces type 1 acute phase proteins (serum amyloid A [SAA] and C-reactive protein) within 4 hours. Interleukin-6 induces haptoglobin at a later stage with serum concentrations remaining elevated for up to 2 weeks. A clinically important issue is that IL-1β is the primary initiator of fever as well as an important upstream initiator of the acute phase response; therefore, it remains to be determined whether laboratory measurement of acute phase reactant concentration in plasma provides practical information beyond that provided by rectal temperature alone. It should be recognized that although the liver plays a central role in the acute phase response, extrahepatic tissues, such as the bovine mammary gland, can also synthesize acute phase reactants.

Fibrinogen is the most widely studied positive acute phase protein in large animals. The interpretation of plasma fibrinogen concentration is complicated by its involvement in the clotting cascade (and potentially decreasing in animals with severe coagulopathies such as disseminated intravascular coagulation) and its relatively narrow range of increase (typically no more than a three- to fourfold increase). Moreover, the plasma fibrinogen concentration is slower to increase in inflammatory conditions than other acute phase reactants, typically taking 24 hours to increase with peak values at 2 to 3 days.

The **SAA** is a positive acute phase protein (apolipoprotein) that is rapidly synthesized and released primarily by hepatocytes in response to inflammation or bacterial infection. The specific role of SAA in the inflammatory response is incompletely understood, but amyloid A is thought to have immune-related functions including opsonization of gram-positive and gram-negative bacteria, increased chemotaxis of neutrophils and monocytes, and the clearance of plasma endotoxin and high-density lipoproteins including cholesterol.

Haptoglobin is a positive acute phase protein and is thought to provide an exquisitely sensitive screening test for the release of endogenous glucocorticoids and proinflammatory cytokines. Haptoglobin is the principal scavenger of free hemoglobin in plasma and therefore decreases growth of most bacteria by decreasing the availability of iron. A major confounder for the interpretation of an increased serum haptoglobin concentration is that trauma, and increased plasma cortisol and estradiol concentrations associated with parturition, increase serum haptoglobin concentrations.[2]

Lipopolysaccharide binding protein (LBP) is an antiinflammatory in low concentrations and proinflammatory in high concentrations. It binds to the lipopolysaccharide portion of gram-negative bacteria and the bound complex then attaches to membrane or soluble CD14 receptors, initiating a signaling cascade. **C-reactive protein** and **α1-acid glycoprotein** are also positive acute phase proteins that have been extensively investigated in humans but have not been well investigated in large animals.

Several positive acute phase proteins have been evaluated in horses including SAA, C-reactive protein, haptoglobin, and fibrinogen. The most clinically relevant acute phase reactant in the horse appears to be SAA, because SAA concentrations are extremely low in healthy horses, increase markedly and rapidly during the acute phase of inflammation, and decrease rapidly after recovery because of its short half-life.[1,3,4] The clinical utility of SAA as a marker of infection is decreased in neonatal foals because SAA concentrations increase for up to 7 days in response to inflammation associated with vaginal delivery and absorption of amyloid A present in colostrum.[5]

Serum amyloid A, haptoglobin, and fibrinogen are important positive acute phase proteins in cattle and are produced by the liver in response to endogenous release of glucocorticoids and proinflammatory cytokines. Of these acute phase reactants, SAA is considered to have the most diagnostic utility in cattle. A potential confounder for the interpretation of SAA concentration in cattle is that its concentration normally increases at calving.[6] This means that an increased SAA concentration is not specific for inflammation or bacterial infection in the postparturient dairy cow and may be more associated with the extent of hepatic lipidosis than the presence of an inflammatory process in early lactation.[6,7]

Serum or plasma haptoglobin concentration is increased in cows with hepatic lipidosis, displaced abomasum, traumatic reticuloperitonitis, respiratory disease, mastitis, metritis, pododermatitis, and renal amyloidosis.[6,8-12] More research is needed to increase our understanding of changes in the concentration and kinetics of haptoglobin in cattle. C-reactive protein does not appear to be an acute phase reactant in cattle. The increase in SAA and haptoglobin in cattle appears to be dose dependent; therefore, the magnitude of the increase reflects the severity of the underlying inflammatory process.[13,14]

Important **negative acute phase proteins** in cattle include **albumin**, transferrin, and **paraoxonase**.[8] Albumin does not appear to be as sensitive an acute phase reactant as SAA in cattle. Moreover, serum albumin concentrations are decreased for 2 weeks after calving in lactating dairy cattle, partly as a result of increased plasma volume and decreased albumin synthesis,[6] further decreasing the clinical utility of serum albumin concentration as an acute phase reactant in postparturient cattle. The acute phase response in sheep appears similar to that in cattle.[15]

Plasma or serum iron concentrations decrease as part of the acute phase response; this has been attributed to sequestration of iron stores by the animal to make less iron available for bacterial growth.[16] Inflammation causes the release of IL-6 that stimulates hepatocytes to release the peptide hormone **hepcidin,** which blocks iron efflux from macrophages, directly resulting in hypoferremia.[16] Plasma iron concentration appears to be a better acute phase reactant than fibrinogen concentration in horses.[16]

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Sepsis, Septicemia, and Viremia

Sepsis is a suspected or proven bacterial infection in conjunction with the presence of **systemic inflammatory response syndrome (SIRS)**, which is defined as systemic inflammation in response to injury, being caused by infectious agents (e.g., bacteria, viruses, protozoa, fungi) or by noninfectious causes (e.g., trauma, toxins, hyperthermia, burns). Accurate criteria for SIRS have yet to be identified in domestic animals, but the presence of at least two of the following abnormalities is used to identify the presence of SIRS in humans:

- Hyperthermia or hypothermia
- Tachycardia
- Tachypnea or hyperventilation
- Leukopenia, leukocytosis, or >10% band neutrophils

These criteria for SIRS should not be applied when environmental conditions impact the measurement (such as heat stress or environmental cold or the presence of pain).

Severe sepsis is sepsis accompanied by organ dysfunction. **Septic shock** is defined as severe sepsis with hypotension (mean arterial blood pressure <65 mm Hg) despite aggressive intravenous fluid therapy. **Septicemia** is the acute invasion of the systemic circulation by pathogenic bacteria accompanied by septic shock with possible bacterial localization in various body systems or organs. It is a common cause of morbidity and mortality in newborn farm animals that have not received a sufficient quantity of colostrum in the first 24 hours after birth. **Bacteremia** is different from septicemia in that bacteremia is not accompanied by sepsis or septic shock. The difference between septicemia and bacteremia is one of degree. In bacteremia, bacteria are present in the bloodstream for only transitory periods and do not produce clinical signs; for example, a clinically unimportant bacteremia probably occurs frequently after rectal examination or other manipulations in which the mucosa is disturbed. In septicemia, the pathogen is present throughout the course of the disease and is directly responsible for initiation of the disease process. There is a current movement to eliminate the term septicemia from use and use the term **multiple organ dysfunction syndrome**, which indicates dysfunction to two or more organ systems, but the definitions stated earlier are clinically useful.

Viremia is the invasion of the systemic circulation by pathogenic viruses with localization in various body tissues and in which the lesions produced are characteristic of the specific virus. Many infections associated with rickettsias, protozoa, and fungi are also spread hematogenously throughout the body but usually do not initiate a systemic inflammatory response syndrome.

ETIOLOGY: ALL SPECIES

Many different infectious agents can result in septicemia or viremia. Some of the notable examples of septicemias and viremias are outlined next. Anthrax, pasteurellosis, and salmonellosis are found in all species of food animal.

Neonatal Septicemias

Neonatal septicemias are caused most commonly by gram-negative bacteria.

Calves

Bacteremia and septicemia are often associated with *Escherichia coli* and *Salmonella* spp. *E. coli* is most frequently isolated from the blood of calves, but gram-positive infections may be found in 10% of septicemic calves and polymicrobial infections in 28%. Calf septicemia is infrequently caused by bacteria similar to *Actinobacillus suis* bacteria. Thirty percent of severely ill calves with or without diarrhea are bacteremic, and the risk of bacteremia is higher in calves with failure of transfer of colostral immunoglobulins.

Piglets

Septicemia caused by *E. coli* is possible along with septicemia with localization in the joints, endocardium, and meninges associated with *Streptococcus suis* type 1.

Foals

Septicemia with localization associated with *E. coli, A. equuli, Klebsiella pneumoniae,* α-hemolytic *Streptococcus,* and *Salmonella* spp. are seen.

Lambs

Septicemia associated with *E. coli* occurs most frequently.

Cattle

Histophilus somni, Pasteurella multocida, Mannheimia haemolytica, Pasteurella (Yersinia) pseudotuberculosis, acute and chronic infections with bovine virus diarrhea virus, and bovine malignant catarrh are encountered.

Sheep (Young Lambs)

H. somni is the main pathogen.

Pigs

Hog cholera and African swine fever viruses and *Erysipelothrix insidiosa* are encountered.

Horses, Donkeys, and Mules

African horse sickness and *M. haemolytica* infection are implicated.

Secondary Septicemias

The principal cause of death in subacute radiation injury is septicemia resulting from loss of leukocyte production because of injury to bone marrow. Septicemia may also result when there is a congenital defect in the immune system or when immunosuppression occurs in older animals as a result of corticosteroid therapy or toxin such as bracken.

EPIDEMIOLOGY

Systemic infections associated with bacteria, viruses, rickettsia, protozoa, and other pathogens occur in animals of all ages and under many different circumstances. The epidemiologic characteristics for each entity are presented under each disease described in this book. The risk factors for each infectious disease are categorized according to

- Animal risk factors
- Environmental risk factors
- Pathogen risk factors

For example, colostrum-deprived newborn animals are highly susceptible to septicemia. **Failure of transfer of passive immunity** (FTPI) in foals is defined by serum IgG_1 concentrations of ≤400 mg/dL and partial failure of transfer of passive immunity between 400 and 800 mg/dL. Serum IgG concentrations of ≥800 mg/dL are less frequently associated with sepsis in foals, and this is considered the threshold concentration for prophylaxis in foals.

PATHOGENESIS

Two mechanisms operate in septicemia: the **exotoxins** or **endotoxins** produced by the infectious agents initiate a profound toxemia and high fever because of their initiation of the release of host mediators and because of the rapidity with which the agents multiply and spread to all body tissues (see also Toxemia, Endotoxemia, and Septic Shock). The clinical manifestations are the result of the effect of the pathogens on monocytes and lymphocytes, which initiate **SIRS**. TNF-α is associated with clinical septicemia in

newborn foals and calves, and plasma TNF-α concentration is associated with the severity of clinical signs.

Localization of certain pathogens occurs in many organs and may produce severe lesions in animals that survive the toxemia. Direct endothelial damage and hemorrhages may also be caused. The same general principles apply to a viremia, except that toxins are not produced by viruses. It is more likely that the clinical manifestations are the result of direct injury of the cells invaded by the virus. **Transplacental infection** can occur, resulting in fetal **mummification**, **abortion**, or **infection of the fetus that may be carried to term**.

Disseminated Intravascular Coagulation

Progression of SIRS can result in disseminated intravascular coagulation (DIC) caused by intravascular fibrin formation, particularly in severe septicemic diseases. Disseminated intravascular coagulation is initiated by vascular injury with partial disruption of the intima, caused by the circulation of foreign materials such as bacterial cell walls, antigen–antibody complexes, and endotoxin, with subsequent platelet adherence and the formation of platelet thrombi. Severe, uncontrolled hypercoagulation results in a high mortality rate caused by MODS. Once coagulation proceeds, the initial hypercoagulable state changes to hypocoagulation as clotting factors and platelets are consumed. The activation of the fibrinolysis system can be a major cause of the hemorrhagic diathesis present in this syndrome.

CLINICAL FINDINGS

The major clinical findings in septicemia are **fever**, **cardiovascular dysfunction and shock**, and **submucosal and subepidermal hemorrhages** that are usually petechial and occasionally ecchymotic. The hemorrhages are best seen under the conjunctiva and in the mucosae of the mouth and vulva. Tachycardia, tachypnea, and shock-induced organ dysfunction with cardiovascular hypotension, myocardial asthenia, and respiratory distress may occur in severe cases if the pathogen initiates the release of the host mediators, causing **SIRS**. These features are described under Toxemia, Endotoxemia, and Septic Shock.

Specific signs may occur as the result of localization of the infection in joints, heart valves, meninges, eyes, or other organs. The clinical findings characteristic of each disease in which septicemia and viremia occur are presented under each disease heading in this book.

Neonatal Septicemia

Neonatal septicemia is common in all farm animal species from a few hours up to several days of age. The following features are common:

- Recumbency
- Depression
- Absence or marked depression of the suck reflex
- Dehydration
- Fever
- Diarrhea
- Injected or congested mucous membranes
- Weakness
- Rapid death

Colostrum-deprived foals are commonly very ill and become comatose and die within several hours. Localized infections in the joints and lungs are frequent in foals that survive for several days. Septic polyarthritis is common and is characterized by heat, pain, synovial distension, and lameness, and occurs in 14% to 38% of neonatal foals with sepsis. About half the foals with septic arthritis have two or more joints clinically infected, with the femoropatellar and tarsocrural joints being most commonly involved. Pneumonia is often observed and is characterized by dyspnea and abnormal lung sounds. The survival rate of foals with confirmed septicemia in one series was 70%.

In calves under 30 days of age with septicemia clinical findings can include evidence of shock with cold extremities, dehydration, weak pulse, prolonged capillary refill time, weakness, and recumbency. Findings indicative of localization include ophthalmitis, neurologic abnormalities, omphalophlebitis, and polyarthritis.

Clinical Sepsis Score

A **clinical sepsis score** for the early diagnosis of septicemia in newborn foals has been evaluated and validated. It should be recognized that application of such scoring systems is statistically flawed, even if they assign different weights to predictors, because they assign equal weights to the change in severity within a given predictor. Nevertheless, such sepsis scores have been adopted by some and do have the value of facilitating the identification of neonates at risk for being septicemic. A score for predicting bacteremia in neonatal dairy calves from 1 to 14 days of age has also been suggested to predict clinically whether a sick calf has bacteremia. The calves are scored according to degrees of **hydration status**, **fecal appearance**, **general attitude**, **appearance of scleral vessels,** and **umbilical abnormality**. However, the sensitivity, specificity, and positive predictive value are too low to be of diagnostic value.

CLINICAL PATHOLOGY

Blood Culture

Isolation of the causative bacteria from the bloodstream should be attempted by culture. Ideally, blood cultures should be obtained just before the onset of fever and from a major vein or any artery. The standard is three blood cultures or animal inoculation at the height of the fever. A minimum of 10 mL of blood (preferably 30 mL) should be collected anaerobically after aseptic preparation of the venipuncture site by clipping and scrubbing with povidone iodine scrub. Blood samples should be inoculated into a broth medium with the ratio of blood to broth being 1:10 to 1:20, and the culture bottles should be examined for growth daily for up to a week. Growth is manifested as turbidity and possibly by the presence of hemolysis.

Hemogram

The presence of **leukopenia** or **leukocytosis** is an aid in diagnosis and the type and degree of leukocytic response may be of prognostic significance, particularly the presence of band neutrophils, metamyelocytes, or toxic neutrophils.[1]

Plasma fibrinogen concentrations may be increased. Consumption coagulopathy is detected by falling platelet counts, prothrombin and fibrinogen concentrations, and by the presence of fibrin-linked degradation products such as **D-dimer**. In neonatal calves, plasma activated partial thromboplastin time was prolonged in calves suspected to have septic shock.[1]

Immunoglobulin Status

Low concentrations of serum protein and immunoglobulins are associated with failure of transfer of colostral immunoglobulins in newborn farm animals with consequent septicemia caused, most commonly, by gram-negative bacteria.

Biomarkers

Biomarkers of sepsis are becoming increasingly used to guide diagnosis and treatment in humans. The main challenges with the use of biomarkers of sepsis in domestic animals are their availability, cost, and time required to obtain a result. Calves with abnormal coagulation profile results indicating the presence of severe hemostatic dysfunction were much more likely to die despite intensive therapy.[1] Plasma or serum biomarkers that show promise for diagnosing sepsis in foals or adult horses are SAA,[2] a soluble form of the CD14 molecule that binds endotoxin in plasma,[3,4] adrenomedullin,[5] arginine vasopressin,[6] and adrenocorticotropin hormone (ACTH).[6] C-reactive protein[7] and haptoglobin[7] do not currently appear to be useful biomarkers for sepsis in foals.

Serology

Serologic tests are available for most infectious diseases described in this book; however, the rapid onset of septicemia in most instances precludes the use of immunoglobulin tests, with the possible exception of IgM.

Necropsy Findings

The lesions will reflect the specific disease causing the septicemia. Subserous and submucosal hemorrhages may be present, together with embolic foci of infection in

various organs accompanied by the lesions typical of the specific pathogen.

TREATMENT

The principles of treatment are similar to those described for the treatment of toxemia, endotoxemia, fever, and septic shock, and treatment should focus on broad-spectrum antimicrobial agents and general supportive measures. For neonatal septicemia the provision of a source of immunoglobulins by plasma or blood transfusion is thought to be advantageous when there is FTPI. Whether such treatment alters the mortality rate is uncertain. Intensive care of the newborn with septicemia is described in Chapter 19. The frequency of bacteremia (approximately 30%) is sufficiently high in calves with diarrhea that are severely ill (as manifested by reduced suckle reflex, >6% dehydration, weakness, inability to stand, or clinical depression) that affected calves should be routinely treated for bacteremia, with emphasis on treating potential *E. coli* bacteremia. Strict hygienic precautions to avoid spread of infection are also necessary.

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Toxemia, Endotoxemia, and Septic Shock

Toxemia is a clinical systemic state caused by widespread activation of host defense mechanisms to the presence of toxins produced by bacteria or injury to tissue cells. Toxemia does not include the diseases caused by toxic substances produced by plants or insects or ingested organic or inorganic poisons. Theoretically, a diagnosis of toxemia can be made only if toxins are demonstrable in the bloodstream. Practically, toxemia is often diagnosed when the endotoxemia is present. In most cases there is contributory evidence of a probable source of toxins, which in many cases are virtually impossible to isolate or identify.

The most common form of toxemia in large animals is **endotoxemia**, caused by the presence of lipopolysaccharide cell-wall components of gram-negative bacteria in the blood and characterized clinically by abnormalities of many body systems. Because of the overwhelming importance of endotoxemia in large animals with gram-negative bacterial infections, the focus of this discussion will be on endotoxemia. The abnormalities of endotoxemia include the following:

- Marked alterations in cardiopulmonary function
- Abnormalities in the leukon (neutropenia and lymphopenia) and thrombocytopenia that may lead to coagulopathies
- Increased vascular permeability
- Decreased organ blood flow and metabolism, leading to heart and renal failure
- Decreased gastrointestinal motility
- Decreased perfusion of peripheral tissues, leading to shock
- The need for intensive and complex therapy
- A high case fatality rate

Current therapeutic regimens are only moderately successful in treating endotoxic large animals with clinical signs of **septic shock** (severe sepsis with hypotension [mean arterial blood pressure <65 mm Hg] despite aggressive intravenous fluid therapy).

Gram-negative bacteria such as *E. coli*, *Salmonella* spp., *Pasteurella* spp., and *H. somni*, as examples, cause many diseases of ruminants in which endotoxemia is common. Varying degrees of severity of toxemia occur in diseases such as mastitis, peritonitis, pneumonia and pleuritis, pericarditis, septic metritis, septicemia of neonates, myositis, meningoencephalitis, and some enteritides. Endotoxemia is also one of the most common causes of death in horses affected with gastrointestinal disease from a physical obstruction causing strangulation and ischemic necrosis.

ETIOLOGY

Toxins can be classified as antigenic or metabolic.

Antigenic Toxins

These are produced by bacteria and to a lesser extent by helminths. Both groups of pathogens act as antigens and stimulate the development of antibodies. Antigenic toxins are divided into exotoxins and endotoxins.

Exotoxins

These are protein substances produced by bacteria that diffuse into the surrounding medium. They are specific in their pharmacologic effects and in the antibodies that they induce. The important bacterial exotoxins are those produced by *Clostridium* spp., for which commercial antitoxins are available. They may be ingested preformed, as in botulism, or produced in large quantities by heavy growth in the intestines, such as in enterotoxemia, or from growth in tissue, as in blackleg and black disease.

Enterotoxins

These are exotoxins that exert their effect principally on the mucosa of the intestine, causing disturbances of fluid and electrolyte balance. The most typical example is the enterotoxin released by enterotoxigenic *E. coli,* which causes a hypersecretory diarrhea in neonatal farm animals.

Endotoxins

The endotoxins of several species of gram-negative bacteria are a major cause of morbidity and mortality in farm animals. The endotoxins are lipopolysaccharides found in the outer wall of the bacteria. Endotoxins are released into the immediate surroundings when the bacteria undergo rapid proliferation with production of unused sections of bacterial cell wall or, most commonly, when the bacterial cell wall breaks. Endotoxin gains access to the blood when there is a severe localized infection, such as a coliform mastitis in dairy cattle, or a disseminated infection, such as coliform septicemia in newborn calves.

Gram-negative bacteria are present in the intestinal tract as part of the normal microflora and endotoxins are also present. The endotoxins are not ordinarily absorbed through the intestinal mucosa unless it is injured, as in enteritis or more particularly in acute intestinal obstruction. Ordinarily, small amounts of endotoxin that are absorbed into the circulation are detoxified in the liver but, if hepatic efficiency is reduced or the amounts of toxin are large, a state of endotoxemia is produced. Endotoxins may also be absorbed in large amounts from sites other than the intestine including the mammary gland, peritoneum, abscesses and other septic foci, or from large areas of injured or traumatized tissue. The best known endotoxins are those of *E. coli,* which have been used extensively as models for experimental endotoxemia, and *Salmonella* spp.

The most common causes of endotoxemia in horses are associated with diseases of the gastrointestinal tract including colitis, intestinal strangulation, or obstruction and ileus. Complications associated with foaling and grain overload are also common causes.

Metabolic Toxins

These may accumulate as a result of incomplete elimination of toxic materials normally produced by body metabolism, or by abnormal metabolism. Normally, toxic products

produced in the alimentary tract or tissues are excreted in the urine and feces or detoxified in the plasma and liver. When these normal mechanisms are disrupted, particularly in hepatic dysfunction, the toxins may accumulate beyond a critical point and the syndrome of toxemia appears. In obstruction of the lower alimentary tract there may be increased absorption of toxic phenols, cresols, and amines that are normally excreted with the feces, resulting in the development of the syndrome of autointoxication. In ordinary circumstances in monogastric animals these products of protein putrefaction are not absorbed by the mucosa of the large intestine but when regurgitation into the small intestine occurs there may be rapid absorption, apparently because of the absence of a protective barrier in the wall of the small intestine.

In liver diseases, many of the normal detoxification mechanisms, including oxidation, reduction, acetylation, and conjugation with such substances as glycine, glucuronic acid, sulfuric acid, and cysteine, are lost and substances that are normally present in insufficient quantity to cause injury accumulate to the point where illness occurs. The production of toxins by abnormal metabolism includes the production of histamine and histamine-like substances in damaged tissues. Ketonemia caused by a disproportionate fat metabolism, and lactic acidemia caused by acute ruminal acidosis (grain overload), are two common examples of toxemia caused by abnormal metabolism.

PATHOGENESIS

The specific effects of the particular bacterial exotoxins and metabolic toxins are presented in the relevant sections of specific bacterial diseases in this book. The principles of the effects of bacterial endotoxemia will be presented here.

The total toxic moiety of the lipopolysaccharide molecule is generally similar regardless of the bacterial source. Endotoxemia results in an extraordinary array of pathophysiologic effects, involving essentially all body systems. Of the endotoxins produced by bacteria, the most is known of those produced by *E. coli*.

Endotoxins are normally present in the intestine and, although the intestinal mucosa provides a highly efficient barrier, limiting transmural movement of endotoxins, small quantities are absorbed into the portal blood. These endotoxins are removed by the liver and do not reach the peripheral blood. In hepatic failure the level of endotoxins in plasma is increased. Significantly greater quantities of endotoxins escape the intestine when the mucosal barrier is disrupted by intestinal ischemia, trauma, ionizing radiation, bacterial overgrowth, reduced luminal pH, or inflammatory intestinal disease. These conditions not only temporarily overwhelm the capacity of the liver to remove endotoxin from the portal circulation but also allow transmural movement of endotoxins into the peritoneal cavity from which they reach the peripheral blood.

Endotoxemia may also occur when gram-negative bacteria gain access to tissues and/or blood. Most of these organisms liberate endotoxin during rapid growth and gain access to the blood from primary foci of systemic or superficial tissue infections. One example is coliform septicemia in newborn farm animals. Once the endotoxins gain access to the blood, they are removed from the circulation by the mononuclear phagocyte system, and the response of these phagocytes to the lipopolysaccharides determines the severity of the clinical illness.

Biochemical Mediators

Endotoxins do not cause their effects via direct toxic effect on host cells; instead they induce the production of soluble and cell-bound mediators from a broad range of host cells, including endothelial and smooth muscle cells, polymorphonuclear granulocytes, platelets, thrombocytes, and cells of the monocyte/macrophage lineage. These cells release a series of phlogistic biochemical mediators, which include cytokines, platelet-activating factor, thromboxane A_2, prostaglandins, leukotrienes, proteinases, toxic oxygen metabolites, and vasoactive amines. Macrophages become highly activated for enhanced secretory, phagocytic, and cidal functions by the lipopolysaccharide. The cytokines derived from the macrophages are responsible for many of the pathophysiologic consequences of endotoxemia. Pulmonary intravascular macrophages are the most important producers of cytokines in large animals.

Animals have evolved to recognize and respond to the lipopolysaccharide of gram-negative bacteria. Although lipopolysaccharides may directly injure the host tissue, many of its effects are indirectly mediated through inappropriate activation of host defense mechanisms, culminating in multiple organ dysfunction and failure. Importantly, the response to endotoxin can be attenuated with certain substances. Experimentally, the use of detergents, such as a nonionic surfactant, can attenuate the response of the horse given endotoxin. There is a large individual variability in the response to endotoxin administration. Much of the variability remains unexplained but appears to have a genetic component.[1] Circulating lipopolysaccharide forms complexes in plasma with high-density lipoproteins or a unique plasma protein termed LBP and bound lipopolysaccharide is cleared from plasma within a few minutes by fixed and circulating macrophages in the bovine lung and liver that recognizes the lipopolysaccharide–LBP complex. The lipopolysaccharide–LBP complex binds to a membrane-bound receptor (**mCD14**) on mononuclear cells via a secreted linking protein called MD-2 and then attaches to **toll-like receptor-4** (TLR-4) on the mononuclear cell membrane; the lipopolysaccharide–LBP–mCD14–MD-2 complex is then internalized and lipopolysaccharide is thought to be destroyed in the process. Internalization of lipopolysaccharide activates the intracellular signaling pathway via nuclear factor κB (**NF-κB**), which translocates to the nucleus and causes the transcription of many cytokine genes and release of proinflammatory cytokines, of which **TNF-α**, **IL-1,** and **IL-6** are the most important. Some of the genes activated include those that code for cyclooxygenase 2 (**COX-2**, the inducible form of cyclooxygenase); inducible nitric oxide; **endothelial adhesion molecules**, which promote the adhesion of neutrophils to endothelial surfaces; and chemokines. Some of the membrane-bound receptors (mCD14) are shed from the cell surface into the plasma; in plasma the shed receptors are termed soluble CD14 receptors (sCD14), which play a crucial role in the pathophysiology of endotoxemia. This is because sCD14 receptors can transfer bound lipopolysaccharide directly to mCD14 or the MD-2/TLR-4 complex, activating the intracellular signaling pathway. Increased serum concentrations of sCD14 are associated with the severity of some clinical signs in critically ill horses.[2]

The plasma concentrations of the **arachidonic acid metabolites**, **thromboxane A_2** and **prostacyclin**, increase in several species during endotoxemia, and these eicosanoids are probably responsible for the hemodynamic abnormalities caused by endotoxin. Endotoxin initiates cellular events that activate a cell-membrane enzyme known as phospholipase A_2. Activation of this enzyme leads to the hydrolysis of membrane-bound phospholipids; arachidonic acid is released from the phospholipid portion of damaged mammalian cell membranes. The enzyme cyclooxygenase converts arachidonic acid into intermediate endoperoxides, which are substrates for the formation of prostaglandins, thromboxane, and prostacyclin, by specific synthetases. Platelets are the principal source of thromboxane, which acts as a potent vasoconstrictor and induces platelet aggregation. Most prostacyclins are synthesized in vascular endothelial cells and cause vasodilation and inhibit platelet aggregation. The generalized endotoxin-induced production of cyclooxygenase products may contribute to the multisystemic organ dysfunction, shock, and disseminated coagulopathy that culminates in death.

Tumor necrosis factor-α is released by macrophages and monocytes in a dose-dependent manner early in the course of endotoxemia, and circulating TNF-α activity correlates with the severity and outcome of disease. Infusion of TNF induces an endotoxemic-shock–like syndrome and TNF-α blockade confers marked protection against the effects of gram-negative sepsis and

lipopolysaccharide administration. Experimentally, pretreatment of horses with monoclonal antibody to TNF-α can reduce the hematologic and clinical effects of endotoxin-induced TNF activity and IL-6 activity can be reduced by neutralization of TNF-α. Interleukin-1 release is proinflammatory and leads to pyrexia and the hepatic **acute phase response**. Interleukin-6 contributes to the hepatic acute phase response and promotes B-lymphocyte proliferation. Interleukin-6 may have value as a prognostic indicator, because its plasma concentration appears to be a better predictor of mortality in humans than TNF-α or IL-1.

The systemic effects of endotoxemia can be demonstrated experimentally by parenteral injection of purified endotoxin, TNF-α, or IL-1. In naturally occurring disease, however, the total effect includes those of bacterial toxins plus those of mediators produced by tissues in response to the toxins and the counterbalancing effects of antiinflammatory molecules that are also secreted during sepsis such as IL-4, IL-10, IL-11, and IL-13, and soluble CD14 receptors. The pathophysiologic effects of endotoxemia associated with gram-negative bacteria are summarized here according to their effects on various body systems or functions.

Cardiopulmonary Function

The hemodynamic effects of endotoxemia are manifested in two phases. In the early stages, heart rate and cardiac output commonly increase, although systemic blood pressure remains near or slightly less than normal. This is known as the **hyperdynamic phase** of endotoxemia. Oxygen demands of peripheral tissues are increased during the hyperdynamic phase, resulting in compensatory mechanisms that increase blood flow in an attempt to meet the increased metabolic demands. However, despite the absolute increase in cardiac output and oxygen delivery during this hyperdynamic phase, blood flow still may be inadequate to meet the needs of tissues in a hypermetabolic state. During the hyperdynamic state, affected animals hyperventilate and have decreased capillary refill time and red, congested mucous membranes. Microcirculatory shunting of blood continues in organs such as the gastrointestinal tract and kidney. Ischemia of intestinal mucosa is manifested clinically by ileus and diarrhea may occur. Decreased renal perfusion will result in decreased urine output.

With uncontrolled endotoxemia, the hyperdynamic phase progresses to the **hypodynamic phase** of shock. Changes include decreased cardiac output, systemic hypotension, increased peripheral resistance, and decreased central venous return. Hypothermia, rapid irregular pulses, prolonged capillary refill time, pale to cyanotic mucous membranes, acidemia, and hypoxemia provide clinical evidence of this advanced stage of endotoxemia. The skin and extremities are cool. Severe pulmonary edema and increasing pulmonary hypertension occur. In horses, administration of endotoxin at high dosages can induce circulatory shock with increased heart rate, decreased cardiac output and stroke volume, and concomitant increases in peripheral vascular resistance. The slow intravenous infusion of low doses of endotoxin into conscious horses results in pulmonary hypertension without causing hypotensive hypovolemic shock. Intestinal vasoconstriction occurs as part of the compensatory response to endotoxemia following slow infusion of low dosages of endotoxin.

Infusion of endotoxin into swine induces widespread changes including intense pulmonary vasoconstriction and hypertension, bronchoconstriction, increased vascular permeability, hypovolemia, systemic hypotension, pulmonary edema, hypoxemia, granulocytopenia, and thrombocytopenia. The vascular changes in endotoxemia include increased vascular permeability, changes in vascular tone, and microvascular obstruction. Increased capillary permeability promotes transmural movement of albumin and other colloids that carry water to the interstitial space. The result is hypoalbuminemia, hypoproteinemia, interstitial edema, pulmonary edema, relative hypovolemia, decreased return to the heart, and further decreases in cardiac output. Arterial and arteriolar vasoconstriction develops in the systemic and pulmonary circulations. Prolonged infusion of endotoxin into sheep causes systemic hypotension, pulmonary hypertension, and acute lung injury with progressive respiratory failure.

Activation of the Renin–Angiotensin–Aldosterone System and Dysfunction of the Hypothalamic–Pituitary–Adrenal Axis

The renin–angiotensin–aldosterone system (RAAS) system is activated in critically ill foals, characterized by increased plasma angiotensin-II and aldosterone concentrations. Critically ill foals also have hypothalamic–pituitary–adrenal (HPA) axis dysfunction, which was originally called **relative adrenal insufficiency** (defined as an inappropriately low plasma cortisol concentration or a low ACTH to cortisol ratio).[3] In 2008 a consensus statement developed by human critical care specialists recommended that the preferred term for the HPA axis dysfunction in septic shock is critical illness-related corticosteroid insufficiency, which reflects an inadequate corticosteroid activity for the severity of the patient's illness.

Leukocytes and Platelets

Foals in septic shock most commonly have gram-negative septicemia, but a minority have gram-positive septicemia or mixed bacterial isolates identified on blood culture. The presence of leukopenia or lymphopenia in a foal with presumed sepsis makes it more likely that a gram-negative septicemia is present.[4] Endotoxemia causes an acute and severe neutropenia, which precedes neutrophilia and hemoconcentration. Neutropenia is caused mainly by leukocyte margination and sequestration; persistence of severe neutropenia is a poor prognostic indicator. Hemoconcentration is caused by movement of fluid from the vascular to extravascular spaces. Endotoxin administration causes an immediate accumulation, margination, and activation of leukocytes in the microcirculation, particularly in the alveolar capillaries. This is followed by degranulation and leukocyte migration into the interstitium and endothelial cell damage. Pulmonary sequestration of neutrophils is preceded by endotoxin uptake by pulmonary intravascular macrophages, indicating that the pulmonary macrophage response is pivotal to the subsequent inflammatory response. Leukopenia appears to be an immediate response to endotoxin administration and is observed as early as 5 minutes after infusion. The rebound leukocytosis is caused by humoral effects on the bone marrow; a neutrophil-releasing factor that promotes release of neutrophils from bone marrow; and macrophage colony-stimulating factor, which stimulates granulopoiesis. Colostrum-fed calves have a greater neutrophilia in response to endotoxin than colostrum-deprived calves, possibly because of absorption of a granulopoietic factor from colostrum. Endotoxemia also induces a lymphopenia that is secondary to the release of endogenous corticosteroids and redistribution of lymphocytes from peripheral blood and the spleen to lymphatic tissue.

Thrombocytopenia is consistently observed after endotoxin administration, but occurs later than neutropenia, although it is sustained for a longer period of time. Endotoxin affects platelet function by a number of different mechanisms.

Hemostatic System

Endotoxins cause endothelial injury directly or indirectly, exposing subendothelial collagen and tissue thromboplastin, initiating the intrinsic and extrinsic coagulation cascades, respectively. Endotoxin can initiate the coagulation cascade directly by activation of factor XII or by inducing platelet release of thromboxane and other procoagulant substances. Endotoxin may induce coagulopathy indirectly by endothelial damage with secondary factor XII activation, or through the effects of complement activation. Macrophages and leukocytes have been shown to release a procoagulant substance in response to endotoxin, which functions similarly to factor VII and may also have a role in perpetuating coagulopathy in endotoxemia via the extrinsic pathway.

Disseminated intravascular coagulation is the cause of diffuse microvascular

thrombosis and eventual organ failure subsequent to endotoxemia. The experimental injection of endotoxin can cause diffuse microthrombosis in multiple organ systems. The principal clinical finding of DIC in horses is petechial and/or ecchymotic hemorrhages on mucous membranes and sclerae with a tendency to bleed from venipuncture sites. Spontaneous epistaxis or prolonged hemorrhage after nasogastric intubation may also occur. The result of exaggerated thrombin formation during DIC is widespread fibrin deposition in the microcirculation causing circulatory obstruction and organ hypoperfusion that may lead to ischemic necrosis and failure. The ultimate consequences are multiple organ failure and death.

Thermoregulation

Bacterial endotoxins are potent stimulators of macrophage interleukins, which belong to a family of polypeptides functioning as key mediators of various infectious, inflammatory, and immunologic challenges to the host. Interleukin-1 induces fever, an increase in the number and immaturity of circulating neutrophils, muscle proteolysis through increased prostaglandin E_2 production, hepatic acute phase protein production, and reduced albumin synthesis. Interleukin-1 participates in the acute phase response, which is characterized by fever, hepatic production of acute phase proteins, neutrophilia, and procoagulant activity.

Endotoxins commonly cause a fever followed by hypothermia. Serum IL-6 concentrations are lower in endotoxin-induced colostrum-deprived foals and take longer to reach peak levels compared with colostrum-fed foals. The higher and more rapid concentrations in colostrum-fed foals may be part of a resistance factor in equine neonates. Interleukin-6 plays a key role in host defense, regulating antigen-specific immune responses, hematopoiesis, cellular differentiation, and the acute phase reaction subsequent to an inflammatory insult. Serum TNF-α responds in a similar pattern in colostrum-deprived and colostrum-fed foals given endotoxin, and the mean rectal temperature in colostrum-deprived foals is significantly less than in colostrum-fed foals.

Gastrointestinal Function

Endotoxemia can cause a profound inhibition of gastrointestinal motility, including the stomach and small and large intestines. Postoperative ileus is a frequent and serious complication of equine colic surgery, and there is a good correlation between the incidence of ileus and the presence of ischemic intestine. Low doses of endotoxin infused into ponies produced profound disruption of normal fasting intestinal motility patterns, with an inhibition of gastric contraction amplitude and rate, left dorsal colon contraction product, and small-colon spike rate. In the small intestine, there is an increase in abnormally arranged regular activity and a decrease in irregular activity. Experimental endotoxemia in the horse causes cecal and proximal colonic hypomotility (ileus) by a mechanism involving α-adrenergic receptors, which is reversible by yohimbine. Numerous mediators may interact with the sympathetic nervous system to induce this effect.

The administration of endotoxin to adult dairy cows can reduce the frequency of reticulorumen contractions; this is caused by endotoxin-induced mediators and the effect can be abolished by flunixin meglumine. Endotoxemia also decreases the abomasal emptying rate in cattle and is suspected to play a role in the development of left displaced abomasum.

Carbohydrate Metabolism

The effects on carbohydrate metabolism include a fall in plasma glucose concentration, the rate and degree varying with the severity of endotoxemia; a disappearance of liver glycogen; and a decreased glucose tolerance of tissues so that administered glucose is not used rapidly. Endotoxic shock can result in lactic acidemia and both hyperglycemic and hypoglycemic responses. **Hyperglycemia** occurs early and transiently in endotoxic shock,[5] is accompanied by increased rates of glucose production, and is dependent on mobilization of hepatic glycogen. **Hypoglycemia** is very common in prolonged or severe endotoxemia caused by decreased suckle and septicemia, and hypoglycemia, hypertriglyceridemia, and low plasma insulin concentrations are commonly present in septic foals.[6] Plasma insulin and leptin concentrations may have predictive utility of clinical outcome in critically ill foals.[6] Experimental infusion of endotoxin into sheep results in transient hyperglycemia associated with increased hepatic glucose production followed by hypoglycemia 3 to 8 hours later, when hepatic glucose production decreases. Sympathetic activation occurs early in endotoxemia and is probably responsible for the initial hyperglycemia and glycogenolysis. Blood pyruvate and lactate concentrations increase as a result of poor tissue perfusion and the anaerobic nature of tissue metabolism.

Protein Metabolism

There is an increase in tissue breakdown (catabolism) and a concomitant increase in serum urea nitrogen concentration. The changes observed include alterations in individual plasma amino acid concentrations, increased urinary nitrogen excretion, and increased whole-body protein turnover. The time course changes in the concentrations of plasma amino acids and other metabolites during and after acute endotoxin-induced fever in mature sheep have been described. Rapid and extensive changes occur in the patterns of tissue protein metabolism in the ruminant in response to endotoxin administration, and these changes may contribute to economic losses incurred during infectious disease outbreaks. There is also an alteration in the aminogram (the relative proportions of the amino acids present in blood) and the electrophoretic pattern of plasma proteins. The globulins are increased and albumin decreased as part of the acute phase reaction.

Mineral Metabolism

Negative mineral balances occur. These include hypoferremia and hypozincemia as part of the acute phase reaction as the animal attempts to sequester these microminerals from invading bacteria, but blood copper concentrations are commonly increased concurrently with an increase in blood ceruloplasmin levels.

Reproduction and Lactogenesis

Endotoxemia can cause pregnancy failure in domestic animals, particularly when pregnancy is corpus luteum–dependent. In horses and cattle, experimentally induced endotoxemia causes an immediate and pronounced release of prostaglandin $F_{2\alpha}$. The intravenous administration of endotoxin may influence luteal function by the activation of the arachidonic acid cascade, by a direct effect of prostaglandin $F_{2\alpha}$ on the corpus luteum. The administration of endotoxin to mares pregnant 21 to 35 days results in a decrease in progesterone and fetal death, which can be prevented by daily treatment with a progesterone compound. Similar results have been produced in pregnant dairy cows during the first 150 days of lactation, and coliform mastitis in the first 5 months of lactation is becoming an increasingly important cause of early embryonic death and return to estrus. The uterus of the early postpartum cow is capable of absorbing endotoxin, which may provoke changes in the serum concentrations of prostanoids and is thought to contribute substantially to the systemic signs of toxic metritis in cows. Endotoxin has a negative effect on the genital functions of the ram; the changes in luteinizing hormone and testosterone are similar to those seen after heat-induced stress.

In recently farrowed swine with the mastitis–metritis–agalactia syndrome, it is suggested that the endotoxin from the mammary glands affected with mastitis may be important in the pathogenesis of the agalactia.

Combined Effects on Body Systems

The combined effects of the hypoglycemia, hyper L-lactatemia, and acidemia interfere with tissue enzyme activity and reduce the functional activity of most tissues. Of these factors, acidemia is probably the most important in adult animals; in neonates low plasma glucose concentrations are probably

as important as acidemia because profound hypoglycemia is more commonly encountered in neonatal animals.[5] Experimental endotoxemia in calves at 24 to 36 hours of age causes severe hypoglycemia, lactic acidemia, and hypotension commonly associated with moderate to severe sepsis. The myocardium is weakened, the stroke volume decreases, and the response to cardiac stimulants is diminished. There is dilatation and in some cases damage to capillary walls, so that the effective circulating blood volume is decreased; this decrease, in combination with diminished cardiac output, leads to a fall in blood pressure and the development of circulatory failure. The resulting decline in the perfusion of tissues and oxygen consumption contributes greatly to the animal's decline and to the clinical signs, such as the dark red coloration of the oral mucosa. Respiration is little affected except as it responds to the failing circulation.

There is decreased liver function, and the damage to renal tubules and glomeruli causes a rise in plasma nonprotein nitrogen and the appearance of albuminuria. The functional tone and motility of the alimentary tract is reduced and the appetite fails; digestion is impaired, with constipation usually following. A similar loss of tone occurs in skeletal muscle and is manifested by weakness and terminally by prostration.

Apart from the effects of specific toxins on the nervous system, such as those of *Clostridium tetani* and *C. botulinum,* there is a general depression of function attended by dullness, depression, and finally coma. Because of the suspected role of *E. coli* in the etiology of edema disease of swine, it is noteworthy that some of the characteristic nervous system lesions of that disease are missing from experimentally induced porcine colitoxicosis. Changes in the hemopoietic system include depression of hemopoiesis and an increase in the number of leukocytes—the type of cell that increases often varies with the type and severity of the toxemia. Leukopenia may occur but is usually associated with aplasia of the leukopoietic tissue associated with viruses or specific exogenous substances such as radioactive materials. Most of these pathophysiologic effects of endotoxicosis have been produced experimentally, and it is apparent that very small amounts of endotoxin can contribute greatly to the serious effects of intestinal disease, especially in the horse.

Endotoxin Tolerance

The repeated administration of lipopolysaccharide results in attenuation of the host response, which is known as endotoxin tolerance. This refractoriness to endotoxin-mediated effects comprises two phases. Early phase tolerance is transient, occurs within hours or days, and is not associated with antiendotoxin antibody production. Late phase tolerance requires several days to develop and is long lasting, antigen specific, and the result of antibody production. By this mechanism it is possible for individual animals to survive a dose of endotoxin lethal to the nontolerant individual. Experimentally, horses develop endotoxin tolerance following sequential sublethal infusions of endotoxin.

Hypersensitivity

A secondary effect produced by some toxins is the creation of a state of hypersensitivity at the first infection so that a second infection, or administration of the same antigen, causes anaphylaxis or an allergic phenomenon such as purpura hemorrhagica. Also, a generalized Schwartzman reaction can be induced in pigs by an injection of *E. coli* endotoxin, especially if there are two injections properly spaced (in time). Pigs on a vitamin E–deficient diet are much more severely affected than pigs on a normal diet. Vitamin E is protective, but selenium is not.

Other Infectious Toxins

In mycoplasmosis (*Mycoplasma mycoides* var. *mycoides*), at least part of the toxic effect is attributable to galactans contained in the toxins. These have a noticeably local effect in causing hemorrhages in alveolar ducts and pulmonary vessel walls so that pulmonary arterial blood pressure rises as systemic blood pressure falls. Later lesions are pulmonary edema and capillary thrombosis, which are characteristic of the natural disease of pleuropneumonia. Disseminated intravascular coagulation is also a characteristic of the lesions associated with the toxin of *Pseudomonas* spp.

CLINICAL FINDINGS

Acute Toxemia

The clinical findings of acute toxemia in most nonspecific toxemias are similar. The syndrome varies with the speed and severity of the toxic process but the variations are largely of degree. **Depression**, **anorexia,** and **muscular weakness** are common in acute endotoxemia. **Calves do not suck voluntarily** and may not have a suck reflex. Scant feces are common but a low-volume diarrhea may also occur. The heart rate is increased and initially the intensity of the heart sounds is increased, but later as the toxemia worsens the intensity may decrease. The pulse is weak and rapid but regular. A **fever** is common in the early stages of endotoxemia but later the temperature may be normal or subnormal. In neonatal calves, foals, and lambs a fever may not occur because of failure of thermoregulation or deprivation of colostrum. Terminally, there is muscular weakness to the point of collapse, and death occurs in a coma or with convulsions.

Anterior uveitis, manifested as lacrimation, blepharospasm, photophobia, corneal edema, conjunctival hyperemia, and fibrin in the anterior chamber are commonly present in septicemic foals.[7] Posterior segment lesions, such as multifocal hemorrhages, exudates, and focal retinal detachments may also be visible during ophthalmic examination in foals with minor anterior segment changes. The presence of uveitis is associated with a lower survival rate in foals.[7]

Endotoxemia

When toxin formation or liberation into the circulation is rapid and the toxicity of the toxin high enough, the onset of cardiovascular collapse is rapid enough to cause a state of *toxic* or *septic* shock. The remarkable clinical findings are

- Severe **peripheral vasodilatation** with a consequent fall in blood pressure
- **Pallor of mucosa**
- **Hypothermia**
- **Tachycardia**
- **Pulse of small amplitude**
- **Muscle weakness**

The syndrome is discussed also in the section on Shock, Endotoxemia, and Septic Shock. Endotoxemia is most commonly associated with bacteremia or septicemia caused by infection with gram-negative organisms, especially *E. coli.*

The clinical findings of severe endotoxemia include the following:

- Depression
- Hyperthermia followed by hypothermia
- Tachycardia followed by decreased cardiac output
- Decreased systemic blood pressure
- Cool skin and extremities
- Diarrhea
- Congested mucosae with an increased capillary refill time
- Muscular weakness, leading to recumbency

Renal failure is common and is characterized by anuria. If DIC develops, it is characterized by petechial and ecchymotic hemorrhages on mucous membranes and sclerae with a tendency to bleed from venipuncture sites.

Chronic Toxemia

Lethargy, separation from the group, inappetence, failure to grow or produce, and emaciation are characteristic signs of chronic toxemia.

Localized Infection

With localized infections there are, in addition to the general signs of toxemia, the clinical effects of a space-occupying lesion. These are presented under Localized infections.

CLINICAL PATHOLOGY

Hematology

Changes in total and differential leukocyte numbers occur in endotoxemia. Leukocytosis and neutrophilia occur with mild endotoxemia and leukopenia, neutropenia, and lymphopenia increase in severity and duration with increasing severity of endotoxemia. Endotoxin-induced rebound neutrophilia

may occur and is attributed to an accelerated release of neutrophils from the bone marrow reserve into the circulation through generation of the neutrophil-releasing factor.

In experimental sublethal endotoxemia in foals 3 to 5 days of age, there is leukopenia followed by leukocytosis, hypoglycemia, increased prothrombin time and partial thromboplastin time, and mild hypoxemia.

Coagulopathies are common in critically ill foals, particularly those with sepsis and septic shock.[8,9] Clinical evidence of bleeding is associated with severity of shock in neonatal foals, and is present in 67% of septic shock foals, 39% of septic foals, and 13% of nonseptic foals.[8] Septic foals demonstrate marked activation of the coagulation and fibrinolytic systems, and many meet the criteria for DIC. As a consequence, plasma concentration of D-dimer, a fibrin-linked degradation product from fibrinolysis, is increased in septic foals, with a normal plasma D-dimer concentration having clinical utility as a predictor for the absence of sepsis.[9]

Serum Biochemistry

A low plasma glucose concentration, high serum urea concentration, and a low serum albumin and total protein concentration are usually present in acute endotoxemia. Decreased albumin and total protein concentrations are in response to increased capillary permeability, whereas the azotemia reflects a decreased glomerular filtration rate. Adult herbivores have a mild hypocalcemia, hypomagnesemia and hypokalemia, and hypophosphatemia, which most likely reflects inappetence and decreased gastrointestinal tract motility. Plasma iron concentration is decreased, which reflects redistribution of iron to intracellular storage sites, particularly in the liver. Plasma zinc concentration is decreased via a cytokine-mediated redistribution of zinc to the intracellular compartment, possibly through the zinc transporter Zip14.[10] Hypoferremia and hypozincemia are focused on decreasing the availability of important mineral elements for bacterial replication. High plasma cortisol concentrations are associated with a higher mortality rate in sick neonatal foals.[11]

In more chronic toxemic states, a high serum total protein concentration, with globulins noticeably increased on electrophoretic examination, is more common.

Endotoxin

Endotoxin can be detected in the platelet-rich plasma of critically ill horses and cattle using the chromogenic Limulus amoebocyte lysate (LAL) assay, which is a biologic test using the hemolymph of the horseshoe crab. The results of most studies indicate that higher plasma endotoxin concentrations in critically ill animals are associated with an increased mortality rate.[12] However, the LAL assay is not widely available and is usually run as a research test.

NECROPSY FINDINGS

Gross findings at necropsy are limited to those of the lesion that produces the toxin. Microscopically, there is degeneration of the parenchyma of the liver and the glomeruli and tubules of the kidney and the myocardium. There may also be degeneration or necrosis in the adrenal glands.

TREATMENT

The principles of treatment of endotoxemia or septic shock include (1) removal of the foci of infection; (2) administration of antimicrobial agents with a gram-negative spectrum; (3) aggressive fluid and electrolyte therapy to combat the relative hypovolemia, systemic hypotension, hypoglycemia, and electrolyte and acid-base disturbances; and (4) NSAIDs or glucocorticoids for the inhibition of products of the cyclooxygenase pathway. These four treatments are routinely applied and are called goal-directed therapy. Other treatments that may be applied in selected cases include the administration of inotropic agents or vasopressors, intravenous or intramammary administration of polymyxin B, continuous rate infusion of lidocaine, and intravenous administration of hyperimmune plasma containing antibodies directed against core lipopolysaccharide antigens. Potential therapeutic agents under investigation (such as pentoxifylline, dimethyl sulfoxide,[12a] tyloxapol, and insulin) cannot be currently recommended for treating endotoxemic animals because of the lack of clinical studies in animals with naturally acquired endotoxemia.

Endotoxemic or septic shock occurs when the animal is overwhelmed by an infection or endotoxemia. This is a complex disease that requires a rapid and comprehensive treatment plan, including those interventions in the following sections.

Removal of Foci of Infection

Removal of endotoxin before it can be absorbed is an important cornerstone of treatment in foals and calves with omphalophlebitis, horses with ischemic or necrotic bowel, and lactating dairy cattle with coliform mastitis.

Antimicrobial Agents

Bactericidal gram-negative antimicrobial agents are always indicated whenever there is evidence of septicemia or a localized infection causing endotoxemia. The choice and route of administration will depend on the pathogens suspected of causing the infection and endotoxemia and the site of infection. The speed of kill of gram-negative bacteria may be an important clinical issue, because antimicrobial agents with a rapid kill (such as moxalactam) can produce a bolus release of endotoxin into the bloodstream by punching multiple holes in the bacteria, causing a rapid explosion of the bacteria caused by osmotic fluid shifts and bolus release of endotoxin. Antimicrobial agents that alter the cell wall of gram-negative bacteria can theoretically produce a bolus release of endotoxin when administered to animals with gram-negative septicemia. On this basis, β-lactam antibiotics effective against gram-negative bacteria should theoretically be avoided; however, clinical experience has not indicated deleterious effects following administration of β-lactam antibiotics. Moreover, coadministration of aminoglycosides blocks the potential bolus release of endotoxin by β-lactam antibiotics. However, it is clinically prudent to ensure that whenever antimicrobial treatment is initiated in endotoxemic animals that NSAIDs are administered concurrently. It is also important to adjust dosage rates of water-soluble antibiotics in neonatal animals because some antibiotics, such as gentamicin in foals and ceftiofur in calves, have a larger volume of distribution and slower clearance in neonatal animals.[13]

Aggressive Fluid Therapy

The intravenous infusion of large quantities of fluids and electrolytes is a high priority in the management of endotoxemia. Maintenance of peripheral perfusion is essential to any therapeutic regimen for treatment of endotoxic shock. Large volumes of isotonic fluids have been standard practice. Recent studies have identified concerns with bolus fluid resuscitation in septic patients, such as 20 to 40 mL/kg in the first hour.[14,15] These findings suggest that rapid resuscitation should focus on the use of low-volume hypertonic saline, and that traditional high-volume crystalloid solution resuscitation should not use bolus administration. Instead, traditional high-volume crystalloid fluid resuscitation should focus on slower rates of administration (<20 mL/kg/h); lactated Ringer's solution or other balanced electrolyte solution should therefore be administered over several hours. A beneficial response is noted by the following:

- Correction of peripheral vasoconstriction
- Restoration of an acceptable pulse quality
- Return of urine output
- Increase in the central venous pressure
- Restoration of mean arterial blood pressure to >65 mm Hg
- Restoration of cardiac output
- Restoration of oxygen delivery to acceptable levels

It may be necessary to deliver fluids in amounts equivalent to 0.5 to 1.0 times the estimated blood volume of the animal over a period of several hours.

Hypertonic Solutions

The use of hypertonic saline, 7.5% NaCl, may enhance tissue perfusion and decrease the volume of subsequent fluids required for a beneficial response. Experimentally, the use

of hypertonic saline in sublethal *E. coli* endotoxemia in mature horses was associated with a more effective cardiovascular response than was an equal volume of isotonic saline solution. Cardiac output is increased and peripheral vascular resistance is decreased compared with results for isotonic saline controls. Hypertonic saline rapidly expands the plasma volume and increases preload by acting as an effective osmotic agent in the extravascular compartment, causing a translocation of fluid from the intracellular space and gastrointestinal tract.

Hypertonic sodium bicarbonate is widely used for the initial treatment of metabolic acidosis in endotoxemic adult horses. However, in horses with experimental endotoxemia, hypertonic sodium bicarbonate did not normalize blood pH, and it increased blood L-lactate concentrations and caused hypokalemia, hypernatremia, and hyperosmolality.

Glucose and Insulin Administration

Glucose should always be included in the infusion fluids because hypoglycemia, increased glucose utilization, and inappetence are usually present in endotoxemic animals. The appropriate target range for plasma glucose concentration in septic humans and domestic animals is unknown. Hyperglycemia, hyperinsulinemia, and low leptin concentrations are associated with increased morbidity and mortality in horses, and endotoxemic horses have impaired glucose metabolism and decreased insulin sensitivity.[6,16] Originally, blood glucose concentration was maintained at <180 to 200 mg/dL, but recent approaches have focused on maintaining blood glucose concentrations within the reference range for each species.[17] Coadministration of glucose (37 mg/kg/h, equivalent to 30 kcal/kg/day) and insulin (0.07 U/kg/h) as continuous rate infusions is effective in preventing hypoglycemia in healthy adult horses and adult horses with experimentally induced endotoxemia.[17] Continuous rate infusions of insulin appear to provide better glycemic control than intermittent subcutaneous insulin injections.[17] It should be noted that insulin has an affinity for binding to fluid administration lines.

Inotropic Agents, Vasopressors, and Local Anesthetics

Critically ill neonates and adults may require the administration of positive inotropic agents and vasopressor agents. Inotropic agents increase cardiac contractility, increasing cardiac output and oxygen delivery. Vasopressor agents increase systemic arterial blood pressure. Inotropic and vasopressive agents are usually administered for short periods of time during anesthesia or recovery from anesthesia.

Dobutamine (0.5–1 µg/kg BW/min in adults and 1–3 µg/kg BW/min in neonates) is the inotropic agent of choice in large animals, although human studies prefer dopamine and norepinephrine. Dobutamine should be diluted in 0.9% NaCl, 5% dextrose, or lactated Ringer's solution and the dose carefully titrated by monitoring heart rate and rhythm and blood pressure. **Norepinephrine** (0.01–1 µg/kg BW/min) is the vasopressor agent of choice in hypotensive animals that have not responded to intravenous fluid loading or dobutamine. Norepinephrine should be diluted in 5% dextrose and the dose titrated because there is marked individual variability in the response to norepinephrine administration.

Lidocaine 1.3 mg/kg as bolus intravenous injection followed by a continuous rate infusion of 0.05 mg/kg/minute mitigated some of the effects of endotoxin administration in healthy adult horses, but the effects were not profound and lidocaine was administered 20 minutes after endotoxin administration.[18] Clinical studies of animals with naturally acquired endotoxemia or septic shock are needed before lidocaine administration can be recommended.

Nonsteroidal Antiinflammatory Drugs

The NSAIDs have been in general use for the treatment of endotoxemia because of their analgesic, antiinflammatory, and antipyretic properties. They suppress production of thromboxane and prostaglandins and reduce the acute hemodynamic response to endotoxemia. Although NSAIDs are routinely administered to endotoxemic animals, a large-scale study in humans with severe sepsis failed to demonstrate an effect of ibuprofen on mortality, despite improvement in a number of clinical indices and decreased production of arachidonic acid metabolites.

Flunixin meglumine is the NSAID most commonly used in the treatment of endotoxemia in horses and cattle and remains the NSAID of choice for treating this condition. It is a potent inhibitor of cyclooxygenase and its action on this enzyme to inhibit the synthesis of eicosanoids, such as prostaglandin E_2, may explain the antiinflammatory action of the drug. Flunixin meglumine also modulates the acute hemodynamic changes and hyper L-lactatemia commonly seen during endotoxemia, which may increase survival rate. Endotoxin-stimulated production of thromboxane B_2 (a metabolite of thromboxane) and prostaglandin $F_{1\alpha}$ are blocked by flunixin meglumine at 0.25 and 0.1 mg/kg, respectively, which resulted in a widespread clinical use of an antiendotoxemic dose of 0.25 mg/kg. However, the term *antiendotoxemic effect* should be discouraged because it is misleading, and a dose rate of 1.1 mg/kg BW IV every 12 hours is recommended in horses. Care should be taken to ensure adequate hydration in endotoxemic animals receiving multiple doses of flunixin meglumine. It is usually given intravenously US label is only for IV use in cattle at 1.1 to 2.2 mg/kg BW every 24 hours. The oral administration of flunixin meglumine at 2.2 mg/kg BW before experimentally induced endotoxemia in cattle exerted an effect equal to that after intravenous administration by minimizing the fever and prostaglandin $F_{2\alpha}$ metabolite concentration induced by the endotoxin administration. However, flunixin meglumine did not prevent the decrease in peripheral mononuclear cells and polymorphonuclear leukocytes seen after endotoxin administration. The bioavailability of flunixin meglumine in cattle ranges from 53% to 60% in cattle and 80% to 86% in horses.

Flunixin meglumine was superior to prednisolone and dimethylsulfoxide in providing protection and mitigating the effects of experimental endotoxemia in calves, but it was only partially protective against the hypotension and hyper L-lactatemia and failed to alter the hypoglycemic effect. Although flunixin meglumine is the most widely used NSAID in endotoxemia, there is little experimental evidence demonstrating its efficacy over other NSAIDs. Ketoprofen, flunixin meglumine, ketorolac, and phenylbutazone have been compared for treating experimental endotoxemia in calves. Each drug modified the response to endotoxin but none was clearly superior to the others in modulating the clinical signs. Phenylbutazone given to calves at 5 mg/kg BW/day intravenously for 5 days suppressed the clinical response to experimental endotoxin in neonatal calves with progressively increasing amounts of endotoxin until large amounts were given. There were no significant differences between ketoprofen and flunixin meglumine in in vitro studies of the effects of the drugs on equine peripheral blood monocytes. An interesting finding in adult dairy cows with experimentally induced endotoxemia was that flunixin meglumine and phenylbutazone delayed the plasma clearance of endotoxin by 2 to 3 and 6 to 12 times, respectively, suggesting that both NSAIDs may prolong the clinical signs of endotoxemia in cattle, possibly by interfering with hepatic metabolism. The clinical significance of this finding is unknown. Flunixin meglumine has been associated with impaired healing of the intestinal tract, injury to the gastrointestinal tract and kidneys, and increased intestinal permeability to lipopolysaccharide.[19]

Glucocorticoids

Glucocorticoids (corticosteroids) have been used extensively in the past for the treatment of endotoxemia and shock. The rationale for the use of glucocorticoids includes the following:

- Organelle and cell-membrane stabilization
- Improved cellular metabolism and gluconeogenesis
- Improved microcirculation

- Decreased production of endogenous toxins such as myocardial depressant factor
- Decreased leukocyte activation and degranulation
- Minimal reticuloendothelial depression and histologic organ damage

The corticosteroids most commonly used in endotoxic shock were hydrocortisone, prednisolone, methylprednisolone, and **dexamethasone**. However, these corticosteroids have been most beneficial therapeutically when given as a pretreatment in experimental situations. Published evidence, based on controlled clinical trials, that corticosteroids are efficacious in naturally occurring cases of endotoxemic shock in humans and farm animals is lacking.

Glucocorticoids improve capillary endothelial integrity and tissue perfusion, decrease activation of complement and the clotting cascade, decrease neutrophil aggregation, stabilize lysosomal membranes, protect against hepatic injury, and improve survival rate. However, there are concerns about their use in septicemic animals because they may cause immunosuppression. Large doses are required, which are cost-prohibitive in farm animals when they are used most commonly in acute cases and in doses such as 1 mg/kg BW of dexamethasone intravenously every 24 hours. It is currently thought that glucocorticoids, if they are to be clinically effective, **must be given as early as possible** to endotoxemic animals. Glucocorticoids are less frequently administered to endotoxemic animals as a result of a number of studies supporting the use of NSAIDs.

Polymyxin B

Polymyxin B is a cationic antibiotic that has an appropriate charge distribution to stoichiometrically bind to the lipid A moiety of lipopolysaccharide. Parenteral administration of antimicrobial doses of polymyxin can lead to nephrotoxicity, neurotoxicity, and ototoxicity, but lower, nonnephrotoxic doses are effective in ameliorating the effects of endotoxin in horses. Specific endotoxin binding agents, such as intravenous polymyxin B, are therefore theoretically beneficial and have shown some efficacy in endotoxemic foals and adult horses when administered at a recommended dose of 1 mg (6000 U)/kg BW administered at 8-hour intervals.[20,21] The benefits attributed to polymyxin B administration in endotoxemic animals are not profound, and definitive efficacy studies have not been completed in endotoxemic calves or horses with naturally acquired endotoxemia. In particular, because the efficacy of polymyxin B is focused against circulating lipopolysaccharide before it is bound to LBP, it is currently thought that polymyxin B, like glucocorticoids, must be given as early as possible to endotoxemic animals if it is to be clinically effective. Attractive features of polymyxin B are its shelf-life and ease of storage, ease of administration (intravenous bolus), cost, and 8-hour duration of effect.

Hyperimmune Serum and Plasma Transfusion

Hyperimmune serum is commercially available for the treatment of endotoxemia in the horse. The rationale is that antilipid A antibodies bind circulating lipopolysaccharide, preventing the subsequent inflammatory cascade. On theoretical grounds it is difficult for an antibody to competitively inhibit the strong binding affinity and high specificity between lipopolysaccharide and LBP. There are also difficulties with spatial hindrance between IgG and the R-core subfraction of lipopolysaccharide that contains lipid A. It is therefore difficult to think that antiserum against core lipopolysaccharide antigens will ever be therapeutically successful in animals with naturally acquired endotoxemia, and large-scale studies in septic humans have failed to observe a decrease in mortality following the administration of hyperimmune core-lipopolysaccharide plasma. However, the administration of plasma containing antiserum has many theoretical advantages separate from those of endotoxin neutralization, and it may be that plasma transfusion alone is beneficial.

The use of antiserum to the rough mutant of *E. coli* 0111:B4(J-5) as a treatment of experimental or naturally acquired endotoxemia has been demonstrated in some, but not all, studies in adult horses but not in foals and calves. One study in foals indicated that the administration of hyperimmune serum resulted in a worsening of the clinical signs and augmented release of TNF-α and IL-6. A later study identified a higher survival rate to discharge for septic and critically ill foals receiving hyperimmune plasma rich in anti-endotoxin antibodies; however, survival rate in a subset of the foal population that had gram-negative septicemia was not significantly altered by plasma administration.[22] Antiserum does not appear as rational a treatment for neutralizing circulating lipopolysaccharide as polymyxin B and, for this reason, the administration of hyperimmune plasma or serum should probably be reserved for animals that fail to improve after polymyxin B administration.

Pentoxifylline and Ethyl Pyruvate

Pentoxifylline is a methylxanthine derivative that has been used in foals with septicemia because it has been shown to suppress production of TNF-α in a dose-dependent manner. Oral administration of pentoxifylline at 10 mg/kg BW produces serum concentrations similar to those achieved at therapeutic levels in humans when administered every 12 hours.[23] Clinical trials administering pentoxifylline in large animals with naturally occurring endotoxemia or septic shock have not been performed.

Ethyl pyruvate is a stable derivative of pyruvate that has been shown to diminish the clinical effects of endotoxemia when rapidly administered to horses intravenously at 150 mg/kg BW in lactated Ringer's solution immediately after endotoxin administration.[15,24] The mechanism of action is thought to be via binding to NF-κB and diminished expression of proinflammatory cytokines. There is a potential for synergism between ethyl pyruvate and flunixin meglumine in the treatment of endotoxemia in horses, but clinical trials have not been performed.

Anticoagulants

Disseminated intravascular coagulation (hypercoagulative states) can be treated with heparin in an attempt to impair intravascular coagulation. Much of the knowledge regarding DIC in endotoxemia has been extrapolated from species other than large animals, and there is little objective information available to guide the clinical use of anticoagulants in endotoxemic large animals. Instead, the focus of treatment should be aggressive intravenous fluid administration to maximize microcirculation.

CONTROL OF ENDOTOXEMIA

The hallmarks of a control program are to decrease the risk or prevent neonatal septicemia, institute early and aggressive treatment of gram-negative bacterial infections, and ensure prompt surgical removal of ischemic and damaged intestine. Vaccines based on core lipopolysaccharide antigens are widely used in North America to decrease the incidence and severity of gram-negative mastitis in lactating dairy cows (see Chapter 20) and gram-negative infections in pigs, but similar vaccination protocols have not been developed for horses, small ruminants, and New World camelids, which are also at risk for endotoxemia.

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Toxemia in the Recently Calved Cow

A special occurrence of toxemia of major importance in food-animal practice is that caused by several diseases in the period immediately after calving in the dairy cow (and less frequently the beef cow). The syndrome is characterized clinically by lack of appetite, marked reduction in milk yield, reduced ruminal and intestinal activity, dullness, lethargy, and a fever. The term *parturition syndrome* has been used in the past but is no longer recommended, because its general adoption could dissuade clinicians from seeking more accurate identification of the component disease.

The diseases commonly included in the broad category of periparturient toxemia are as follows:

- Acetonemia
- Fat cow syndrome and pregnancy toxemia
- Mastitis
- Peritonitis
- Puerperal metritis

A brief account of puerperal metritis in cattle is provided here because of the common occurrence of puerperal metritis and the profound nature of the systemic signs of illness in affected cattle. All the other diseases are described under their respective headings in this book.

PUERPERAL METRITIS IN CATTLE

Puerperal metritis occurs primarily in dairy cows within the first 7 days after parturition (but up to 21 days after parturition) and is characterized clinically by systemic signs of sickness including fever (≥39.5°C); dullness; inappetence; increased heart rate; low milk production; an enlarged uterus for the number of days postpartum with poor uterine tone; and a copious, foul-smelling red-brown watery uterine discharge, with or without retention of the fetal membranes. Puerperal metritis is one of the most costly diseases of dairy cattle, with an estimated total cost per case of $329 to $386. **Clinical metritis** is defined as the presence of an abnormally enlarged uterus and a purulent uterine discharge detectable in the vagina within 21 days postpartum in an animal that is not systemically ill. This should be compared with **clinical endometritis**, which is characterized by the presence of a purulent (>50% pus) uterine discharge detectable in the vagina 21 days or more after parturition, or the presence of a mucopurulent (approximately 50% pus and 50% mucus) discharge detectable in the vagina 26 days or more after parturition.

ETIOLOGY

The etiology is multifactorial. It is assumed that a combination of impaired neutrophil function; abnormal postpartum uterine involution, often with retained fetal membranes; and infection of the uterus precipitates the disease. A mixed bacterial flora is common, which includes organisms such as *Trueperella* (*Arcanobacterium* or *Actinomyces* or *Corynebacterium) pyogenes, Fusobacterium necrophorum, Prevotella melaninogenica, Bacteroides* spp. *Streptococcus uberis;* these commonly predominate as a mixed flora in cows with retained placenta and postpartum metritis, particularly after 5 to 7 days postpartum. Other observations found that *E. coli* predominates in cows with retained placenta, particularly in the first 5 to 7 days postpartum. *Staphylococcus* spp., *Streptococcus* spp., *Pseudomonas aeruginosa, Proteus* spp., and occasionally *Clostridium* spp. are also present; the last can occasionally result in tetanus if *C. tetani* proliferates. High-throughput automated DNA pyrosequencing of uterine fluid from dairy cows with metritis on postpartum days 1 to 3 and 8 to 10 indicated that *Fusobacterium* and *Bacteroides* accounted for more than 83% of all bacterial DNA.[1] Slow-growing facultative anaerobic gram-positive bacteria (*Helcococcus kunzii* and *H. ovis*) have also been cultured from the uterine fluid in dairy cows with puerperal metritis.[2]

The current view is that *E. coli* colonization within the first 3 days after parturition creates a suitable intrauterine environment that leads to puerperal metritis by facilitating the establishment and persistence of *F. necrophorum* and other gram-negative anaerobic bacteria in the endometrium and uterine lumen. Early intrauterine colonization with *E. coli* strains that carry the virulence factor *fimH* that facilitate adhesion to endometrial epithelial and stromal cells increases the odds of developing metritis by 4.6 to 4.7.[3] Clinical signs of puerperal metritis are most likely caused by intrauterine colonization with the strict anaerobic bacteria *F. necrophorum* and the facultative anaerobe *T. pyogenes,* which are the most likely source for the fetid odor of affected cattle. Another important virulence factor for developing metritis appears to be *lktA* (leukotoxin) of *F. necrophorum.*[3] Together, this sequential colonization pathway suggests that decreasing fecal contamination of the vagina and uterine lumen (and therefore the colonization by *E. coli*) in the immediate postpartum period should decrease the incidence of puerperal metritis in cattle. Interestingly, it appears that uterine colonization by *E. coli* in the early postpartum period increases the risk of puerperal metritis but decreases the risk of clinical endometritis, whereas uterine colonization by *S. uberis* in the early postpartum period increases the risk of clinical endometritis.[4]

EPIDEMIOLOGY

The disease occurs in cows of all ages but is most common in mature dairy cows within 2 to 10 days of parturition. Factors strongly associated with an increased incidence of puerperal metritis include:

- Large herds
- Dystocias
- Retained fetal membranes
- Decreased feed intake in the last 2 weeks before parturition[5]
- Overconditioning or underconditioning of cows

Puerperal metritis is most common in cows with fetal membranes retained for more than 24 hours following parturition. Several cause and effect relationships have been implicated for retained placenta in cattle, with impaired neutrophil function being the most likely underlying cause.

Retention of fetal membranes is associated most commonly with abortion, dystocia, and multiple births. The most commonly used definition is the presence of fetal membranes 12 hours or more following parturition but retention for more than 6 to 8 hours is the time limit set, particularly in older cows. Approximately 10% of dairy cows have retained fetal membranes after parturition. The incidence between herds ranges from 3% to 27%. In single calvings the incidence is about 10% and in twin calvings 46%. Puerperal metritis occurs in about 50% of cows with retained placenta, and puerperal metritis is 25 times more likely to occur with retained placenta than without. Other less common risk factors for retained placenta include the following:

- Old age
- Increased gestation length
- Hormone-induced parturition
- Fetal anasarca
- Uterine prolapse
- Fetotomy

The factors that are associated with retention of the placenta are indirectly associated with the development of puerperal metritis. The forceful removal of retained placenta, particularly in the first 4 days postpartum, is also considered to be a major predisposing factor to puerperal metritis. Recent work indicates that the fundamental cause of retained placenta is impaired neutrophil function, in which the ability of the maternal immune system to recognize the placenta as "foreign" tissue is impaired. Specifically, the separation of a placenta from healthy caruncles in a normal calving depends on incompatibility between maternal and fetal major histocompatibility complex Class I expressed on the epithelium within the fetomaternal unit.[5] In other words, retained placenta is an indication of an impaired immune system, which may be secondary to periparturient deficiency of vitamin E or selenium, or a greater degree of negative energy balance prepartum. Lack of uterine motility is thought to play a minimal to no role in the development of retained placenta and puerperal metritis.

Uncomplicated cases of retained fetal membranes in cattle have no significant effect on subsequent fertility and the calving-to-conception interval. However, it is significantly increased in cows that develop puerperal metritis as a sequel to retained fetal membranes. Vitamin E and selenium deficiency, placentitis, and vitamin A deficiency have also been suggested as factors.

PATHOGENESIS

Failure of normal uterine involution combined with retention of the fetal membranes and infection of the uterus with a mixed bacterial flora results in puerperal metritis and a severe toxemia. There is diffuse necrosis and edema of the mucosa and wall of the uterus. There is marked accumulation of foul-smelling fluid in the uterus and enlargement of the uterus. Absorption of toxins results in severe toxemia, particularly in fat cows, which may develop irreversible fatty degeneration of the liver.

CLINICAL FINDINGS

Affected cows become acutely anorexic and toxemic within 2 to 10 days after parturition. There is a marked drop in milk production. The temperature is usually elevated, in the range of 39.5 to 41.0°C, but may be normal in the presence of severe toxemia. A consensus has not been reached on the threshold rectal temperature cut point for a diagnosis of toxic metritis, because increased ambient temperatures in summer also increase core body temperature, and dystocia-related trauma in primiparous cattle appears to increase rectal temperature. The optimal rectal temperature cut point indicating a cow has puerperal metritis during the first 10 days in milk in dairy cattle is approximately ≥39.5°C (range is >39.2°C to >39.7°C), with the cut point higher for primiparous than multiparous cattle.[6,7] It has become popular on some large dairies to measure the rectal temperature each morning for the first 10 days of lactation, primarily as a screening test for puerperal metritis. One study suggested that rectal temperature measurement from day 5 to 10 of lactation was sufficient, because this protocol did not negatively impact the ability to successfully treat cases of puerperal metritis that are diagnosed before day 5 of lactation.[8] Although an elevated rectal temperature is considered a requirement for a diagnosis of **puerperal metritis**, it is important to recognize that some cows can have systemic signs of illness and a serosanguinous uterine discharge and a normal rectal temperature. An elevated rectal temperature in the 5 to 10 day postpartum period should not be used as the sole criteria for a diagnosis of **clinical metritis**, because this will lead to overtreatment of healthy cows. For example, 14% to 66% of healthy cattle exhibit at least one rectal temperature ≥39.5°C in the first 10 days of lactation, 59% of cows with clinical metritis maintain a rectal temperature <39.5°C, and rectal temperature is impacted by the age of the animal, environmental conditions, and the method used to measure rectal temperature.[9]

The heart rate is usually elevated and may range from 96 to 120 beats/min. The respiratory rate is commonly increased to 60 to 72 breaths/min, and the breath sounds may be louder than normal. Rumen contractions may be markedly depressed or absent. A foul-smelling fluid diarrhea may occur. Mild to moderate dehydration is common because affected cows do not drink normally.

Retention of the fetal membranes is common, and manual examination of the vagina reveals the presence of copious quantities of foul-smelling, dark brown to red fluid containing small pieces of placenta pooled in the vagina. When the fetal membranes are retained and protruding through the cervix, the hand can usually be inserted through the cervix and into the uterus. Manual exploration of the uterine cavity will usually reveal the state of adherence of the fetal membranes. Often the fetal cotyledons are firmly attached to the maternal caruncles, but occasionally they have separated from the caruncles and the placenta can be removed by simple traction.

Rectal examination usually reveals that the uterus is large, flaccid and lacks the longitudinal ridges that indicate normal rate of involution. In large cows the enlarged, flaccid uterus may be situated over the pelvic brim extending into the ventral part of the abdomen and thus may not be easily palpable and examined. This is an important finding because the fetal membranes may be fully retained in the uterus and no evidence of their presence may be detectable on examination of the vagina and the cervix, which may be almost closed, making examination of the uterus impossible.

The presence of viscid, nonodorous mucus in the cervix and anterior part of the vagina usually, but not always, indicates that the fetal membranes have been expelled. When evidence of a retained placenta and puerperal metritis cannot be found on examination of the reproductive tract, either by rectal palpation or vaginal examination, and if the history indicates some uncertainty about the disposition of the placenta, a retained placenta and puerperal metritis should be considered until proven otherwise. Persistent toxemia, tachycardia (100–120 beats/min), anorexia, and rumen stasis that cannot be explained by any other disease should arouse suspicion of septic metritis until proved otherwise.

Tenesmus occurs most commonly when the fetal membranes are retained and this causes irritation in the vagina. Manual examination of the vagina may also stimulate tenesmus.

The course of the disease varies from 2 to 10 days. Those cases with retained fetal membranes may be toxemic and not return to normal appetite until the membranes are fully expelled, which may take up to 10 days. Necrotic pieces of placenta may be passed for 10 to 14 days after treatment is begun.

CLINICAL PATHOLOGY

Hematology

Leukopenia, neutropenia, and a degenerative left shift occur in acute cases and the degree of change parallels the severity of the disease and reflects the absorption of endotoxin from the uterine lumen. Bacteremia caused by *Bacillus* spp. has been identified in 53% (9/17) of cattle with puerperal metritis; however, bacteremia did not reflect the most common isolates from the uterus of affected cattle.[10] The prevalence of bacteremia in healthy dairy cattle at the same stage of lactation (53%, 8/15) was similar to that of cattle with puerperal metritis.

Vaginal/Uterine Fluid

Samples of fluid from the vagina and uterus reveal a mixed bacterial flora including *E. coli, F. necrophorum, T. pyogenes, Proteus* spp., *Staphylococcus* spp. and *Streptococcus* spp., with the predominant bacteria varying mainly with time since parturition. Generally, *E. coli* predominates in the first 5 days after parturition, whereas *F. necrophorum* and *T. pyogenes* predominate after the first 5 days in cattle with retained placenta. Uterine lochia of cattle with retained placenta had a much higher endotoxin concentration in the first 2 days postpartum than did lochia of healthy cattle or cattle that had undergone a dystocia but did not have retained placenta. Endotoxin was not detected in the plasma of cattle with high

lochial endotoxin concentrations, indicating effective systemic clearance.

Other Samples and Tests

Ketonuria may occur in animals that are overconditioned and mobilize excessive quantities of depot fat, resulting in ketosis. **Liver function tests** reveal a decrease in liver function, which may be irreversible in excessively fat cows. A study evaluating the detection of the fetid smell of puerperal metritis indicated considerable subjectivity into the classification of healthy and diseased animals, whereas an instrument that acted as an "electronic nose" was more repeatable but not sufficiently accurate for on-farm use.[11] A subsequent reanalysis focusing on days 2, 5, and 10 using a proprietary algorithm suggested that test performance could be improved.[12]

NECROPSY FINDINGS

The uterus is enlarged, flaccid and may contain several liters of dark brown, foul-smelling fluid with decomposed fetal membranes. The uterine mucosa is necrotic and hemorrhagic and the wall of the uterus is thickened and edematous. In severe cases, fibrin may be present on the serosal surface of the uterus. The liver may be enlarged and fatty and there is usually mild degeneration of the myocardium and kidneys. The presence of perineal, perivulvar, and perivaginal gelatinous or hemorrhagic edema along longitudinal vulvar, vaginal, cervical, and uterine body tears is suggestive of infection with *C. septicum*.[13]

Fat Cow Syndrome

This is characterized by excessive body condition, anorexia to inappetence, ketonuria, a marked loss in milk production, decreased rumen movements, and delayed involution of the uterus. The temperature is usually normal but the heart and respiratory rates may be increased. The prognosis is poor in cows that are totally anorexic; those that are inappetent will usually recover after 5 to 7 days of supportive therapy.

Acute Diffuse Peritonitis

This may occur in cows within a few days postpartum and is characterized by anorexia, toxemia, a spontaneous grunt, or one that can be elicited by deep palpation, rumen stasis, fever and the presence of an inflammatory exudate in the peritoneal fluid.

Peracute and Acute Mastitis

This occurs in cows within a few days after parturition and is characterized by severe toxemia, swelling of the affected quarters, and abnormal milk.

TREATMENT

Conservative Therapy

Uncomplicated cases of retained fetal membranes without any evidence of clinical toxemia usually do not require parenteral or intrauterine treatment. The placenta is typically retained for an average of 7 days. Cows with retained fetal membranes and tenesmus should be examined vaginally to ensure that there is no evidence of injury to the vagina or cervix. In cows with tenesmus, if the placenta is detached and loose it should be removed by careful traction. Forceful removal of the placenta should be avoided.

Antimicrobial Agents

Cows with retained fetal membranes but **without systemic illness** should be monitored, but treatment with antimicrobial agents is not indicated. Antibiotic treatment with IV or IM oxytetracycline (10 mg/kg BW, daily) before placental shedding delays detachment of the placenta; this finding is consistent with the concept that intrauterine bacterial infection facilitates placental detachment.

Cows with retained fetal membranes **complicated by septic metritis and toxemia** should be treated with antimicrobial agents daily for several days or until recovery occurs. Death can occur in untreated animals. Because of the mixed bacterial flora in the postpartum uterus with a retained placenta, broad-spectrum antimicrobials are recommended. Procaine penicillin (22,000 U/kg BW intramuscularly every 12–24 h) and ceftiofur (1–2.2 mg/kg BW intramuscularly every 24 h) for 3 to 5 days are preferred treatments, with some support from clinical trials for the administration of ampicillin (10–11 mg/kg BW intramuscularly)[14] or oxytetracycline (11 mg/kg BW intravenously every 24 h) for 3 to 5 days. Ceftiofur increases the cure rate and milk yield and decreases rectal temperature when administered to dairy cows with fever and vaginal discharge or dystocia. Subcutaneous administration of ceftiofur (1 mg/kg BW) achieves concentrations of ceftiofur derivatives in uterine tissue and lochial fluid that exceeded the reported minimal inhibitory concentrations for common metritis pathogens. Treatment with a longer acting formulation of ceftiofur (ceftiofur crystalline free acid) subcutaneously into the base of the ear at 6.6 mg/kg may not provide an adequate duration of antibiotic concentration in endometrial tissue and lochia in cows with puerperal metritis, and current data do not support using this one-dose ceftiofur treatment regimen instead of daily subcutaneous ceftiofur injections for 3 to 5 days.[15] A recent randomized clinical trial indicated that the administration of ceftiofur crystalline free acid (6.6 mg/kg) subcutaneously twice into the base of the ear on days 0 and 3 was effective in treating puerperal metritis, with the second dose given in the opposite ear.[16] Care should be exercised when injecting ceftiofur crystalline free acid subcutaneously into the base of the ear because acute death has been associated with neurologic sequelae caused by intraarterial injection. Ampicillin increased the pregnancy rate and decreased the cure rate, compared with ceftiofur, in cattle that were also treated with intrauterine ampicillin and cloxacillin. Generally, oxytetracycline use should be confined to the first 5 to 7 days postpartum when *E. coli* predominates, because it is likely to be ineffective against *T. pyogenes* in the endometrium. Oxytetracycline at 30 mg/kg BW intravenously as a single dose in cows with retained fetal membranes resulted in concentrations of the antimicrobial in uterine secretions, placenta, and cotyledon for 32 to 36 hours. Two intramuscular injections of regular formulations of oxytetracycline at 25 mg/kg BW resulted in lower peak concentrations, but these were maintained for 144 hours. Parenteral oxytetracycline appears to decrease endotoxin production, as indicated by the severity of leukopenia in cattle with retained placenta.

In **severely affected cases**, large amounts of balanced isotonic crystalloid fluids, electrolytes, and glucose by continuous intravenous infusion may be necessary and often result in a marked beneficial response within 24 to 48 hours. The uterus should always be examined by palpation per rectum and vaginally to determine the degree of uterine involution, the thickness of the uterine wall, the volume of the uterus, the nature of the luminal contents, and the degree of attachment of the placenta to the cotyledons. This can be done daily to assess progress. Uterine fluids should be drained by creating a siphon if sufficiently liquid in nature, although care must be taken to ensure that the tube does not penetrate a friable uterine wall. The placenta will invariably be expelled within 6 to 8 days, and usually within 4 to 6 days, if parenteral antimicrobial and supportive therapy is provided. The use of antimicrobial agents must be accompanied by appropriate withdrawal periods for the milk produced by treated animals.

Intrauterine Medication

The necessity for intrauterine medication is controversial. There is limited evidence, if any, that the intrauterine infusion of antimicrobial agents with or without lytic enzymes and estrogens has any beneficial effect on the treatment of puerperal metritis. Nevertheless, a wide variety of antimicrobial agents have been used for intrauterine medication for retained placenta and metritis in cows, although generally β-lactam–resistant antibiotics should be administered because the uterine lumen can contain β-lactamase–producing bacteria. Intrauterine infusion of 0.5 g of the first-generation cephalosporin cephapirin improved the reproductive performance of cows with metritis, but only when administered after 26 days in milk. Intrauterine infusion of 1 g of the third-generation cephalosporin ceftiofur in 20 mL of sterile water once between 14 and 20 days of lactation had no effect on reproductive performance but decreased the risk of culling and increased the time to culling.

Tetracycline products (5–6 g) are commonly administered but should be administered as a powder dissolved in an appropriate volume of 0.9% NaCl, because vehicles such

as propylene glycol can irritate the endometrium. Intrauterine infusion of oxytetracycline decreases lochial odor and the incidence of fever in cattle with retained placenta. The combination of 8 g of oxytetracycline dehydrate (40 ml of solution) by intrauterine infusion through a disposable uterine catheter twice at 72 to 96 h apart and amoxicillin trihydrate (15mg/kg BW intramuscularly every 48 hours for a total of three injections) increased conception rate at first insemination and percent pregnant at 150 days in milk compared with treatment with amoxicillin alone.[17] In cattle with retained placenta, intrauterine administration of a povidone-based oxytetracycline solution (5 g daily until expulsion) combined with fenprostalene (1 mg subcutaneously) did not alter the time to detachment of the placenta but increased the frequency of pyometra; this finding was consistent with the concept that intrauterine bacterial infection facilitates placental detachment. Milk from cows treated by intrauterine infusion of antimicrobial agents should be discarded for an appropriate period of time to avoid illegal residues. Generally, intrauterine treatment may achieve effective endometrial antibiotic concentrations, but antibiotic concentrations in deeper myometrial tissue are usually too low to be effective, hence, the preference for systemic treatment in cattle with puerperal metritis.

Intrauterine administration of antiseptics (0.5% povidone iodine, 0.1% chlorhexidine), hyperosmotic agents (7.2% NaCl solution, 50% dextrose), and proprietary organic formulations[18] as a lavage or infusion has been done, particularly on organic dairies, but studies with a negative control group demonstrating efficacy are lacking.

Ancillary Treatment and Control

Portions of retained placenta protruding from the vagina should be wrapped in a plastic rectal sleeve to minimize wicking of fecal bacteria after defecation, although this supposition has not been verified. Alternatively, protruding remnants of placenta can be excised, although this may prolong to the time to expulsion because the decreased placental weight may interfere with traction on the remaining placenta in the uterine lumen. Complete manual removal is often requested by the producer but is not recommended because studies have not demonstrated its efficacy.

Nonsteroidal antiinflammatory drugs are often administered as part of the initial treatment of toxic metritis, purportedly to address fever and clinical signs of endotoxemia. The administration of one dose of the NSAID flunixin meglumine (2.2 mg/kg intravenously) at the start of treatment of puerperal metritis in dairy cows in addition to antibiotics did not improve the outcome compared with administration of antibiotics alone.[19] The addition of flunixin meglumine (1.1 mg/kg, route not stated, daily for 3 days) to the treatment of puerperal metritis in dairy cows with parenteral ceftiofur (1 mg/kg, subcutaneously or intramuscularly [route of administration not clear] daily for 5 days) did not improve the clinical cure rate, serum or blood concentrations of inflammatory biomarkers such as serum amyloid A and fibrinogen, or the elimination of bacteria from the uterus.[20]

The infusion of collagenase solution (200,000 U dissolved in 1 L of 0.9% NaCl containing 40 mg calcium chloride and sodium bicarbonate) into the umbilical arteries within 12 hours of parturition is an effective treatment for retained placenta. Collagenase injection therefore provides an effective method for preventing septic metritis in cattle with retained placenta. However, the collagenase solution is expensive and not widely available, and the technique is difficult in some animals because of difficulty in identifying intact umbilical arteries for injection. As a result, collagenase injection is rarely performed in clinical veterinary practice. The efficacy of umbilical artery infusion with antimicrobial agents has not been adequately evaluated.

Ecbolic drugs have been proposed for the prevention and treatment of retained placenta in cattle. These include prostaglandins, ergot derivatives, oxytocin, and β_2-adrenoceptor antagonists. The rationale for their use is that they stimulate uterine contractions and physically aid in the expulsion of the fetal membranes. Generally, the consensus is that they are ineffective after the diagnosis of a retained placenta is recognized. However, their use may be effective if used immediately after calving. In particular, the frequent intramuscular administration of oxytocin appears to provide the most effective means of preventing metritis, with a recommended protocol of 20 IU every 3 hours for postpartum days 0 to 3, 30 IU every 2 hours for postpartum days 4 to 6, and 40 IU every 2 hours for postpartum days 7 to 10. A large study found that intramuscular injection of oxytocin (30 IU) immediately after parturition and 2 to 4 hours later decreased the incidence of retained placenta and the calving-to-conception interval. Fenprostalene at 1 mg subcutaneously, 25 mg dinoprost tromethamine intramuscularly, or 20 IU oxytocin given to a large number of dairy cows in five commercial dairy herds did not reduce the incidence of retained fetal membranes or improve reproductive performance. A detailed review failed to identify any evidence supporting the use of estrogen or prostaglandins in the first 7 to 10 days postpartum.[21]

The finding that retained placenta can be caused by neutrophil dysfunction at calving provides the basis for epidemiologic evidence that deficiency of trace minerals or vitamins (such as selenium and vitamin E) is associated with an increased incidence of retained placenta. In regions deficient in selenium, supplementation of the diet up to 0.3 ppm can decrease the incidence of retained placenta in herds that are fed a total mixed ration. Selenium can also be administered by intraruminal boluses or parenteral administration of vitamin E/selenium preparations during the dry period.

Subcutaneous vaccination with protein subunits or inactivated bacterial components of *E. coli* (expressing the *fimH* virulence factor), *F. necrophorum* (producing the protein leukotoxin), and *T. pyogenes* (producing the protein pyolysin) can prevent puerperal metritis and result in improved reproductive performance.[22] It is anticipated that a commercial vaccine will be produced incorporating one or more of these agents.

Identification of Affected Cows

Cows affected with retained placenta and puerperal metritis should be identified and recorded in the records system and examined 30 to 40 days after parturition for evidence of further complications such as pyometra.

TREATMENT AND CONTROL

Treatment

For cows with fetid smelling metritis and rectal temperature ≥39.5°C:
- Procaine penicillin (22,000 U/kg body weight [BW] intramuscularly [IM] every 12–24 h for 3–5 days). (R-1)
- Ceftiofur (1.1–2.2 mg/kg BW IM every 24 h for 3–5 days). (R-1)
- Ceftiofur crystalline free acid (6.6 mg/kg BW subcutaneously every 3 days for two treatments). (R-2)
- Ampicillin (10–11 mg/kg BW IM every 24 h for 3–5 days). (R-2)
- Oxytetracycline (11 mg/kg BW IV every 24 h for 3–5 days). (R-2)
- Oxytetracycline dihydrate (8 g) by intrauterine infusion twice at 72 to 96 h apart combined with amoxicillin trihydrate (15 mg/kg BW IM every 48 hours for a total of three injections). (R-2)
- Carefully siphon off voluminous uterine fluid. (R-2)
- Administer intrauterine treatment and manual removal of placenta. (R-3)
- Parenteral administration of nonsteroidal antiinflammatory drugs. (R-3)

For cows with metritis and rectal temperature <39.5°C:
- Monitor rectal temperature daily, institute treatment when temperature >39.5°C. (R-1)

Control

Ensure adequate vitamin E and selenium status. (R-1)

Wrap retained placenta with palpation sleeve or remove placenta hanging from perineum. (R-2)

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Hypovolemic, Hemorrhagic, Maldistributive, and Obstructive Shock

SYNOPSIS

Etiology Shock caused by a reduction in venous return (circuit failure) secondary to hypovolemia, hemorrhage, maldistribution of blood or obstruction, to venous return.

Clinical findings Depression and weakness, subnormal temperature, elevated heart rate with weak thready pulse, cold skin and extremities, prolonged capillary refill time. Progressive development without aggressive fluid therapy and collapse and death from irreversible shock.

Clinical pathology Increased blood or plasma L-lactate concentration, decreased venous oxygen tension, evidence of multiple organ dysfunction. Decreased central venous pressure, low mean arterial blood pressure terminally. Changes in heart rate, activity level, and blood or plasma L-lactate concentration indicate the efficacy of treatment.

Necropsy findings None specific for hypovolemic or maldistributive shock; the source of hemorrhage may be apparent in hemorrhagic shock.

Diagnostic confirmation Clinical signs, blood or plasma L-lactate concentrations, venous oxygen tension.

Treatment Aggressive fluid therapy based on intravenous isotonic crystalloid solutions and possibly colloid solutions. Blood transfusion or stroma-free hemoglobin administration for hemorrhagic shock. Initial treatment by rapid infusion with small-volume hypertonic saline solutions gives rapid but transient resuscitative effect. Antimicrobial agents and nonsteroidal antiinflammatory drugs in maldistributive shock caused by endotoxemia.

ETIOLOGY

The circulatory system consists of a pump (the heart) and a circuit (the vasculature). Circulatory shock can result from abnormal functioning of the pump or circuit, or both. It is clinically very important to differentiate **pump failure** (cardiogenic shock caused by acute or chronic heart failure) from **circuit failure**, because the diagnosis and treatment of cardiogenic shock is vastly different from that of circuit shock. Cardiogenic shock is covered in detail in Chapter 10, whereas circuit failure is addressed in the following section.

Circuit failure occurs whenever the cardiac output is reduced below a critical point because of inadequate venous return to the heart. There are four main ways that circuit failure occurs:

1. **Hypovolemic shock** occurs when there is a reduction in circulating blood volume caused by loss of blood, plasma, or free water.
2. **Hemorrhagic shock** occurs when there is a reduction in circulating blood volume caused by the rapid loss of blood.
3. **Maldistributive shock** occurs when there is a reduction in circulating blood volume caused by increased capillary permeability, pooling of blood in capacitance vessels (such as the veins in the splanchnic circulation), or pooling of plasma in a large third space such as the thoracic or abdominal cavities.
4. **Obstructive shock** occurs when there is an acute reduction in venous return caused by a mechanical obstruction, such as pericardial tamponade or pulmonary artery thrombosis. Obstructive shock is extremely rare in large animals.

Regardless of the initiating cause for circuit failure and inadequate venous return, tissue hypoperfusion results, leading to impaired oxygen uptake and anaerobic metabolism. The end result of inadequate tissue perfusion is the development of multiple organ failure, L-lactate acidemia, and strong ion (metabolic) acidosis, manifested as the **hypodynamic stage** of shock. Hypovolemia and poor tissue perfusion result in cold extremities, elevated heart rate, a weak thready pulse, decreased capillary refill times, and altered mental status. Cardiac arrhythmias may occur because of myocardial ischemia and electrolyte and acid-base disturbance. There is anorexia and gastrointestinal stasis. Signs of renal failure include anuria or oliguria and azotemia.

Common causes of circuit failure in large animals are as follows.

Hypovolemic Shock

- Fluid loss and dehydration, such as in neonatal calf diarrhea and burn injury, especially when fluid loss is severe and rapid
- Fluid loss into the gastrointestinal tract caused by acute intestinal obstruction

Hemorrhagic Shock

Acute hemorrhage with loss of 35% or more of total blood volume, equivalent to an acute blood loss of 2.8% of BW (assuming blood volume is 8% of BW) will lead to clinical signs of severe hemorrhagic shock. In contrast, acute hemorrhage with loss of less than 10% of total blood volume (equivalent to an acute blood loss of less than 0.8% of BW) produces minimal detectable clinical changes.

Traumatic injury or spontaneous rupture of a large blood vessel are common reasons for acute hemorrhage. Any sort of minor surgical wound, e.g., castration or dehorning, may lead to excess hemorrhage after which there is a hemorrhagic tendency caused by defects of clotting. Some of the more common causes of hemorrhagic shock are as follows.

Cattle, Sheep, and Goats

- Spontaneous pulmonary hemorrhage associated with caudal vena caval syndrome
- Abomasal ulcer, sometimes originating from a bovine viral leukosis lesion (cattle)
- Enzootic hematuria with bleeding from a bladder lesion (cattle)
- Pyelonephritis with bleeding from a renal lesion (cattle)
- Intraabdominal hemorrhage as a result of arterial aneurysm, possibly associated with copper deficiency (cattle)
- Laceration of arteries in the wall of the vagina as a result of dystocia
- Ruptured middle uterine artery during uterine prolapse or torsion of uterus
- Cardiac tamponade caused by rupture of the coronary artery or ventricular chamber, rupture of the aorta (see Chapter 1)

- Rupture of liver associated with dystocia in lambs, and in older lambs possibly associated with vitamin E deficiency

Horses
- Ethmoidal hematoma
- Exercise-induced pulmonary hemorrhage
- Rupture of the middle uterine, uteroovarian (especially right side), or iliac artery associated with parturition, more commonly in aged mares
- Nasal bleeding from hemorrhage into the guttural pouch, from carotid or maxillary arteries with guttural pouch mycosis or associated with rupture of the longus capitis muscle following trauma
- Rupture of mesenteric arteries secondary to strongyle larval migration
- Splenic hematoma or rupture following blunt trauma
- Rupture of liver with hyperlipemia
- Hemangioma, hemangiosarcoma, squamous cell carcinoma of the stomach, and other neoplasia
- Persistent bleeding from the vulva in association with ulcerated varicose veins on the dorsal wall of the vagina
- Congenital venous aneurysm (rare)

Pigs
- Esophagogastric ulceration
- Proliferative hemorrhagic enteropathy
- Rupture of liver in hepatosis dietetica
- Congenital neonatal bleeding, e.g., umbilical hemorrhage

Maldistributive Shock
- Endotoxemia in neonatal septicemia, salmonellosis, coliform mastitis in lactating dairy cattle, toxic metritis in cattle
- Septic shock caused by gram-positive bacterial septicemia
- Too sudden reduction of pressure in a body cavity, e.g., by rapid withdrawal of ascitic fluid

Obstructive Shock
- Pericardial tamponade

PATHOGENESIS
Hypovolemic Shock
When cardiac output falls as a result of decreased venous return, the carotid and aortic baroreceptors stimulate the sympathetic nerves and adrenal medulla to release catecholamines resulting in vasoconstriction in vessels with α-adrenergic receptors. Vasoconstriction leads to **decreased renal perfusion**, which activates the RAAS, inducing sodium and water retention. The decrease in renal perfusion can result in renal ischemia and nephrosis if the ischemia is sufficiently severe and prolonged (see Chapter 13). Hypovolemia also stimulates the release of antidiuretic hormone (vasopressin). There is contraction of the spleen and venous capacitance vessels, an increased peripheral vascular resistance, and an increase in heart rate in an attempt to maintain cardiac output and blood perfusion through the coronary and cerebral blood vessels.

Water shifts from the interstitial space to the vascular space in response to the contraction of precapillary arterioles. In the initial stages of hypovolemic failure the primary signs are those of interstitial fluid depletion and dehydration, with dry mucous membranes, sunken eyes, and decreased skin turgor. Peripheral vasoconstriction in the face of continued hypovolemia and falling cardiac output results in the opening of arteriovenous shunts and decreased perfusion of organ systems, with resultant damage from hypoxia and tissue acidosis and the development of clinical signs of peripheral vascular failure and shock. Arterial blood pressure falls terminally, and a decrease in mean arterial pressure indicates a complete lack of cardiovascular reserve. The rate at which hypovolemia develops profoundly affects the outcome because compensatory mechanisms are more readily overcome by acute than chronic changes.

Hemorrhagic Shock
The major effects of hemorrhage are loss of blood volume (hypovolemic shock), loss of plasma protein (decreased plasma oncotic pressure), and loss of erythrocytes (decreased oxygen-carrying capacity and buffering capacity).

With acute and severe hemorrhage, the rapid loss of blood volume results in hypovolemic shock and the loss of erythrocytes in anemic anoxia. The combination of these two factors is termed hemorrhagic shock and is often fatal. With less severe hemorrhage, the normal compensatory mechanisms, including release of blood stored in the spleen and liver and the withdrawal of fluid from the tissue spaces, may maintain a sufficient circulating blood volume, but the anemia is not relieved and the oncotic pressure of the blood is reduced by dilution of residual plasma protein. The resulting anemia and edema are repaired with time provided the blood loss is halted.

Maldistributive Shock
In normal animals the healthy intestinal mucosa is an effective barrier to the absorption of endotoxin that is present in the gut, and the small amounts of endotoxin that are absorbed into the portal blood are cleared by the liver and do not reach the systemic circulation. When the integrity of the intestine is compromised by factors such as ischemia, trauma, or inflammation, sufficient endotoxin can be absorbed to overwhelm the clearance mechanisms of the liver, and endotoxin may also leak to the peritoneal cavity, gaining access to the systemic circulation. Endotoxin can also be absorbed from sites of local infection, as with diffuse peritonitis, coliform mastitis, and toxic metritis, or released from gram-negative bacteria in the bloodstream. Intestinal mucosal integrity is lost in the terminal stages of circulatory shock caused by tissue hypoxia, and endotoxin translocation from the intestinal tract is markedly increased in the terminal stages of shock, independent of the initiating cause.

Endotoxin and other bacterial toxins cause direct endothelial damage. Endotoxin also activates macrophages and neutrophils provoking the release of a multitude of **inflammatory mediators**, including TNF, IL-1, IL-6, and platelet-activating factor, which lead to endothelial damage, leaky vessels, hypotension and vasculitis, and eventually decreased intravascular volume. Inadequate perfusion of tissue with appropriately oxygenated blood impedes oxidative cellular metabolism and leads to the release of arachidonic acid, which is metabolized by the cyclooxygenase pathway to yield prostaglandins and thromboxane A_2 or by the lipoxygenase pathway to yield leukotrienes. These **eicosanoids** are potent vasoactive compounds. They can act locally or be carried in the circulation to act at distant sites to further adversely affect vascular reactivity and vascular permeability. Endotoxin itself also provokes increased synthesis and release of eicosanoids, and many of the early effects of endotoxin are mediated by these metabolites of arachidonic acid.

A further consequence to tissue hypoxia is damage to endothelium with exposure of collagen; tissue thromboplastin can initiate the intrinsic and extrinsic coagulation cascades, leading to damage to other organ systems and further complications from the development of coagulopathies, including DIC, which may be central to the development of irreversible shock.

In the early **hyperdynamic stage** of endotoxemia and sepsis, there is an increased oxygen demand by peripheral tissue and an increase in heart rate and cardiac output with pulmonary and systemic vasoconstriction. Pulmonary hypertension increases transvascular fluid filtration in the lung, and pulmonary edema can develop when hypertension is accompanied by increased vascular permeability. There is systemic arterial hypoxemia caused by ventilation-perfusion inequalities in the lung and, despite the increase in cardiac output, blood flow may be inadequate to meet the needs of tissue in a hypermetabolic state. The **late hypodynamic** stage of endotoxemia and sepsis is characterized by decreased venous return, decreased cardiac contractility, decreased cardiac output and oxygen delivery, systemic arterial hypoxemia, and decreased mean arterial pressure.

Obstructive Shock
In severe pericardial tamponade, the rapid increase in pericardial fluid volume impedes

diastolic filling of the heart, resulting in decreased cardiac output. A similar response occurs in advanced traumatic reticulopericarditis in cattle that have ingested a wire; however, in the latter condition the obstruction is slow to develop.

CLINICAL FINDINGS

Depression, weakness, and listlessness are accompanied by a fall in temperature to below normal. The skin is cold and skin turgor is decreased. The mucosae are pale gray to white and dry, and capillary refill time is extended beyond 3 to 4 seconds.

There is an increase in heart rate to 120 to 140 beats/min in horses and cattle, with abnormalities of the pulse including small and weak pressure amplitudes (manifested as a "thready" pulse). Cardiac arrhythmias are present terminally. Venous blood pressure is greatly reduced in hypovolemic and hemorrhagic shock and the veins are difficult to raise in response to obstruction. Arterial blood pressure, measured either directly by arterial puncture or by indirect oscillometric methods, is decreased terminally and fails to provide an early indicator of the severity of the circulatory failure.

Anorexia is usual but thirst may be evident and there is anuria or oliguria. Nervous signs include depression, listlessness and obtusion, and coma in the terminal stages.

During the early hyperdynamic stage of maldistributive shock the temperature is normal or elevated, mucous membranes are injected and brick-red in color, there is tachycardia but normal capillary refill time, and the extremities (particularly ears) are cool to the touch. Although these signs are not specific for shock, the recognition of this stage in animals that are at risk for maldistributive shock, such as the neonate or animals with early signs of acute intestinal accident, can allow the early institution of therapy, which will frequently result in a better outcome than therapy instituted when the later stages of shock have manifested.

Therapeutic reversal of maldistributive shock in its later stages is difficult. In contrast, circulatory failure that is a result of hypovolemic or hemorrhagic shock is relatively easily treated and can be successfully reversed, even at stages of profound depression.

CLINICAL PATHOLOGY

The use of clinical pathology is directed at determining the cause and severity of shock and at monitoring the effectiveness of therapy. Volume expansion and restoration of tissue perfusion will usually correct acid-base and strong ion (metabolic) acidosis in the majority of animals with shock, and abnormalities are addressed once fluid balance is established.

Examination of the blood to determine the hematocrit and plasma protein concentration is invaluable in indicating the magnitude of the blood loss in hemorrhagic shock and providing a clinically useful index to the progress of the disease. However, there can be a **delay in the fall** of the hematocrit following hemorrhage for up to 4 to 6 hours because splenic contraction temporarily augments circulating red cell numbers. The hematocrit and plasma protein concentrations usually fall to their lowest levels 12 to 24 hours following hemorrhage, and determination at this time provides a clinically useful index of the amount of blood lost. Signs of a regenerative response (increased hematocrit, presence of reticulocytes, and increased red blood cell volume) should be seen within 4 days of an acute hemorrhage in ruminants and pigs but cannot be used as a guide in the horse. Generally, the hematocrit increases by 1% per day following acute hemorrhage in ruminants.

Abdominocentesis, **thoracocentesis,** and **ultrasound** are used to identify sites of internal bleeding. **Thrombocyte** and **clotting factor** examinations are indicated in cases in which unexplained spontaneous hemorrhages occur.

Monitoring in Shock

Clinical parameters of heart rate, pulse character, mucous membrane color, temperature of the extremities (particularly the ears), and activity level provide extremely useful guides to the efficacy of treatment when performed serially over time. The single most valuable index is the **heart rate**, although, in animals housed in a stable ambient temperature, **peripheral skin temperature** is also a useful clinical guide but not during rapid intravenous fluid administration, because there is a thermal lag of at least 30 minutes before increased blood and heat flow to the periphery is manifested as an increase in skin surface temperature. Blood or plasma **L-lactate concentration** and **venous oxygen tension** provide the most useful measures of the adequacy of oxygen delivery and tissue perfusion and therefore the efficacy of treatment. These two laboratory parameters are much more informative than measurement of **central venous pressure** or **mean arterial blood pressure**, and blood pressure measurement is discussed mainly for historical interest.

Blood or plasma L-lactate concentration, preferably measured in arterial blood or blood from a large vein such as the jugular vein, provides an indication of prognosis and an even more valuable serial measure of the efficacy of treatment. In general terms, plasma L-lactate concentrations are normally less than 1.5 mmol/L and fluctuate slightly depending on diet and time since feeding. Plasma L-lactate concentrations of more than 4 mmol/L indicate the presence of widespread anaerobic metabolism and the need for aggressive therapy, and plasma L-lactate concentrations above 10 mmol/L are associated with a high mortality in humans, pigs, cattle, and horses. Blood L-lactate concentrations are increased in cows with abomasal volvulus; however, blood lactate concentration did not provide an accurate prognostic indicator for survival. Generally, it is the **change in plasma L-lactate concentration after initiation of therapy** that provides the most useful guide to treatment. This change may be monitored by the actual plasma L-lactate concentration or the area under the plasma L-lactate concentration-time relationship. In particular, failure to decrease the plasma L-lactate concentration despite aggressive and appropriate therapy is a poor prognostic sign.

Venous blood oxygen tension (Po_2), preferably measured in a large vein such as the jugular vein, provides an indication of the adequacy of oxygen delivery and is a useful guide to the efficacy of treatment. In general terms, venous Po_2 is normally 35 to 45 mm Hg, arterial Po_2 is normally 90 mm Hg, and the difference between the venous and arterial Po_2 depends on the amount of oxygen extracted by tissues. The oxygen extraction ratio increases in tissues receiving inadequate blood flow as a consequence of the inadequate oxygen delivery; this results in an increased difference between arterial Po_2 and venous Po_2 and a lower value for venous Po_2. **Venous Po_2 below 30 mm Hg** indicates inadequate oxygen delivery and the need for aggressive therapy, such as hemoglobin in erythrocytes or stroma-free solution in hemorrhagic shock and plasma volume expansion in hypovolemic and maldistributive shock. A venous Po_2 below 25 mm Hg indicates severe abnormalities in oxygen delivery, and venous Po_2 below 20 mm Hg indicates impending death. Aggressive resuscitation should always increase venous Po_2 to more than 40 mm Hg, and failure to substantially increase venous Po_2 despite aggressive and appropriate therapy is a poor prognostic sign.

Central venous pressure (CVP) is another measure of hypovolemia, but individual measurements can be misleading and serial measurements should be used. By definition, CVP can only be measured by a catheter placed in a blood vessel within the thorax (typically the cranial vena cava), because this permits measurement of negative values for CVP. Central venous pressure is frequently measured in the jugular vein through a short intravenous catheter; this pressure is more correctly termed jugular venous pressure and, because it cannot be negative, is of much less clinical value than measuring CVP in shocked animals. A general rule of thumb in horses is to administer fluids as long as the CVP remains below 2 cmH_2O (0.2 kPa), and to immediately discontinue fluid administration whenever CVP exceeds 15 cmH_2O (1.5 kPa). The main clinical utility of CVP measurement is

ensuring that volume overload is not occurring. More details on measuring CVP are available in Chapter 10.

Mean arterial blood pressure is an insensitive but specific method for determining the severity of shock and the efficacy of therapy, because mean arterial blood pressure only decreases in the terminal stages of shock, indicating a complete lack of cardiovascular reserve. More details on measuring mean arterial blood pressure are available in Chapter 10.

NECROPSY FINDINGS

In **hemorrhagic shock** there is extreme **pallor** of all tissues, and a thin **watery appearance of the blood** may be accompanied by large extravasations of blood if the hemorrhage has been internal. When the hemorrhage has been **chronic**, anemia and edema are characteristic findings. In obstructive shock there is a large increase in pericardial fluid (usually blood), or the presence of a large thrombus in the cranial or caudal vena cava or pulmonary circulation, or evidence of severe abdominal distension (such as in ruminal tympany). There are **no specific findings** in hypovolemic or maldistributive shock, although in maldistributive shock the capillaries and small vessels of the splanchnic area may be congested and there may be evidence of pulmonary edema. With death from septic shock the major findings relate to the changes as evidence of pulmonary edema. With death from septic shock the major findings relate to the changes associated with the infectious disease. Dehydration is evident in animals dying from hypovolemic shock.

DIFFERENTIAL DIAGNOSIS

Circulatory failure caused by a circuit abnormality can be diagnosed when there is no detectable primary cardiac abnormality and when a primary cause such as hemorrhage, dehydration, or endotoxemia is known to be present. Ideally, endotoxemic or septic shock should be diagnosed in its early hyperdynamic stage and aggressively treated at this stage. This requires knowledge of the risks for shock with various conditions in each of the animal species. Hypovolemic, hemorrhagic, or maldistributive shock should be anticipated:

- In septicemic disease, especially of the neonate
- In acute localized infections
- With intestinal disease, but especially with those in the horse that have acute intestinal accident as part of the differential diagnosis
- When severe trauma occurs
- Where there is severe fluid loss for any reason
- Where decompression of an area is to be practiced (i.e., removal of fluid from a body cavity)
- When there is to be a significant surgical procedure

TREATMENT

Identification of Cause

The identification and, if possible, the immediate elimination of the precipitating cause of the shock is important in cases in which circulatory failure is initiated by conditions that are amenable to surgical correction. Prompt surgical intervention coupled with aggressive fluid therapy may save an animal, whereas delaying surgery until shock is advanced is almost always followed by fatality. This requires a full clinical examination and often ancillary laboratory examination to accurately identify the cause.

The identification of cause will also give some indication of the likelihood of success in treatment. Generally, there is greater success in the treatment and management of hypovolemic and hemorrhagic shock, especially if treatment is instituted early in the clinical course. Effective treatment and management of maldistributive shock is less successful unless the sepsis can be controlled and the source of the endotoxemia eliminated.

Hypovolemic and Maldistributive Shock

The rapid administration of intravenous fluids is the single most important therapy in animals with hypovolemic or maldistributive shock. The goal is to increase venous return, restoring circulatory function and tissue perfusion. Crystalloid solutions (fluids that contain electrolytes) and colloid solutions (fluids that increase the plasma oncotic pressure and expand plasma volume) can be used. The general principles and practice of fluid therapy are extensively discussed in Chapter 5.

Isotonic Crystalloid Solutions

These are the least expensive and most commonly used treatments for hypovolemic and maldistributive shock in large animals. Balanced electrolyte solutions, such as lactated Ringer's solution, are preferable to 0.9% NaCl solutions. Fluids for the restoration of the extracellular fluid volume must contain sodium, but glucose solutions (fluids that provide free water when the glucose is metabolized) are not indicated in the treatment of shock. **Large volumes** of isotonic crystalloid fluids are required. There is no set dose and each case needs to be assessed individually; an initial administration of 1\00 mL/kg by rapid intravenous infusion is not unusual and 50 mL/kg is probably the minimum. Isotonic crystalloid solutions expand the interstitial fluid volume and promote urine flow; however, beneficial responses are absent shortly after the cessation of fluid administration unless the syndrome is resolved.

More fluids are administered as required on the basis of clinical response and the monitoring measures discussed earlier; generally, this involves continuous intravenous infusion during the clinical course. In calves, ruminants, and horses the reestablishment of adequate tissue perfusion by intravenous fluid therapy can often be sustained by oral administration of large volumes of electrolyte solutions.

The disadvantages of the use of isotonic crystalloid solutions are the large volume required for treatment, the requirement for repeated treatment, and a sustained increase in pulmonary artery pressure with the risk for production of pulmonary edema in animals with maldistributive shock caused by endotoxemia. Moreover, the delivery of large volumes of isotonic fluid to large animals takes time and is difficult to accomplish in the field. This has led to the widespread use of **small-volume hypertonic saline solutions** for the initial resuscitation of shocked animals. The intravenous administration of small volumes of hypertonic salt solutions results in a transcompartmental and transcellular shift of fluid into the vascular compartment, with an increase in the circulating volume, cardiac output, and stroke volume and an increase in blood pressure with a reduction in peripheral and pulmonary vascular resistance. However, there is little improvement in renal function, the improvement in hemodynamic function is very **short lived,** and their use must be followed by intravenous isotonic crystalloid fluids.

Hypertonic Saline Solution

This has been used successfully in fluid therapy of hypovolemic, maldistributive, and hemorrhagic shock and is of value for the rapid resuscitative effect and the lower risk for induction of pulmonary edema in animals with endotoxemia. Small volumes (4–5 mL/kg) of hypertonic saline (7.2%, 2400 mOsm/L) are infused intravenously over 4 to 5 min, and the animal is allowed access to fresh water immediately upon completion of the injection.[1] Too rapid an infusion will result in vasodilation and death and too slow an infusion will diminish the resuscitative effect. There is a risk of phlebitis if there is perivascular deposition of hypertonic fluid. Hypertonic sodium lactate solution has been shown to improve fluid balance and mean arterial pressure in pigs with experimentally induced endotoxic shock.[2]

Colloids

The intravenous administration of colloid solutions (plasma, dextran, gelatin polymers, and hydroxyethyl starches) induces a more sustained increase in plasma volume than crystalloid solutions and smaller volumes are required for therapy, but colloid solutions are expensive and are rarely used in cattle and occasionally used in horses, with the exception of blood transfusion. Hydroxyethyl starches, such as hetastarch and tetrastarch, can interfere with coagulation but for the most part the effects are minor and clinically

inapparent.[3] Colloid solutions also have a risk for the induction of pulmonary edema and may also increase risk for coagulopathy. For horses, equine plasma is available commercially but is expensive. The use of hypertonic saline in combination with colloids or infusions containing albumin gives a more sustained response and hypertonic saline-dextran solution (2400 mOsm/L sodium chloride with 6% Dextran 70) at a dose of 5 mL/kg is more effective than hypertonic saline alone.

Hemorrhagic Shock

The source of the hemorrhage should be determined and the cause corrected. The other immediate concern is to replenish the blood volume and a decision must be made if this will be with fluids, whole blood, or stroma free hemoglobin solutions. Blood transfusion replaces all elements of the blood and in cases of severe hemorrhage blood transfusion is the most satisfactory treatment. However, a decision for **blood transfusion** should not be made lightly because the procedure is time-consuming, costly, and carries some risk. The decision to use whole blood in addition to fluids for treatment is based on the need to replace erythrocytes. The hematocrit can be a guide, in combination with clinical assessment, if the hemorrhage started at least 4 hours previously. With acute hemorrhage (<4 hours), transfusion is indicated solely on the basis of the severity of clinical signs. In the period immediately following hemorrhage a hematocrit of 20% is indicative of a significant loss of erythrocytes and the hematocrit should be monitored over the next 24 to 48 hours. If there is a fall to less than 12%, a transfusion of blood is indicated, but a stable packed cell volume (PCV) between 12% and 20% is not usually an indication for transfusion.

The best **anticoagulant** for immediate **blood transfusion** is **sodium citrate,** which is widely available and inexpensive. Citrate complexes calcium and inhibits coagulation; as such the amount of sodium citrate mixed with a volume of blood must be accurately known because excess sodium citrate will induce hypocalcemia when collected blood is transfused into the recipient. Sodium citrate (purchased as a white powder) is dissolved in sterile water to provide a stock solution of 3.85% (weight/volume), which can be autoclaved; the stock solution is subsequently mixed at one part solution to nine parts blood. As an example, 500 mL of 3.85% stock sodium citrate solution is placed at the bottom of a glass bottle and 4.5 L of blood collected to provide a final blood volume of 5 L. Approximately 20 mL of blood for each kg BW can be safely collected from a healthy blood donor (equivalent to 10 L from a 500-kg horse or cow). Do not exceed this volume of collection from the donor, because 40 mL of blood for each kg BW can be lethal. Heparinized blood is not recommended for immediate transfusion because heparin has a much longer half-life in domestic animals than citrate; consequently, if hemorrhage is not controlled there is the potential for heparin to facilitate additional blood loss.

If blood transfusion is to be delayed, then **acid citrate dextrose (ACD)** also known as anticoagulant citrate dextrose is widely recommended based on the addition of dextrose, which purportedly supports erythrocyte metabolism. The beneficial effect of dextrose has probably been overemphasized in domestic animals relative to humans, because human erythrocytes have a similar glucose concentration to plasma. In contrast, erythrocytes from adult domestic animals have a glucose concentration that is much lower than that in plasma and, consequently, a much lower rate of glucose metabolism,[4] potentially minimizing the need for additional glucose. Enthusiastic supporters of using ACD solution can purchase commercial plastic collection kits (usually 450 mL) with the appropriate volume of ACD solution present, but this becomes expensive when contemplating transfusion of an adult horse or cow. Alternatively, 3.6 mL of 50% dextrose solution, 1.6 g of sodium citrate, and 0.5 g citric acid can be dissolved in distilled water to a total volume of 50 mL, which is sufficient to collect 450 mL of blood.

The blood donor should be healthy and easily restrained during collection and free of infectious agents that can be transferred during blood transfusion, including prions. Crossmatching is not routinely performed in cattle, sheep, goats, or alpacas/llamas because these species have a large number of blood group factors and transfusion reactions are rare on the first transfusion. Consideration regarding crossmatching is required in these species if the animal in hemorrhagic shock has been previously transfused; however, often the results are not available fast enough to impact the decision to transfuse animals in shock. Crossmatching is routinely performed in horses if available in a timely manner because the incidence of incompatibility on the first transfusion is much higher in this species. The incidence of adverse events during transfusion in horses was 16% (7/44), characterized by mild urticarial reactions, acute anaphylactic shock, and exacerbation of intravascular hemolysis.[5] Five of the seven horses had some level of incompatibility on major or minor crossmatching, confirming that crossmatching would be beneficial if there is sufficient time and the test is available.

The jugular vein (or both veins) should be aseptically prepared and a bleb of 2% lidocaine placed under the skin to facilitate creating a 5-mm long stab incision through the skin over the site of the jugular vein in the midcervical region (the skin is moved dorsally away from the vein while making the incision). The jugular vein should be distended by application of a knotted rope around the distal cervical region so the knot occludes the jugular vein and facilitates sustained venous distention. A sterilized **12-gauge bleeding trocar** is then placed through the incision and advanced into the lumen of the jugular vein until the hub of the trocar is at skin level. Blood is collected directly into the glass jar as it flows freely, with gentle swirling of the jar contents to mix collected blood with citrate and minimize clot formation. The addition of a connecting tube from the bleeding trocar to the glass jar is not recommended because such tubes usually result in a narrowing of the blood flow with marked slowing of blood collection. Collection of blood into plastic bags is preferred to collection into glass bottles because hemolysis is decreased and clotting factors are maintained and the plastic bag is not easily broken when dropped; however, suitably sized plastic bags may not be readily available. At the completion of blood collection, sustained venous distention is released, the bleeding trocar removed, and one or more sutures are placed in the skin over the site of venipuncture to facilitate hemostasis. The bleeding trocar must be thoroughly cleaned and sterilized after use because plasma adheres tenaciously to the lumen of the trocar; the presence of foreign plasma protein will promote clotting and decreased luminal volume and flow rate when the trocar is used to collect blood from a different animal.

Blood should be administered to the recipient intravenously with an in-dwelling 14-gauge catheter through a commercially available in-line filter that will trap small blood clots. A test administration of 20 mL of blood should be administered and the animal monitored for clinical signs of anaphylaxis, including tachypnea, tachycardia, urticaria, and edema. If these signs are observed the blood transfusion should be immediately stopped. Administration of blood at too rapid a rate may cause overloading of the circulation and acute heart failure, particularly in animals with both circuit and pump failure. An infusion rate of 10 to 20 (mL/kg BW)/h is recommended and 5 to 10 L of blood usually requires an hour to administer to a cow or horse.

Hypertonic saline solution is recommended in the initial treatment of hemorrhagic shock and has been shown to be effective in the treatment of experimental hemorrhagic shock in large animals. Hypertonic saline can be of particular value to the ambulatory clinician, because this therapy can be used in emergency situations for the initial resuscitation of cases of hemorrhagic shock pending transfusion. A further advantage to the ambulatory clinician is the ease of portability of this fluid. The use of hypertonic saline is contraindicated when the hemorrhage has not been controlled, because its use in these cases will result in more protracted bleeding.

Drugs to assist coagulation and arrest hemorrhage are used in some cases, but there is limited information on their efficacy. **Aminocaproic acid** (10 g in 1 L of saline for an adult horse, administered intravenously) has been recommended for the management of hemoperitoneum in the horse. **Formalin** has traditionally been used to control hemorrhage and 10 mL of a 37% solution of formaldehyde or 30 to 150 mL of buffered 10% formalin in 1 L of 0.9% NaCl solution administered rapidly intravenously through an intravenous catheter has been recommended for the control of hemorrhage in horses; however, administration of formaldehyde at levels that did not induce an adverse reaction did not alter measured hemostatic variables in healthy horses. Formaldehyde treatment for hemostasis cannot be recommended for use in horses with the current available data. However, administration of a 5% solution of formalin to healthy goats (at 1.1 mL/kg intravenously) had a transient but detectable effect on decreasing both clotting time and bleeding time. This suggests that the effect of intravenous formalin on hemostasis may be dose dependent, and the optimal dose has yet to be identified in horses. **Ergonovine maleate**, 1 to 3 mg intramuscularly at 3-hour intervals, has also been used to control hemorrhage in the postparturient mare.

Animals should be kept quiet and in a dark stall to minimize excitement and the risk of further hemorrhage. Analgesic drugs should be given with hemorrhagic disease when there is pain, such as rupture and hemorrhage of the broad ligament of the uterus.

Obstructive Shock

The source for the obstruction should be identified and specific remedies applied. Obstructive shock is a rare cause of shock in large animals.

Ancillary Treatment

A large number of drugs have been shown to influence various components of the inflammatory response in septic shock, but none has been shown to alter the eventual outcome, and the interference of one aspect of the inflammatory cascade triggered by endotoxin should not be expected to improve overall survival. The specific treatment of maldistributive shock has been discussed earlier in this chapter.

Corticosteroids

There is considerable controversy over the use of corticosteroids in shock. Experimental studies have shown that they may have value in the prevention of maldistributive shock, but for this to occur corticosteroids must be given before the bacterial or endotoxin challenge. There is little evidence that they are of value in the treatment of hypovolemic, hemorrhagic, or maldistributive shock in animals once clinical signs have developed. Despite this, corticosteroids are frequently used in the treatment of shock in animals. The dose that is used is considerably higher than that used for other indications, for example, a dose of 1 to 2 mg/kg BW of dexamethasone intravenously, which is expensive in adult cattle and horses.

Cyclooxygenase Inhibitors

The use of cyclooxygenase inhibitors such as IV flunixin meglumine (0.25 mg/kg BW) and IM ketoprofen (0.5–2.2 mg/kg BW) has attractions in that they inhibit the production of the vasoactive prostaglandins and thromboxane A_2. This may not be entirely advantageous because the alternate path of metabolism of arachidonic acid is to leukotrienes, which are also potent mediators of inflammation. Treatment of horses with endotoxemia with cyclooxygenase inhibitors does result in a better maintenance of blood pressure and tissue perfusion but does not influence the eventual mortality. Tirilazad mesylate suppresses eicosanoid production and TNF-α activity and has been shown to be of benefit in the treatment of experimental endotoxemia in calves.

Antibiotic Therapy

With maldistributive shock the appropriate antibiotic therapy should be immediately instituted. Antibiotic therapy will not counteract the immediate effects of endotoxin and may theoretically increase the release of endotoxin in the short term, but this should not be a contraindication to antibacterial therapy. Pending the result of bacterial culture and susceptibility testing a broad-spectrum bactericidal antibiotic, or a combination of antibiotics to achieve a broad spectrum, should be used. Gram-negative septicemia in calves or foals, or acute–diffuse peritonitis, must be treated with antibiotics as well as by aggressive fluid therapy if there is to be any chance of survival.

Vasoconstrictors and Vasodilators

The administration of vasoconstrictors and vasodilators in cases of shock remains problematic unless the patient's cardiovascular status is accurately known and can be continuously monitored. Generally, their use is not currently recommended. The administration of a vasoconstrictor substance in a case of low-pressure distributive shock might seem rational because blood pressure would be elevated but it could reduce tissue perfusion still further. α-Adrenergic blockers improve tissue perfusion and cardiac function once the circulating blood volume has been restored, but if hypotension is already present it will be further exacerbated. Dopaminergic agonists may be useful in the early stages of maldistributive shock as long as monitoring is adequate. This is seldom possible in large-animal ambulatory practice and their use in large animals is confined to referral hospitals.

Immunotherapy

Immunotherapy with antibody directed against the **core lipopolysaccharide antigens** of gram-negative bacteria may be of value in the therapy or prevention of shock produced by endotoxin in some diseases but not in others. Immunotherapy has shown some promise in the treatment of shock associated with experimental endotoxemia in horses but none for the control of maldistributive shock associated with gram-negative sepsis in the neonate. Hyperimmune serum is available commercially and may be indicated in those cases when endotoxemia is a risk, in which case it is given before the onset of severe signs. Vaccination with these antigens has proved of value in the reduction of clinical disease produced by endotoxemia and in a reduction of the occurrence of endotoxin-induced shock associated with gram-negative mastitis in cows, although it does not reduce the occurrence of infection of the udder.

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Localized Infections

Localized infections are common in farm animals and many are bacterial infections secondary to traumatic injuries. Because most of them have a surgical outcome, by incision and drainage or by excision or amputation, they are not usually included in medical textbooks. They are presented briefly here because of their importance in the differential diagnosis of causes of toxemia and also because of their space-occupying characteristics, which cause compression of other structures. Also, the initial treatment is often medical, especially if the location of the lesion cannot be identified.

ETIOLOGY

Abscesses and similar aggregations of pyogenic material in certain anatomic locations are described elsewhere in this book. The common ones include pharyngeal,

submandibular,[1] retroperitoneal, hepatic,[2,3] splenic, pulmonary, cerebral, pituitary, spinal cord, and subcutaneous abscesses. Other similar lesions include embolic nephritis, guttural pouch empyema, lymphadenitis, pharyngeal phlegmon, osteomyelitis tooth root abscesses, and infections of the umbilicus and associated vessels.

More widespread accumulations of necrotic/toxic pyogenic debris occur and are described under the headings of pericarditis, pleurisy, peritonitis, metritis, mastitis, meningitis, and pyelonephritis.

Other pyogenic lesions worthy of note include the following:

- **Inguinal abscess in horses.** Some of these probably originate as postcastration infections, but some obviously have other origins, possibly as a lymphadenitis arising from drainage of a leg with a chronic skin infection.
- **Traumatic cellulitis and phlegmon in soft tissue,** especially skeletal muscle. The neck is a common site of infection in the horse, with lesions resulting from infected injection sites or the injection of escharotic materials, e.g., iron preparations intended only for intravenous administration. Penetrating traumatic wounds, often severely infected, are among the serious occurrences to the legs and hooves of horses and cattle. These commonly penetrate joint capsules, bursae, and tendon sheaths, and underrun periosteum. In cattle, the common causes are agricultural implements; in horses they are more commonly caused by running into protruding objects, including stakes and fencing material.
- **Abscessation and cellulitis of the tip or the proximal part of the tail.** This occurs in steers in feedlots and rarely extends to the hindquarters and the scrotum; the cause is presumed to originate from the presence of an aggregate of feces on the tip of the tail (manure ball) that gets caught in fencing material. Bacteria isolated from the lesion indicates a mixed infection.
- **Perirectal abscess** occurs in horses, caused usually by minor penetrations of the mucosa during rectal examination. Some of these rupture into the peritoneal cavity, causing acute, fatal peritonitis. Others cause obstruction of the rectum and colic because of the pain and compression that result. They are readily palpable on rectal examination.
- **Perivaginal abscess** occurs in heifers and cows, caused by vaginal tears during parturition, particularly after dystocia. Occasionally these rupture into the peritoneal cavity, causing acute, fatal peritonitis. More commonly, the abscess causes obstruction of the rectum and urethra, with the animal exhibiting signs of abdominal pain and stranguria because of the resultant pain and compression during posturing for defecation and urination. Perivaginal abscesses are readily palpable on rectal and vaginal examination.
- **Urachal abscess.** See omphalitis.
- **Pituitary abscess** occurs in cattle, sheep, and goats[4] as a single entity or in combination with other lesions. Pituitary abscesses cause a wide range of signs with emphasis on dysphagia caused by jawdrop, blindness, and absence of a pupillary light reflex, ataxia, and terminal recumbency with nystagmus and opisthotonus.
- **Facial abscess in cattle and goats.** Facial abscesses secondary to injury of the cheek mucosa caused by plant awns are common in beef cattle being fed hay containing a variety of awns that may penetrate the oral mucosa. *T. pyogenes* (formerly *Arcanobacterium* or *Actinomyces* or *Corynebacterium pyogenes*) is the commonly isolated bacterium. Localized abscesses of the face and neck are common in some flocks of goats and sheep.[5,6] *Corynebacterium pseudotuberculosis* is most commonly isolated, followed by *T. pyogenes* and *Staphylococcus* spp. The abscesses are most common on the jaw and sternal, facial, and cervical regions.
- **Tooth root abscesses in llamas, alpacas, goats, and sheep.** Tooth root abscesses are a common dental disease of llamas and alpacas and are thought to be caused by ingestion of rough or stemmy forages when permanent molars are erupting.[7] Tooth root abscesses can arise without a known cause or may result from trauma, foreign body migration (such as grass seeds), malocclusion and abnormal tooth wear, and periodontal disease. *T. pyogenes* and *F. necrophorum* are most commonly isolated from tooth root abscesses in New World camelids. Tooth root abscesses are most frequently found in mandibular molar teeth in New World camelids,[7] the mandibular incisors in pigs, and the first maxillary molar in horses.

Bacterial Causes of Localized Infection

These include those bacteria that are common skin contaminants in animals, including *T. pyogenes, F. necrophorum,* streptococci, and staphylococci. Clostridial infections are common but occur sporadically. They are described under Malignant edema. *Clostridium pseudotuberculosis* is common as a cause of local suppuration in horses and is the specific cause of caseous lymphadenitis of sheep. *Rhodococcus equi* also causes pulmonary and subcutaneous abscesses in horses and cervical lymphadenitis in pigs. Strangles (*Streptococcus equi* subsp. *equi*), *R. equi* infection in foals, melioidosis, and glanders are all characterized by extensive systemic abscess formation. *Histophilus somni* causes systemic abscess formation in sheep. *Mycobacterium phlei* and other atypical mycobacteria are rare causes of local cellulitis and lymphadenitis/lymphangitis manifesting as "skin tuberculosis" in cattle. Streptococcal cervical abscess in pigs is another specific abscess-forming disease.

PORTAL OF ENTRY

Most localized infections begin as penetrating wounds of the skin, caused accidentally or neglectfully because of failure to disinfect the skin adequately before an injection or incision, as in castration, tail docking, and so forth.

Metastatic implantation from another infectious process, especially endocarditis, carried by blood or lymph, is the next most common cause. In this way a chain of lymph nodes can become infected. Cranial and caudal vena caval syndromes produce similar embolic showers in the lungs.

PATHOGENESIS

The local infection may take the form of a circumscribed aggregation of bacterial debris and necrotic tissue, known as an **abscess**. This may be firmly walled off by a dense fibrotic capsule or be contiguous with normal tissue. When such an abscess occurs in a lymph node it is called a **bubo**; when the infective material is purulent but diffusely spread through tissues, especially along fascial planes, it is known as a **phlegmon**; and when it is inflammatory but not purulent the same lesion is called **cellulitis**.

The species of bacteria in the abscess determines the type of pus present and its odor. Staphylococci produce large quantities of thick yellow pus, and streptococci produce less pus and more serous-like exudates. Pus associated with *T. pyogenes* is deep-colored, yellow or green in color and very thick and tenacious. The pus of *F. necrophorum* is very foul-smelling and usually accompanied by the presence of gas.

Deposition of bacteria in tissues is sufficient to establish infection there in most instances. Conditions that favor abscess development include ischemia, trauma, and the presence of a cavity or a hematoma. A continuing process of pus formation results in enlargement to the stage of pointing and rupturing of an abscess, or spread along the path of least resistance into a nearby cavity or vessel, or discharge to the exterior through a sinus. Continuing discharge through a sinus indicates the persistence of a septic focus, usually a foreign body, such as a grass seed, a sequestrum of necrotic bone, or an osteomyelitis lesion.

CLINICAL FINDINGS

The clinical signs of abscesses and other local aggregations of pyogenic lesions were

described earlier. General clinical findings that suggest the presence of a localized infection, which is not readily obvious clinically, include the following:

- Fever, depression, lack of appetite, all are signs of toxemia.
- Pain resulting in abnormal posture, e.g., arching of the back, or gait abnormality, including severe lameness.
- Weight loss, which can be dramatic in degree and rapidity.
- Obstruction of lymphatic and venous drainage, which can cause local swelling and edema. Sequels to these developments include extensive cellulitis if there is a retrograde spread of infection along lymph drainage channels and phlebitis and thrombophlebitis when there is stasis in the veins.
- Careful palpation under anesthesia or heavy sedation may be necessary to overcome the muscle spasm caused by pain. Calves with extensive abscessation emanating from the navel, and horses with inguinal abscesses, can only be satisfactorily examined by deep abdominal and rectal palpation.
- Radiologic examination may elicit evidence of osteomyelitis, and examination of a fistulous tract may be facilitated in this way, especially if a radiopaque material is infused into the tract.

CLINICAL PATHOLOGY

Hemogram

A complete blood count is helpful in supporting a diagnosis of local abscess. Unless the infection is completely isolated by a fibrous tissue capsule or is small in size relative to the size of the animal (tooth root abscess or osteomyelitis), there will be a leukocytosis with a left shift and an elevation of polymorphonuclear leukocytes in acute lesions or of lymphocytes and monocytes in more chronic ones. A moderate normochromic anemia is usual in chronic lesions, and mild proteinuria is common.

Sample of Lesion for Culture and Staining

Attempts to identify the presence of an infectious agent and to establish its identity are usually undertaken, but care is necessary to avoid spreading infection from a site in which it is presently contained. Techniques used include paracentesis, careful needle aspiration from an abscess, blood culture (with the chances of isolation of bacteria being very small unless there is phlebitis or endocarditis), and aspiration of cerebrospinal fluid. Ultrasonographic guidance is helpful for percutaneous aspiration of deeper seated abscesses.[8]

The isolation of bacteria from a well-contained abscess may be difficult because of the paucity of organisms. Special techniques may be necessary and examination of a smear stained with Gram stain, and perhaps also with Ziehl–Neelsen stain if the circumstances suggest it, is an essential part of the examination. Determination of sensitivity of the bacteria to antibiotics is usually undertaken.

Necropsy Findings

The presence and location of the local infection can be demonstrated at necropsy.

TREATMENT

Drainage of Abscesses

Surgical drainage of readily accessible intact abscesses is the treatment of choice and in most cases the only effective method of therapy. A needle aspirate may be indicated when the nature of the lesion is uncertain. The site is prepared surgically and the abscess is drained, flushed, and topically medicated, usually with a roll of gauze soaked in a 1% povidone iodine solution, which is a stable chemical complex of polyvinylpyrrolidone and elemental iodine, for the first 24 to 48 hours. One roll is used to ensure that all the gauze is removed from the abscess. If the abscess is large then gauze rolls should be tied together to ensure all gauze is removed at the same time. If the abscess has not yet pointed with a soft spot, hot fomentations and hydrotherapy may aid in the maturation of a superficial abscess. An analgesic may be required during this stage of therapy. Deep-seated abscesses may benefit from ultrasonographic-guided aspiration, lavage of the abscess cavity with 0.9% NaCl solution, removal of the remaining saline solution, and injection of potassium penicillin into the abscess cavity.[8] Some abdominal abscesses may only be accessible by surgery.[4,9] Tooth root abscesses require extraction of the affected tooth to effect a cure.

Antimicrobial Agents

Antimicrobial agents given parenterally can be used for the treatment of deep abscesses not readily accessible to surgical drainage. Ideally, a sample of the contents of the abscess should be cultured and antimicrobial susceptibility determined. The agent must achieve high plasma concentrations to facilitate penetration into an abscess, and daily treatment for several days is usually necessary. However, antimicrobial agents alone may be ineffective, even if the organism appears sensitive to the drug in vitro in cases when the abscess is surrounded by a dense capsule—presumably the capsule prevents diffusion of the drug into the abscess cavity. Lipophilic antibiotics, such as rifampin, florfenicol, or macrolides, are theoretically advantageous in penetrating into abscesses. Rifampin should be administered with another antimicrobial agent to delay the development of antibiotic resistance.

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Pain

THE PROBLEM OF PAIN

Pain has been described in animals as "an aversive sensory and emotional experience representing an awareness by the animal of damage or threat to the integrity of its tissues." Pain is basically a protective mechanism to ensure that the animal moves away from noxious (damaging) influences, but endogenous pain, arising from internal damaging influences, causes its own physiologic and pathologic problems that require the veterinarian's intervention. In humans, there is an additional psychological parameter to pain and, although it is customary to transpose attitudes from pain in humans to animals, this is a courtesy rather than an established scientific principle.

A major difficulty with pain in animals is the difficulty of pain measurement. Pain is a subjective sensation known by experience that can be described by illustration, but measurement of pain is an indirect activity related to its effects and is an objective phenomenon. A panel report on recognition and alleviation of pain in animals proposed a simplified classification for animal pain and distress as pain, anxiety and fear, stress, suffering, comfort, discomfort, and injury. The recommendations are directed at academics, teachers, and researchers using laboratory animals, as well as the pharmaceutical industry.

Pain is assessed in animals by three methods: (1) **observation of behavior**; (2) measurement of physiologic parameters, including heart rate, blood pressure, sweating and polypnea, that indicate **sympathetic activation**; and (3) measurement of the plasma concentration of factors that indicate sympathetic activation, such as plasma cortisol, epinephrine, norepinephrine, and nonesterified fatty acid concentrations. Behavioral changes are increasingly being used as indirect indicators of pain, but studies lack standardization with respect to definition of behaviors, frequency and duration of monitoring, and interpretation of results. More objective indirect techniques for quantifying pain include the use of force meters, vocalization measures, stride length, and activity using pedometers and

accelerometers.[1] Because of the lability and expense of epinephrine and norepinephrine analyses, and the poor specificity of increased plasma nonesterified fatty acid concentration for pain, the most commonly used laboratory measure of pain is **plasma cortisol concentration**. Cortisol concentrations have also been measured in saliva, urine, and feces to provide a more accurate indicator of basal stress, because plasma cortisol concentrations increase rapidly in response to handling and restraint for blood sampling.

Pain in agricultural animals is a matter of ever-increasing concern, and there is an obvious need to identify, evaluate, prevent, and manage pain in large animals. Many agricultural practices that are thought to be necessary to avoid later painful disease or injury (e.g., disbudding or dehorning of cattle, sheep, and goats;[2] tail docking in piglets and lambs;[3] the Mules operation in Merino sheep;[4] and tooth clipping in baby pigs), to improve animal production and minimize fighting or reproductive-related injuries (e.g., castration, spaying), or to facilitate in animal identification (branding, eartagging, tattooing, or ear notching) are performed by producers without provision of an analgesic agent. It is not our purpose to engage in a discussion on the subject of animal welfare or the prevention of cruelty.

ADVANCES IN ATTITUDE TOWARD PAIN

There is now a greater awareness of the existence and detrimental effects of pain in animals, which has led to widespread implementation of postoperative pain control. New and improved analgesics are being developed and marketed as a result of increased basic and clinical research in pain. The detrimental effects of pain include the following:

- Suffering and stress resulting in delayed healing
- Increased catabolism and decreased feed intake
- Prolonged recovery and longer recumbency, with a greater risk of postoperative complications
- The potential to cause ineffective respiratory ventilation with the development of respiratory acidosis and acidemia
- Self-mutilation
- The potential of acute pain to lead to chronic pain

Pain may be clinically beneficial by acting as a protective mechanism by moving the animal away from the noxious stimulus and providing immobility of the affected part, promoting healing. Pain is a valuable diagnostic aid but, once identified, it is necessary to treat the pain and remove or modify its source if possible.

Once it is accepted that pain is detrimental it then becomes important to recognize and evaluate the severity of the pain. In the past, veterinary science has used an anthropomorphologic approach to the assessment of whether or not an animal is in pain. It is a reasonable elementary approach to compare the effects of pain in animals with those in humans because there are many more similarities in the neuroanatomical, physiologic, and behavioral data between humans and animals than there are differences. However, because of the inherent behavioral and social differences between humans and animals, this approach is limited.

Current research on pain in animals includes visual and subjective assessment of pain supported by physiologic and clinicopathologic measurements. These studies have increased the awareness of the problem of pain in veterinary medicine and resulted in improved information on the use of appropriate analgesics. Analgesics are now more commonly used perioperatively in food-producing animals and horses in New Zealand, Scandinavia, the United Kingdom, and the United States undergoing surgical and painful procedures.[5-8] More research is needed to develop optimal analgesic protocols.

ETIOLOGY

Pain sensations are aroused by different stimuli in different tissues, and the agents that cause pain in one organ do not necessarily do so in another. In animals there are three types of pain:

1. Cutaneous (or superficial)
2. Visceral
3. Somatic (or musculoskeletal)

The causes of each type of pain are listed in the following sections.

Cutaneous or Superficial Pain

Cutaneous or superficial pain is caused by agents or processes that damage the skin, such as burning, freezing, cutting, and crushing. Fire burns, frostbite, severe dermatitis, acute mastitis, laminitis, infected surgical wounds, foot rot, crushing by trauma, conjunctivitis and foreign body in the conjunctival sac are all common causes of pain.

Visceral Pain

Examples of visceral pain include the following:

- Inflammation of serosal surfaces, as in peritonitis, pleurisy, and pericarditis
- Distension of viscera, including the stomach, intestines, ureters, and bladder
- Swelling of organs as in hepatomegaly and splenomegaly
- Inflammation, as in nephritis, peripelvic cellulitis, and enteritis
- Stretching of the mesentery and mediastinum

In the nervous system, swelling of the brain caused by diffuse edema, or of the meninges caused by meningitis, are potent causes of pain. Inflammation of (neuritis) or compression of (neuralgia) peripheral nerves or dorsal nerve roots are also associated with severe pain.

Musculoskeletal (Somatic) Pain

Muscular pain can be caused by lacerations and hematomas of muscle, myositis, and space-occupying lesions of muscle. Osteomyelitis, fractures, arthritis, joint dislocations, and sprains of ligaments and tendons are also obvious causes of severe pain. Among the most painful of injuries are swollen, inflamed lesions of the limbs or joint caused by deep penetrating injury or, in cattle, by extension from foot rot. Amputation of a claw, laminitis, and septic arthritis are in the same category. Ischemia of muscle and generalized muscle tetany, such as occurs in electroimmobilization, also appear to cause pain.

The trauma of surgical wounds is a controversial topic in animal welfare, especially that associated with minor surgical procedures such as dehorning, tail docking, and castration in farm animals. From clinical observation supported by some laboratory examinations, e.g., salivary cortisol concentrations after castration in calves and lambs, it appears that pain after these procedures is short-lived, up to about 3 hours, and the perception of pain is age dependent.[1,9]

PATHOGENESIS

Pain receptors are distributed as end organs in all body systems and organs. They are connected to the CNS by their own sensory nerve fibers with their cell bodies in the dorsal root ganglion of each spinal nerve and via some of the cranial nerves. Intracord neurons connect the peripheral neurons to the thalamus, where pain is perceived, and to the sensory cerebral cortex, where the intensity and localization of the pain are appreciated and the responses to pain are initiated and coordinated.

The stimuli that cause pain vary between organs. The important causes include the following:

- **Skin:** cutting, crushing, freezing, burning
- **Gastrointestinal tract:** distension, spasm, inflamed mucosa, stretching of mesentery
- **Skeletal muscle:** ischemia, traumatic swelling, tearing, rupture, hematoma
- **Synovial membranes and cartilage of joints:** inflammation

Nociception is the normal physiologic process by which pain is perceived. When a tissue is injured by mechanical, thermal, or chemical means, **peripheral nociceptors** (specialized free nerve endings of afferent neurons) are depolarized and the initial stimulus is felt as pain.

Peripheral nociceptors are located in skin, fascia, muscles, tendons, blood vessels, joint capsules, periosteum, subchondral bone, pleura, peritoneum, and viscera. Five

classes of peripheral nociceptor are currently recognized: (1) thermal nociceptors activated by temperatures above 52°C or below 5°C, (2) mechanoheat nociceptors activated by pressure and temperature, (3) polymodal nociceptors, (4) visceral nociceptors, and (5) silent nociceptors. The **first pain** or initial sharp stinging following injury is caused by activation of large-diameter fast-conduction myelinated nerve fibers called **Type IAδ fibers** (thermal nociceptors) or **Type IIAδ fibers** (mechanoheat nociceptors). The **second pain** or slow pain following injury is caused by activation of small-diameter unmyelinated slow-conduction fibers called **C-fibers**; these fibers transmit a painful stimulus that is perceived as a sustained burning sensation that persists past cessation of the initial sharp painful sensation. Visceral nociceptors are activated by diffuse stimulation instead of direct local noxious stimuli. Silent nociceptors are mechanoheat nociceptors activated when sensitized by release of proinflammatory mediators (such as bradykinin, histamine, leukotrienes, eicosanoids, serotonin, substance P, adenosine triphosphate [ATP], low tissue pH, and other constituents of inflammation) into damaged tissues, establishing **peripheral hyperalgesia**. The hyperalgesia during acute pain is thought to promote healing at the injured site.

Central Hypersensitivity and Preemptive Analgesia

A state of altered central processing can also occur in response to chronic activation of peripheral nociceptors, which is called **central hypersensitivity** or "wind up." This central hypersensitivity results in a modified response to subsequent afferent inputs, which last between 10 and 200 times the duration of the initiating stimulus. The net result is that stimuli previously perceived as innocuous, such as touch or pressure, become perceived as painful after the system is sensitized. Preinjury treatment with opioids or local anesthetics prevents or decreases the development of central hypersensitivity and behavioral indicators of pain, but opioids and local anesthetics are less effective if administered after the injury is initiated. It is the establishment of central hypersensitivity that makes pain much more difficult to control once it is established and why analgesics are less effective at this time. Thus the combination of peripheral hyperalgesia (particularly associated with substance P) and central hypersensitivity results in what is called clinical pain.

It has been suggested that by preventing the surgical afferent stimuli from entering the spinal cord, the facilitation of spinal nociceptive processing could be prevented and this would decrease the severity of postoperative pain. This is known as the concept of **preemptive analgesia**. Preoperative administration of an analgesic is more effective than postoperative administration of the same dose; this is relevant to the control of pain associated with elective surgery. Many studies (primarily in humans) have demonstrated that preoperative administration of local anesthetic agents and the administration of NSAIDs or opioids before the patient is recovered from anesthesia are appropriate methods for instituting preemptive analgesia.

The physiologic responses to pain are described in the following sections. Normal responses include the release of the morphine-like endorphin from the brain, providing an endogenous analgesic system, and also cortisol release from the adrenal cortex in response to any stress. The clinical response to pain varies not only with the personality of the patient (some are more stoic than others) but also with various other influences. For example, distraction, as in walking a horse with colic, application of an alternative pain in the forced elevation of the tail of a cow (tail jack), and application of local anesthetic agents all tend to relieve pain. In agricultural animals pain elicits behavioral, physiologic, and clinicopathologic changes. The behavioral responses can be interpreted as a form of distraction, a displacement activity, or as providing an alternative pain. The physiologic and clinicopathologic responses are part of the fight or flight phenomena and reflect sympathetic activation.

CLINICAL FINDINGS

The general clinical findings of pain are described here and the indications of pain associated with individual body systems or organs are described within each category.

Physiologic Responses

Physiologic responses to pain are manifested by the following signs, and the severity of the pain determines the degree of response:

- Tachycardia
- Polypnea
- Pupillary dilatation
- Hyperthermia
- Sweating

The cardiovascular responses of tachycardia and hyperthermia may contribute to a fatal outcome in animals with reduced cardiovascular reserve, for example, when dehydration, acid-base imbalance, and endotoxic shock are also present.

Behavioral Responses

These include abnormal posture and gait when the pain is musculoskeletal (e.g., somatic). The gait abnormalities include lameness, a shuffling gait, and rapid shifting of weight from one leg to another. These are subjects of importance in orthopedic surgery.

The behavioral responses to pain may also include unrelated activities such as **rolling, pawing, crouching, or grinding of teeth** when the pain is visceral. However, the behavioral activities may also be related to the site of the pain, e.g., the horse with colic that looks at its abdomen, or to a particular function, such as pain manifested on coughing, walking, defecating, urinating, and so forth. The behavioral aspects of severe pain are very important in the horse with severe unrelenting visceral pain caused by colic. The rolling, falling, and lunging upward and backward (often falling against walls) can result in severe injury and causes panic in many owners.

Generally, somatic pain is more localized and easily identified than visceral pain. Injuries to limbs are usually identifiable by fractures or localized tendon strain or muscle injury. With severe somatic pain, as with a fracture or septic arthritis, the limb is carried off the ground and no weight is taken on the limb. With lesser lesions more weight-bearing activity is undertaken.

One of the notable factors affecting pain in animals is the analgesic effect of the animal lying on its back or of its adopting a defeated, supine posture. This may be related to the release of endorphins.

More general behavioral responses to pain include **decreased appetite** and average daily rate of gain, adoption of an anxious expression (ears retracted), disinclination to be examined, and aversion to returning to a particular location in which pain has been experienced previously. **Moaning, grunting, and grinding of the teeth** (odontoprisis or bruxism) are generally indicative of pain. If vocalization occurs with each respiration or rumination, the pain appears likely to arise from a lesion in the thoracic or abdominal cavities. When teeth grinding is associated with head pressing it is thought to indicate increased intracranial pressure such as occurs with brain edema or lead poisoning. Grinding of the teeth as a sole sign of pain is usually associated with subacute distension of segments of the alimentary tract. More extreme kinds of vocalization caused by pain include moderate bellowing by cattle, bleating in sheep and goats, and squealing in pigs.

Elicitation of Pain by the Veterinarian

This is an essential part of a clinical examination. The techniques include the following:

- Pressure by palpation, including firm ballottement with the fist and the use of a pole to depress the back in a horse or to arch the back upward from below in a cow
- Pressure by compression, as with hoof testers for detecting the presence of pain in the hoof
- Movement by having the animal walk actively or by passively flexing or extending limbs or neck
- Stimulation of pain related to coughing by eliciting the cough reflex
- Relief of the pain by correction of the lesion

Periodicity and Duration of Pain

Limited duration of pain can be the result of natural recovery or of surgical or medical correction of the problem. Constant pain results from a static state, whereas periodic or intermittent pain is often related to periodic peristaltic movement. In humans and in companion animals some importance also attaches to observing the time of onset of pain, whether it is related to particular functions or happenings and whether the patient gains relief by adopting particular postures or activities. These factors are unlikely to be of importance as an aid to a diagnosis in agricultural animals.

TREATMENT

Several aspects concerning the relief of pain in agricultural animals are important. Cost has always been a deterrent to the use of local anesthetics and analgesics. However, with changing attitudes toward animal pain, this issue is more frequently examined. Treatment of the causative lesion is a major priority, but the treated lesion may remain painful for varying lengths of time. Relief and the control of pain should be a major consideration and the following principles require consideration:

- Relief of pain is a humane act. Improved, less painful methods of castration,[9] dehorning,[2] tail docking,[3] Mules operation in sheep,[4] spaying cattle, and treating painful lesions of the hooves of farm animals must be explored and implemented. Surgical operations, such as laparotomies, must be performed using appropriate analgesia.
- Analgesia may obscure clinical findings that may be necessary to observe, properly diagnose, or maintain surveillance of a case. This is of major importance in equine colic.
- Control of pain is necessary to prevent animals from inflicting serious self-injury associated with uncontrollable behavior as a result of severe visceral pain.
- Analgesics for visceral pain are readily available and relatively effective.
- A major problem in the clinical management of pain is for cases of severe, slowly healing, infected traumatic wounds of the musculoskeletal system. Pain is likely to be very severe, continuous, and to last for periods of up to several weeks. Affected animals cannot bear weight with the affected limb, have great difficulty in moving, lose a great deal of weight, and prefer prolonged recumbency. At the present time, there are no effective analgesics available that can be administered easily and daily for a few weeks without undesirable side effects. The development of such products is urgently required.

Analgesia

The analgesic agents and techniques available include the following:

- Surgical procedures, e.g., neurectomy by section of peripheral nerves, as practiced in horses
- Local destruction of peripheral nerves by chemical means, e.g., the epidural injection of agents such as ethyl alcohol may prevent straining
- Local destruction of peripheral nerves by thermal means, e.g., cautery of the wound edge after gouge dehorning in calves
- Analgesia using nonopioid drugs when sedation is not required or is contraindicated
- Opioid analgesics (narcotic analgesics)

Analgesic Agents

There are seven main types of analgesic agent administered parenterally or topically to large animals:

1. **Local anesthetic agents** such as lidocaine (lignocaine), mepivacaine, and bupivacaine
2. **NSAIDs** such as flunixin meglumine, ketoprofen, phenylbutazone, carprofen, and meloxicam
3. **α_2-Agonists** such as xylazine and detomidine
4. **Opioids** such as morphine, fentanyl, butorphanol, and buprenorphine
5. ***N*-methyl-D-aspartate receptor antagonists** such as ketamine
6. **Vanilloids** such as capsaicin
7. **γ-Aminobutyric acid analogs** such as gabapentin

Generally, local anesthetic agents, α_2-agonists, and opioids are used to provide short-term analgesia (hours), parenteral NSAIDs and topical vanilloids are used to provide long-term analgesia (days to months), and **γ-aminobutyric acid analogs are investigational**. Effective analgesia is best achieved using a **multimodal approach** that incorporates the administration of two or more pharmaceutical agents that attenuate or abolish the transmission, modulation, and perception of pain, providing optimal pain relief (Fig. 4-2). Standard anesthesiology texts should be consulted regarding techniques for local analgesia using regional or peripheral nerve blocks and local anesthetic agents, or for general analgesia using α_2-agonists and opioids.

Local Anesthetic Agents

Lidocaine, mepivacaine, and bupivacaine exert their analgesic effect by addressing both the first pain and second pain after injury by blocking the voltage-gated sodium channels in peripheral nerves, preventing propagation of depolarization. Types IAδ and IIAδ and C-fibers are blocked before other sensory and motor fibers, meaning that it is possible (but sometimes a clinical challenge) to selectively block pain while maintaining the animal's normal motor function. The main advantages of local anesthetic agents are their cost and predictable and local effect, and the main disadvantage is short duration of action. They are usually administered by perineural infiltration in specific or regional nerve blocks. One challenge with lidocaine injection is that formulations are acidic and, consequently,

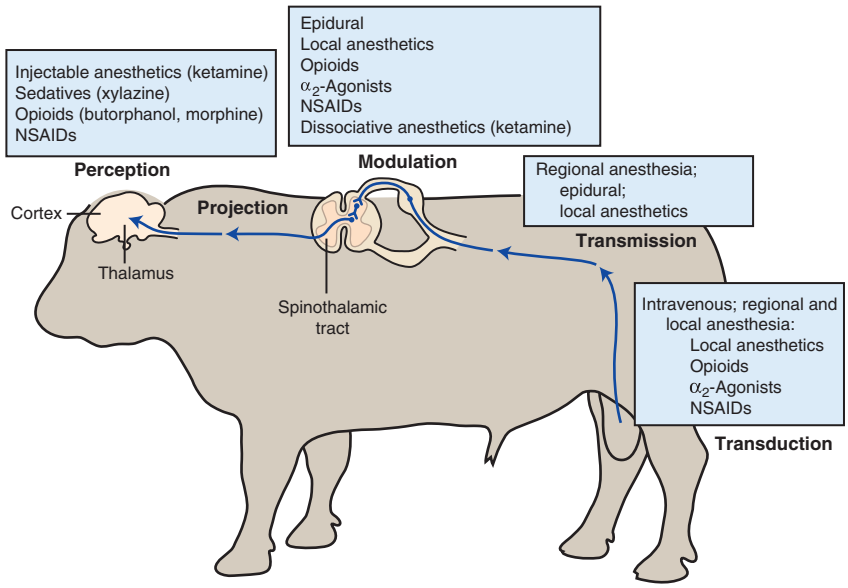

Fig. 4-2 The nociceptive pathway in cattle, identifying the anatomic location of analgesic drug activity. Effective analgesia is best achieved using a multimodal approach that incorporates the administration of two or more pharmaceutical agents that attenuate or abolish the transmission, modulation, and perception of pain. (Reproduced with permission from Coetzee JF. *Vet Clin North Am Food Anim Pract* 2013;29:13.)

burn when injected. The injection pain can be mitigated by mixing 1 mL of 8.4% sodium bicarbonate solution with 10 mL of 2% lidocaine in a 12-mL syringe; this increases the solution pH and reportedly decreases the immediate pain associated with lidocaine injection. The bicarbonate–lidocaine mixture should be used immediately and not stored because the higher pH causes the lidocaine to come out of the solution. Topical formulations of lidocaine (2.5%) and prilocaine (2.5%) are available that appear to be useful for transdermal administration of a local anesthetic in large animals before intravenous catheter placement, venipuncture, arthrocentesis, or collection of cerebrospinal fluid. There is concern in the European Union regarding the use of lignocaine (lidocaine) in food-producing animals because of mutagenic activity and genotoxic characteristics of a lignocaine metabolite, 2,6-xylidine. Procaine is not metabolized to the same metabolite and offers a suitable alternative if lignocaine use is curtailed in food-producing animals.

Nonsteroidal Antiinflammatory Drugs

These drugs appear to exert most of their analgesic effect by addressing the **second pain** (slow pain) caused by sensitization of C-fibers by eicosanoids; NSAIDs are not currently thought to exert a central analgesic effect. Animals receiving NSAIDs should be normally hydrated to minimize potential renal effects such as tubular nephrosis and papillary necrosis (see diseases of the kidney). Combined administration of a systemic NSAID with an intraarticular corticosteroid appeared to be more successful in the treatment of joint pain in horses than single treatment of either agent alone.[10]

Although parturition is painful, current data do not support the routine administration of NSAIDs at parturition because most of the studies completed in cattle have reported an increased incidence of retained placenta in animals treated with NSAIDs; this result is consistent with the current understanding that $PGF_{2\alpha}$ plays an important role in placental detachment.[11] Whether NSAIDs are beneficial in cattle experiencing dystocia remains to be determined.[12,13]

Flunixin Meglumine

This NSAID has excellent antiinflammatory, antipyretic, and analgesic properties, and is the preferred NSAID for acute soft tissue or visceral pain, although it is also efficacious against musculoskeletal pain. Flunixin meglumine provides excellent analgesia in equine colic and postoperative pain. In a comparison of three NSAIDs used to minimize postsurgical pain in horses, flunixin meglumine (1 mg/kg BW), phenylbutazone (4 mg/kg BW), or carprofen (0.7 mg/kg BW) were administered once intravenously. All three NSAIDs were effective in controlling postoperative pain, but the duration of clinical effect was longer for flunixin meglumine (12.8 hours) than carprofen (11.7 hours) or phenylbutazone (8.4 hours). Flunixin meglumine (1.1 mg/kg intravenously) was an effective analgesic in 2- to 3-month-old bull dairy calves undergoing surgical castration; flunixin meglumine administration attenuated the cortisol response and avoided some of the behavioral changes observed in calves castrated without drugs or with lidocaine infusion alone.[1]

The usual loading dose for flunixin meglumine is 1.1 to 2.2 mg/kg BW IV (ruminants) or 1.1 mg/kg BW (horses) followed by a maintenance dose of 1.1 mg/kg BW every 24 hours, although some studies have administered repeated injections at 8 to 12 hours. Flunixin meglumine is usually administered once or twice a day for its analgesic effect and is usually administered parenterally (preferably intravenously because of the rare instances of myonecrosis following intramuscular injections, particularly in horses), although oral formulations exist. Intramuscular doses are rapidly absorbed, with the maximal concentration occurring within 1 hour. Large doses given to individual ponies may, however, be toxic. Toxic effects are similar to those with phenylbutazone and include ulceration of the colon, stomach, and mouth; the latter two are most evident when administered orally. The major disadvantage with flunixin meglumine is the relatively short duration of action and label requirements for intravenous injection in the United States.[14]

Ketoprofen

This NSAID has antiinflammatory, antipyretic, and analgesic properties and is labeled in Europe for the treatment of pain in cattle associated with mastitis, lameness. and trauma (3.3 mg/kg BW intravenously or intramuscularly, every 24 hours for 3 days). Oral formulations are also available in Europe for the treatment of suckling calves. On theoretical grounds, ketoprofen may have analgesic properties superior to currently available NSAIDs because it blocks both the cyclooxygenase and 5-lipoxygenase branches of the arachidonic acid cascade as well as potentially having antibradykinin activity. However, the latter two effects have not been demonstrated in large animals at recommended dose rates. Ketoprofen has been shown to provide analgesia for several hours after gouge dehorning of calves and surgical castration of calves.

Phenylbutazone

This NSAID is used extensively as an oral analgesic for horses, especially for long-term treatment of musculoskeletal pain. It is most effective for the relief of mild to moderate musculoskeletal pain. The half-life of the drug in plasma is about 3.5 hours so that repeated treatment is recommended. A plasma concentration of 20 µg/mL appears to be clinically effective in horses, whereas a plasma concentration of 60 to 90 µg/mL appears to be clinically effective in cattle. After oral use in horses the peak levels in plasma are reached at 2 hours, but after intramuscular injection this does not occur until after 6 hours; thus, the oral or intravenous routes are the usual routes of administration. Unless care is taken to inject the drug slowly when using the intravenous route, severe phlebitis, sometimes causing complete obstruction of the jugular vein, may result. For horses the recommended dose rate is 4.4 mg/kg BW daily for 5 days orally or intravenously. Treatment on day 1 may be at 4.4 mg/kg BW twice, constituting a loading dose. Treatment beyond 5 days may be continued at minimal effective dose rates. However, prolonged use, especially in ponies, at a dose of 10 to 12 mg/kg BW daily for 8 to 10 days, may be followed by ulceration of alimentary tract mucosa, including the oral mucosa, and fatal fluid retention caused by hypoproteinemia. The pathogenesis of these lesions is thought to be caused by a widespread phlebopathy. Phenylbutazone should not be used if there is preexisting gastrointestinal ulceration, clotting deficits, or cardiac or renal dysfunction. Its use should be under close veterinary supervision so that the dose rate may be kept to a minimal effective level and so that it is used only when there is a clear clinical indication to do so. It should be withdrawn if there is no indication of a therapeutic response or if signs of toxicity appear. If there is doubt about toxicity or a prolonged course is advised, periodic hematologic examinations are recommended.

For cattle, the recommended oral dose is 10 to 20 mg/kg BW initially followed by daily doses of 4 to 6 mg/kg BW or every other day dose of 10 to 14 mg/kg BW. Clearance is slowed in neonates, so the dosage protocol would need to be adjusted in suckling calves. The general clinical impression is that phenylbutazone is the most effective analgesic available for the treatment of cattle with painful musculoskeletal conditions. Phenylbutazone is no longer permitted to be administered to female dairy cattle > 20 months of age in the United States because of concerns about meat and milk residues; phenylbutazone is known to induce blood dyscrasias in humans, including aplastic anemia, leukopenia, agranulocytosis, thrombocytopenia, and death. In addition, phenylbutazone is a carcinogen, as determined by the National Toxicology Program. Because of these concerns, phenylbutazone should not be administered to food-producing animals.

Meloxicam

Meloxicam is a longer acting NSAID than flunixin meglumine and has the additional advantage that it can be administered intramuscularly. Meloxicam preferentially binds to COX-2 (the inducible isoform) and

therefore theoretically has decreased side effects in large animals that may result from constitutive COX-1 isoform inhibition, including gastric or abomasal ulceration and proximal tubular injury of the kidneys. Meloxicam has been shown to be an effective analgesic in ruminants undergoing surgical procedures such as dehorning or castration, and it is effective when administered at 0.5 to 1 mg/kg BW orally every 1 to 2 days. However, based on prescription guidelines in the United States, oral meloxicam should only be administered to ruminants when sustained analgesia (>3 days) is needed.

Salicylates

Aspirin or acetylsalicylic acid is the most commonly administered analgesic in cattle but is not very effective, and there is limited clinical evidence of its efficacy. The recommended dose rate is 100 mg/kg BW orally every 12 hours, and oral administration is most common. Because there may be limited absorption from the small intestine, the salicylates may be given intravenously (35 mg/kg BW every 6 hours in cattle; 25 mg/kg BW every 4 hours in horses), but this is no longer practiced with the widespread availability of flunixin meglumine and phenylbutazone.

Carprofen

This is the safest NSAID, because of its weak inhibition of peripheral prostaglandins.

Diclofenac

This NSAID, when given to lambs before castration with bloodless castrators, significantly reduced the time spent trembling or in abnormal postures following the castration procedure. Diclofenac was widely administered to cattle and water buffalo in south Asia until catastrophic declines in the local vulture populations was identified. It was determined that vultures scavenging on cattle carcasses that had been unsuccessfully treated with diclofenac were dying from diclofenac-induced renal failure. Diclofenac was subsequently banned for veterinary use across south Asia in 2006, and since that time vulture populations have made a remarkable comeback.

α_2-Agonists

Xylazine

Xylazine was the first widely used α_2-agonist in large animals and remains the most commonly administered α_2-agonist in ruminants. Xylazine has been shown to be the most effective analgesic for the relief of experimentally induced superficial, deep, and visceral pain in ponies when it was compared with fentanyl, meperidine (pethidine), methadone, oxymorphone, and pentazocine. However, its short duration of action and the accompanying sedation and decreased gastrointestinal motility, respiratory activity, and increased urine formation limit its use as a short-term analgesic. Xylazine appears to produce minimal sedation and analgesia in pigs when administered as a sole agent.

Xylazine is widely used in the horse. Medetomidine and dexmedetomidine are used in the horse when a longer duration of analgesia is required.[15]

Narcotic Analgesics

Meperidine (Demerol, pethidine) is extensively used as an analgesic for visceral pain in the horse. Methadone hydrochloride and pentazocine are also used, to a limited extent, and their use is detailed in the treatment of colic in the horse. Butorphanol, a synthetic narcotic used alone or in combination with xylazine, provides highly effective analgesia in horses.[16]

Generally, narcotic analgesics are not as effective in ruminants as in horses and pigs because they have a distribution of μ and κ receptors different from monogastric animals. In ruminants, opioids produce brief analgesia or no analgesia (depending on the type of stimulus) and higher doses are needed for an effect than in monogastric animals. Opioids also produce behavioral side effects in ruminants. Concern that most opioids are scheduled drugs necessitating extensive record keeping and secure storage, and about meat and milk residues in food-producing animals, further limit the use of opioids in ruminants.

Narcotic agents are used in somatic pain in humans and may have wider applicability in animals. A recent clinical application has been transdermal delivery of fentanyl, which is a potent μ and κ agonist opioid analgesic drug that is highly lipid soluble. Fentanyl patches have been applied to the skin of horses, pigs, sheep, goats, and llamas. The rate and magnitude of uptake is dependent on core temperature and environmental temperature (and therefore blood flow to the skin at the site of the patch), thickness of the skin at the site of the patch, and adherence of the patch to the skin. A significant limitation to the use of opioids is their addictive nature in humans, necessitating storage under strict control with written records of their usage required in most countries.

N-methyl-D-aspartate receptor antagonists

The prototype *N*-methyl-D-aspartate receptor antagonist is ketamine, which modulates central sensitization at subanesthetic doses exerting an antihyperalgesic effect. The analgesic effects of ketamine are most evident in animals with moderate to severe pain or those animals that appear hypersensitive to pain.

Vanilloids

Capsaicin is derived from hot chili peppers (*Capsicum annuum*) and is the main vanilloid used in horses; these agents are characterized by their ability to activate a subpopulation of nociceptor primary afferent neurons. Capsaicin induces a transient primary hyperalgesia that is followed by a sustained period of desensitization that is species, age, dose, and route of administration dependent. The sustained desensitization is responsible for capsaicin's efficacy as an analgesic agent. Capsaicin therefore has dual effects: initial transient primary hyperalgesia (manifested as a burning sensation) and long-term desensitization. Topical application of capsaicin ointment over the site of the palmar digital nerves has been used in horses as an adjunctive method of analgesia in equine laminitis, with demonstrated efficacy. The major clinical disadvantage of using capsaicin is the initial transient primary hyperalgesia.

γ-Aminobutyric Acid Analogs

Gabapentin is the class representative and was originally developed as an antiepileptic agent in humans because it is a structural analog of the inhibitory neurotransmitter γ-aminobutyric acid (GABA). The analgesic effect of gabapentin is focused primarily at chronic or neuropathic pain or as part of multimodal therapy, particularly with NSAIDs. The pharmacokinetics of gabapentin has been determined in horses,[17] beef cattle,[18] and dairy cattle.[19] Generally, gabapentin is rapidly but poorly absorbed in horses when administered orally at 5 mg/kg BW and is rapidly cleared in the horse with an apparent plasma elimination half-life of 3.4 hours. This suggests that gabapentin must be administered frequently (at least every 8 hours) when administered orally to horses.

Balanced (Multimodal) Analgesia

Because multiple mechanisms for pain modulation all act together, the concept of **balanced or multimodal analgesia** has been proposed, similar to the way in which the use of different combinations of sedative and anesthetic agents results in the best aspects of each agent producing balanced anesthesia. Among horses receiving NSAIDs at the end of an anesthetic, those that received butorphanol during surgery required less additional analgesia compared with those that did not receive any opioid. Thus combinations of drugs can be used to produce sequential blocks in nociceptive pathways.

Acupuncture is a popular complementary treatment option for pain in human medicine. Adequate randomized clinical trials that have an appropriate control group, use blinding, and have clinically relevant primary endpoints have yet to be conducted in large animals to determine whether acupuncture is an effective analgesic agent.

Administration Routes

The main routes used for administration of analgesics have been local infiltration, subcutaneous, intramuscular, and intravenous. Other routes, including **oral, epidural, intraarticular,** and **topical**, are now being explored.

Xylazine and **lidocaine** given as **epidural analgesia** abolished pain and tenesmus in cows with acute tail-head trauma, which was characterized by acute, intense pain and discomfort, severe tenesmus, and a limp tail. Extended pain relief was required for up to 3 weeks. Xylazine in the epidural space has also been used to provide analgesia for the castration of bulls. In the horse epidural analgesia using a combination of butorphanol and local anesthetics has been used to provide perineal analgesia.

Supportive Therapy

The application of moist heat to a local lesion causing pain is effective and makes medical sense. Its value depends on how frequently and for how long it can be applied. Providing adequate bedding is important for an animal that is recumbent for long periods or that is likely to injure itself while rolling. A thick straw pack is most useful if it can be kept clean and densely packed. Sawdust is most practical but gets into everything, especially dressings and wounds. Rubber floors and walls, as in recovery wards, are effective but are usually available only for short periods. Distracting a horse with colic by walking it continuously is a common practice to prevent the animal from behavioral activities such as rolling, which may cause self-inflicted injuries. Walking is valuable, but has obvious limitations.

The provision of adequate amounts and quality of feed and water is essential, especially if the animal is immobilized and because appetite is often poor.

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Stress

Stress is a systemic state that develops as a result of the long-term application of stressors. It includes pain, which was discussed earlier. **Stressors** are environmental factors that stimulate homeostatic, physiologic, and behavioral responses in excess of normal. The most objective measures of the presence and magnitude of acute stress are activation of the **sympathoadrenal medullary system** and the **HPA axis**, manifested as increases in the plasma concentrations of catecholamines and cortisol, respectively. The importance of stress is that it may

- Lead to the development of psychosomatic disease
- Increase susceptibility to infection
- Represent an unacceptable level of consideration for the welfare of animals
- Reduce the efficiency of production

The general adaptation syndrome, described in humans, has no counterpart in animals, and it is lacking in accurate definitions, precise pathogenesis, and general credibility.

CAUSES OF STRESS

For animals, a satisfactory environment is one that provides thermal comfort, physical comfort, control of disease, and behavioral satisfaction. An environment that is inadequate for these factors will lead to stress. The environmental influences that elicit physiologic responses from animals are outlined next and some can be classified as stressors. The effects of most of these influences on production or performance indices have been measured quantitatively, and many of them have been equated with blood levels of adrenal corticosteroids, which quantify them as stressors in the different species:

- **Road transportation** for prolonged periods, especially during inclement weather and when overcrowded, is considered to be a major stress associated with an increased incidence of infectious disease in all farm animal species. The effects of prolonged road transportation have been measured in young calves, cattle, sheep, and horses.
- **Climate**, especially temperature, either as excessive heat or cold, is a stressor. In particular, a change of climate places great pressure on heat production and conservation mechanisms in, for example, conditions of sudden wind and rain, which affect the comfort of animals.
- **Excessive physical effort**, as in endurance rides for horses, struggling in restrained animals, fear, and the excitement and fear in capture myopathy syndrome in wildlife, are all potential stressors.
- **Pain**, especially analgesia-masked pain in severe colic in horses, is a stressor. The pain of dehorning and castration of farm animals is also a transient stressor, depending on the species and method used.
- **Crowding factors,** such as temperature, humidity, the physical exhaustion associated with standing up for long periods, being walked on, difficulty in getting to food and water, and so forth, are relevant. Two other factors could be important. One is the effect of crowding on behavior; for example, pigs in overcrowded pens appear to bite one another more than when they are housed at lower densities, and are more restless than normal when temperatures in the pens are high. The biting is much more severe between males than between females. Also, it is known that pigs bite each other when establishing precedence in a group, e.g., after mixing of batches, and that this is more severe when feed is short. The other possible factor that might affect the animal's response to crowding is a psychological appreciation of the unattractiveness of crowding (or of isolation). This, however, is an unknown phenomenon in animals.
- **Presence or absence of bedding**. This is a comfort factor separate from temperature and wetness. Whether comfort affects physiologic mechanisms is not currently known.
- **Housing** generally includes the matter of comfort as well as that of maintaining moderate temperatures, but whether there is a factor other than the physical is not known.

- **Nutritional deficiencies** including lack of energy, bulk, and fluid.
- **Quietness versus excitement.** Harassment by humans or other animals sufficient to cause fear does elicit stress response in animals, and this is thought to be one of the significant causes of stress-related diseases in animals. Thus transportation, entry to saleyards, feedlots, fairs, and shows, and simply the mixing of several groups so that competition for superiority in the social order of the group is stimulated, are causes of stress. Entry to an abattoir, which has the additional fear-inspiring factors of noise and smell, is likely to be very stressful for those reasons, but it is unlikely that a fear of impending death is relevant. Such situations are stressful to the point of causing marked elevation of plasma epinephrine concentrations.
- **Herding and flocking instincts**. Animal species that are accustomed to be kept as herds or flocks may be distressed for a period if they are separated from the group.

PATHOGENESIS

Stress is thought to develop when the animal's mechanisms concerned with adapting its body to the environment are extended beyond their normal capacities. The daily (circadian) rhythm of homeostatic and physiologic changes in response to normal daily changes in environment requires the least form of adaptation. Marked changes in environment, such as a dramatic change in weather, on the other hand, place a great strain on adaptation and are classified as stressors.

The body systems that are principally involved in the process of adaptation to the environment are the endocrine system for the long-term responses and the nervous system for the sensory inputs and short-term responses. The endocrine responses are principally the adrenal medullary response, related to the "flight or fight" situation, which requires immediate response, and the adrenal cortical response, which becomes operative if the stressful situation persists.

In humans, a large part of the "stress" state is the result of stimuli arising in the cerebral cortex and is dependent on the capacity to develop fear and anxiety about the effect of existing or anticipated stressful situations. Whether or not these psychological inputs play any part in animal disease is important, but undecided. The evidence seems to suggest that psychic factors do play such a part but that it is relatively minor.

The critical decision in relating stress to disease is to decide when an environmental pressure exceeds that which the animal's adaptive mechanisms can reasonably accommodate, in other words, to define when each of the pressures outlined earlier does, in fact, become a stressor. There is a great dearth of definition on the subject. Probably the most serviceable guideline is "stress is any stimulus, internal or external, chemical or physical or emotional, that excites neurons of the hypothalamus to release corticotrophin-releasing hormone at rates greater than would occur at that time of the day in the absence of the stimulus." This definition uses stress where stressor would have been more commonly used. Other than that, it is acceptable. The critical threshold of stress occurs in the adrenal cortex, and its physical determination is subject to a chemical assay of ACTH. This was the basis of the original "stress and the general adaptation syndrome" as set down by Selye in 1950. The original concept is still attractive because of its simplicity and logic. However, evidence supporting the hypothesis remains limited. The importance of the concept for our animals is unproven. The deficiency in evidence is that of obtaining a standard response to a standard application of a stimulus. There is a great deal of variation between animals, and stimuli that should be significant stressors appear to exert no effect at all on adrenocortical activity.

Stress and Road Transportation

The response of different farm animal species to the effects of road transportation has been examined. In unaccustomed cattle that are forced to run and are then herded together, there are increases in the hematocrit and blood concentrations of catecholamines, cortisol, total lipid, glucose, and lactose. Transportation of calves, 4 to 6 months of age, for only 4 hours results in a leukocytosis with neutrophilia, a decrease in T-lymphocyte population, a suppression of lymphocyte blastogenesis, and enhancement of neutrophil activity. The effect of road transportation on cattle varies according to age: the transportation of 1- to 3-week-old calves for up to 18 hours was not as stressful as in older calves. The lack of response of the younger calves to transport may be caused by their lack of physiologic adaptation to coping with the transportation. During transportation, plasma cortisol concentrations and serum creatine kinase (CK) activities increase. There is clinical evidence of dehydration and increases in serum nonesterified fatty acid, β-hydroxybutyrate, and urea concentrations, which reflect changes in normal feeding patterns. Based on the physiologic measurements and subjective measurements of behavior, a 15-hour transportation period under good conditions is not unacceptable regarding animal welfare. Transportation is exhausting and causes dehydration, but lairage facilitates recovery from both. When sheep are subjected to a journey of up to 24 hours it is best to be done as an uninterrupted trip, because it is the initial stages of loading and transport that are most stressful. In a 15-hour road journey with sheep, the major change in hormone release occurs during the first 3-hour period and is much less in the remaining 12 hours.

The effects of road transport on indices of stress in horses have been examined. A road journey lasting up to 24 hours is not particularly stressful for horses, if they are healthy, accustomed to the trailer and their travel companions, permitted to stop at least as frequently as every 3.75 hours, and traveling in a well-ventilated trailer. There was no indication that road transport was a risk factor for pulmonary disease; however, confinement of horses with their heads elevated for up to 24 hours (similar to during transportation) results in bacterial colonization and multiplication within the lower respiratory tract. Horses are also less physically stressed when facing backward in a trailer.

Based on plasma cortisol concentrations, confinement of young bulls on a truck and motion are considered stressful factors in road transport. Transport stress increases fecal, urine, and tissue losses, with most of the increased loss taking place during the first 5 to 11 hours of transport. During transportation of feeder calves (195 kg) the major portion of transport stress occurs during the early phases of transport; longer periods may not add significantly to the overall stress imposed on the calf. It is possible that the major stress may be related to the handling of the animals during loading and unloading.

Other Possible Sources of Stress

Dehorning dairy calves at 8 weeks of age resulted in an increase in plasma cortisol concentration within 1 hour after the procedure but there was no evidence of prolonged stress.

The effects of maternal dietary restriction of protein and/or metabolizable energy on the humoral antibody response in cows and the absorption of immunoglobulins by their cold-stressed calves indicates that there were no major or sustained differences compared with controls.

Different types of stress also result in distinctive changes in the plasma concentrations of metabolites and hormones. An environmental stress, such as noise, will stimulate a hypothalamic–adrenal–cortex response, whereas a sympathetic–adrenal–medulla response occurs with a stressor such as transportation.

CLINICAL PATHOLOGY

The direct criterion of stress is the assay of plasma ACTH; stress may be indirectly assayed using plasma cortisol concentration, which is a less expensive and more widely available assay. Salivary or fecal cortisol concentration is a good indicator of stress in sheep and cattle. Salivary and fecal samples are easy to collect, and the laboratory assay is simple to perform. Remember that elevation of plasma, salivary, and fecal cortisol concentrations are a normal physiologic

response and do not necessarily imply the existence of a damaging state in the environment. Assays of plasma catecholamines (epinephrine and norepinephrine) are confined to the research setting because these hormones are unstable using standard storage conditions.

Stressors such as weaning, placement in solitary housing or with a new group, and transportation lead to an acute phase response, which is manifested as an immediate increase in serum amyloid A concentration and a slightly delayed increase in serum haptoglobin concentration.[1] The mechanism of the increase is not directly linked to an increased plasma cortisol concentration. Endogenous cortisol release also results in an acute neutrophilia with no left shift.[1]

During prolonged periods of road transportation of cattle and sheep, there are significant changes in serum concentrations of total proteins, nonesterified fatty acids (NEFAs), glucose, CK, β-hydroxybutyrate, and urea. These changes can be used to assess the degree of nutritional stress and the deprivation from feed and water during transportation.[2] Prolonged feed deprivation reduces liver glycogen stores and increases concentrations of NEFAs and ketones in the plasma. Dehydration will elevate the concentrations of plasma proteins and the osmolality of the blood. Physical stress, such as fatigue or exercise, will result in increases in CK. Psychological stressors such as fear result in elevations of cortisol and corticosterone.

STRESS SYNDROMES

Stress-Related Psychosomatic Disease

In humans there is a significant neuronal input from the cerebral cortex to the hypothalamus in response to the psychological pressure generated by stress. The inability to monitor anxiety and feelings of harassment in our animals makes it impossible to determine the presence of psychological stress in them. However, psychosomatic diseases as they occur in humans are almost unknown in farm animals. The pathogenesis of psychosomatic disease appears to be based on the ability of the cerebral cortex to effectively override the normal feedback mechanisms by which the pituitary gland regulates the secretion of corticosteroids from the adrenal cortex. In other words, the normal adaptive mechanisms do not operate and hyperadrenocorticism and adrenal exhaustion develop.

Stress and Susceptibility to Infection

Field observations support the view that stress reduces resistance to infection. This seems to be logical in the presence of higher than normal adrenocortical activity. The most intensively explored relationship of this kind has been that of exposure of calves to weaning and transportation and their subsequent susceptibility to shipping fever. The prevalence appears to be increased and is still further enhanced by the introduction of other stress factors.

Stress and Animal Welfare

The perceived harassment of domesticated animals by humans has become a matter of great concern for the community at large. Intensive animal housing has become an accepted part of present-day agribusiness, but sections of the consuming public are inclined to the view that these practices are cruel. The literature that has built up around this argument sets out to demonstrate that environmental stress in the shape of intensive housing, debeaking, tail docking, and so on, is sufficient to cause a stress reaction as measured by increased corticosteroid secretion. This has not turned out to be the case, and it is understandable in the light of the known variation among animals in their response to environmental circumstances requiring their physiologic adaptation. If it could be shown that this relationship did exist and that the increased adrenocortical activity caused reduction in resistance to infection, the task of the responsible animal welfare person would be much easier. The absence of this experimental data makes the continuing argument less resolvable, but it is now generally accepted that producers have a responsibility to their animals and to society generally to maintain an acceptable standard of humane care of animals. These arguments are usually expressed as codes of animal welfare, to which most concerned people conform. However, they are not statutory directives and are not capable of active enforcement. Some courts of law accept them as guidelines on what the human–animal relationship in agriculture should be. Many aspects of the codes are arbitrary and are understandably heavily sprinkled with anthropomorphic sentiments. The study of ethology, which has expanded greatly during the recent past, may eventually provide some answers to this active, often bitterly fought-over field.

There has been increased adoption of the belief that an animal's welfare, whether on a farm, during transportation, or at a market or slaughterhouse, should be considered in terms of **five freedoms** that reflect ideal states rather than legal standards. The Five Freedoms concept originated with the Brambell Report released in 1965 (Report of the Technical Committee to Enquire into the Welfare of Animals kept under Intensive Livestock Husbandry Systems). This report indicated that livestock should have the freedom "to stand up, lie down, turn around, groom themselves and stretch their limbs." The five freedoms are currently stated as follows:

- **Freedom from Hunger and Thirst:** Ready access to fresh water and a suitable diet that maintains full health and vigor.
- **Freedom from Discomfort:** Provide an appropriate environment including shelter and a comfortable resting area.
- **Freedom from Pain, Injury, or Disease:** Prevent or rapidly diagnose and treat disease.
- **Freedom to Express Normal Behavior:** Provide sufficient space, proper facilities, and an appropriate group structure.
- **Freedom from Fear and Distress:** Ensure that conditions and treatment avoid mental suffering.

Animal welfare can also be viewed using a conceptual framework, with three such frameworks being widely advocated (biological functioning, affective state, and natural living). In the **biological functioning** framework, animals use a variety of behaviors and physiologic responses to cope with the environment; poor production or injury occurs in severe circumstances in which they are unable to adapt to the environment. This framework has been criticized because it does not include an emotional component, although such activation may be inferred by evaluating the magnitude of sympathoadrenal medullary and HPA axes. In the **affective state** framework, animal welfare is viewed as the "net sum of the magnitude of pleasant and unpleasant experiences." Although this is a useful concept, it has been difficult to quantify. Finally, the **natural living** framework is based on the concept that welfare is improved whenever animals can express their normal behaviors; this is best illustrated by "welfare-friendly" production systems, such as free range grazing of sheep flocks and beef cattle herds. When practiced to extremes, natural living can result in animal welfare concerns, such as increased neonatal losses caused by hypothermia in ruminants exposed to cold and windy weather.

The status of animals used in research has always been a bone of contention between the experimenters and some sections of the general public. Generally, these arguments revolve around anthropomorphic propositions that animals are subject to fear of pain, illness, and death in the same way as humans. There is no consistent evidence in physiologic terms that supports these views. However, the public conscience has again achieved a good deal of acceptance to the view that animal experimentation should be controlled and restricted and carefully policed to avoid unnecessary experiments and hardship in animals under our control.

Stress and Metabolic Disease

There is an inclination to label any disease caused by a strong pressure from an environmental factor as a stress disease, for instance, hypocalcemia of sheep and hypomagnesemia of cattle in cold weather, acetonemia and pregnancy toxemia of cattle and sheep on deficient diets, and white muscle disease of

calves and lambs after vigorous exercise. These diseases do have environmental origins, but their causes are much simpler than a complex interaction of the cerebral–cortical–hypothalamic–adrenocortical axis. They can be prevented and cured without any intervention in the stress disease pathogenesis. This is not to say that there is no adrenocortical basis for the pathogenesis of the previously listed diseases, but attempts to establish the relationship have so far been unsuccessful.

Stress and Its Effect on Economic Performance

The constant struggle for domination of other animals in an animal population is most marked in chickens and pigs, and the relationship between status in the hierarchy and productivity in these species has been established with the low-status animals producing less well. It is also known that birds that are highly sensitive and easily startled are poor producers, and they are easily identified and culled.

The relationship between stress and production appears to be a real one. For example, heat stress in the form of high environmental temperatures reduces roughage intake and hence milk production in lactating dairy cows, and the relationships between stress and infertility and stress and mastitis in cattle are also well documented. The sensitivity of animals to environmental stress is greatest at times when they are already affected by metabolic stresses, e.g., during late pregnancy and early lactation. The adoption of a policy of culling erratic, excitable animals appears to have an economic basis.

MANAGEMENT OF STRESS

The widespread public debate about the welfare of food-producing domestic animals dictates that veterinarians, animal scientists, and the livestock industry must develop systems of handling and housing that will minimize stressors and provide an environment that makes the animals most content and at the same time most productive. In civilized human society it should be realistic to expect that the animals that are used for food production or as companions should live their lives free from abuse or adverse exploitation. It will be necessary to determine how best to monitor the well-being of animals and determine whether or not they are under stress. Guidelines dealing with codes of practice for livestock production are available in many countries. In addition to housing, handling, and experimental intervention, it will also be important to give due care to the appropriate selection and use of anesthetics and analgesics when pain is being inflicted, such as in dehorning and castration. The effect of sedatives, such as acepromazine and xylazine on the stress response in cattle, has been examined but the results are inconclusive.

The welfare of animals during transportation is a major issue that has resulted in legislation governing the transport of animals and to define acceptable and unacceptable procedures. Welfare is determined by the length of the trip and the conditions under which animals are transported, including stocking density, ventilation, temperature and humidity, noise, and vibration. Prolonged deprivation of feed and water during long transportation results in hunger and thirst, and methods to minimize these consequences have been developed.

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Disturbances of Appetite, Food Intake, and Nutritional Status

Hunger is a purely local subjective sensation arising from gastric hypermotility caused in most cases by lack of distension by food.

Appetite is a conditioned reflex depending on past associations and experience of palatable foods, and is not dependent on hunger contractions of the stomach. The term appetite is used loosely regarding animals and really expresses the degree of hunger as indicated by the food intake. When variations from normal appetite are mentioned, it means variations from normal food intake, with the rare exception of the animal that demonstrates a desire to eat but fails to do so because of a painful condition of the mouth or other disability. Variation in appetite includes increased, decreased, or abnormal appetite.

Hyperorexia, or increased appetite, caused by increased hunger contractions, is manifested by **polyphagia** or increased food intake. Partial absence of appetite (**inappetence**) and complete absence of appetite (**anorexia**) are manifested by varying degrees of decreased food intake (**anophagia**). **Undernutrition** can be defined as a prolonged inadequate supply of nutrients to sustain good health and, in the case of immature or underweight animals, growth potential. For comparison, **malnutrition** is a deficit, imbalance, or excess of nutrients with consequential adverse effects on health and growth potential.[1]

Abnormal appetites include cravings for substances, often normally offensive, other than usual foods. The abnormal appetite may be perverted, a temporary state, or depraved, the permanent or habit stage. Both are manifested by different forms of **pica** or **allotriophagia**.

THIRST

Thirst is an increased desire for water manifested by excessive water intake (polydipsia). The two main stimuli for thirst are increased plasma osmolality and hypovolemia/hypotension. Osmolality is monitored by receptors in the anterior hypothalamus that are outside the blood-brain barrier, whereas "pressure" is monitored by high- and low-pressure baroreceptors in the vascular system and heart. Clinically, diabetes insipidus produces by far the most exaggerated polydipsia.

Specific observations in ponies have shown that water intake is increased in response to either an increase in the osmotic pressure of tissue fluid (from previous water deprivation) or a decrease in the volume of their body fluids (such as from intravenous furosemide administration). Equidae can accommodate and rapidly recover after 72 hours of water deprivation, particularly donkeys and burros, and, consequently, can be considered desert-adapted animals.

The clinical syndrome produced by water deprivation is not well defined. Animals supplied with saline water will drink it with reluctance and, if the salinity is sufficiently great, die of salt poisoning. Cattle at pasture that are totally deprived of water usually become quite excited and are likely to knock down fences and destroy watering points in their frenzy. On examination they exhibit a hollow abdomen, sunken eyes, and the other signs of dehydration. There is excitability with trembling and slight frothing at the mouth. The gait is stiff and uncoordinated and recumbency follows. Abortion of decomposed calves, with dystocia caused by failure of the cervix to dilate, may occur for some time after thirst has been relieved and cause death in survivors. At necropsy there is extensive liquefaction of fat deposits, dehydration, and early fetal death in pregnant cows.

Experimental water deprivation has been recorded in camels, lactating and nonlactating dairy cows, and sheep. In camels death occurred on the seventh to ninth day of total deprivation; BW loss was about 25%. Lactating cows allowed access to only 50% of their regular water supply become very aggressive about the water trough, spend more time near it, and lie down less. After 4 days milk yield is depressed to 74% and body weight to 86% of original figures. There is a significant increase in serum osmolality with increased concentrations of urea, sodium, total protein, and copper. The PCV is increased, as are

activities of creatinine kinase and serum aspartate aminotransferase (AST) activity. With complete deprivation for 72 hours, the changes are similar but there are surprisingly few clinical signs at that time. The composition of the milk does not change markedly and plasma electrolyte concentrations return to normal in 48 hours. Sheep, even pregnant ewes, are capable of surviving even when access to water is limited to only once each 72 hours, but there is a significant loss (26%) of BW. Deprivation of water that allows access to water only once every 96 hours is not compatible with maintaining the pregnancy.

POLYPHAGIA

Starvation, functional diarrhea, chronic gastritis, and abnormalities of digestion, particularly pancreatic deficiency, may result in polyphagia. Metabolic diseases, including diabetes mellitus and hyperthyroidism, are rare in large animals but are causes of polyphagia in other species. Internal parasitism is often associated with poor growth response to more than adequate food intakes.

Although appetite is difficult to assess in animals, it seems to be the only explanation for the behavior of those that grossly overeat on concentrates or other palatable feed. The syndromes associated with overeating are dealt with in Chapter 8.

ANOPHAGIA OR APHAGIA

Decreased food intake may be caused by physical factors, such as painful conditions of the mouth and pharynx, or to lack of desire to eat. Hyperthermia, toxemia, and fever all decrease hunger contractions of the stomach. In species with a simple alimentary tract a deficiency of thiamin in the diet will cause atony of the gut and reduction in food intake. In ruminants a deficiency of cobalt and a heavy infestation with Trichostrongylidae helminths are common causes of anophagia, and low plasma levels of zinc have also been suggested as a cause. In fact alimentary tract stasis from any cause results in anophagia. Some sensations, including severe pain, excitement, and fear, may override hunger sensations and animals used to open range conditions may temporarily refuse to eat when confined in feeding lots or experimental units. Some sheep that have been on pasture become completely anophagic if housed. The cause is unknown and treatment, other than turning out to pasture, is ineffective.

A similar clinical sign is feed aversion, seen most commonly in pigs, which is rejection of particular batches of feed that are contaminated by fungal toxins, e.g., *Fusarium* spp., or by the plant *Delphinium barbeyi.*

One of the important aims in veterinary medicine is to encourage adequate food intake by sick and convalescing animals. Alimentary tract stimulants applied either locally or systemically are of no value unless the primary disease is corrected first. To administer parasympathomimetic drugs parenterally when there is digestive tract atony caused by peritonitis is unlikely to increase food intake. In cattle, the intraruminal administration of 10 to 20 L of rumen juice from a normal cow will often produce excellent results in adult cattle that have been anorexic for several days, provided the primary cause of the anorexia is corrected. The provision of the most palatable feed available is also of value.

Parenteral or oral fluid and electrolyte therapy is indicated in animals that do not eat or drink after a few days. For animals that cannot or will not eat, or in those with intractable intestinal disease, the use of total intravenous feeding (parenteral nutrition) may be indicated. The subject of therapeutic nutrition for farm animals that cannot or will not eat appears to have been ignored. However, in most cases farm animals will begin to eat their normally preferred diets when the original cause of the anophagia or aphagia is removed or corrected. Intensive fluid therapy may be necessary during the convalescence stage of any disease that has affected feed intake and that may result in a mild depression of serum electrolytes.

A reduced feed intake in high-producing dairy cattle during the first few days or weeks of lactation and in fat beef cattle in late pregnancy may result in fatty infiltration and degeneration of the liver and high mortality. Treatment with glucose parenterally and propylene glycol orally to minimize the mobilization of excessive amounts of body fat is indicated.

In nervous anophagia the injection of insulin in amounts sufficient to cause hypoglycemia without causing convulsions is used in human practice, and in animals the use of tranquilizing drugs may achieve the same result.

In ruminants the effects of blood glucose levels on food intake are controversial, but it seems probable that neither blood glucose nor blood acetate levels are important factors in regulating the appetite. The anorexia that is characteristic of acetonemia and pregnancy toxemia of ruminants appears to be the result of the metabolic toxemia in these diseases. Electrolytic lesions in the hypothalamic region can stimulate or depress food intake depending on the area affected. This indicates the probable importance of the hypothalamus in the overall control of appetite.

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PICA OR ALLOTRIOPHAGIA

Pica is the ingestion of materials other than normal food and varies from licking to actual eating or drinking. It is associated in most cases with dietary deficiency, either of bulk or, in some cases, more specifically fiber, or of individual nutrients, particularly salt, cobalt, or phosphorus. It is considered as normal behavior in rabbits and foals, where it is thought to be a method of dietary supplementation or refection of the intestinal bacterial flora. Boredom, in the case of animals closely confined, often results in the development of pica. Chronic abdominal pain caused by peritonitis or gastritis and CNS disturbances, including rabies and nervous acetonemia, are also causes of pica.

The type of pica may be defined as follows: **osteophagia,** the chewing of bones; **infantophagia,** the eating of young; **coprophagia,** the eating of feces. Other types include wood eating in sheep, bark eating, the eating of carrion, and cannibalism. Salt hunger can result in coat licking, leather chewing, earth-eating, and the drinking of urine. Urine drinking may also occur if the urine is mixed with palatable material such as silage effluent. Bark eating is a common vice in horses, especially when their diet is lacking in fiber, e.g., when they are grazing irrigated pasture.

CANNIBALISM

Cannibalism may become an important problem in housed animals, particularly swine, who bite one another's tails, often resulting in severe local infections. Although some cases may be caused by dietary deficiencies in protein, iron, or bulk, many seem to be the result of boredom in animals given insufficient space for exercise. A high ambient temperature and generally limited availability of food also appear to contribute. Male castrates are much more often affected than females, and the bites are also much more severe in males. Provision of larger pens or a hanging object to play with, removal of incisor teeth, and the avoidance of mixing animals of different sizes in the same pen are common control measures in pigs. In many instances only one pig in the pen has the habit and his removal may prevent further cases. One common measure that is guaranteed to be successful in terms of tail biting is surgical removal of all tails with scissors during the first few days of life, when the needle teeth are removed. Unfortunately the cannibalistic tendency may then be transferred to ears. As in all types of pica, the habit may survive the correction of the causative factor.

INFANTOPHAGIA

Infantophagia can be important in pigs in two circumstances. In intensively housed sows, especially young gilts, hysterical savaging of each pig as it is born can cause heavy

losses. When sows are grazed and housed at high density on pasture it is not uncommon to find "cannibal" sows who protect their own litters but attack the young pigs of other sows. This diagnosis should be considered when there are unexplained disappearances of young pigs.

SIGNIFICANCE OF PICA

Pica is defined as a depraved or abnormal appetite and may result from a nutritional deficiency or boredom. It may have serious consequences: cannibalism may be the cause of many deaths; poisonings, particularly lead poisoning and botulism, are common sequelae; foreign bodies leading to reticuloperitonitis[1] or lodging in the alimentary tract leading to a luminal obstruction; accumulations of wool, fiber, or sand may cause obstruction; perforation of the esophagus or stomach may result from the ingestion of sharp foreign bodies; and grazing time is often reduced and livestock may wander away from normal grazing. In many cases the actual cause of the pica cannot be determined and corrective measures may have to be prescribed on a trial and error basis.

The majority of observational studies identify a relationship between phosphorus deficiency and pica, particularly in ruminants. Horses exhibiting pica may have iron or copper deficiencies.[2]

STARVATION

Complete deprivation of food causes rapid depletion of glycogen stores and a change-over in metabolism to fat and protein. In the early stages there is hunger, increase in muscle power and endurance, and a loss of body weight. In sheep there is often a depression of serum calcium levels sufficient to cause clinical hypocalcemia. The development of ketosis follows associated with increased fat utilization and an increased serum concentration of NEFAs. Plasma and urine concentrations of allantoin are decreased in goats and sheep during fasting as a result of depressed microbial protein production in the forestomach.[3]

A marked reduction in feed intake in pony mares in late pregnancy is often a precursor of hyperlipemia, a highly fatal disease discussed in Chapter 17. In a case series of chronically starved horses, a low body condition score was accompanied with a lower serum urea nitrogen concentration (caused by low protein intake), a normocytic and normochromic anemia, and an increased serum total bilirubin concentration.[4] The serum urea nitrogen to creatinine concentration ratio is considered a better index of protein wasting than serum albumin or total protein concentrations, with a ratio <15 mg/dL being indicative of protein deprivation or starvation in horses.[4] The most pronounced biochemical changes in ponies and mares occurring as a result of experimental food deprivation is increased serum concentrations of triglycerides, cholesterol, and glutamate dehydrogenase,[5] which reach a peak by the eighth day of fasting but quickly return to normal when feeding is resumed. This degree of change in blood lipids appears to be a characteristic of ponies and horses; it is much higher than that in pigs.

In lactating cows, a short period of starvation results in depression of plasma glucose and an increase in plasma lipid concentrations. Milk yield falls by 70%. On refeeding most levels return to normal in 5 days but blood lipid and milk yield may take as long as 49 days to recover to normal levels. In horses, fecal output falls to zero at day 4 and water intake is virtually zero from that time on, but urine volume is maintained. In spite of the apparent water imbalance there is no appreciable dehydration, and plasma protein levels and PCV stay at normal levels. A significant loss of skin turgor (increase in skin tenting) caused by the disappearance of subcutaneous fat as cachexia develops may occur. Muscular power and activity decrease and the loss of body weight may reach as high as 50% to 60%. The metabolic rate falls and is accompanied by a slowing of the heart and a reduction in stroke volume, amplitude of the pulse, and blood pressure. The circulation is normal as indicated by mucosal color and capillary refill.

In the final stages, when fat stores are depleted, massive protein mobilization occurs and a premortal rise in total urinary nitrogen is observed, whereas blood and urine ketones are likely to diminish from their previous high level. Great weakness of skeletal and cardiac musculature is also present in the terminal stages and death is caused by circulatory failure. During the period of fat utilization there is a considerable reduction in the ability of tissues to use glucose and its administration in large amounts is followed by glycosuria. In such circumstances readily assimilated carbohydrates and proteins should be given in small quantities at frequent intervals but fatty foods may exacerbate the existing ketosis. Diets for animals that have been through a period of great nutritional stress because of deprivation of food or because of illness are described in the following section.

Starvation of farm livestock is an animal welfare issue with economic and ethical considerations. When starving animals are identified by a neighboring farmer or veterinarian they are commonly reported to the appropriate authorities, which may be provincial or state-appointed inspectors (animal care officers) who have the authority to take appropriate action. The animals are examined and corrective action is taken, including possession of the animals and relocating them to a commercial feeding facility. Predicting survival of starved animals is a major challenge. Economics becomes an important aspect because the financial costs of stabilizing a group of starved horses may exceed their free market price. Responsible management of chronically starved commercial animals should include options for immediate euthanasia. Ethical considerations include deciding if certain severely starved animals should be euthanized. In some cases, enforcement officers may be reluctant to recommend mass euthanasia of otherwise healthy horses based on personal aversion.

Chronically starved horses lose body weight, become weak, and their body condition score may decline to below 2 on the basis of 1 to 9, and death is common, especially during cold weather. Chronically starved horses frequently respond poorly to refeeding. About 20% of severely malnourished horses can be expected to die in spite of attempts at refeeding. Recovery of severely malnourished horses to an average body condition score may require 6 to 10 months.

INANITION (MALNUTRITION)

Incomplete starvation—inanition or malnutrition—is a more common field condition than complete starvation. The diet is insufficient in quantity; all essential nutrients are present but in suboptimal amounts. This condition is compatible with life, and generally the same pattern of metabolic change occurs as in complete starvation but to a lesser degree. Thus ketosis, loss of body weight and muscular power, and a fall in metabolic rate occur. As a result of the reduction in metabolic activity there is a fall in body temperature and respiratory and heart rates. In addition there is mental depression, anestrus in cows but not ewes, and increased susceptibility to infection. This increased susceptibility to infection that occurs in some cases of malnutrition cannot be accepted as a general rule. In the present state of knowledge it can only be said that *some* nutritional influences affect resistance to *some* forms of infection.

A significantly reduced food intake also increases susceptibility to some poisons, and this has been related to the effects of starvation on hepatic function. In ruminants, the effects of starvation on the activity of liver enzymes is delayed compared with the effects in monogastric animals, apparently because of the ability of the ruminal store of feed to cushion the effect of starvation for some days. The most striking effect of short-term malnutrition in sheep and cattle compared with rats was the very rapid and large accumulation of neutral fat in hepatocytes. If there is a relative lack of dietary protein over a long period of time, anasarca occurs, particularly in the intermandibular space.

Malnutrition makes a significant contribution to a number of quasispecific diseases, "weaner ill-thrift" and "thin sow syndrome" among them, and these are dealt with in the following section.

Controlled malnutrition in the form of providing submaintenance diets to animals during periods of severe feed shortage is now a nutritional exercise with an extensive supporting literature. For pastured animals it is a fact of economic life that significant loss of body weight is planned and tolerated for some parts of each year because the well-known phenomenon of compensatory growth enables the animal to make up the lost weight, with no disadvantage, during the times of plenty. Animals fed on submaintenance diets undergo metabolic changes reflected in blood and tissue values as well as the more significant changes in weight. Experimental restriction of feed intake to 65% of normal levels in nonlactating, nonpregnant heifers does not cause significant falls in serum calcium and phosphorus levels, nor in plasma AST, lactate dehydrogenase (LDH), or CK activities. Serum alkaline phosphatase (ALP) activity was also maintained. In sheep that are losing weight because of undernutrition there is a significant decrease in plasma creatinine concentration.

Experimental feed restriction, followed by fasting, followed by *ad libitum* access to feed, such as might occur in nature, had no serious ill effects on goats. The goats lost weight significantly but did not overeat on being allowed access to feed.

A deficiency of one or more specific dietary essentials also causes a form of partial starvation (see Chapter 4).

Outbreaks of incomplete starvation may occur in cattle, sheep, and horses that are kept outdoors during the cold winter months in regions of the Northern Hemisphere. The feed usually consists of poor-quality grass hay or cereal grain straw and no grain supplementation. During prolonged exposure to the cold environment the animals will increase their daily intake in an attempt to satisfy maintenance requirements and, in cattle, abomasal impaction with a high case of mortality may occur. Field and postmortem findings indicate complete mobilization of fat in affected animals, including serous atrophy of fat in the bone marrow, and an inability to maintain core body temperature in cold ambient temperatures. The fat percentage in the bone marrow of the femur offers an excellent test to quantify whole-body fat reserves. The test requires drying a bone marrow sample to constant temperature; bone marrow percent fat = (dry weight × 100)/wet weight. Normal animals have a percent fat of 70% to 80% in femur bone marrow; animals dying of starvation usually have a bone marrow percent fat <10% and very low body condition score.[6] Serous atrophy can also be quantified by magnetic resonance imaging of bone marrow fat in the distal limbs,[7] but this appears to provide a complicated and expensive method compared with weighing to constant weight. Animals affected with severe inanition are usually weak and recumbent and may or may not eat when offered a palatable feed.

Malnutrition and starvation may occur in calves under 1 month that are fed poor-quality milk replacers containing excessive quantities of nonmilk carbohydrates and proteins. The diet is not well digested by young calves and chronic diarrhea and gradual malnutrition occur. Affected calves recover quickly when fed cows' whole milk for several days. At necropsy there is a marked reduction in muscle mass, lack of depot fat, and serious atrophy of fat. Starvation may also occur in beef calves sucking poorly nourished heifer dams with an insufficient supply of milk. The mortality will be high during cold weather when the maintenance requirements are increased. Affected calves will initially suck vigorously and persistently, they will attempt to eat dry feed, drink surface water and urine, and bawl for several hours. Eventually they lie in sternal recumbency with their head and neck turned into their flanks and die quietly. The response to therapy is usually unsatisfactory and the case fatality rate is high. The convalescence period in survivors is prolonged and treatment is usually uneconomic. Affected animals must be brought indoors and kept warm and well bedded during treatment and realimentation. Initially, fluid therapy using balanced electrolyte solutions containing glucose and amino acids may be necessary to restore the animal's strength and appetite. This is followed by the provision of controlled amounts of a highly palatable digestible diet. High-quality legume hay is excellent, small amounts of ground grain are of value, and the daily administration of a multiple B vitamin and mineral mixture will replenish those lost during inanition. Skim-milk powder is an excellent source of carbohydrate and protein for young animals that have been partially starved. Adult animals cannot digest large quantities of milk powder because of the relative lack of appropriate digestive enzymes.

Horses that have been ill with a poor appetite should be tempted with green grass first, and failing that tried with good-quality hay, preferably alfalfa. It is best to dilute it with good grass hay to begin with, and increase the mix to 100% legume hay over a week. An average horse will require 1.5 to 2 kg BW/day. Grain can be added mixed with molasses or as a mash. Low-fiber diets are recommended to ensure maximum digestibility. A supplement of B vitamins may be advantageous until full appetite and intake are regained. Horses with broken jaws or that are unable to eat at all for some reason can be allowed to go without food for 3 days, but beyond that time they should be fed by stomach tube. A suitable ration is as follows:

- Electrolyte mixture (NaCl, 10 g; $NaHCO_3$, 15 g; KCl, 75 g; K_2HPO_4, 60 g; $CaCl_2$, 45 g; MgO, 24 g): 210 g
- Water: 21 L
- Dextrose, increased from 300 g/day in 7 days to 900 g
- Dehydrated cottage cheese, increased from 300 g/day in 7 days to 900 g

The ration is divided into two or three equal amounts and fed during 1 day. Adult horses that are weak and recumbent may be supported in a sling to avoid decubitus ulceration and other secondary complications associated with prolonged recumbency.

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Weight Loss or Failure to Gain Weight (Ill-Thrift)

This section is concerned with the syndrome of weight loss, or low body condition score (BCS), in the presence of an apparently adequate food supply and a normal appetite. In the absence of any primary disease, an animal or group of animals that presents with this as the problem is a major diagnostic dilemma. Several poorly identified diseases in this category are weaner ill-thrift, thin sow syndrome, thin ewe syndrome, and weak calf syndrome (see other sections of this chapter).

Body weight and **BCS** are sometimes used interchangeably and regarded as synonymous. This is incorrect as body weight, per se, is not a good indicator of BCS because it is closely related to the height and girth of the animal and provides only limited information about body composition.[1] Body weight (live weight) reflects changes in protein and in fat but is influenced by the relative percentages of protein, fat, and water in the body, which can vary depending on physiologic status. Body weight is not a good indicator of energy content per kilogram of body weight, and proportions of fat, protein, and water are highly variable in animals of the same weight.[2] For example, when body mass is depleted there can be selective depletion of fat mass with partial replacement by water so that the amount of mobilized fat can be larger than the loss of body weight.[1-3] Additionally, body weight is substantially influenced by gut fill, and short periods of feed or water withholding, or feed supplementation, can result in marked changes in

body weight without similar changes in body energy content.[2,4] Pregnancy can increase body weight, especially during mid to late gestation, solely because of the growing fetus.

Body condition score is a more useful indicator of both fat-free mass and fat mass in many species. These variables, and in particular fat mass, are closely associated with nutrient requirements, reproductive efficiency, cull value, and risk of disease (for example, laminitis in fat horses) of animal, and estimation of body fat from the BCS or back fat thickness is increasingly important in management of animals.[1,2,4-9] The ideal body condition of an animal must be determined while considering many factors including species, sex, age, reproductive status, lactation status, disease risk, and intended use. For example, the ideal body condition of dairy cows during each stage of lactation is that which optimizes milk production, minimizes reproductive and health disorders, and maximizes economic returns.[2,8]

Body condition score is determined subjectively by observers using a standardized grading system. These grading systems were not developed to assess the fat content (proportion) of the animal but rather to assess "flesh" or the general body condition and are limited because of their subjective nature.[10] Additionally, body condition scoring systems do not provide an assessment of regional adiposity, which might have greater clinical relevance in some species, including horses.[5] Body condition scoring systems have not been validated in all major breeds and uses of animals (validation determines the relationship between BCS and a gold standard measure of body fat, such as deuterium dilution space or carcass analysis) nor has their reliability (intrarater and interrater agreement/repeatability expressed as an intraclass correlation coefficient or, less optimally, a κ or weighted κ statistic) been demonstrated over large numbers of raters. There are reports of an intraclass correlation coefficient of 0.74 for four raters of 21 mares and 75 ponies, and of 0.92 (without details).[11,12] Interrater agreement (weighted κ statistic) among three trained observers for dairy cattle was 0.67 for exact agreement, 0.82 for ± 0.25, and 0.96 for ± 0.5 BCS, based on a <2 to 5 scale.[13] Training of observers markedly improved both interobserver and intraobserver repeatability.[13]

Furthermore, differing rating systems might be used within an industry or between countries such as the use of different body condition scoring methodologies in the United Kingdom (UKBCS) and the United States (USBCS) resulting in the need to develop conversion factors (R^2 = 0.56):[14] USBCS = 1.182 + 0.816 × UKBCS and, UKBCS = 0.131 + 0.681 × USBCS.

A rating system for dairy cattle developed by Elanco Animal Health and subsequently modified is used in the United States (Fig. 4-3) and a methodology for equids is described in Chapter 17).[13] A similar BCS system in dairy cattle is depicted in Fig. 4-4.

Estimation of body composition, including proportions of fat and fat-free mass, can be made using tracer dilution technologies (isotopes or chemical traces such as urea or antipyrine) or ultrasonographic imaging. The gold standard is the analysis of carcass composition, but this technique requires the death of the animal and is time-consuming and expensive. Use of tracer technologies and in particular deuterium oxide has become more common in experimental studies but has limited utility in clinical practice situations.[4] More practical is the use of ultrasound to determine subcutaneous fat thickness, or retroperitonal fat depth (usually perirenal), as an indicator of body energy stores. This methodology has been well

BCS	3.0	2.75	2.5	2.25	2.0	< 2.0
Pelvic area	V	V	V	V	V	V
Hook bones	Rounded	Angular	Angular	Angular	Angular	Angular
Pin bones	Padded	Padded	Angular, fat palpable	Angular, no fat palpable	Angular, no fat palpable	Angular, no fat palpable
Ribs	Corrugations non visible	Corrugations non visible	Corrugations non visible	Corrugations visible 1/2 way between tips and short ribs	Corrugations visible 3/4 way between tips and short ribs	Corrugations visible 3/4 way between tips and short ribs
					Thurl non prominent	Thurl prominent

BCS	3.25	3.5	3.75	4.0	4.25	4.5	4.75	5.0
Pelvic area	U	U	U	U	U	U	U	U
Tailhead ligament	Visible	Barely visible	Not visible	Not visible	Not visible	Not visible	Not visible	Not visible
Sacral ligament	Visible	Visible	Barely visible	Not visible	Not visible	Not visible	Not visible	Not visible
Thurl	Non flat	Non flat	Non flat	Non flat	Flat	Flat	Flat	Flat
Tips short ribs	Visible	Visible	Visible	Visible	Barely visible	Barely/not visible	Barely/not visible	Barely/not visible
Pin bones	Visible	Visible	Visible	Visible	Visible	Buried	Buried	Buried
Hook bones	Visible	Visible	Visible	Visible	Visible	Visible	Barely visible	Barely/not visible
								All bony prominences well bounded

Fig. 4-3 Summary of system to estimate body condition scoring (BCS) in dairy cattle, ranging in score from 1.0 (could not be skinnier) to 5.0 (could not be fatter).

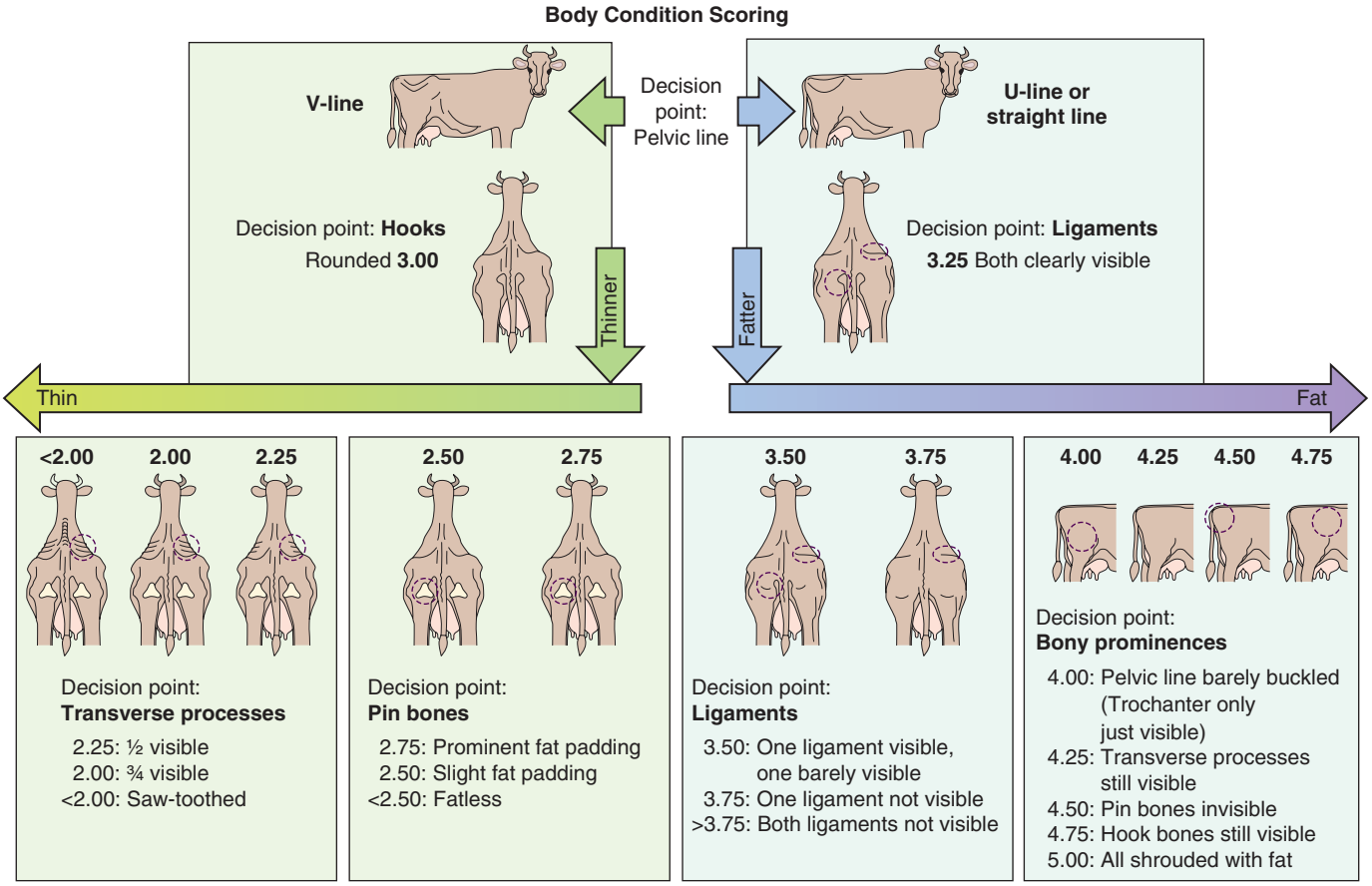

Fig. 4-4 Body condition scoring system modified from earlier work. (From Isensee A et al. *Animal* 2014; 8(12):1971-1977.)

developed in cattle (Fig. 4-5) and pigs and less so in horses.[3,5,7,16-18]

Measurement of bioelectrical impedance is used to assess carcass composition of cattle and to estimate changes in body water in horses.[19-21] Thermal imaging and use of digitized images have been investigated for the assessment of BCS in dairy cows, with a view toward developing automated systems.[17,22]

Detailed next is a checklist of causes that should be considered when an animal has a weight loss problem in the absence of signs indicative of a primary wasting disease.

NUTRITIONAL CAUSES

"Hobby farm malnutrition" is a surprisingly common cause of poor body condition, especially in companion horses. Inexperienced owners keep their animals where they are not able to graze pasture and are entirely dependent on stored feed but underfed for economy's sake or out of ignorance of the nutritional requirements of the animal. Knowledge of the animals' needs and of the approximate energy and protein values of feeds is necessary to prepare an appropriate ration.

The feed and feeding conditions must be inspected as the first step in the diagnostic process to rule out malnutrition (broadly defined as either provision of insufficient feed or of feed that is not appropriate for the species, age, reproductive status, and use of the animal) as a cause of poor body condition. Mature meadow hay might not provide sufficient calorie or protein intake for some animals and "shy" animals or those low in the hierarchy (pecking order) in group-fed animals can be physically prevented from getting a fair share of available feed, especially if **trough space** is inadequate.

This problem is also common when urban people try to raise a few veal calves or sheep to help defray the costs of their rural acreage. It is common in these circumstances to equate rough meadow grass with proper nutrition for young or pregnant ruminants.

Other considerations are as follows:

- Diets that are inadequate in total energy because they cannot replace the energy loss caused by the animal's level of production can be important causes of weight loss in heavy producing animals. This subject is discussed under the heading of production disease. An example is acetonemia of high-producing cows in which body stores of fat and protein are raided to repair the energy deficiency of the diet.
- Malnutrition as a result of a ration that is deficient in an essential trace element is unusual in the management situation being discussed. A nutritional deficiency of cobalt does cause weight loss in ruminants but is likely to have an area effect rather than cause weight loss in single animals. Copper, salt, zinc, potassium, selenium, phosphorus, calcium, and vitamin D deficiencies are also in this category. Experimental nutritional deficiencies of riboflavin, nicotinic acid, pyridoxine, and pantothenic acid in calves and pigs can also be characterized by ill-thrift.
- Inadequate intake of an adequate supply of feed is dealt with under diseases of the mouth and pharynx and is not repeated here, but it is emphasized that the first place for a clinician to look in a thin animal is its mouth. The owner might have forgotten just how old the animal is and one often finds a cow without any incisor teeth attempting to survive on pasture.
- Other factors that reduce an animal's food intake when it is available in adequate amounts include anxiety, the excitement of estrus, new surroundings, loss of a newborn, bad weather, tick or other insect worry, and abomasal displacement.

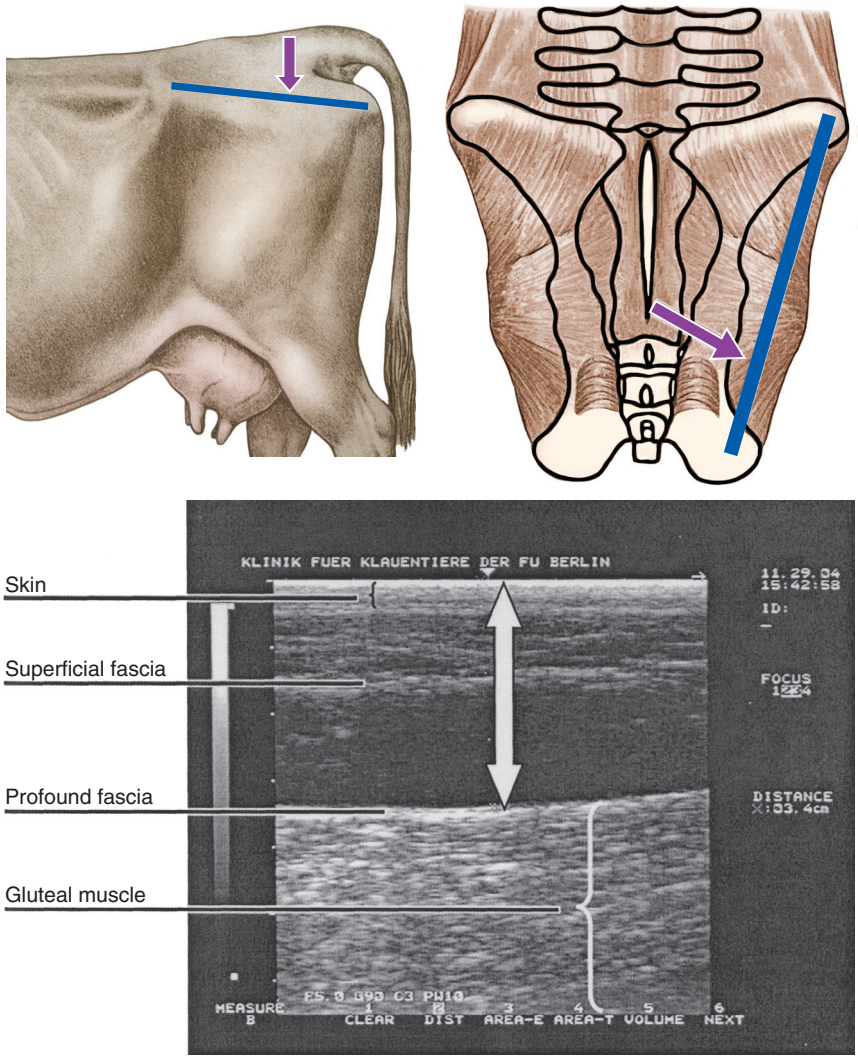

Fig. 4-5 Location of the site for ultrasonographic measurement of backfat thickness in dairy cattle from the left lateral and dorsal views (top two panels) and ultrasound image from an overconditioned cow with a back fat thickness of 34 mm. (Reproduced with permission from Schroder UJ, Staufenbiel R. *J Dairy Sci* 2006;89:1-4.)

EXCESSIVE LOSS OF PROTEIN AND CARBOHYDRATES

- **Protein loss in the feces**. Cases of protein-losing gastroenteropathy are not unusual and can be caused by diseases as common as gastrointestinal parasitism or bovine or ovine paratuberculosis (Johne's disease). The loss can occur through an ulcerative lesion, via a generalized vascular discontinuity, or by exudation through intact mucosa as a result of hydrostatic pressure in blood vessels, e.g., in verminous aneurysm, or lymphatics in cases of lymphangiectasia of the intestine. The identification of a neoplasm (lymphosarcoma or intestinal or gastric adenocarcinoma are the usual ones) or of granulomatous enteritis is not possible without laparotomy and biopsy of the alimentary segment. One is usually led to the possibility of this as a diagnosis by either a low serum total protein or low albumin level in a normal total protein level, and in the absence of other protein loss.
- **Proteinuria** for a lengthy period can cause depletion of body protein stores, resulting in weight loss. Chronic glomerulonephritis is the usual cause. Examination of the urine should be part of every clinical examination of an animal being investigated for weight loss.
- **Internal and external parasitoses** in which blood sucking is a part of the pathogenetic mechanism can result in severe protein loss, as well as anemia per se.

FAULTY DIGESTION, ABSORPTION, OR METABOLISM

Faulty digestion and absorption are commonly manifested by diarrhea, and diseases that have this effect are dealt with under the heading of malabsorption syndromes (see Chapter 7). In grazing ruminants, the principal causes are the nematode worms *Ostertagia, Teladorsagia, Nematodirus, Trichostrongylus, Chabertia, Cooperia,* and *Oesophagostomum* and the flukes *Fasciola* and *Paramphistomum*. In cattle the additional causes are tuberculosis, coccidiosis, sarcosporidiosis, and enzootic calcinosis. In sheep and goats there are Johne's disease, viral pneumonia without clinical pulmonary involvement, and hemonchosis. In horses there are strongylosis, habronemiasis, and heavy infestations with botfly larvae. In pigs there are stephanuriasis, hyostrongylosis (including the thin sow syndrome), infestation with *Macracanthorhynchus hirudinaceus,* and ascariasis. Gastrointestinal neoplasia must also be considered as a possible cause.

- Chronic villous atrophy occurs most severely with intestinal parasitism or as a result of a viral infection.
- Abnormal physical function of the alimentary tract, as in vagus indigestion of cattle and grass sickness in horses, is usually manifested by poor food intake and grossly abnormal feces.
- Inadequate utilization of absorbed nutrients is a characteristic of chronic liver disease. It is usually distinguishable by a low serum albumin concentration (although this is an uncommon manifestation of liver diseases in horses), by liver function tests, and by measurement of activity in serum of liver-derived enzymes. A clinical syndrome including edema, jaundice, photosensitization, and weight loss is a common accompaniment.
- Neoplasia in any organ. The metabolism of the body as a whole is often unbalanced by the presence of a neoplasm so that the animal wastes even though its food intake seems adequate.
- Chronic infection, including specific diseases such as tuberculosis, sarcocystosis, East Coast fever, trypanosomiasis (nagana), maedi-visna, caprine arthritis–encephalitis, enzootic pneumonia of swine, metastatic strangles in horses, and nonspecific infections such as atrophic rhinitis of pigs, abscess, empyema, and chronic peritonitis reduce metabolic activity generally as well as reducing appetite. Both effects are the result of the toxemia caused by tissue breakdown and of toxins produced by the organisms present. Less well understood are the means by which systemic infections, e.g., equine infectious anemia, scrapie in sheep, and other slow viruses, produce a state of weight loss progressing to emaciation.
- Food refusal is a well-recognized syndrome in pigs, which in some cases

is caused by mycotoxins in the feed, and "off feed effects" are similarly encountered in feedlot cattle on rations containing a large proportion of wheat grain.
- Many diseases of other systems, e.g., congestive heart failure, are manifested by weight loss.
- Determination of the **specific cause of weight loss in an individual animal** depends first on differentiation into **one of the three major groups**:
  - Nutritional causes, diagnosed by assessment of the animal's total food intake
  - Protein or carbohydrate loss in the animal's excretions, diagnosed by clinicopathologic laboratory tests
  - Faulty absorption of the food ingested diagnosed by tests of digestion, as set out in Chapter 7.

SHORTFALLS IN PERFORMANCE

The need for economically efficient performance by farm animals introduces another set of criteria, besides freedom from disease, to be taken into consideration when deciding an animal's future. The same comment applies, and much more importantly, when a herd's productivity is being assessed. This is usually done by comparing the subject herd's performances to that of peer herds, or animals in similar environmental and management conditions.

It is usual to use the production indexes that are the essential outputs of the particular enterprise as the criteria of productivity. Thus in dairy herds the criteria could be as follows:
- Milk or butterfat production per cow per lactation (liters per cow or liters per hectare)
- Reproductive efficiency as the mean intercalving interval
- Percentage calf survival to 1 year of age
- Longevity as percentage mortality per year or average age of cows in herd plus culling rate per year
- The culling rate needs to differentiate between sale because of disease or poor production and sale as a productive animal
- Acceptability of product at sale, as indicated by bulk tank milk somatic cell count and rejection of milk because of poor-quality, low-fat content, and low solids-not-fat content

If it is decided that performance falls too far short of the target, an investigation is warranted. Some targets for productivity in each of the animal industries are available, but they vary a great deal between countries depending on the levels of agriculture practiced and the standards of performance expected. For this reason, they are not set down here and neither is the degree of shortfall from the target that is acceptable, which depends heavily on the risk aversion or acceptability in the industry in that country. For example, if the enterprise is heavily capitalized by high-cost housing and land, the standard of performance would be expected to be higher than in a more exploitative situation in which cattle are pastured all year. In the latter, a reasonable flexibility could be included in the assessment of productivity by permitting it to fall within the scope of 2 standard deviations of the mean productivity established by peer herds.

If the performance is below permissible standards, then an investigation should be conducted that should include the following groups of possible causes:
- **Nutrition:** Its adequacy in terms of energy, protein, minerals, vitamins, and water
- **Inheritance:** The genetic background of the herd and the quality of its heritable performance
- **Accommodation:** To include protection from environmental stress by buildings for housed animals and terrain and tree cover for pastured animals; also consideration of population density as affecting access to feed, water, and bedding areas
- **General managerial expertise:** The degree of its application to the individual flock or herd; this is difficult to assess and then only indirectly, e.g., the efficiency of heat detection and achievement of planned calving pattern
- **Disease wastage:** As clinical disease or, more particularly, subclinical disease; the latter may include such things as quarter infection rate as an index of mastitis, fecal egg counts relative to parasite burden, metabolic profile relative to metabolic disease prevalence rate, and so forth

These investigations tend to require special techniques in addition to the clinical examination of individual animals. They are mostly self-evident, but attention is drawn to the section on examination of a herd or flock in Chapter 2. It will be apparent that there is a great deal of merit in having herds and flocks under constant surveillance for productivity and freedom from disease, such as is practiced in modern herd health programs. Monitoring performance and comparing it with targets is the basis of that system.

The specific syndromes that fall within this category of disease, and which are dealt with elsewhere in this book, are ill-thrift of weaner sheep, thin sow syndrome, weak calf syndrome, poor performance syndrome of horses, and low butterfat syndromes and summer slump of milk cows. Two performance shortfalls encountered commonly by field veterinarians are ill-thrift in all species and poor performance syndrome in horses.

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UNTHRIFTINESS IN WEANER SHEEP (WEANER ILL-THRIFT)

ETIOLOGY

Several factors have been associated with this syndrome in lambs, goat kids, and calves. Contributing causes include intestinal parasitism, coccidiosis, infection with *Mycoplasma ovis* (eperythrozoonosis), suboptimal animal husbandry, and nutritional deficiencies. The latter can be in the form of inadequate gross nutrition (a lack of energy or protein) or a deficiency of trace elements (copper, cobalt, selenium, and zinc) or vitamins (thiamin, vitamin A, vitamin D, and vitamin E).

The syndrome is often multifactorial, with a combination of management, nutritional, and infectious causes involved that can be a challenge to identify and correct.[1]

SYNOPSIS

Etiology Several, often interacting causes, including poor management and animal husbandry; parasitism; trace element and vitamin deficiencies; the amount, quality, and palatability of pasture and fungal infestations of pasture.

Epidemiology Loss of weight after weaning, hence failure to achieve target

weights for adequate survival and mating. This is often despite the presence of ample feed and at times when adult sheep are faring well.

Clinical findings Poor body condition and wool growth, failure to thrive, and gradually accumulating mortalities.

Lesions Inanition; little body fat, involution of rumen papillae, and poor mineralization of long bones and ribs, often with evidence of healing fractures.

Diagnostic confirmation Examination of weight profile of mob and pastures being grazed. Laboratory testing for contributing causes, such as worm egg counts for internal parasitism or blood and tissue tests for trace element status. Response to treatment or provision of the required nutritional supplement, such as energy (usually most cost-effectively in the form of cereal grains), protein (legume grains such as field peas or lupins), trace elements, or vitamins.

Treatment and control Correction of gross nutritional or trace element deficiencies and review of the management calendar, including length of mating period, month of lambing, and proactive monitoring of body weights and worm egg counts at and after weaning. "Imprint feeding" of cereal grains to lambs while they are still on the ewes; 20 g per head on at least three occasions will help weaner sheep recognize and start consuming supplementary grain rations before they start losing excessive weight.

Poor quality or unpalatable pasture can be a cause of ill-thrift, or at least associated with it, and moving animals to a better quality pasture will often help alleviate the problem. This has been observed with many pasture species, especially rank or senescent swards, including phalaris (*Phalaris aquatica*), perennial rye grass (*Lolium perenne*), setaria grass (*Setaria sphacelata*), tall fescue (*Festuca arundinaceae*), and turnips (*Brassica repens*). Infestation of pasture grasses with endophyte fungi may be a contributing factor to ill-thrift and poor growth rates, such as with *Acremonium lolii* in perennial rye grass and "summer syndrome" of calves associated with *A. coenophialum* infestation of tall fescue. Infection of pasture species with toxigenic *Fusarium* spp. has been associated with ill-thrift in lambs in South Africa, New Zealand, and Australia. Pasture and soil fungi have also been suspected of being associated with ill-thrift in sheep in eastern Canada.

EPIDEMIOLOGY

The syndrome appears to be most severe in the Southern Hemisphere, but this may be because Merino sheep are more prevalent. The disease is most common in this breed, which may be due in part to their timorous nature, which makes weaning, and the need to graze as a mob by themselves, more stressful and traumatic than for most other breeds. For example, the average postweaning mortality in a national survey of 1400 sheep producers in Australia was 4.6%, with 44% of farms having "high" mortalities (exceeding a benchmark of 4% per annum).[1] High mortality was reported on 50% of farms with predominantly Merino sheep, but also on 32% of farms with predominantly crossbreeds, and there was a postweaning mortality >10% on 14% of farms.

Factors that contribute to weaner ill-thrift include the following:

- Overstocking (overcrowding) on pasture.
- Poor quality or an inadequate amount of pasture.
- Lambs that are light (<20 kg) at weaning, with the lightest 20% of a mob having three times the risk of mortality than the middle 20%. A target for a weaning weight of at least 22 kg for Merinos, or 45% of mature weight, is commonly used.[2-4]
- Merino ewes often have poor milk production, hence management of the ewe flock, such as maintaining ewes at target condition scores from mating and throughout pregnancy, is critical to achieve target weaning weights.[4]
- Postweaning growth rate: Increasing growth from 10 to 20 g/day reduces the risk of mortality by 70%[3] and a target for growth in the immediate postweaning period of 30g/day (1 kg/month) is sufficient to significantly reduce the risk of mortality.[2,4]
- Other management factors likely to lead to low weaning weights and subsequent unthriftiness are extended mating periods (lambs born late in the season), ewes in low condition score (light lambs and poor milk supply), and multiple birth lambs.

Weaner ill-thrift does occur in breeds other than the Merino[1] and is also reported in the Northern Hemisphere. The economic effects can be disastrous for individual flocks and have been estimated at up to USD$58M over the entire industry in Australia.[5] Decreased growth and delayed maturation can mean a poor performance at the first (maiden) lambing. A high proportion of weaner deaths in wool flocks reduces the ability to select replacement ewes, decreasing the rate of genetic gain (although ram genetics are overwhelmingly more important in a wool flock). There is also a substantial decrease in the amount and quality of weaner wool which, in Merino flocks, is usually the finest and most valuable from any age group.

CLINICAL AND NECROPSY FINDINGS

As the name indicates, this syndrome in weaned sheep is manifested primarily by poor body condition and a failure to thrive. Within an affected group not all lambs are equally affected and there will be a range of weight or condition scores. Those lambs in very poor condition are often anemic, may have diarrhea, and there are sporadic but continuing mortalities. The sheep will often have been treated with anthelmintics with no favorable response. There are often no abnormal findings at gross postmortem, other than those associated with emaciation. Poor development of rumen papillae may be obvious grossly, villous atrophy is often found on histologic examination of the small intestine, and the mineralization of long bones and ribs may be reduced because of chronic malnutrition. This can lead to thin cortices and fractures when sheep are handled, such as for shearing or crutching.

DIFFERENTIAL DIAGNOSIS

When faced with this problem the initial approach should be to examine for the most likely cause, namely a deficiency in energy or protein intake. A physical examination of affected sheep should include an examination of the teeth to ensure that there is no excessive wear, or even breaking of the incisors (e.g., if the sheep are being fed roots).

The internal parasite status of the group should be examined by appropriate techniques, such as worm egg counts or total worm counts. Clinical or subclinical infestations with nematodes are common occurrences at this time in the sheep's life, before immunity is properly developed and when pasture contamination can be high.

Infections with coccidia, cryptosporidia, or *Mycoplasma* (*Eperythrozoon*) *ovis* are significant causes of ill-thrift and should be examined by fecal flotation and blood smears, respectively.

The trace element status of the group should be examined if the cause cannot be attributed to gross nutritional deficiencies (inadequate energy or protein) or internal parasites. The most common trace element deficiencies are copper, selenium, and cobalt. These are typically associated with specific geographic areas, soil types, and differing patterns of soil ingestion through wet and dry seasons. If trace element deficiency is a contributing factor it is likely that there will be some prior history of this problem in the area. Diagnosis by response to supplementation is a common approach, and the diagnostic aspects of the trace element deficiencies are outlined under their specific headings.

Examination of the previously mentioned possible causes can be time-consuming and costly, and there are a proportion of cases in which no clear cause can be identified.

Infectious agents can produce enteric lesions and ill-thrift (e.g., coronavirus and yersiniosis), with the malabsorption of nutrients manifested by weight loss and by chronic diarrhea. These can be differentiated on the initial gross postmortem or in samples submitted for culture and histopathology.

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PORCINE FAILURE TO THRIVE

This is a clinical syndrome recognized in the United States and Canada since 2007[1] and in Spain.[2] It has also been called porcine cachectic syndrome or porcine cachexia. It is characterized by anorexia of nursery piglets, progressive loss of bodily condition, and lethargy over the next 1 to 3 weeks. Morbidity may be low but the case mortality is high and many require culling.

ETIOLOGY

The etiology for porcine failure to thrive has not yet been established. It may include both infectious and noninfectious factors. This syndrome was first identified in a high-health herd and all the usual culprits were ruled out, although both viral and bacterial agents were found.[3,4] Some eminent pig veterinarians think that the disease is related mainly to suboptimum management before weaning.

EPIDEMIOLOGY

It occurs around weaning not just postweaning. Villous atrophy and enteritis are the main features.

PATHOGENESIS

Some think porcine failure to thrive is a postweaning location issue, whereas others think it is a source farm issue. There are no infectious, nutritional, managemental, or environmental factors to explain the clinical signs.

CLINICAL SIGNS

At weaning affected pigs are of average to above average weight. Within 60 to 72 hours of weaning they are still active, alert, and without fever, but they are flat-sided and have an empty abdomen. Within 7 days they are anorectic with rough hair coats and lethargic. Their heads are down and their muscles are slack. They are unwilling to move and often sneeze. The pigs deteriorate and die within 2 to 3 weeks.

Some groups from the same source are affected but not others. It may occur several times and then disappear for a long period. Some pigs on the affected farms show repetitive oral behavior such as licking, chewing, or chomping. The crucial time appears to be around 96 hours postweaning. At this time the pigs rest their heads on the backs of their fellows and start chomping.

PATHOLOGY

It is difficult to say whether the lesions are the cause of the condition or are the result of inappetence and starvation. Subgross pathology shows a severe villous atrophy, rhinitis, and gastritis but not in the *pars esophagea*. There are no fat reserves remaining in the carcass.

In the early cases in 2007, the most obvious lesions were histologic and included superficial lymphocytic fundic gastritis, atrophic enteritis with many immature cells, villous atrophy, superficial colitis, lymphocytic and neutrophilic rhinitis, mild nonsuppurative meningoencephalitis, and thymic atrophy.

TREATMENT

Until a cause is found it is difficult to work out a reliable treatment, and in many cases pigs are too badly affected for anything other than euthanasia. It is essential that pigs find food and water and it may be necessary to introduce gruel feeding. Few pigs respond to the special care they might have in hospital accommodation (supplemental heat, electrolytes, special high-milk feed supplements, moistened feed, and individual pig feeding).

CONTROL

There is none at the moment.

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Physical Exercise and Associated Disorders

The act of performing physical work requires expenditure of energy at rates above the resting metabolic rate. Increases in metabolic rate can be supported by anaerobic metabolism through the use of intramuscular ATP stores and conversion of glycogen or glucose to lactate for short periods of time. Ultimately, however, all energy is derived by aerobic metabolism and is limited by the rate of delivery of oxygen to tissue and its utilization in mitochondria. To support the increased energy expenditure required to perform work, such as racing, carrying a rider, or pulling a cart, the metabolic rate is increased. Increases in metabolic rate are supported by increases in oxygen delivery to tissue and carbon dioxide removal. Increased oxygen consumption is dependent on an increase in oxygen delivery to tissues, which is possible by increases in cardiac output, muscle blood flow and, in horses, an increase in hemoglobin concentration with a concomitant increase in the oxygen-carrying capacity of blood. The increased transport of oxygen from the air to the blood is accomplished principally by increases in respiratory rate and tidal volume. Factors that affect oxygen transport from the air to the mitochondria have the potential to impair performance. For instance, laryngeal hemiplegia reduces minute ventilation and exacerbates the normal exercise-associated hypoxemia in horses, atrial fibrillation decreases cardiac output and hence oxygen delivery to tissues, and anemia reduces the oxygen-carrying capacity of the blood.

The increase in cardiac output with exercise of maximal intensity in horses is very large; horses have a cardiac output of about 75 (mL/min)/kg at rest and 750 (mL/min)/kg (300 L/min for a 400-kg horse) during maximal exercise. Associated with the increase in cardiac output are increases in right atrial, pulmonary arterial, and aortic blood pressures. Systemic arterial blood pressure during exercise increases as the intensity of exercise increases with values for systolic, mean, and diastolic pressures increasing from 115, 100, and 80 mm Hg (15.3, 13.3, and 10.6 kPa) at rest to 205, 160, and 120 mm Hg (27.3, 21.3, and 16kPa), respectively, during intense exercise.

Pulmonary artery pressure increases from a mean of approximately 25 mm Hg (3.3 kPa) to almost 100 mm Hg (13.3 kPa) during intense exercise. The increase in pulmonary artery pressure with exercise may contribute to exercise-induced pulmonary hemorrhage.

The increase in metabolic rate during exercise causes a marked increase in metabolic heat generation with a subsequent increase in body temperature. The increase in body temperature is dependent on the intensity and duration of exercise and the ability of the horse to dissipate heat from the body. Intense exercise of short duration is associated with marked increases in body temperature but such increases rarely cause disease. However, prolonged exercise of moderate intensity, especially if performed in hot and humid conditions, may be associated with rectal temperatures in excess of 42.5°C (108.5°F). Heat is dissipated primarily by evaporation of sweat from the skin surface. Sweating results in a loss of body water and electrolytes, including sodium, potassium, calcium, and chloride. The size of these losses can be sufficient to cause dehydration and abnormalities of serum electrolyte concentrations and also impaired cardiovascular and thermoregulatory function.

Recovery from exercise is influenced by the fitness of the individual, with fitter horses recovering more rapidly; the intensity and

duration of the exercise bout; and activity during recovery. Horses allowed to walk after a bout of intense exercise recuperate more quickly than do horses that are not allowed to walk. Recovery is delayed if the horse cannot drink to replenish body water or in hot and humid conditions.

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EXERCISE-ASSOCIATED DISEASES

Many exercise-induced diseases are associated with specific activities. For instance, heat stroke and exhaustion are very rare in Standardbred and Thoroughbred horses raced over distances of up to 3 miles (5km) but common in horses participating in endurance races (50–100km) or the second day of 3-day event competitions. Conversely, exercise-induced pulmonary hemorrhage occurs only in horses that race or compete at high speed and is very uncommon in draft breeds. The exercise-associated diseases exertional rhabdomyolysis, synchronous diaphragmatic flutter, hyperthermia, and exercise-induced pulmonary hemorrhage are dealt with in other sections of this book.

EXHAUSTION

All physical work, if of sufficient intensity and duration, causes fatigue. The mechanisms underlying fatigue vary with the type of work or exercise performed. Thus fatigue in a racehorse running 3 km at high speed has a different genesis from fatigue than an endurance horse that has run 100 km at low speed. Typically, Standardbred and Thoroughbred racehorses recover quickly and exhaustion rarely occurs. However, horses performing endurance exercise require longer to recover, and the processes associated with fatigue may progress to the extent that recovery is delayed or impossible without treatment.[1] This results in illness in some competitors after racing and elimination of some horses from competition during the endurance race.[2] The failure to recover and the clinical and clinicopathologic signs associated with this have been labeled *exhausted horse syndrome*.

The exhausted horse syndrome is associated with endurance races, 3-day eventing, trail riding, and fox and bird hunting; these are all activities in which there is prolonged submaximal exercise. The likelihood of the disorder is increased in unfit horses or when horses are exercised in hot and humid conditions, especially if they are not accustomed to such conditions.

PATHOGENESIS

The pathogenesis of exhaustion is complicated but probably involves depletion of body glycogen and electrolytes, especially sodium, chloride, and potassium; hypovolemia caused by large losses of water in sweat; hyperthermia; and acid-base disturbances. Endurance exercise is associated with the production of large amounts of heat, which are dissipated primarily by evaporation of sweat. Approximately 11 L of sweat are lost each hour during submaximal exercise, and this loss causes a significant decline in total body water, sodium, potassium, and chloride content and serum concentrations of these ions. Loss of chloride causes a metabolic alkalosis. Hypovolemia impairs thermoregulation by reducing blood flow to the skin and probably results in a reduction in gastrointestinal blood flow contributing to intestinal ischemia and development of ileus. Body temperature increases to dangerous levels (43°C; 109°F), and the horse cannot continue to exercise. Excessive increases in body temperature can overwhelm mechanisms to ensure that the brain of horses does not overheat, resulting in signs of CNS dysfunction.[1] If the exercise-induced abnormalities are sufficiently severe then the combination of hyperthermia and dehydration can initiate a cascade of events terminating in shock, multiple organ failure, and death.

CLINICAL SIGNS

The clinical signs of the exhausted horse syndrome include failure to continue to exercise, depression, weakness, failure to eat and drink, delayed return of heart rate and rectal temperature to normal values, poor skin turgor and capillary refill time, a stiff stilted gait consistent with rhabdomyolysis, and decrease or absent borborygmi. Urine is concentrated and the horse ceases to urinate.

Colic occurs in horses after endurance racing and can be related to abnormalities in gastrointestinal motility secondary to fluid and electrolyte abnormalities and hyperthermia.[3-6] Lesions in horses taken to surgery most commonly involve the small intestine, and affected horses have signs typical of acute small intestinal obstruction compounded by signs of exhaustion.[3] Most endurance horses with postracing colic respond to cooling and correction of fluid and electrolyte abnormalities with development of surgical lesions.[4]

Clinicopathologic examination reveals hemoconcentration, hypochloremia, hypokalemia, and variable changes in serum sodium concentration. There is usually a metabolic alkalosis (increased blood bicarbonate concentration), although some severely affected horses will also have a metabolic acidosis associated with increased blood lactate concentration. Serum creatinine and urea nitrogen concentrations are increased because of dehydration and/or renal disease. Serum creatine kinase activity is markedly increased in horses with rhabdomyolysis.

TREATMENT

Treatment consists of rapid restoration of hydration status, correction of electrolyte and acid-base abnormalities, and reduction in body temperature. Fluid therapy is addressed in detail in Chapter 5. Suitable fluids for administration to exhausted horses are Ringer's solution, isotonic sodium chloride with added potassium chloride (10 mEq/L), and calcium gluconate (10–20 mL of 24% solution per liter). Theoretically, lactated Ringer's solution should not be given to horses with metabolic alkalosis, but clinical experience indicates its safety and efficacy.

Horses should be aggressively cooled by application of cold water or water and ice. In spite of folklore to the contrary, application of ice cold water to hyperthermic horses is not dangerous or associated with rhabdomyolysis. The NSAIDs for pain relief can be given when the horse is no longer hypovolemic. Horses with colic should have a full examination for that condition, including passing of a nasogastric tube to ensure that there is no distension of the stomach.

PREVENTION

Prevention rests in ensuring that participating horses are adequately trained for the event and acclimated to the environmental conditions. Horses should be healthy, preferably as determined by a veterinary examination before the race, and should be monitored during the event for signs of excessive fatigue, dehydration, or hyperthermia.

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POOR RACING PERFORMANCE AND EXERCISE INTOLERANCE IN HORSES

The definition of poor racing performance is difficult. Horses that have a proven record of performing well and then fail to perform at their previous level are readily apparent, and a physical cause of the reduction in performance can often be identified. More difficult are the horses that do not have a history of satisfactory performance and are best labeled as *failure to perform to expectation*. Horses in this group might indeed have a clinical abnormality, but commonly the reason is lack of innate ability or inadequate training. Both of these causes must be raised with the owner and trainer carefully and tactfully, and only after a thorough examination of the horse.

Exercise intolerance in racehorses is best defined as the inability to race at speeds previously attained by that horse or attained by peers. In its most extreme form exercise intolerance is evident as failure to complete the race, whereas its mildest form is evident as a slight decrement in performance, such as losing a race by several lengths or 1 or 2 seconds, or failure to perform to expectation.

APPROACH TO THE HORSE WITH EXERCISE INTOLERANCE

Horses with a history of a recent decrement in performance or those that are not performing to expectation should be examined in a systematic fashion.

History

A detailed history should be collected that focuses on documenting the reduction in performance, its time course, and the presence and evolution of any clinical signs. This can be accomplished by asking the following questions of the owner or trainer:

- **What evidence is there of poor performance?** This query should focus on providing objective evidence of a reduction in performance through examination of race times or results. This also allows the severity of the reduction in performance to be documented.
- **What is the horse's training schedule?** The training regimen should be appropriate for the horse's level of competition.
- **Describe the horse's exercise intolerance**. Does it start the race strongly and "fade" in the last part of the race, or is it unable to maintain a suitable speed for the complete race? Is the horse slow to recover its normal respiratory rate after exercise? Can it sweat? Does it consistently veer or "pull" toward one side?
- **Is there any history of illness in this horse or other horses in the same stable or at the race track**? Has the horse had a fever or been inappetent? Is the horse on any medication? Specific attention should be paid to any history of respiratory disease.
- **Does the horse make an unusual noise associated with respiration when running?** Horses with upper airway obstructions almost always make an abnormal noise during exercise.
- **Does the horse cough either at rest, during, or after exercise?** Coughing can be an indication of lower respiratory tract disease.
- **Has the horse ever had blood at the nostrils after exercise or has it been diagnosed as having exercise-induced pulmonary hemorrhage?**
- **Is the horse lame?** Does it ever show signs of muscle stiffness or abnormal gait?
- **What is the history of anthelmintic administration?**

Clinical Examination

A thorough clinical examination should be performed. The physical examination should include a detailed examination of the musculoskeletal, cardiovascular, and respiratory systems and should include the collection of samples of body fluids for laboratory analysis as indicated by the historical data or clinical examination. Ancillary testing, such as radiography, endoscopy, nuclear scintigraphy, and stress testing, are available at larger centers and might be indicated in some cases.

The horse should be examined at rest for evidence of musculoskeletal disease and then should be observed at the walk and trot for signs of lameness. Subtle lameness that is sufficient to impair performance can be difficult to detect in a horse slowly trotting, and other examinations, such as observation during and after high-speed running at a track, radiography, and nuclear scintigraphy, can be necessary. The major muscle groups, including the quadriceps, should be palpated for firmness or pain suggestive of rhabdomyolysis.

The heart should be auscultated carefully for evidence of valvular incompetence or arrhythmias. Mild (grade II–III/VI) systolic ejection murmurs heard loudest on the left thorax are common in fit racehorses and should not be mistaken for evidence of valvular disease. Electrocardiography to diagnose abnormalities of rhythm (for example, atrial fibrillation) or echocardiography to demonstrate the extent of valvular lesions are indicated if abnormalities are detected on cardiac auscultation.

The respiratory system should be carefully examined by auscultation of the thorax in a quiet area. The thorax should be auscultated initially with the horse at rest; if no abnormalities are detected the horse's tidal volume should be increased by rebreathing air from a large bag held over its nose, or by exercise. Radiography of the thorax may demonstrate changes consistent with exercise-induced pulmonary hemorrhage, recurrent airway obstruction, or pneumonia. Aspirates of tracheal fluid or bronchoalveolar lavage fluid should be examined for evidence of inflammation or hemorrhage.[1,2] The upper respiratory tract, including pharynx, larynx, trachea, and carina, should be examined with a flexible endoscope.

Laboratory Testing

Collection of blood and urine samples for laboratory analysis is indicated if specific abnormalities are detected on physical examination or there is historical data suggesting the need to more closely examine some body systems. For instance, exercise-associated rhabdomyolysis can be confirmed by measurement of serum CK and AST activity. However, blood samples are often submitted for analysis as a matter of routine. Specific attention should be paid to the hemogram, in particular the white blood cell count, for evidence of inflammation and the hematocrit for evidence of anemia. Care should be taken to not assign minor abnormalities an undue importance until corroborating evidence is obtained. Tracheal or bronchoalveolar lavage fluid can provide evidence of lower respiratory tract disease.[2] Examination of feces for helminth ova might demonstrate parasitism.

Exercise Stress Testing

Examination of horses during and after high-speed exercise is now routine in many referral centers and practices specializing in sports medicine. Such examinations in the past had to be conducted on a treadmill if dynamic endoscopic examinations or electrocardiographic examinations were to be performed, but this is no longer the case. Endoscopic and electrocardiographic examinations of horses exercising in the field, and ideally undertaking exercise tasks that mimic their day-to-day activities and competition, are now readily achieved in real time.[3-8] Dynamic endoscopy allows visualization of the upper airway of horses under actual working conditions (racing, dressage, and reining) and avoids the risks and limitations of horses exercising on a treadmill,[3,7,9] although this risk is comparatively small with 0.6% of horses sustaining an important injury during examination.[10] Examination of ridden horses under saddle also provides the opportunity to examine the horse–saddle–rider interaction, including saddle fit and girth tension, which is an important cause of poor performance in some classes of equitation.[11]

Values of a number of performance-related variables have been determined for Standardbred and Thoroughbred racehorses, with better athletes having greater aerobic capacity. However, at this time the main use of high-speed exercise testing is the detection of exercise-induced arrhythmia (such as paroxysmal ventricular tachycardia or atrial fibrillation), rhabdomyolysis, and upper airway obstruction. Upper airway obstruction is a common cause of poor performance that can often be diagnosed by rhinolaryngoscopic examination of horses at rest or after brief nasal occlusion. However, some causes of obstruction are best diagnosed using rhinolaryngoscopy during exercise.[12]

CAUSES OF EXERCISE INTOLERANCE OR POOR PERFORMANCE

Any disease that adversely affects the normal function of a horse has the potential to impair performance, and these are dealt with extensively in textbooks on equine sports medicine. Listed in the following sections are some common causes of exercise intolerance in racehorses.

Musculoskeletal System

- Lameness is a common cause of poor performance. Subtle lameness can be difficult to detect but be sufficient to cause a decrement in performance. Causes and diagnosis of lameness are discussed in textbooks on that topic and are not further covered here.
- Rhabdomyolysis (see Chapter 15)

Cardiovascular System

Poor performance attributable to cardiovascular disease can be caused by the following:

- Atrial fibrillation is usually readily detected on examination of heart sounds or pulse and confirmed by electrocardiographic examination. Paroxysmal atrial fibrillation induced by exercise that resolves soon after exercise ceases causes poor performance and is difficult to diagnose.
- Ventricular arrhythmias[4,5]
- Valvular incompetence, such as mitral or tricuspid regurgitation secondary to acquired or congenital disease; endocarditis is rare in horses.
- Congenital anomalies including ventricular septal defect
- Myocarditis or myocardial disease (rare)
- Aortoiliac thrombosis

Respiratory System

Upper Airways (See Obstructive Diseases of the Equine Larynx)

- Laryngeal hemiplegia
- Intermittent dorsal displacement of the soft palate
- Epiglottic entrapment
- Epiglottic hypoplasia
- Arytenoid chondritis
- Pharyngeal cysts
- Upper air obstruction associated with hyperkalemic periodic paralysis
- Guttural pouch empyema
- Retropharyngeal abscesses
- Redundant or flaccid alar folds

Lower Airways

- Pneumonia secondary to influenza virus or equine herpesvirus-1 or equine herpesvirus-4 infection
- Parasitic pneumonia caused by *Dictyocaulus arnfieldi*
- Severe exercise-induced pulmonary hemorrhage
- Lower airway inflammatory disease and recurrent airway obstruction
- Granulomatous pneumonia

Hematologic and Biochemical Abnormalities

Anemia

- Parasitism, especially caused by *Strongylus* sp. and cyathostomes
- Chronic disease, such as the presence of an abscess
- Equine infectious anemia
- Piroplasmosis
- Gastric ulceration (anemia is an unusual manifestation of this disease)
- Iron deficiency (which is rare)
- Administration of inhibitors of folic acid synthesis or prolonged oral administration of inactive folic acid
- Phenylbutazone toxicity
- Excessive phlebotomy
- Gastric squamous cell carcinoma
- Administration of recombinant human erythropoietin

Hypoproteinemia

- Parasitism, especially caused by *Strongylus* sp. and cyathostomes
- Malnutrition, especially inadequate protein intake
- Protein-losing enteropathy such as lymphosarcoma or granulomatous enteritis

Electrolyte Abnormalities

- Hypokalemia and hyponatremia secondary to excessive losses in sweat and inadequate intake

Nervous System Disease

- Spinal ataxia caused by cervical compressive myelopathy (static or dynamic), equine protozoal myeloencephalitis, and equine degenerative myelopathy
- Sweeney
- Stringhalt

Miscellaneous

- Hypothyroidism (very rare)
- Pituitary tumor (equine Cushing's disease)
- Iatrogenic hypoadrenocorticism
- Hepatic disease of any cause, but beware of iron overload
- Renal disease
- Secondary nutritional hyperparathyroidism
- Malnutrition
- Performance-altering drug administration such as β-adrenergic antagonists (beta blockers) or sedatives

TREATMENT

Treatment should be directed toward correcting the underlying disease. Routine administration of hematinics to horses with a normal hemogram is unnecessary. If after careful and comprehensive examination an organic cause for the poor performance is not found, attention should be given to the horse's training program. Training programs for horses are described in Further reading (see below).

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Sudden or Unexpected Death

When an animal is found dead without having been previously observed to be ill, a diagnosis, even after necropsy examination, is often difficult because of the absence of a detailed history and clinical findings. A checklist of diseases for consideration when sudden or unexpected death occurs in a single animal or group of animals is provided later. All death is sudden, but the focus on an investigation of sudden death is that it was unexpected. Details of each of the diseases listed are available in other sections of this book. This list applies particularly to cattle, but some occurrences in other species are noted. It is necessary to point out the difference between "found dead" and "sudden and unexpected death."

When animals are observed infrequently, for example, at weekly intervals, it is possible for them to be ill with obvious clinical signs for some days without being observed. In these circumstances the list of possible diagnoses is very large. It is also correspondingly large when animals are kept together in large groups and are not observed as individuals. This is likely to happen in beef cattle, especially in feedlots or as calves with dams at pasture, when the animals are unaccustomed to human presence and move away when approached.

SUDDEN OR UNEXPECTED DEATH IN SINGLE ANIMALS

SPONTANEOUS INTERNAL HEMORRHAGE

This condition could be caused by cardiac tamponade in cows, ruptured aorta or atrium, inherited aortic aneurysm, or verminous mesenteric arterial aneurysm in horses and esophagogastric ulcer or intestinal hemorrhagic syndrome in pigs. Aortic rupture and aortopulmonary fistulation should be considered as a potential cause of sudden death in Friesian horses.[1]

RUPTURE OF INTERNAL CAROTID ARTERY ANEURYSM

This condition may occur secondary to mycosis of the guttural pouch of the horse.

In one survey of sudden deaths in horses while racing, most (68%) were undiagnosed, although it was assumed that they died of exercise-associated ventricular arrhythmias. Of those that were diagnosed, most deaths were caused by spontaneous hemorrhage. Similar conclusions have resulted from other surveys. Most reported cases of sudden death in the horse are the result of cardiovascular accidents. Fracture of the pelvis can result in fatal hemorrhage within the gluteal muscles of the horse and rupture of the middle uterine artery at parturition in cattle may occur with uterine prolapse.

PERACUTE ENDOGENOUS TOXEMIA

Peracute endogenous toxemia can arise from rupture of the stomach of horses, abomasum of cows, and the colon in mares at foaling. Large amounts of gastrointestinal contents are deposited rapidly into the peritoneal cavity. In newborn animals, especially foals, fulminating infections are the commonest cause.

Peracute exogenous toxemia in a single animal could be as a result of snakebite, but the snake would have to be very poisonous and the animal of small body weight (such as an adult sheep or goat) to cause death without any observable illness.

TRANSPORTATION STRESS

Transportation can result in sudden death in stress-susceptible animals. The best known example of this is porcine stress syndrome (PSS), during which stress appears to be the sole causative factor in death. Transportation results in a death rate from PSS of 2.0 per 1000 slaughter age pigs in Germany and 0.6 to 3.4 per 1000 slaughter age pigs in the Czech Republic.[2]

TRAUMA

Trauma may cause death by either internal hemorrhage or damage to the CNS, especially the brain or atlantooccipital joint sufficient to damage the medulla oblongata. In most cases the trauma is evident: there has been fighting, or a fall has occurred, or the animal has attempted to jump an obstacle. In horses a free gallop downhill may result in a serious fall or collision with, for example, a wall, especially if the ground is slippery.

Inapparent trauma usually occurs when animals are tied up by halter and rush backward when frightened or are startled by an electric fence and the halter shank is long. Sometimes the animal will plunge forward and hit its forehead between the eyes on a protruding small object such as a bolt used in a fence. Sadism, especially by the insertion of whip handles or pitchfork handles into the anus or vulva, may also be inapparent.

GASTROINTESTINAL CONDITIONS

Gastric rupture in the horse may occur following overeating highly fermentable feed, administration of excessive quantities of fluids by nasogastric tube, gastric impaction, or when gastric motility is markedly reduced in acute grass sickness or gastric distension with fluid. Peracute enteritis in the horse can cause rapid unexpected death.

Volvulus or gastrointestinal accidents account for almost 50% of sudden deaths in sows, followed next by gastric ulceration, retained fetuses, and toxemia.

Recumbent cattle that become lodged in a small hollow in the ground may die of bloat because the cardia becomes covered with ruminal fluid and eructation is not possible.

IATROGENIC DEATHS

Iatrogenic deaths may be caused by overdose with intravenous solutions of calcium salts in an excited cow, too-rapid fluid infusion in an animal with pulmonary edema, intravenous injection of procaine penicillin suspension, and intravenous injections of ivermectin in horses. These are not hard to diagnose and the producer or veterinarian is usually obviously embarrassed.

One of the most sudden death occurrences is the anaphylactoid reaction in a horse to an intravenous injection of an allergen such as crystalline penicillin. Death occurs in about 60 seconds. Intraarterial injections of ceftiofur, penicillin, or phenothiazine tranquilizers have also been reported to cause sudden death. This has been documented in a small number of cattle given subcutaneous injections of ceftiofur crystalline free acid suspension at the base of the ear; 0.1% of cattle in one report died suddenly and unexpectedly because of inadvertent intraarterial injection with migration to the cerebral vasculature.[3]

SUDDEN DEATH IN HORSES

An analysis of the cause of sudden death over a 20-year period was completed in Victoria, Australia. The risk in flat starts was 0.08 to 0.10 per 1000 starts, whereas the risk in jump starts was three to four times higher at 0.26 to 0.36 per 1000 starts.[4] An analysis was made of the causes of death in horses and ponies over 1 year of age that died suddenly and unexpectedly. No cause of death was found in 31% of cases and 16% died from the following causes: hemorrhage in the respiratory tract and CNS and adverse drug reactions. Cardiovascular lesions were the cause in 14% and the remaining 3% had lesions of the gastrointestinal tract.

Sudden death in racehorses is commonly caused by massive hemorrhage into the lungs, abdomen, or brain. In horses that were found dead but appeared normal when last seen, the cause of death was not determined in 33% of cases. Lesions of the gastrointestinal tract were the cause of death in 39% and respiratory tract lesions in 9%. Lesions of both the CNS and cardiovascular system were the cause of death in 5%, and the remaining 10% had miscellaneous causes.

Hyperkalemic periodic paralysis should be considered as a potential cause of sudden death in certain lines of Quarter Horses, Appaloosas, and Paints because of a single point mutation in the α-subunit of the muscle sodium gene.

SUDDEN OR UNEXPECTED DEATH IN A GROUP OF ANIMALS

The following diseases could affect single animals if the animals were housed or run singly.

LIGHTNING STRIKE OR ELECTROCUTION

This usually affects a number of animals that are found together in a pile or group. Rarely, electrical current only electrifies a contact object intermittently and deaths will be intermittent. In most cases the history and an examination of the environment reveals the cause.

NUTRITIONAL DEFICIENCY AND POISONING

At pasture, sudden death may come from the sudden exposure of the cattle to plants that cause bloat, hypomagnesemia, cyanide or nitrite poisoning, fluoroacetate poisoning, microcystins (produced by algae in a stagnant lake or pond), or acute interstitial pneumonia.[5] Acute myocardiopathy in young animals on diets deficient in vitamin E or selenium is in this group, as is inherited myocardiopathy in Herefords. Gross nutritional deficiency of copper in cattle causes "falling disease," which is a manifestation of acute myocardiopathy.

Acute myocardiopathy and heart failure is associated with poisons in *Phalaris* spp. pasture; grass nematodes on *Lolium rigidum;* the hemlocks *Cicuta* and *Oenanthe* spp.; and the weeds *Fadogia, Pachystigma, Pavetta, Asclepius eriocarpa, Cryptostegia* and *Albizia,* and *Cassia* spp. The trees oleander and yew (*Taxus* spp.) may also be causes, and those species containing fluoroacetate, such as the gidgee tree and the weeds *Gastrolobium, Oxylobium, Dichapetalum,* and *Ixiolaena* spp., may be implicated. There are a number of plants that cause cardiac irregularity and some sudden deaths, e.g., *Urginea* and *Kalanchoe* spp., but more commonly congestive heart failure is caused. Monensin, lasalocid, and salinomycin toxicities are increasingly common causes in horses and, to a less extent, cows.[5]

ACCESS TO POTENT POISONS

Access to potent poisons may occur in housed animals or in those fed prepared feeds. A select number of herbicides, insecticides, rodenticides, and metals

account for the majority of poisonings, with country to country variation and species differences.[6,7]

There are few poisons that cause sudden death without premonitory signs. Cyanide is one, but is an unlikely poison in these circumstances. Monensin, mixed in a feed for cattle that is then fed to horses, or fed in excess to cattle, does cause death by heart failure. Organophosphates are more likely, but clinical signs are usually apparent. Lead is in a similar category; however, very soluble lead salts can cause death quickly in young animals.[8]

DISEASES ASSOCIATED WITH INFECTIOUS AGENTS

These diseases cause septicemia or toxemia, and include anthrax, blackleg, hemorrhagic septicemia, and (especially in sheep, but occasionally in cattle) peracute pasteurellosis. In pigs, mulberry heart disease and perhaps gut edema should be considered. In horses, colitis is probably the only disease that will cause sudden death. In sheep and young cattle, enterotoxemia associated with *Clostridium perfringens* should be included and this may be involved in rumen overload in feedlot cattle on heavy grain feed. Circumstances, feeding practices, climate, and season of the year usually give some clue as to the cause of death.

NEONATAL AND YOUNG ANIMALS

In very young, including neonatal, animals, congenital defects that are incompatible with life—prematurity, septicemia because of poor immune status or toxemia associated with particular pathogens, especially *E. coli,* and hypothyroidism—are important causes of sudden death.

ANAPHYLAXIS

Anaphylaxis after injection of biological materials, including vaccines and sera, is usually an obvious diagnosis, but its occurrence in animals at pasture can cause obscure deaths. In these circumstances it usually affects one animal and clinical illness is often observed. A similar occurrence is sudden death in a high proportion of piglets injected with an iron preparation when their selenium–vitamin E status is low.

PROCEDURE FOR INVESTIGATION OF SUDDEN DEATH

The procedure for investigating sudden death is as follows:

- Keep excellent records because of the probability of insurance enquiry or litigation.
- Take a careful history, which may indicate changes of feed composition or source, exposure to poisons, or administration of potentially toxic preparations.
- Make a careful examination of the environment to look for potential sources of pathogens. Be especially careful if electrocution is possible; wet concrete floors can be lethal when combined with electrical current unless rubber boots are worn.
- Carefully examine dead animals for signs of struggle, frothy nasal discharge, unclotted blood from natural orifices, bloat, pallor or otherwise of mucosae, burn marks on the body (especially on the feet), or signs of trauma or of having been restrained. Pay particular attention to the forehead by palpating the frontal bones, because these may have been fractured with a heavy blunt object without much damage to the skin or hair.
- Ensure that typical cadavers are examined at necropsy, preferably by specialist pathologists at independent laboratories, in which opinions are more likely to be considered authoritative and unbiased.
- Collect samples of suspect materials for analysis. Preferably, collect two samples, one to be analyzed and one to be made available to a feed company, if indicated.

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CYANOBACTERIA (BLUE-GREEN ALGAE) TOXICOSIS

SYNOPSIS

Etiology Toxins from cyanobacteria in blooms on stagnant fresh or brackish water in lakes, ponds, reservoir, billabongs

Epidemiology Outbreaks with high mortality when sole source of drinking water is polluted by toxigenic algae

Clinical pathology Elevation of liver enzymes, electrolyte abnormalities, hypoglycemia (microcystins), or possible acetylcholinesterase depression [anatoxin-a(s)]

Lesions Sudden death caused by massive hepatic necrosis (microcystins) or respiratory arrest (anatoxins). Hepatomegaly and hepatic necrosis (microcystins); no lesions (anatoxins); cyanobacteria in alimentary tract (both).

Diagnosis confirmation Positive identification of toxin(s) in water source and animal fluids or tissue confirms diagnosis; liquid chromatography mass spectrometry using animal tissue available for some toxins (microcystins)

Treatment None

Control Avoidance of contaminated water; judicious use of algaecides; watershed management

ETIOLOGY

There are over 2000 species of cyanobacteria with at least 80 known to be toxigenic.[1] The cyanobacteria, commonly referred to as blue-green algae, form dense blooms in fresh or brackish bodies of warm, stagnant water. Ingestion of cyanobacteria or their toxins liberated from ruptured cells results in clinical signs. Toxicity is species specific and some species, such as *Anabaena flos-aquae,* produce more than one toxin. Cyanotoxins associated with large-animal poisonings include:[1-3]

- **Microcystins.** These are potent hepatotoxins produced by many different cyanobacteria including several species of *Anabaena, Anabaenopsis, Microcystis, Planktothrix, Nostoc,* and *Oscillatoria.*
- **Anatoxins.** Toxins in this group are potent neurotoxins produced primarily by several species of *Anabaena* and a few species of *Planktothrix.*
- **Various freshwater toxins.** Included in this group are cyanotoxins known to cause toxicity in animals. Toxins, produced by a variety of cyanobacteria, include saxitoxins, cylindrospermopsin, nodularins, and most recently β-*N*-methylamino-L-alanine (BMAA).[4,5]

EPIDEMIOLOGY

Occurrence

Cyanobacterial toxins are associated with outbreaks of poisoning in farm animals that drink contaminated water. Lakes, reservoirs, ponds, waterholes, and other nonturbulent water sources are all affected, especially when the organisms are concentrated by onshore winds so that large quantities may be ingested. Typically the surface of the water has a bluish green sheen or pea green to iridescent neon green streaks. Often the algae accumulate along the shoreline where animals have easy access and the water is shallow and more stagnant. In small waterholes and reservoirs the surface water is often completely covered with a very thick coat of gelatinous organisms (algae bloom), and animals are unable to drink without ingesting some of the algae. Cyanobacteria are found in every continent except Antarctica and toxicoses has been recorded in most

countries, especially the United States, Canada, Scandinavia, Japan, South Africa, Australia, and New Zealand.[2,3,6,7] The cyanobacterial toxins affect all animals and birds and those found in brackish and marine waters are associated with mortalities in fish.[3] Death, while the normal outcome, occasionally does not occur, especially if animals are able to avoid ingesting large amounts of contaminated water.

Risk Factors

Heavy growth commonly occurs in the late summer to autumn period. Factors promoting growth of the organisms and increasing the chances of animals being poisoned include warm water temperatures, low water depths, sunshine, and onshore winds.[1-3] In addition, a high concentration of other nutrients such as nitrogen and phosphorus associated with fertilizer runoff or feces/urine contamination may play a role.[2,8]

PATHOGENESIS

Microcystins

These toxins are potent hepatotoxins affecting virtually every animal species as well as some plant species. The toxins are found inside the cyanobacteria and released by cell damage or death. When an animal drinks contaminated water, the acid pH of the stomach liberates microcystins from the algae and toxicosis occurs. The toxin enters hepatocytes via the bile acid carriers and inhibits protein phosphatases 1 and 2A resulting in cytoskeleton and actin filament changes, hepatocyte necrosis, and cell death.[1] Other mechanisms such as free radical induction and mitochondrial changes affect the liver as well.[1] Animal death occurs from intrahepatic hemorrhage.

Anatoxins

Three important subgroups of anatoxins, all potent neurotoxins, have been identified in animal poisonings. One subgroup, homoanatoxin-a, has not yet been associated with large-animal poisonings, but with neurotoxicosis and death in New Zealand dogs.[9]

Anatoxin-a

This neurotoxin is a potent agonist at nicotinic acetylcholine receptors both at the neuromuscular junctions and neurons.[1,6] Prolonged and continuous stimulation at the neuromuscular junction results in weakness, respiratory paralysis, and death. Dopamine and norepinephrine are released secondary to modulation at the neuronal nicotinic acetylcholine receptors.[10]

Homoanatoxin-a

Toxicologic properties of this toxin are similar to anatoxin-a.[9]

Anatoxin-a(s)

The chemical structure and mechanism of action of this toxin are different from the other two anatoxins. Anatoxin-a(s) is an irreversible acetylcholinesterase inhibitor with a mechanism of action similar to organophosphorus containing pesticides.[1,11] Continued nicotinic receptor stimulation from increased amounts of acetylcholine result in ataxia, seizures, respiratory arrest, and death. Unlike organophosphorus compounds, anatoxin-a(s) affects only the peripheral nervous system (i.e., no central effects).[11]

Various Freshwater Toxins

The toxins listed next are not as common as microcystins and anatoxins but worthy of note because they have been associated in some manner with large-animal poisonings.

- **Saxitoxins.** Toxins in this group are generally associated with paralytic shellfish poisoning in small animals, but a group of Australian sheep became symptomatic and died after exposure to *Anabaena circinalis*.[3] Saxitoxin, a potent neurotoxin, selectively blocks voltage-gated sodium channels causing neuromuscular weakness, respiratory arrest, and death.[1,6]
- **Cylindrospermopsin.** This toxin, produced by several species of cyanobacteria including *Cylindrospermopsis raciborskii,* has been implicated in the death of cattle. It inhibits protein synthesis and thus affects several organs in the body including the heart, lungs, liver, and kidneys.
- **Nodularins.** This potent hepatotoxin is produced primarily by the cyanobacteria *Nodularia spumigena* and has caused death in sheep and other livestock.[1,3,12] The mechanism of action is similar to microcystins with death the normal outcome.
- **BMAA.** This potent neurotoxin produced by the cyanobacteria *Hydrilla verticillata* was recently associated with the development of avian vacuolar myelinopathy.[4,5] The toxin has also been associated with several degenerative human neurologic diseases, and it has been hypothesized that BMAA may play a role in the onset of equine motor neuron disease.[13]

CLINICAL FINDINGS

Microcystins

The clinical picture has been well described in livestock, swine, and horses.[1,3,8] Most are found dead or die within a few hours. Vomiting, diarrhea, ataxia, and shock occur in early deaths; those that live for a few hours show agitation and irritability, ataxia, recumbency, and seizures before death. In the less acute cases there is severe liver damage manifested by anorexia, stupor or hypersensitivity, ruminal atony, dehydration, recumbency, jaundice, and photosensitization in cattle and sheep. Many apparently unaffected and recovered animals die in the ensuing 3 months. Affected pigs are anorexic and show dullness, vomiting, lethargy, tremor, frothing at the mouth, coughing, sneezing, dyspnea, and dysentery.

Anatoxins

Affected animals are commonly found dead. Clinical signs may become apparent within 15 minutes after exposure. In acute cases the affected animals have muscle tremor, stupor, staggering, recumbency, and in some cases hyperesthesia to touch so that slight stimulation provokes a seizure with opisthotonus. Death is from respiratory arrest. Animals exposed to anatoxin-a(s) also have excess salivation as well as lacrimation, vomiting, and diarrhea.

CLINICAL PATHOLOGY

Microcystins

Chemical analysis shows increased liver enzymes, electrolyte abnormalities (hyperkalemia), hypoglycemia, and hypoalbuminemia in all species.[1,3] Clinical pathologic findings rated in order of frequency in sheep exposed to microcystins are high serum concentrations of bile acids, glutamate dehydrogenase, γ-glutamyl transferase and serum bilirubin, and reduced serum concentration of albumin.

Anatoxins

There are no anatoxins.

NECROPSY FINDINGS

Necropsy findings in microcystin toxicity vary depending on when death occurred. Gross postmortem examinations show enlarged livers with dark-brown to a bluish parenchyma.[14] Microscopic lesions are consistent with centrilobular hepatic necrosis.[1] Other lesions include generalized petechiation, plasma transudates in body cavities, and congestion of most viscera. Severe gastroenteritis with intestinal hemorrhage and severe bloody diarrhea has also been observed in some outbreaks. There are no specific necropsy findings in animals dying of anatoxin toxicity.

Diagnosis

The presence of cyanobacteria in the source water and gastrointestinal tract is not diagnostic. Identification of the specific toxin in the water and animal tissues or fluids is needed to make a diagnosis. The toxins may disappear from the water within 2 to 3 days so samples should be taken as soon as possible after the poisonings occur. A specimen of the bloom material should be immediately preserved for identification, because degeneration of cells is rapid during transport to the laboratory. Laboratory examination for the presence of high concentrations of known toxic cyanobacteria is required. Many assays, including ELISAs, are available to routinely confirm the presence of microcystins in suspect water, but few are useful for

anatoxins.[15] Within the past few years, liquid chromatography mass spectrometry (LC/MS/MS) has been successfully used to measure the microcystin concentration found in body tissues. No such test is routinely available for anatoxins.[16,17] The diagnosis of anatoxin a(s) intoxication may be supported by acetylcholinesterase testing, although the presence of organophosphorus and carbamate pesticides needs to be ruled out.[1]

DIFFERENTIAL DIAGNOSIS

Diagnosis confirmation is made by positive assay for the algal toxins in suspect water and animal body tissues or fluids.

Microcystins
- Alfatoxin toxicosis
- Carbon disulfide ingestion
- Hepatotoxic chemicals (chlorinated hydrocarbons, phenols, etc.)
- Mushroom ingestion (amatoxins)
- Paraquat toxicosis
- Pyrrolizidine alkaloids, other hepatotoxic plants
- Phomopsin toxicosis
- Sporidesmin toxicosis

Anatoxins
- Anthrax
- Atrial fibrillation
- Cyanide toxicosis
- Electrocution or lightning strike
- Ionophore toxicosis
- Plant poisonings
- Rupture of major vessel (aorta, uterine arteries)
- Trauma

TREATMENT

There are no specific antidotes, and treatment is unrewarding.

CONTROL

The two principles involved are prevention of ingestion of floating bloom material by animals and preventing the addition of nutrients that promote cyanobacterial growth to the water.[2,8]

Prevent the Ingestion of Toxins

- Prevent access to contaminated water. Move livestock to a clean water source or draw drinking water from a site away from the bloom.
- Keep bloom away from water intake by use of a floating boom.
- Add precipitants, e.g., lime, ferric alum, and gypsum, which remove algae without release of toxin and remove phosphates (see later).
- Algaecides such as copper sulfate are still used but the routine, unregulated use is no longer recommended. The killed cyanobacteria release toxins into the water, so it cannot be used as drinking water for at least 5 days. The algaecides also damage other vegetation and may ultimately promote further cyanobacterial blooms.

Prevent the Addition of Nutrients to Water

- Fence off water sources from direct livestock access so no manure or urine is added to the watershed or directly to the water.
- Precipitate phosphates with lime, gypsum, and ferric alum. This is useful only for small reservoirs or ponds.
- Mechanically aerate bottom layers of water body; this is useful only for large water reservoirs.
- Exert catchment control and minimize use of phosphate fertilizers and inflow of sewage.
- Filter the inflow by enhancing reed bed and wetland growth.
- Buffer afforestation and vegetation generally along the banks of watercourses.

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PLANTS CAUSING SUDDEN DEATH WITHOUT CARDIOMYOPATHY

In many plant poisonings the identity of the toxin is unknown. The more common of these plants associated with sudden death without evidence of cardiomyopathy are listed next. Because the information about most of them is meager, no attempt is made to provide a complete picture of each of them.

Arrabidaea bilabiata
Burttia prunoides
Eupatorium wrightii
Lamium amplexicaule/dead nettle
Laurelia novae-zealandiae/ pukatea
Nicandra physalodes/apple of Peru
Viguiera annua/ annual goldeneye

Diseases Associated With Physical Agents

LIGHTNING STRIKE AND ELECTROCUTION

SYNOPSIS

Etiology Exposure to high-voltage electric currents

Epidemiology Single or multiple cases. Following a thunderstorm dead animals at pasture may be under trees or along fence lines. Posterior paralysis in housed pigs

Clinical findings Bone fractures, temporary unconsciousness, or immediate death. In recovered animals residual nervous signs may persist. Posterior paralysis in pigs

Necropsy findings Singe and burn marks with some cases. Fractures of long bones in some cases and of lumbar vertebrae in swine

Diagnostic confirmation Difficult. History and environmental evidence of lightning or electric shock exposure and no postmortem lesions of other causes of disease

ETIOLOGY

The three common causes are flashes of linear lightning during thunderstorms, broken overhead electrical transmission wires that usually carry very high voltages, and faulty electrical wiring in cowsheds and barns.

Lightning-related injury or death can occur through five primary mechanisms[1,2]:

1. Direct strikes
2. Side flashes emanating from tall objects such as trees hit by lightning
3. Ground currents (step potentials or step voltages) occur with each strike and are the most common mechanism in four-legged species because after injection of current into the earth, a potential gradient develops that can initiate current entering the animal from one set of feet, leaving the body by the other set of feet. In contrast to humans, this current crosses essential organs, such as the heart and liver, causing death.
4. Contact, from touching long conductors, such as railings, cables, and fences can be fatal.

5. Upward leaders that emanate from high ground and tall objects when downward leaders approach ground

During lightning strike trees, fences, barns, and pools of water may become electrified, and it is not unusual for damp ground to act as a conductor for electricity passing along the roots of stricken trees. Animals electrocuted by standing on electrified earth are unlikely to show burn marks on the body. Oak trees are particularly prone to lightning strike and because of their spreading foliage and extensive root system, are common mediators of electrocution deaths in pastured animals. Poplar, elm, walnut, beech, ash, and conifers are also mediators of electrocution to animals that shelter under them.

Electrical transmission wires are most dangerous when they fall into pools of water, as they are likely to do during the storms that bring the wires down. In such cases, the entire pool is electrified and animals passing through it may be killed instantly. Electrocution can also occur from this source without obvious evidence of line fault.

In accidents caused by **faulty wiring**, voltages of 110 to 220 V are sufficient to kill adult cattle provided they make good contact with the source and the ground. Water pumps and milking machines are the common sources of electricity that may electrify water pipes or the milk line through the earth wire or a short circuit. The use of very heavy fuse wire (30–60 A) may cause continuance of the trouble, which could be avoided if lower capacity fuses were used. In situations of electrical fault, certain farm owners will choose to try to circumvent it by improper use of fuse breakers that can lead to substantial risk of electrocution hazard.

EPIDEMIOLOGY

The area incidence is never high but heavy mortalities may occur on individual farms when a barn or a group of animals sheltering under a tree is struck. Approximately 90% of deaths occur in cattle in Belgium.[2] Risk factors include documented cloud-to-ground lightning strikes at about the time of death of animals and the presence of open water and tall trees.[2] As many as 20 head of cattle may be killed by one lightning flash. Most fatalities caused by lightning strike occur during the summer months when the animals are at pasture.[2,3]

Behavioral abnormalities of housed animals may indicate the presence of faulty wiring in barns. Deaths caused by electrocution in barns can occur at any time.

PATHOGENESIS

Tissue damage from electrical trauma is induced by the direct effects of the electric current and the development of heat and tissue ischemia. Exposure to high-voltage electrical currents causes severe **nervous shock** with complete unconsciousness and flaccid paralysis. In some instances, focal destruction of nervous tissue occurs and **residual signs of damage** to the nervous system persist after nervous shock disappears. Death when it occurs is usually caused by paralysis of vital medullary centers. Ventricular fibrillation can also occur and contribute to death. **Superficial burns** may be evident at the site of contact with the current or along the path of flow from the point of contact to ground. The burn is produced by heat generated from the resistance of tissues to the passage of the electricity. **Fractures** are thought to be the result of sudden and profound muscular contraction.

CLINICAL FINDINGS

Deaths caused by lightning strike can be detected by an examination of the dead animal and its environment with additional information provided by lightning location data.[2]

Varying degrees of shock occur. With high-voltage currents and good earth contacts such as wet concrete floors, water, and damp earth, the animal may fall dead without a struggle. Singeing and burning are likely to occur because of the severity of the shock. The burns may be localized to the muzzle or feet and be in the form of radial deposits of carbon with or without disruption of tissue, or they may appear as treelike, branching patterns of singeing running down the trunk and limbs. Acute blindness linked to lightning flash injury has occurred in a horse. The injuries were consistent with acute and severe flash injury.[4]

In less severe shocks, the animal falls unconscious, **suddenly collapses**, or may struggle, followed by a period of unconsciousness varying from several minutes to several hours. When consciousness is regained, or the animal is removed from the electric field, the animal may rise and be perfectly normal, or show depression, blindness, ataxia, posterior paralysis, monoplegia, and cutaneous hyperesthesia. In some cases there may be more local signs including nystagmus and unilateral paralysis. Sloughing of the skin at the sites of burns may occur after a few days. These signs may persist or disappear gradually over a period of 1 to 2 weeks. With electrocution in **pigs** caused either by lightning strike or wiring faults, the major signs are related to spinal injury or to fracture of the ileum, ischium, and the transverse processes of the lumbar vertebrae with a large number of animals exhibiting apparent lameness and especially posterior paralysis. Vestibular disease is described as a sequela to lightning strike in horses.

The actual occurrence of electric shock often is not observed and electrocution should always be considered in the differential diagnosis of spinal or pelvic fracture or injury in pigs.

With minor shocks, especially as they occur in barns on low-voltage domestic current, the animal may be knocked down or remain standing. Consciousness is not lost and the clinical picture is one of restlessness. The animal may kick violently at the stanchion or the dividing rail. The attacks may be intermittent and occur only when the cattle supply a good ground contact such as standing in the gutter, when they are drinking, or when they are wet. Dairy farmers are often unaffected in the same environment because their boots provide effective insulation.

CLINICAL PATHOLOGY

Laboratory examinations are of no value in diagnosis.

NECROPSY FINDINGS

If electrocution is suspected it is best to ensure that possible **sources of electric power** are shut off before proceeding with a postmortem examination.

Diagnostic lesions are often minimal but singe marks on or under the skin, or damage to the environment, or both, occur in about 90% of lightning deaths. Rigor mortis develops but passes quickly.

In cattle, anthrax is often a consideration as the carcass decomposes rapidly and blood may exude from the external orifices. The pupils are usually dilated and the anus relaxed. All viscera are congested and the blood is dark and unclotted. Petechial hemorrhages may occur throughout the body, including the trachea, endocardium, meninges, and CNS. The superficial lymph nodes, particularly the prescapular and the interior cervical, are often hemorrhagic. Superficial singeing of the hair, burn marks on the feet or muzzle, and internal or subcutaneous extravasations of blood in arboreal patterns also occur.

In some cases of electrocution there are longitudinal **fractures** of long bones and in incidents involving pigs, local hemorrhage and extensive fractures of the bones in the pelvic area are observed. Fractures of the lumbar vertebrae have also been described in electrocuted swine.

Theoretically, the passage of electric current through tissue may cause cell nuclei to elongate and assume orientations parallel to one another. Skin lesions can be examined histologically for this change and hyperconcentration of skeletal muscle fibers may also be observed.

DIFFERENTIAL DIAGNOSIS

Great care must be taken in accepting an owner's suggestion that an animal has been killed or injured by lightning strike. Insurance against loss by lightning is commonly carried and the many other causes of sudden death or injury are seldom covered by insurance. To minimize the possibility of conflict and potential future legal problems it is wise to have a representative of the insurance

company present at the autopsy so that all may agree on the diagnosis.

To make the diagnosis, there should be a history of exposure and evidence of sudden injury or death. In the latter case, half-chewed food may still be present in the mouth. Burns on the skin, scorching of the grass, and tearing of the bark on nearby trees are also accepted as contributory evidence. The possibility of electrocution caused by faulty wiring should be considered when sudden shocks or death occur in animals confined in stanchions. Differentials include:

- Other causes of sudden death
- In pigs, other causes of posterior paresis/paralysis

DIAGNOSIS

A model to predict the likelihood that death of an animal at pasture was caused by lightning strike has been developed. Factors significantly associated with lightning strike death in the multivariable model were age, presence of a tree or open water in the near surroundings, tympany, and presence of feed in the oral cavity at the time of investigation.[2] This basic model had a sensitivity (Se) of 54% and a specificity (Sp) of 88%. The predictive value was improved by combining the model based on the veterinary expert investigation (circumstantial evidence and pathologic findings), together with the detection of cloud-to-ground (CG) lightning at the time and location of death (Se 89%; Sp 67%).[2]

TREATMENT

Central nervous system stimulants and artificial respiration should be provided for unconscious animals, but in most instances the animals are dead or recovered before treatment can be instituted.

CONTROL

Precautions taken to avoid lightning strike in animals are largely ineffective, but proper installation of all electric equipment in barns and milking parlors is essential to prevent losses. All motors should be earthed to a special iron spike or pipe driven at least 2.5 m into the ground, preferably in a damp spot, and electrical machinery that has potential contact with animals should be shielded. Earthing to water pipes should not be permitted. Minimum amperage fuses should be used to provide protection in cases of short-circuiting.

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STRAY VOLTAGE

SYNOPSIS

Etiology Minor voltage (<10 V) in the animal environment causing mild electric shock

Epidemiology Risk with any electrified housing system but most recognized in dairy cattle and pig housing

Clinical findings Behavioral changes in feeding or eating patterns, reluctance to move freely in some areas of buildings at levels of 2 V or higher in some but not all animals. Claims for increased disease incidence and decreased production not substantiated experimentally

Diagnostic confirmation Demonstration of stray voltage with amelioration of the problem when this is corrected

ETIOLOGY

The term *stray voltage* is used to denote minor (<10 V) electrical voltage between two points that can be accessed by an animal resulting in a current flow through the animal. **Other terms** that have been used for stray voltage include *free electricity, tingle voltage,* and *transient voltage.* The terms *neutral to earth voltage* or *neutral to ground voltage* usually apply to the voltage measured between the service entrance neutral bus and a reference ground rod. **Cow contact voltage** refers to voltage measured between a potential cow contact, such as a drinker, and the ground.

The source and cause of the problem is complex. Stray voltage can be caused by leakage of current from electrical installations, electric and magnetic induction from high voltage lines, or faulty connections between the electrical circuit and earth.[1]

Depending on the current, exposure to stray voltage can produce minor electrical shock and discomfort to animals. Voltages occurring in barns at the level of the animal are usually low and are not felt by humans because of the insulation provided by clothing and footwear.

EPIDEMIOLOGY

The potential presence of stray voltage has been recognized for many years. The possible relation to production and disease gained particular attention in the 1980s when different surveys indicated that over 50% of dairy farms had significant cow contact voltage, and more current studies indicate a continuing problem. Deteriorating wiring, poor wire insulation, and older buildings are **risk factors.** Heavy milking cows are thought more sensitive to electric shock; scratched, infected, and sore muzzles and hooves may increase sensitivity.

PATHOGENESIS

The reaction of the animal to stray voltage will depend on the current flow, or shock, which is related directly to the voltage and inversely to the **impedance** to flow in the animal.[2] The impedance decreases as body weight increases because of an increase of the surface of contact and the pressure exerted by the hooves on the floor and, with pigs, current flow at the same voltage is higher through a gilt or sow than through a piglet. There are some differences in impedance between different pathways in animals (e.g., mouth to hooves or udder to hooves), but there can also be individual animal **variation in sensitivity** to stray voltage.[3] Generally, the problem will only be suspected if the stray voltage is high enough so that a significant proportion of the herd shows signs.

The reactivity of **cows** to different voltage levels has been studied, and the **lowest behavioral perception** is observed at 1 to 2 V for the most sensitive cows and moderate behavioral responses at 1.5 to 3 V. With **pigs**, feeding and drinking behavior is affected at 5 V but not at 2 V, and resting time is disturbed at 8 V.

CLINICAL FINDINGS

Behavioral Changes

The behavioral responses exhibited by **cows** exposed to stray voltage depend on the site at which the voltage occurs and the strength of the current flow. Stray voltage in the **milking parlor** results in a reluctance to enter the parlor, a reluctance to cross the floor grids, extreme nervousness while in the parlor, and rapid exit or stampeding from the parlor. Where stray voltage occurs at **drinkers** cows may show reluctance to drink, with lapping of water rather than full drinking and crowding at the drinker resulting in one cow being the ground while others drink. Cows that are experiencing current flow are restless, they may tremble, the back is arched and the head is elevated with the ears held back rigidly, and there is frequent urination and defecation.

In **pigs**, restlessness, increased aggressiveness, and changes in drinking and feeding patterns have been associated with stray voltage.

Effects on Production and Disease

Field observations suggested that stray voltage in the milking parlor at milking time may result in incomplete milk letdown, increased milking times, elevated somatic cell counts, an increased incidence of clinical mastitis, and poor production. However, **controlled trials** have consistently reported behavioral changes, as well as transiently elevated blood cortisol levels in cows exposed to stray voltage above a certain threshold, but failed to identify any effect on somatic cell counts, mastitis incidence, or milk production.[1,2,4] Similarly no effect of stray voltage on the incidence of disease in pigs could be identified. It was concluded that exposure to stray voltage at the levels of 2 to 4 V may be

a mild stressor but does not impair productivity or increase the occurrence rate of production diseases.

DIFFERENTIAL DIAGNOSIS

The presence of stray voltage should be suspected where animals exhibit behavioral abnormalities and for the present, it is probably wise to consider it as part of the differential of problems of production inefficiency.

Cow contact voltage can be measured with a sensitive voltmeter, but the ground must be well established. The measurement of the neutral to earth voltage does not give a good prediction of cow contact voltage and is not recommended as the sole measure for the risk of stray voltage on the farm. In most instances a qualified electrician is required to correct the problem. The use of a commercially available tingle voltage filter has been recorded to significantly reduce stray levels.

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ENVIRONMENTAL POLLUTANTS AND NOISE

Pollution From Outside the Farm

Deposition of contaminants in soil and water and on plants can derive from a large number of sources including atmospheric pollution, residues from the petroleum and metalliferous industries (both mining and smelting), persistent pesticides, and the application of sludge. Deposition in soil, but not on plants, does not preclude poisoning of animals because soil can comprise a significant proportion of the dry matter intake of grazing ruminants. Pollutants exert their effect through direct toxicity, immunosuppression or, in the case of some heavy metals, by the competitive induction of trace element deficiencies.

Mine spills and **smelter emissions** have been associated with soil and water contamination with a number of different heavy metals. Aluminum smelter emissions result in fluorosis in Easter Grey Kangaroos in Australia.[1,2] Cattle grazing near lead, zinc, or vanadium mines have increased concentrations of lead, cadmium, and vanadium in body tissues and biochemical evidence of intoxication.[3-7] Cattle grazing pasture and drinking water near former uranium mines have elevated concentrations of radionuclides.[8] Water from mines is also potentially toxic to livestock that drink it. Pastures adjacent to **major roads** and animals grazing them are also contaminated by heavy metals from vehicle emissions. Blood and tail hair can be analyzed to detect abnormal concentrations of many pollutants, including heavy metals.[9,10] Cattle grazing near a lead and zinc industrial processing area had higher blood concentrations of lead, lower hematocrit and hemoglobin concentration, and higher serum activity of alanine transaminase and AST than did cattle from an uncontaminated area.[11] Similarly, young cattle grazing near a zinc and lead mine had evidence of subclinical toxicosis (blood lead 6–35 µg/dL and elevated blood aminolevulinic acid dehydrogenase activity) compared with reference ranges.[6]

Cattle will readily ingest petroleum products, and the toxicology of **oil field pollutants** has been reviewed. Another important group of compounds is the polychlorinated biphenyls and the **polybrominated biphenyls** and the chlorinated hydrocarbons. These substances are extensively used in agriculture and in industry. They have very long half-lives and, although they are not in themselves dangerous, they cause a great deal of trouble if they get into the human food chain and become deposited in fatty tissues.

Pollution From Farms

Pollution of the environment by animal feces and urine is now a matter of great importance, especially to intensive animal farmers located near population centers. There are increasing regulations governing livestock farming, effluent disposal, nitrogen and mineral cycles, and odor emission, and there are increasing regulatory actions or private lawsuits against farms that offend. This is not a subject for a text on veterinary medicine, although efforts to minimize nitrogen, phosphorus, and potassium fecal outputs by dietary manipulation and water restriction have potential veterinary and welfare implications.

Slurry application to pastures and runoff to streams and groundwater introduce health problems such as salmonellosis, cryptosporidiosis, leptospirosis, and mycobacteriosis. Shallow wells near animal accommodation are also likely to contain high levels of nitrates derived from nitrogen filtering through surrounding earth. Such water is a potential source of nitrate poisoning, especially in pigs.

One of the important pollutants for housed animals is **ammonia** from urine.[12] When it is combined with dust, it can cause severe inflammation of the respiratory mucosae. **Dust** may be the carrier of pathogenic bacteria or viruses or antigens that provoke a hypersensitivity reaction, e.g., interstitial pneumonia. Carbon monoxide and hydrogen sulfide from **slurry pits** can cause mortality in both animals and humans. The highest risk is during agitation of the slurry, when they are released. Sulfur dioxide is also an environmental contaminant capable of causing respiratory tract irritation in animals.

Noise

Animals are more susceptible to high-pitched noise than are humans, and the elimination of such noises in working facilities improves the **orderly handling** of cattle and sheep. Pollution by noise, a matter of increasing importance for veterinarians who police codes of practice for animal welfare and for those who are called upon to act as expert witnesses in cases involving excessive noise and its effects on animals, is also an important subject.

The effects of a sonic bang from **aircraft** are short-lived and are caused by fear reactions but include injury from sudden flight, killing of young by mink and rabbits, suffocation in panic-stricken chickens, and reduced egg production. Cattle and goats are unaffected and the effect on livestock and wildlife from the noise produced by low-flying aircraft appears minimal.[13]

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WIND FARMS AND ELECTRIC AND MAGNETIC FIELDS

Electric and magnetic fields are generated from the transmission of electricity through high tension lines. Electrical transmission lines and electrically powered devices generate an **extremely low frequency magnetic field** (50–60 Hz), whereas electronic devices emit a **high-frequency electromagnetic radiation** (300 MHz to 300 GHz). Livestock are exposed to these fields when high-voltage lines pass through rural areas. German veterinarians have expressed concern for livestock health from the effect of radiofrequency electromagnetic fields associated with the establishment of a national mobile phone network. Current work suggests the major biological effect of high-frequency electromagnetic radiation is localized heating, which is usually very minor relative to diurnal temperature changes and changes in

core temperature in response to different ambient conditions. The evidence supporting an effect of electromagnetic fields on circadian rhythms in a variety of species such as cows and lambs, via alteration in melatonin or cortisol secretion, is contradictory and the consensus view is one of no effect.

There is no apparent effect of high-voltage transmission lines on any health outcome in humans, with the possible exception of an increased risk of childhood leukemia. There appears to be no effect on the behavioral or feeding patterns or the reproductive performance of cattle grazed under or near high-voltage transmission lines. There is no consistent detectable effect of high-voltage transmission lines on reproductive performance or growth rate in animals.

Wind farms have become commonplace in parts of Europe, North America, and Australia as society is becoming increasingly interested in using alternative energy sources to fossil fuels. The environmental concern about wind farms is focused on four alterations produced by wind turbines: (1) an extremely low frequency magnetic field; (2) a high-frequency electromagnetic radiation; (3) a low-frequency noise and shadow flicker; and (4) infrasound, which is a sound wave inaudible to humans because of its extremely low frequency (1–20 Hz). No adverse health effects of exposure to wind farms have been identified, except for increased mortality of specific migrating bird species and bats by hitting rotating wind turbine blades and population shifts as a result of habitat alteration; the latter is primarily the result of building access roads and preparing ground to support large wind farms.

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RADIATION INJURY

SYNOPSIS

Etiology Ionizing radiation from radionuclides in environment or feed resulting from exploded nuclear bombs or nuclear power plant accidents

Epidemiology Type, severity, and extent of exposure will depend on atmospheric conditions and the radionuclides released.

Clinical findings Anorexia, depression, and severe diarrhea in acute sickness. Bone marrow depression with anemia and septicemic disease

Clinical pathology Neutropenia and thrombocytopenia, bone marrow depression

Necropsy findings Hemorrhagic and ulcerative lesions in the alimentary tract. Pneumonia, general septicemia

Diagnostic confirmation Radiation exposure from nuclear disaster

Public health considerations Animals exposed to radioactive material also serve as reservoirs for radioactive material that could be passed to humans in meat, milk, and other animal products. This hazard to humans is a problem of public health and is primarily addressed by establishing tolerance limits for contamination in animal products for human food and by changes in agronomic practices and policy.[1-5] The following discussion is restricted to the effects of irradiation on the health of animals exposed to it.

ETIOLOGY

Radiation injury can be caused in a number of ways including nuclear bombs, contamination from nuclear power plant accidents, and exposure to x-rays, but the effects on the tissues are the same, with differences occurring only in the depth of penetration and the degree of injury caused. The radiation emitted by radionuclides has a similar biological effect to external irradiation by x-rays because both sources are **ionizing**—they remove electrons from their orbits causing atoms within animal tissue to produce pairs of charged ions, which are the instruments of the biological damage. Atomic explosions can also injure through the effects of blast and heat.

EPIDEMIOLOGY

Incidence and Case Fatality

There is considerable variation in the effects of an atomic explosion, or a nuclear power plant accident, depending on the distance from and the time after the blast, whether the explosion occurs in the air or on the ground surface, and the types of radionuclides released. With nuclear explosions, animals within the range of immediate irradiation are more severely affected than those exposed only to the "fallout" of radionuclides on pasture. However, grazing animals are exposed to very great risk because of this fallout. The area in which direct radiation effects occur is significantly smaller than that where "intervention levels" for radionuclides are exceeded.

Risk Factors

Animal

Radiosensitivity differs between animal species when death is defined as the endpoint. Horses are more resistant to whole-body radiation than other animal species. Sheep appear the most susceptible and die earlier than cattle at equivalent exposure doses. Pigs are the least susceptible to low radiation. Age is also a risk factor and calves are more susceptible than adult cattle and are prone to develop respiratory and enteric disease, effects that are uncommon in adult cattle that commonly show hemorrhagic disease.

Nature of Radiation

Of the radioactive materials produced by an atomic explosion, a number of **radionuclides**, including iodine-131, barium-140, strontium-89 and strontium-90, and cesium-134 and cesium-137 are likely to enter biological systems. Of these, radioactive iodine, barium, and strontium-89 are of less importance because of their short **half-lives**. On the other hand, strontium-90, cesium-134, and cesium-137 may occur in very large quantities and have long half-lives and are therefore of greatest biological significance.[6] If a sufficient amount of these radionuclides is ingested and tissue levels of them reach critical points, injury similar to that produced by external irradiation will occur. Cesium-134 and cesium-137 are of particular concern because of their biological mobility. They behave metabolically like potassium and are distributed widely through the body.[6] Both are beta and gamma emitters and effectively will administer a dose of whole-body radiation to an animal ingesting pasture contaminated with them. Iodine-131 behaves like stable iodine and is concentrated in the thyroid gland.

Soil type can influence radionuclide intake by animals grazing contaminated pastures. Persisting concentrations of radiocesium in plants are associated with acid soils with high organic and low clay content. In mineral soils, cesium is strongly bound to clay particles, which limits its uptake by plants; clay minerals, such as bentonite, fed to ruminants will reduce the alimentary absorption of radiocesium. Animal contamination is further influenced by **differences in uptake** of radionuclides by different pasture species and animal breed differences in **grazing behavior.**

Zoonotic Implications

Radionuclides are excreted in the **milk**[2] of animals and are present in the **meat**,[1] posing a risk for humans consuming them. Radioiodine transfer to the milk of sheep and goats is considerably greater than to that of cows. The half-life of radioiodine is sufficiently short that contaminated milk could be diverted to stored dairy products, although this would not have public acceptance. The

maximum permissible concentration of radioactive substances in meat is reached at much lower levels of pasture contamination than would be required to cause physical injury to the cattle or sheep; in most countries it is set at around 1000 to 2000 Becquerels (Bq) per kg fresh weight.[4]

PATHOGENESIS

The acute radiation syndromes from acute radiation usually occur within the first few days after exposure to whole-body radiation to 30 to 60 days depending on the radiation dose. Based on the dose, the major manifestations have been divided into three major presentations, central nervous system (CNS), gastrointestinal, and hemorrhagic, but there is considerable overlap in clinical signs at all but the high doses that result in the peracute CNS syndrome.

Doses greater than 80 to 100 Gray (Gy) induce rapid damage to blood vessels, changes in permeability, and an increase in intracranial pressure with death in 2 to 5 days. Gastrointestinal disease results when the radiation dose ranges between 10 and 80 Gy and results from damage to the rapidly dividing undifferentiated cells in crypts of intestinal villi, which are the progenitor cells to the differentiated enterocytes of the intestinal villi. Damage to bone marrow stem cells is the main cause of death at whole-body doses between 2 and 10 Gy with death in large animals occurring 6 to 8 weeks after exposure. Clinical disease is slow in development after exposure because the effect of this damage is not evident until the death of existing circulating blood cells. The effects are the result of decreased granulocytes, platelets, and red cells and are manifested with increased susceptibility to infection, bleeding syndromes, and anemia.

Initially there is a lymphopenia followed by a depression of granulocyte and platelet counts. The leukopenia permits invasion by bacteria from the alimentary tract and **bacteremia** and septicemia develop 1 to 4 weeks after irradiation. The clotting mechanism and antibody production are impaired and facilitate the invasion. Progressive necrosis of the gut wall without inflammation is characteristic. Thrombocytopenic hemorrhage into the lymphatic system and other tissues leads to the development of a profound anemia.

The activity of **germinative epithelium** is also profoundly depressed; if the animal survives the early stages listed earlier, the hair commences to shed, the skin to ulcerate, and a gross reduction in fertility occurs. Degenerative changes in the lens of the eye, particularly cataract, may also occur. **Long-term effects** in animals are of less concern than in man because of the short life span of animals and any genetic damage can be removed by selective breeding. Very long-term effects of irradiation include a high rate of **mutations** and a high incidence of tumors, mostly of the hemopoietic system, and an increased risk for squamous cell carcinoma of the skin.

Thyroid damage by iodine-131 does not appear a major risk for ruminants. The thyroid gland of the sheep is more radiosensitive than that of the cow but very high and sustained doses of iodine are required to produce damage, and clinical signs in thyroid-damaged ruminants are minimal.

CLINICAL FINDINGS

Acute Syndrome

After immediate irradiation with high doses death occurs from damage to the CNS. At lesser doses damage to the alimentary tract occurs and, particularly in young animals, there is a resulting intense, refractory diarrhea. Death occurs in a few days from dehydration and electrolyte imbalance. Local contact of radioactive materials to skin causes changes within a few hours. Observable lesions vary from depilation and slight desquamation to extensive necrosis, depending on the irradiation dose.

Subacute Syndrome

Immediately after irradiation with median doses there is an **initial phase** of "radiation sickness" characterized by anorexia, vomiting in pigs, and profound lethargy, which lasts from several hours to several days.

The **second phase** is one of apparent normality lasting until 1 to 4 weeks after irradiation. This is followed by a **third phase** in which most deaths occur associated with damage to stem cells in bone marrow and secondary infections. Clinical signs vary with the nature of the infection and the age of the animal. Calves commonly develop respiratory and enteric disease with fever, weakness, and diarrhea developing to melena and dysentery, sometimes with tenesmus. Anorexia is complete but there is great thirst. Weakness, recumbency, and hyperirritability are present. Respiration is rapid with panting and there is a profuse sometimes blood-stained nasal discharge. In adult cattle severe anemia and septicemia occur.

Generally, if the animal survives this period, there is a **long period of convalescence,** which is accompanied by failure to make normal weight gains, alopecia, sterility, and lenticular defects. The sterility may be permanent, or normal fertility may be restored by the end of 8 months in pigs and 2 years in cattle. During the ensuing years, recovered animals may produce mutant offspring. Tumors, especially of the hemopoietic system and of areas of skin that suffer radiation injury, are also likely to occur.

Experimental irradiation of pregnant animals causes fetal death and resorption, defects of individual organ and limb development, decreased survival of young born alive, and depressed growth rate and fertility of surviving young. The type of abnormality depends on the stage of pregnancy at which exposure is experienced.

Chronic Exposure

Chronic exposure to gamma and mixed neutron-gamma radiation for several years produces lenticular opacities. Levels of irradiation that cause lesions in the human lens are the same levels that create similar opacities in the lens of cattle, but are not the same for pigs or burros.

CLINICAL PATHOLOGY

In cattle receiving median somatic doses, the **total leukocyte count** falls precipitately during the first few days after irradiation with the peak of fall at the 15th to 25th post-irradiation (PI) day. In this species, the most sensitive leukocyte is the **neutrophil**, in contrast to the lymphocyte, which is most seriously affected by irradiation in humans.

Platelet counts begin to decrease from a normal of 500,000/mm on PI day 7 to 40,000/mm at about PI day 21.

Erythrocyte counts and hematocrit levels also fall and prothrombin times increase in parallel to the other changes mentioned. The return to preirradiation levels requires about a year for granulocytes and platelets and from 4 to 5 years for agranulocytes.

NECROPSY FINDINGS

Gastroenteritis, varying from hemorrhagic to ulcerative, is constant and ulceration of the pharyngeal mucosa and pulmonary edema occur commonly. Hemorrhages into tissues are also characteristic and include all degrees from petechiae and ecchymoses to hematomas and large extravasations. In experimentally produced irradiation sickness, severe fibrinous pneumonia, pleuropneumonia, and pericarditis are common. Degeneration of many tissues, but especially bone marrow, intestinal mucosa, and lymphoid tissue, is evident histologically. Evidence of secondary bacterial invasion is usually seen. Confirmation of the diagnosis usually requires documentation of exposure to radiation.

Samples for Confirmation of Diagnosis

Histology samples from the jejunum, lymph node, and bone marrow are used for confirmation.

DIFFERENTIAL DIAGNOSIS

The subacute syndrome closely resembles poisoning by bracken fern in cattle and by trichloroethylene-extracted soybean meal, but the diagnosis will usually depend on a knowledge of exposure to irradiation.

CONTROL

The problems of veterinary civil defense in the event of thermonuclear warfare are too extensive to discuss here, and the necessary information is provided by most

governments. The use of clay minerals and iron-hexacyanoferrates in the feed can bind and **restrict the uptake** of radiocesium from the alimentary tract of ruminants but is impractical for widespread use. Long-term control of exposure rests can be accomplished with changes in agronomic practices.

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VOLCANIC ERUPTIONS

Active and potentially active volcanic chains exist in several countries in close proximity to significant livestock production areas. Major volcanic eruptions are rare, but the experiences of the eruptions of Mount Hecla in Iceland, Mount St. Helens in the United States, the Lonquimay complex in the Southern Andes, Mount Ruape hu in New Zealand, and in Eyjafjallajokull, Iceland[1] suggest that while most are inconvenient to orderly livestock production, and usually have minimal effects on animal health, some can cause catastrophic losses of livestock, long-term destocking, and have a large economic impact. The 1991 eruption of the Vulcan Hudson in South America directly killed over one million livestock through deposition of ash on pasture resulting in severe continuing economic loss to the sheep grazing areas of Patagonia.[2] There is also the potential for volcanic ash to leach important mineral nutrients, such as sulfur, from soils, affecting productivity of grazing enterprises.[3]

Blast and Gas Damage

Volcanic eruption can result in devastation of land areas from the effects of lateral blast and pyroclastic, laval, and mudflows. Livestock losses that occur in this way can be total, but the affected areas are restricted to the immediate vicinity of the eruption. Toxic gases from the eruption may accumulate in close low-lying areas and result in the death of animals in those areas.

Ash Hazards

Significantly greater land areas can be affected by tephra fallout consisting of ash and rock fragments from the volcanic eruption. The size of the sector affected by ash fallout will be determined by the strength and direction of winds at the altitude reached by the ash column at the time of the eruption, but several thousand square kilometers can receive ash fallout varying from a light dusting to falls several centimeters in depth.

The hazards to livestock during the fallout period appear minimal, although in areas where the ash fall is heavy, there is virtually total darkness. Animals, particularly sheep, mill about excessively and some die of **suffocation** or **misadventure,** including drowning.

The immediate effect of the fallout is to blanket pastures with ash, and in heavy fallout areas taller succulents may become lodged and unavailable for grazing.[2] Livestock may be forced to graze more robust, but toxic, plant species if stored feeds are not provided, and loss from **plant poisoning** was observed following the Mount St. Helens eruption. **Hypocalcemia**, apparently resulting from food deprivation, was also observed in the immediate postfallout period with Mount St. Helens and was also recorded following the Mount Hecla eruption.

Ash fallout may have a devastating effect on insect life, and this may be followed soon afterward by death from starvation of **insectivorous avian species**. This might be misinterpreted by the public as evidence of ash toxicity.

Toxic Chemicals

Potential hazards to livestock health exist in the chemical composition of ash. In the fallout from Mount St. Helens and from Mount Ruapehu several potentially toxic heavy metals and trace elements were present, but none in a concentration sufficient to be a hazard to livestock health. During the airborne stage, wind sorting of the dust into particles of varying size, shape, and density results in area variation in the composition of the fallout. Consequently, area variations in chemical analysis over the fallout area can occur. Analyses based on acid-leachable or water-soluble analysis are more relevant to immediate animal health than those reporting total content.

Death resulted from acute **fluorine poisoning** in association with high fluoride levels in ash and ash-contaminated grasses and water in the period immediately following the Mount Hecla, Lonquimay, and other eruptions.[4,5] It is therefore advisable to remove livestock from ash-contaminated pastures until this hazard is determined. In most circumstances, this will necessitate removal to indoor housing and ***feeding of stored feed and well water if they are available.***

Physical Properties

The ash particulate count in air and the respiratory exposure to livestock is highest during the fallout period, but can remain high for long periods following the fallout when ground ash is disturbed by animal movement, winds, and normal farming practices. A significant proportion of this material is of **small particulate size** and is **respirable**. Chemical and/or physical irritation of the respiratory tract, with a significant increase in the prevalence of respiratory disease, might be expected in these circumstances. This did not occur following the Mount St. Helens eruption, even in animals with known preexisting respiratory disease, and it was not a reported problem following the eruption of Mount Hecla. Signs of irritation such as lacrimation were observed widely but with no untoward sequelae.

Long-Term Effects

Volcanic ash is composed predominantly of pumiceous volcanic glass and crystalline mineral silicates such as feldspar. These materials have no innate pulmonary toxicity. Volcanic ash may also contain variable amounts of free crystalline silica such as quartz, cristobalite, and tridymite which, if present in respirable-sized particles for prolonged exposure periods, can induce pulmonary fibrosis.

Silicosis is primarily a human health concern, although spontaneous silicosis is recorded in livestock. While it is a concern with all eruptions, the long-term health history of animals and man following volcanic eruptions suggests this hazard is minimal.

In the vicinity of Mount St. Helens there have been two appreciable effects on livestock health:

- There has been a marked increase in the incidence of **hypomagnesemia** in cattle in the semiarid channeled scab lands of central Washington. This has possibly resulted from the reflective nature of the ash layer on the soil reducing soil temperature increase during early grass growth and thus reducing magnesium uptake. Grass magnesium concentrations are low and potassium levels are high, but there are no preeruption values for comparison.
- There has been an increase in the severity of **selenium deficiency**. The association between selenium deficiency and recent volcanic origin soils is well recognized. Problems have been corrected by additional and more intensive selenium supplementation.

Animals might ingest considerable quantities of ash from grazing contaminated pastures or from hay subsequently prepared from these areas. There is little field evidence for disturbance of **digestive function** in livestock following the Mount St. Helens or Mount Ruapehu eruptions, and feeding trials of ash to cattle and sheep have shown no clinical or postmortem evidence of untoward effects or any depression of production except that associated with decreased feed palatability at high ash feed levels. There is evidence that long-term inhalation of volcanic gases exacerbates the lesions caused by lung worm infestation in sheep in Hawaii.[6]

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BUSHFIRE (GRASS FIRE) INJURY (THERMAL BURNS)

SYNOPSIS

Etiology Thermal or smoke inhalation injury from fire

Epidemiology Large numbers of livestock with thermal burns in bush and grass (prairie) fires. Smoke inhalation injury more common in horses rescued from barn fires

Clinical findings Edema and thermal injury in skin. Upper respiratory signs in the short term and lower respiratory disease in the longer term, with smoke inhalation

Treatment Palliative local therapy, fluid therapy to prevent shock with superficial thermal injury. Maintenance of airway and lower respiratory function with smoke inhalation. The major dilemma with treatment is the conflict between the welfare of the animals and the responsibility to the owner.

ETIOLOGY

Heat, carbon monoxide, and toxic gases are the cause of injury and death in fires. Most fire victims have thermal burns. The treatment of burns is usually a surgical subject, but there are aspects of bushfire or forest fire injury that warrant discussion in a textbook of large-animal medicine. For example, when large numbers of animals are affected the most important questions are whether to treat them and what to treat them with. Alternatively, if they are not to be treated a decision must be made as to whether they are humanely destroyed or salvaged for meat. When large numbers of animals are burned there is also often a problem with pastures and supplementary feed, such as hay, being destroyed by the fire. There is also a moral conflict for the veterinarian between the welfare of the animals and his or her responsibility to the owner.

EPIDEMIOLOGY

Forest Fires

Although no written information is readily available about forest fires in softwood forests it is assumed that few animals would survive the suffocating effects of intense heat and high smoke concentration. The intensity of the heat arises from the fact that the entire forest from leaves to trunks is burned.

In hardwood forests, such as eucalyptus forests in Australia, the heat may not be so severe if only the tops of the trees are destroyed. Underbrush is burned but the tree trunks may only be scorched and usually survive to regrow. Depending on the density of the forest and the amount of underbrush, many badly burned animals may survive and will need to be assessed. The most severe burns are on the lower surfaces and undersurfaces of the body and are caused by burning of the litter on the forest floor.

Grass Fires

The most serious situation is caused by a grass or prairie fire which, because of the short period of intense heat generated by the wind-driven fire, will burn but not necessarily kill animals. The fires can be extensive and involve contingent farms and large numbers of animals. Many animals will die of suffocation, especially sheep, but a majority will often survive with various states of burn injury.

Barn Fires

Animals may die of carbon monoxide poisoning and asphyxiation, or be burned all over, but some may be rescued without burns but with the risk of smoke-induced respiratory injury. Animals trapped, but subsequently rescued, in barn fires are usually horses.

There are a number of problems for veterinarians created by a large number of burned livestock:

- National or regional disaster services are usually responsible for dealing with the damage to property and welfare problems of humans. They are often poorly equipped to deal with animal problems, yet assume authority over their fate in the temporary absence of the owners. The normal reaction of the average person is to judge that burn injuries are much more serious than in fact they are, hence many burned animals are often unnecessarily destroyed.
- Facilities for penning and treating burned animals will often have been partially or completely destroyed by the fire, so mustering to inspect the affected animals may need improvised or temporary yards.
- The presence and amount of insurance also exerts an influence on the owner's decision on the course to be followed. If most livestock are protected by fire insurance there will be no argument with a veterinarian's decision that severely burned animals should be immediately destroyed for humane reasons.
- Salvage for slaughter is often difficult to arrange at short notice for such large numbers and often has logistical problems in the form of burned yards and fencing. Public sentiment is also often against this practice, and the quality of meat from burned animals can be severely downgraded. However, subsequent slaughter must be kept in mind as an option for animals that will have impaired functions because of burns, such as ewes and cows with teat injuries and rams and bulls with preputial and scrotal burns.

CLINICAL FINDINGS

Burn Injury

The parts most affected by burning are the face, especially the eyelids; conjunctivae and lips; the undersurface of the body, especially udder, teats, and perineum; and the coronets. Badly damaged corneas take many weeks to heal, but badly swollen lips and eyelids can appear almost normal within 48 hours. Marked edema is always a feature of skin burns in animals, but badly burned skin will be dry and ready to slough in a week.

The teats of dairy cows may be damaged to the point where they will not be milkable by machine, with heifers usually having the worst prognosis. Burns to the prepuce of wethers and rams may induce urethral obstruction. This will usually not be apparent until some days later; thus reinspection of groups assessed as not needing immediate destruction should always be a priority.

Separation of the coronary band from the hoof is commonly seen after burns from grass fires. There is usually a serous exudate at the separation of the hoof and coronet, which can become struck by blowflies. Footbathing in appropriate insecticides, which may be an off-label use, can effectively prevent or treat strikes. Sloughing of the entire hoof may occur, especially following fires that generate intense heat, and secondary infections can exacerbate these lesions.

TREATMENT

Decision Criteria

An accurate assessment and prognosis for survival is essential if suffering is to be kept to a minimum, while at the same time allowing as many livestock that can be economically salvaged the chance to recover. The extent of burns varies widely, depending on the nature of the fire and location of individuals within a mob of sheep or cattle as the fire passes. Except for recently shorn sheep, the fleece, although charred, protects the sheep's body from intense heat. Critical areas for burns are the bare areas of skin, such as on the legs, udder, and breech.

Burned skin is inflamed and hot immediately after the fire, then blackens over the next 2 to 3 days and goes hard and dry, with a leathery feel. Thus burns inspected within 24 hours of a fire will appear progressively worse over the next few days.

A major decision must be made at the outset whether to treat each affected animal or whether to destroy it on humane grounds. This decision is more easily made when assessing individual animals rather than mobs or whole flocks/herds.

Recommended criteria for deciding the fate of sheep burned by pasture fire depend

Table 4-1 A simple method of categorizing livestock affected by burns and appropriate actions for each category

	Prognosis	Action
Group 1	Survival unlikely	Immediate humane destruction. If large numbers they are usually shot and buried in a pit.
Group 2	Better than a 50–75% chance of survival	Treat and monitor in smaller paddocks on the farm; check every 1–2 days for dyspnea and recumbency; some may need to be subsequently destroyed and/or some sent for salvage slaughter at an abattoir; remainder retained in flock
Group 3	Minimal skin damage: often scorched wool and face/ears (check feet)	Minimal supervision; let out into a larger paddock and check for dyspnea and lameness (initially at 4–7 days)

on the presence of burns to the hooves and legs below the carpal and tarsal joints, which cause local swelling and a dry leathery appearance of the skin. Such sheep are often recumbent or immobile, unable to graze, and likely to die and should be humanely destroyed as soon as practicable. Burns that do not cause swelling of the lower limbs, or to other parts of the body, are not likely to be fatal or to produce chronic ill health, unless they affect a large part (more than 15% to 20%) of the body surface. A simple key for categorizing large numbers of sheep into three groups after a fire is shown in Table 4-1.

Animals that are unconscious or very distressed, cannot walk, or have severe difficulty in breathing are poor prospects for recovery and are best euthanized as soon as possible. It may be necessary to monitor sheep after a fire before deciding what to do with them. Several reinspections of a mob at 7 to 14 days, and then progressively longer intervals, may be required. It is necessary at all times to consider the need to avoid inflicting suffering on the animals and to consider the farmer's need to retrieve his assets and recover his business after the fire. If the animals are insured against fire it is also highly desirable to keep written records and advise the insurer of what recommendations have been made.

Animals that have been trapped in a burning building are likely to be burned all over and to have upper and lower respiratory damage from smoke inhalation. With individual animals of high value, bronchoscopy can aid in establishing the severity of this injury. Burning insulation and material from the ceiling can fall on animals and inflict severe (third-degree) burns along the back.

The disposal of euthanized livestock also requires appropriate planning. In large events this is often in a pit constructed by local authorities on the farm or on nearby public land.

Skin Burns

Extensive skin burns are accompanied by fluid shifts, vascular leakage, protein loss, and the potential for hypovolemia. The initial therapy is with crystalloid and colloid fluids as discussed earlier. Tetanus prophylaxis and topical antibiotics, silver sulfadiazine, and aloe vera gel are appropriate therapies. Nonsteroidal antiinflammatory agents can decrease the inflammatory response and help in pain management, but glucocorticoids may potentiate burn sepsis and so prophylactic antibacterial treatments are often advisable. In horses, euthanasia is recommended if greater than 50% of the body surface is affected.

Smoke Inhalation

Tracheostomy may be required to maintain the upper airway. Bronchodilators such as aminophylline or terbutaline sulfate are used to relieve reflex bronchoconstriction and humidified oxygen and local hydration by fluid nebulization to relieve hypoxemia. Corticosteroids are used to reduce airway inflammation in animals with minimal cutaneous burns.

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Diagnosis of Inherited Disease

Genetic disorders are a small but important cause of wastage in farmed animals and, with increasing access to genomic analysis and technology, are more readily recognized and categorized. Most occur in purebred animals and the simplest to understand and control are inherited as autosomal recessive traits with a clear phenotype and expression in the young animal. The recessive mode of inheritance means that heterozygotes can, in the absence of available testing, remain in the population, with disease only occurring when homozygous-affected animals are produced as a result of mating of heterozygous parents. An example of this situation is that of severe combined immunodeficiency syndrome in Arabian foals.

Dominant disorders tend to be self-limiting because of lack of viability of affected offspring or because affected animals are readily identified and excluded from the breeding pool.

A more complex situation is when heterozygotic animals have characteristics that are desired and when the homozygotic animal is severely or lethally affected. In this situation there is an imperative to select for the mutation by breeding desired heterozygotes. An example is Quarter Horses with hyperkalemic periodic paralysis (see Chapter 15) in which the heterozygote is favored because it performs better in halter class competitions. Another example is in the original Dexter cattle in which the slightly dwarfed Dexter phenotype is dominant to the normal and is selected for. Animals homozygous for the gene abort with a nonviable "bulldog" type fetus. Sex-linked disorders may occur but are uncommon. Some monogenic disorders may arise de novo because of new mutations of germ plasm. Those with a dominant mode of inheritance are present in offspring of the animal in question, usually affecting genes for structural proteins such as collagen. A new mutation should be considered with disorders such as osteogenesis imperfecta or skin fragility. The proportion of offspring with the defect may vary depending on what stage of gametogenesis the mutation occurred.

Inbreeding, knowingly or unknowingly practiced, is an important feature in the manifestation of most outbreaks of a recessive disorder. Founder effect is an aspect of this that has been important when new breeds have been introduced to a country by importation of genetic material from a small number of individuals. Artificial breeding on a large and international scale has sometimes exacerbated this, particularly in cattle but also in horses.

Genetic disorders can be manifested as disease or bodily malformation. When diagnosed, an entity may reflect the tip of an iceberg only, and it can be expected that many other cases go undiagnosed. Spread across an industry their economic importance may be limited, but as particular disorders tend to be concentrated in certain herds/flocks they may have considerable importance to an individual breeder, particularly those involved with pedigree breeding. Animal welfare is also a concern to be

addressed, which is driven by a greater awareness of ethical standards in livestock production and by potential market access requirements.

The advent of genome-wide association studies has allowed the detection of polygenic associations with production traits or propensity for disease.[1-3] Examples include double muscling in Belgium Blue cattle,[3] recurrent laryngeal neuropathy[4-7] and guttural pouch tympany in horses,[7] and mastitis[2] and resistance to mycobacterial disease in cattle.[2] Although these analyses are useful, the emphasis on genetic disease remains the determination of associations with mutations in single genes. This situation is changing as more complex genomic analyses become more widely available.

The two main problems for the clinician investigating a suspected inherited disorder are to confirm a primary genetic cause and then to institute control in a cost-effective manner.

DIAGNOSIS

For a number of inherited diseases or malformations known to occur in a breed, morphology or histopathology may be so characteristic as to be essentially pathognomonic. However, for some disorders environmental agents (teratogens) may cause similar morphologic anomalies, e.g., arthrogryposis, so care should be taken. Pedigree analysis may help if there are sufficient animals of known breeding to show that the incidence of the disorder follows a Mendelian pattern. However, in many herds/flocks animals may be closely related and pedigree analysis can sometimes be misleading and produce a fictitious relationship between inheritance and disease. As the biochemical anomaly is now known for many diseases, or perhaps can be deduced from histopathologic lesions, laboratory tests may confirm a presumptive diagnosis. Test mating of a sire to daughters, related females, or females that have given birth to an affected animal is the ultimate confirmation of the genetic nature of a disorder, provided the appropriate numbers of progeny are generated. Disproving a genetic cause of a disorder may be as important as proving it. Matings of a sire to produce a minimum of 24 progeny from his daughters or 12 from putative heterozygotes (females that have given birth to affected individuals) are usually considered satisfactory numbers to exclude a likely inherited cause if no affected individuals are born ($P < 0.5$). The birth of a proportion of affected offspring is strong evidence of inheritance. The use of superovulation and embryo transfer techniques may facilitate this, particularly if insufficient daughters or putative heterozygotes are available. The time to accomplish this may be decreased by caesarian section of the surrogate dams if the defect can be detected in the fetuses.

The degree of inbreeding is an important indicator of whether a congenital disorder is inherited or not. Consistency of the defect is a characteristic of inherited disorders, but there may be some variation in age of onset or expressivity of lesions. Other epidemiologic factors include the occurrence of the defect over more than 1 year and occurrence or repetition of it in the same mating group, but not in others on the property.

CONTROL OF INHERITED DISEASE

Appropriate control measures may vary, depending on the importance of the disorder, and may be aimed at the herd/flock level or at the breed as a whole. It may be prospective but, at the farm level, it is mainly reactive with the purpose of preventing further losses by immediate action. This should include not breeding from putative heterozygous sires or females that should preferably be culled. Replacement sires are best acquired from another breeder but, if the defect is common in the breed, then the risk may remain and crossbreeding with a sire from another breed may be considered if the type of farm operation permits it. If a test is available for detecting heterozygous animals then this can be used in new sire selection.

Control of genetic disorders in pedigree herds is more complex and to be effective depends on ability to detect heterozygotes or prove animals do not carry the recessive gene in question. Test mating is time-consuming, expensive, and of limited application. The explosion of knowledge concerning the biochemical and molecular genetic basis of inherited diseases across species has opened up effective means of diagnosing genotype for many of them. Control may be at an individual herd/flock level or applied to all at risk. It is best instigated with the help of breed societies who may exert control over the fate of animals diagnosed as heterozygous through control of registrations. Apart from the accuracy of genetic tests in genotype diagnosis, there is the added advantage that particularly valuable animals may be kept within the herd/flock for breeding because their offspring can in turn be tested as normal or heterozygous.

The first generation of tests for heterozygotes was biochemical based on knowledge of the enzyme deficiency and the gene dosage phenomenon. Heterozygous animals with one normal and one mutant gene have enzyme values midway between normal and diseased values, although there may be some overlap. Supplementary tests or knowledge of the parents' genotype may assist with clarification of equivocal results. Such tests were used to control the economically important lysosomal storage diseases α-mannosidosis in Angus and Murray Grey cattle in New Zealand and Australia and glycogen storage disease type II in Shorthorn and Brahman cattle in Australia. These have now given way to more accurate second-generation technology based on DNA for these diseases as well as a number of others.

The genome for the major farm species is known and genome-wide analyses now routine. When the abnormal gene or genes is known then it is much simpler to define the mutation and through molecular diagnostics detect affected or carrier animals.

Artificial breeding techniques have the capacity to spread undesirable genotypes widely before they are recognized. Many artificial breeding organizations involved in the dairy industry prospectively screen for genetic disorders by mating prospective sires over a proportion of their daughters. This is possible because of the time taken to prove a sire before he enters the industry on a large scale.

ONLINE MENDELIAN INHERITANCE IN ANIMALS

Online Mendelian Inheritance in Animals (OMIA) is a database of genes, inherited disorders, and traits in animal species (other than human and mouse) authored by Professor Frank Nicholas of the University of Sydney, Australia, with help from many people over the years.[8] The database contains textual information and references as well as links to relevant records from Online Mendelian Inheritance in Man (OMIM), PubMed, Gene, and soon to be NCBI's phenotype database.

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