PATHOLOGY OF SELECTED INFECTIOUS DISEASES IN DOMESTIC ANIMALS

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Preface

Pathological morphology is a basic method in the veterinary medicine for determination of final diagnosis, above all in diagnostics of infectious diseases. Morphological features of diseases are always a result of complex interactions between host organism, pathogen and environmental conditions. Every pathological process has its own cause – etiology and disease is always a consequence of alteration of homeostasis.

Infectious diseases are transmitted to susceptible animals either directly – through contact with diseased animal or indirectly – through various reservoir hosts or vectors. The outbreak of a disease depends on many factors, such as virulence of etiological agent, its quantity, effectiveness of defensive ability of organism, its susceptibility, positive or adverse effects of environmental conditions and others. Important factor at the beginning of an infectious process is also the entering gate of infection, such as peroral, aerogenous, genital, umbilical, intrauterine way of infection or through wounds etc. After the penetration of pathogenic microorganism into a host organism there is farther spreading, settling and replication of causative agents in different organs and tissues. This process of penetration of pathogens to the organism, their farther spreading, replication and causing of morphological changes is described as a pathogenesis of the disease. The way of progression of various diseases depends on the species of pathogen and on its localization in the host organism, while considerably influenced by the immune system of an animal.

Lecture notes on the pathology of infectious diseases should help to provide an overview of modern findings in the veterinary medicine, easier orientation in the results of complex interactions between various pathogens and host organisms. We also hope, that it would be an useful help for other specialists working in any field of veterinary medicine and veterinary hygiene.

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1. Actinobacillus pleuropneumoniae infection

**Etiology and pathogenesis:** *Actinobacillus pleuropneumoniae* (APP) causes contagious pleuropneumonia, an important cause of severe, often fatal, pneumonia in growing pigs. The disease is most common in 6-week to 6-month-old hogs. The severity is highly variable, but case fatality rates of 20-80% are common in acute outbreaks. Clinical signs in severely affected swine include fever, lethargy, severe dyspnea, cyanosis, bloody discharge from the nose, and occasionally vomiting or diarrhea. Convalescent pigs with chronic pneumonia may fail to thrive and display exercise intolerance and coughing.

APP is a gram-negative coccobacillus of the family Pasteurellaceae. APP benefits from a rich spectrum of virulence factors - toxins. The toxins are potent inducers of cytolysis in porcine neutrophils, alveolar macrophages, erythrocytes, and epithelial cells. Low concentrations induce an oxidative burst in porcine neutrophils. These toxins appear critical to development of disease. Lipopolysaccharide induces macrophage activation and secretion of neutrophil chemoattraktants, procoagulant activity, and complement activation, similar to that described for *M. haemolytica*. The capsule impairs phagocytosis by macrophages and may prevent complement activation. APP produces superoxide dismutase, catalase, and hydroperoxide reductase, which may protect against oxidative killing by neutrophils and macrophages. Other virulence factors include fimbrial adhesins, outer membrane proteins, iron-binding proteins, metalloproteinase, and urease.

Infection is acquired by direct contact with infected pigs or by spread of aerosol droplets over short distances. The bacteria may be carried in the nasopharynx of apparently healthy animals, and these carriers are the principal method of introduction onto a naive farm. In contrast to *Pasteurella multocida* and *Bordetella bronchiseptica* in pigs and *M. haemolytica* of cattle, APP often causes disease in the absence of predisposing factors. Nevertheless, disease severity is enhanced by *Mycoplasma hyopneumoniae* or pseudorabies infections, and by factors that cause ciliary stasis. Following inhalation, APP rapidly binds to the epithelium lining terminal bronchioles and alveoli. Neutrophil infiltration and alveolar exudate develop as early as 90 minutes after infection. Neutrophil recruitment is primarily due to secretion of neutrophil chemoattraktants by macrophages in response to infection, for bacterial products themselves do not directly induce neutrophil chemotaxis. Leukocyte necrosis is a prominent feature of the histologic lesions, and is presumably mediated by the cyto-toxins.

**Gross lesions and histopathology:** Gross findings in pigs that die of contagious pleuropneumonia are typified by fibrinosuppurative, hemorrhagic, and necrotizing lobar pneumonia or pleuropneumonia. Identical gross lesions may be caused by *Actinobacillus suis* and, less frequently, by *Salmonella choleraesuis*; these are important differential diagnoses in minimal-disease herds expected to be free of APP. The le-
sions commonly affect the middle or caudal lung lobes, and may be unilateral or bilateral. Lesions are deep red, firm to hard, protrude above the surrounding lung, and cut crisply. The cut surface often exhibits sharply demarcated, irregularly shaped, 1-10 cm foci of coagulative necrosis that are friable and pale. In peracute cases, interlobular septa are expanded by fibrin and edema, and fibrinous exudate on the pleural surface ranges in appearance from a haze resembling ground glass to mats of elastic fibrin. The bronchi may contain bloody fluid, and blood may ooze from the nostrils. Bronchial and mediastinal lymph nodes are enlarged, edematous, and congested. The pericardial and peritoneal cavities may contain scant serosanguineous fluid. Lesions in chronic survivors include fibrous pleural adhesions, sequestra that develop from large foci of coagulative necrosis, and locally extensive pulmonary fibrosis or abscessation. Acutely affected pigs occasionally develop hyaline thrombi and fibrinoid necrosis of glomerular capillaries, afferent arterioles, and interlobular renal arteries, perhaps mediated by endotoxemia.

Microscopic investigation of these lesions reveals filling of alveoli and terminal bronchioles by fibrin, neutrophils, fewer macrophages, and many necrotic leukocytes that are probably neutrophils. The foci of necrosis, which are often centered on alveolar septa, are delineated by a basophilic band of intense neutrophil infiltration and extensive neutrophil necrosis. In the center of the necrotic areas, the exudate varies from protein-rich edema, to fibrin, to leukocytes. As in other areas of the lung, many of the leukocytes contain streaming, lightly basophilic, homogeneous chromatin debris. These neutrophils are in an apparent state of activation, and express tumor necrosis factor-α, IL-1, and IL-8 mRNA at high level. The mucosa of bronchi and bronchioles may be invaded by neutrophils with fewer macrophages and neutrophils, and bronchiolar epithelium may be necrotic or sloughed. Nevertheless, a discovery of extensive bronchiolar necrosis should prompt a search for concurrent viral infection, such as influenza. Thrombi may develop in small venules and capillaries in the alveolar and interlobular septa, and fibrinoid vasculitis has been infrequently described. Lymphatics in the alveolar septa are distended by serofibrinous exudate with variable numbers of neutrophils. Extrapulmonary lesions are uncommon, but include renal glomerular thrombosis, renal vasculitis, or osteomyelitis.

Definitive diagnosis depends on isolation of the agent, and microscopic identification of suppurative bronchopneumonia with neutrophil necrosis.

2. Actinomycosis

**Etiology and pathogenesis:** Actinomycosis is subacute to chronic opportunistic cutaneous, alimentary, and disseminated infection that develop secondary to wound contamination or ingestion. *Actinomyces* species are gram-positive, non-acid fast, filamentous anaerobic or microaerophilic rods that are commensal inhabitants of the oral cavity, intestine, and upper respiratory tract. Cutaneous infection is usually secondary to bites, penetrating wounds caused by foreign bodies such as quills or grass
awns, and wounds contaminated by licking. Cutaneous actinomycosis occurs in dogs, cats, horses, and cattle. Infection in pigs usually involves the mammary gland.

Mandibular osteomyelitis is primarily a disease of cattle caused by Actinomyces bovis, but occasionally occurs in horses, pigs, deer, sheep, and dogs. In cattle, the disease is known as "lumpy jaw," and the classic lesion is confined to the mandible. The maxilla is rarely involved and the organism rarely spreads even to regional lymph nodes, which, although large and indurated, are not infected. A. bovis is probably an obligate parasite of the oropharyngeal mucosa in a number of animal species, and most infections involve the buccal tissues. The organism is not particularly virulent, and in most, perhaps all cases, the surface tissues must be injured by some other agent or by a foreign body for invasion to occur. The osteomyelitis follows direct extension of the infection from the gums and periodontium. Extension to the periosteum causes actinomycotic periostitis, and the infection may not progress any further. Similar lesions may be produced by A. pyogenes. Actinomyces bovis may invade bone directly though the periosteum, but osteomyelitis usually develops from periodontitis, presumably via lymphatics, which drain into the mandibular bone. Grass awns or other plant matter may be wedged into pockets between teeth and the alveolar bone, providing a route of entry for opportunistic bacteria into the mandible.

Gross lesions and histopathology: They consist of abscesses, cellulitis, ulcerated nodules, draining fistulous tracts, and dense fibrous masses. When the triad of clinical signs consisting of tumefaction, draining sinuses, and tissue grains is present, the lesion can be termed an actinomycotic mycetoma. Lesions progress slowly by local extension. They occur most commonly on the head, neck, and extremities. The exudate is variable and ranges from thin serosanguineous to thick purulohemorrhagic. It may be odorless or foul-smelling and contain white, yellow, tan, or gray "sulfur granules." Regional lymphadenopathy frequently accompanies skin lesions. In cats, lesions on the ventral abdomen resemble mycobacterial infections. Actinomycosis in cattle usually involves the mandible or maxilla causing proliferative osteitis ("lumpy jaw"); the infection may extend from the bone to the overlying skin to form firm nodules, abscesses, and draining sinus tracts with extensive fibrosis. The cutaneous lesions of bovine farcy are typically associated with lymphangitis and lymphadenitis and are clinically similar to those caused by tuberculosis.

Microscopically, A. bovis causes a chronic, pyogranulomatous inflammatory reaction. Suppurative tracts permeate the medullary spaces leading to multiple foci of bone resorption and proliferation. Large sequestra do not develop, even when the cortex is invaded, probably because of the slow, progressive nature of the disease. Fistulae often extend into the overlying soft tissue and may discharge through the skin or mucous membranes. Periosteal proliferation is excessive and the bone may become enormously enlarged, the normal architecture of the mandible being destroyed. The teeth in the affected portion of the jaw become loosened, lost, or buried in granulation tissue. On cut surface, the affected mandible has a "honeycomb" appearance with reactive bone surrounding pockets of inflammatory tissue. Fragments of necrot-
ic trabecular bone accumulate in purulent exudate as "bone sand." The pus is also likely to contain many 1-2 mm diameter, soft, light yellow granules referred to as "sulfur granules." These consist of an internal mass of tangled, gram-positive filaments mixed with some bacillary and coccoid forms, and a periphery consisting of closely packed, club-shaped, gram-negative bodies.

A similar tissue reaction, accompanied by club-colonies, occurs in association with some other bacteria, in particular *Actinobacillus lignieresii*. Actinobacillosis is typically a disease of soft tissue, spreading as a lymphangitis and usually involving the regional lymph nodes. *A. lignieresii* is part of the normal oral flora, and in cattle is associated with deep stomatitis. When introduced into the submucosa, it causes pyogranulomatous inflammatory loci centered on club colonies containing gram-negative coccobacilli. Microscopic examination of these lesions reveals well-demarcated submucosal granulomas with plant fibers in the center, surrounded by a marked neutrophilic reaction. The tongue is often involved in actinobacillosis, and the chronic condition produces clinical "wooden tongue". Oral actinobacillosis in pigs causes lesions similar to those in cattle, including glossitis.

3. African swine fever

**Etiology and pathogenesis:** African swine fever (ASF) is an acute-to-chronic, febrile, viral disease of swine, characterized by high fever, cutaneous hyperemia, abortions, edema, and hemorrhage in internal organs, particularly lymph nodes. African swine fever virus (ASFV) infects only members of the Suidae family and is a harmless companion of the warthog (*Phacochoerus aethiopicus*) and the bush pig (*Potamochoerus porcus*). However, the virus is a constant and major threat to domestic pigs. Originally limited to sub-Saharan Africa, the disease has appeared in southern and western Europe, but remains endemic only in Sardinia outside Africa. International spread of ASF is primarily through infected pork products in garbage fed to pigs. Once a focus of infection is established, spread is most likely to occur by direct or indirect contact. In Africa, the transmission of the virus from wild Suidae to domestic pigs is primarily by the argasid tick *Ornithodoros moubata*, a true biological vector and a reservoir of the virus in nature. Additional arthropod vectors exist.

The causative agent, ASFV, is an enveloped DNA virus, family Asfarviridae, genus *Asfivirus*. It is a relatively resistant virus that may survive in the environment or in uncooked pork products for prolonged periods. In an area free of the disease, ASF is typically seen as a peracute or acute disease with high morbidity and mortality, but as virulence diminishes with time, subacute, chronic, and inapparent forms become increasingly evident. Survivors remain persistently infected.

Susceptible animals infected develop rarely neutralizing or protective antibodies. The animals remain viremic and usually die within 7 to 10 days. Pigs that recover are resistant to infection with the homologous virus. There is no cross-protection conferred by infections by Classical swine fever virus (CSFV) and ASFV. Failure of swine that
are immune to CSFV to survive challenge with ASFV is the critical test for establishing the diagnosis of ASF in a suspected outbreak. The ASFV replicates in and activates monocytes and macrophages of various lymphoid tissues and organs, resulting in release of cytokines such as interleukin-1 and tumor necrosis factor, and hence causes widespread cell death through apoptosis of T and B lymphocytes in lymphoid tissue and of endothelial cells in arterioles and capillaries, accounting for the lesions of the acute disease. Activation of pulmonary intravascular macrophages and release of cytokines incites pulmonary edema, neutrophil sequestration, and formation of microthrombi in septal capillaries. It also appears that the virus modulates signaling pathways in macrophages, hence interfering with the expression of host immunomodulatory genes; this evasion of host defences allows infections to be persistent.

The peracute form of ASF is a severe acute viral hemorrhagic fever characterized by a 1 to 3 day course of pyrexia, hyperpnea, and cutaneous hyperemia, with morbidity and mortality approaching 100%. The usual clinical course of ASF is acute. Following an incubation period of 4 to 10 days, there is a reduction in appetite, pyrexia, marked cutaneous reddening, dyspnea, and severe leukopenia. Pregnant sows may abort. Death may occur during one of the periods of pyrexia. It is important to realize that the clinical signs of chronic ASF may be indistinguishable from those seen in classical swine fever (CSF).

**Gross lesions and histopathology:** The ASFV tends to affect the same organs and tissues as does the CSFV. The anatomical differences tend to be quantitative and dependent on the more fulminating nature of ASF; only splenomegaly and hematoma-like visceral lymph nodes are particularly characteristic of ASF. The vascular lesions that can develop rapidly, namely hemorrhage and edema, are apt to be more severe in ASF than in CSF whereas the lesions that develop more slowly, such as infarction, tend to be absent.

The pig dead from acute ASF shows few or no signs of recent wasting. Gastrosplenic and renal lymph nodes are usually intensely hemorrhagic, and ecchymotic hemorrhages may be present on the serous membranes. The spleen is usually enlarged and may be markedly enlarged and friable; infarction cannot usually be recognized grossly. Pulmonary edema, not common in CSF is present frequently in pigs with ASF. The pulmonary septa are thickened by a yellow gelatinous infiltrate. Pulmonary hemorrhage is also common. The gallbladder is often edematous, and the vessels of the wall are engorged and conspicuous. Both petechiae and ecchymoses are present on the serosal and mucosal surfaces. In some outbreaks of the disease, there are extensive pancreatic hemorrhages and necrosis. The renal changes are similar to those of CSF and consist of subcapsular petechiae. The stomach often contains ingesta, but the mucosa is apt to be inflamed and eroded. Changes in the small intestine may be absent or consist of segmental areas of congestion and mucosal petechiation. More severe intestinal changes may be found in the large intestine; these may include large areas of hemorrhage, severe congestion, and ulceration. Lesions suggesting "button
ulcer" are very rare in this disease, presumably because few animals survive long enough for their development.

The postmortem appearance of subacute and chronic cases of ASF varies considerably. In the subacute cases that die after 3 to 4 weeks of illness, there may be lymph node and renal hemorrhage, an enlarged, but not congested spleen, lobular consolidation of cranial lung lobes, and intestinal mucosal hemorrhage. Prominent features of the chronic form include fibrinous pericarditis and pleuritis; splenic and lymph node enlargement; lobular consolidation of the lungs, which may progress to necrosis and mineralization of an entire lobe; skin lesions ranging from raised hyperemic plaques to necrotic areas; swollen joints; and arthritis. The meningoencephalomyelitis and periporal hepatitis observed in the acute disease persist in the chronic disease. Lesions in aborted fetuses are inconsistent but include petechiation of placentas, skin, and myocardium, mottled lungs and liver, and anasarca.

Histologically, infection by a highly virulent strain of ASFV causes extensive necrosis of cells of the mononuclear phagocyte system, whereas infection with a moderately virulent strain causes little necrosis. The histologic findings in acute ASP are very similar to those of CSF, but there are important differences. A major difference is that ASFV does not infect epithelium. Necrosis with karyorrhexis in lymphoid tissue everywhere is often very obvious in ASF; frank necrosis is quite rare in CSF, although mature lymphocytes are apt to be absent in lymphoid tissue. Renal tubular degeneration with amorphous casts in the medulla is frequent in ASF but rare in CSF. In ASF necrosis of periporal hepatocytes and infiltrating lymphocytes is common, whereas microscopic hepatic lesions are usually absent in CSF. The vascular cuffs in the brain in ASF contain much more necrotic debris than do the lesions in CSF. The degeneration of vascular endothelium and the fibrinoid arterial changes are identical. Vascular endothelial damage in the lung may cause thrombosis of vessels and thickening of alveolar walls. Pigs dead of acute ASF may have glomerular capillary thrombosis; surviving pigs may develop focal segmental glomerulonephritis.

4. Anthrax

**Etiology and pathogenesis:** Anthrax is caused by *Bacillus anthracis*, a large, gram-positive, spore-forming bacteria that is highly pathogenic for most herbivorous animals and humans, whereas carnivorous birds and reptiles are resistant. Domestic animals are susceptible to *B. anthracis* in the decreasing order of goats, sheep, cattle, horses, pigs and dogs. Farmed mink are highly susceptible. In ruminants, the disease is usually brief and septicemic; in horses, pigs, and dogs, it is frequently localized to the throat or intestine and may be fatal before invasion of the blood occurs. When the disease is septicemic, as it usually is in herbivores, the blood and tissues of the animal swarm with vegetative organisms which, when exposed to air or oxygen, form spores of most remarkable durability. It is the combination of these two factors, the number of organisms and the resistance of spores, which is of paramount importance.
in the epidemiology of the disease. The spores are known to remain viable in soil for at least 15 years, and probably much longer, since they have been noted to retain their vitality and virulence for 50 years in the laboratory. In the terminal stages of the disease, large numbers of bacilli are excreted in all natural excretions, as well as pathological exudates, and these organisms sporulate and perpetuate infections. As a general rule, the spores are very resistant to methods of disinfection, with the exception of chemical disinfectants which are oxidizing agents. Spores on skin have even survived tanning processes to become a hazard for humans.

Dogs and pigs acquire the infection as a result of eating an animal that had anthrax, and deaths in humans have occurred after eating inadequately cooked meat from a goat dead of anthrax. Anthrax in pigs has been traced to the ingestion of bone meal which was not sufficiently sterilized. Vegetative bacilli are unlikely to cause the disease since they are rapidly destroyed in the acid medium of the stomach. Cattle and sheep are presumed to obtain the infection by ingestion of contaminated food and water, entry through mucous membranes possibly being aided by local trauma. Pulmonary anthrax resulting from the inhalation of spore-laden dust can occur. Infection through the skin is occasionally seen in sheep, and may be assisted by grass seed infestation. Ingestion is an important mode of infection in horses and dogs, as indicated by the common occurrence of lesions in the throat. It is also thought that infection can be transmitted to horses by blood-sucking insects. Intestinal anthrax in pigs probably reflects infection by ingestion.

The pathogenesis of anthrax is an initial lymphangitis and lymphadenitis, which develops into septicemia. Spores that are inhaled are ingested by cells lining alveoli and transported in them to the tracheobronchial nodes, in which vegetation and true initiation of the infection occur. Spread to the blood is via lymphatics as well as by lymphovenous connections within lymph nodes, and numerous bacilli spread in the lymph from node to node as the filtering mechanism of each is successively swamped. Bacilli that enter the blood are taken up in other parts of the mononuclear phagocyte system, especially the spleen, to establish secondary centers of infection and proliferation.

Physiological disturbances, clinical signs and death depend on the development of a massive septicemia. Vegetative cells produce a small array of toxins. The combined effects of toxins are injury and inactivation of phagocytes, increased capillary permeability and impairment of coagulation.

When an animal is suspected of having died of anthrax, organisms should be detected in smears of blood or local exudate. All bacilli in internal organs are likely to be destroyed in 48 hours or less by putrefaction. Hence, it is best to obtain blood for diagnostic purposes from close to the coronet or the tip of the tail, places that are likely to be involved last by putrefactive processes that destroy the vegetative bacilli. *Bacillus anthracis* occurs in blood in pairs or in short chains of 3 to 4 cells. They are large truncate organisms that are easily observed. They are differentiated from putrefac-
tive bacteria by their distinct capsule, which stains pink with old methylene blue, and by having square ends when these are apposed.

**Gross lesions and histopathology:** The carcass of an animal dead of this disease putrefies quickly, becomes very rapidly distended with putrefactive gases, and blood exudes from the natural orifices. These changes are not diagnostic, but when they are observed in an animal that has died suddenly in an area in which anthrax is endemic or has at any time occurred, the examination of smears of blood should always precede autopsy. Anthrax in the fulminating disease is very largely an intravascular infection with most of the organisms in the blood and the rest in the spleen. Septicemia in anthrax is a terminal event, and smears of blood may not be helpful when prepared more than a few hours before death.

The morbid picture of the disease in cattle is characterized by splenomegaly, multiple hemorrhages, and edematous effusions in connective tissues. A very large soft spleen is the most significant lesion, and very rarely is it absent. Splenomegaly occurs in other diseases of cattle, but rarely is it as large in association with sudden death. In anthrax the spleen is soft, sometimes it ruptures spontaneously, and when it is incised the pulp exudes very thick black-red blood which brightens in color on exposure to air. Smears and sections of the spleen reveal very large numbers of bacilli if the carcass is fresh but, when decomposition is advanced, they are destroyed by putrefactive changes. In some cases, splenomegaly is the only lesion.

The histology of the spleen is not revealing. The sinus areas are distended with sludged red cells and the lymphoid follicles are widely separated and hypocellular, but numerous leukocytes and bacilli in chains are present. It is typical of septicemic anthrax that the organisms are always intravascular.

The blood is dark, and either it is not clotted or the clots are very soft and friable, compatible with the effects of the combined toxins in inhibiting the clotting system. Small hemorrhages are common in the mucous and serous membranes and in the subcutaneous connective tissues. Loose connective tissues in any location may be infiltrated with gelatinous fluid, and accumulations of such fluid in serous cavities are stained with blood. There is congestion, swelling, and degeneration of parenchymatous organs. The myocardium is dull and flabby.

Cattle are moderately resistant to *B. anthracis* so that local lesions may occur at the site of entry. Local lesions are usually in the small intestine and take the form of ulcerative hemorrhagic enteritis, but acute inflammation in the abomasum and large intestine may also occur. The most severe lesions may be over the lymphoid tissues of the intestine, or extend for a considerable distance from these. The mucous membrane is intensely red, and at a greater distance is sprinkled with small hemorrhages. The contents of the intestine are then deeply stained with blood. Superficial necrosis and ulceration occur in some areas of most intense hyperemia. The corresponding mesentery, up to the regional nodes, is infiltrated with gelatinous fluid as a result of acute lymphangitis, and the fluid may be stained with blood. The regional nodes have
the appearance of the spleen. They are enlarged, red-black, and on cut surface are moist and shiny. The vessels are intensely congested, and hemorrhage extends into the peripheral sinuses and cortex. Bacilli are numerous and leukocytes are present, but there is no necrosis. In some cases in which the organisms gain entry through the oropharynx, there is hemorrhagic lymphadenitis of the nodes of the throat and edema of the connective tissues in these regions. The occasional case of pulmonary anthrax in cattle is characterized by acute congestion and consolidation of a portion of the lung with larger areas of interstitial edema, edema of the mediastinum, and regional hemorrhagic lymphadenitis.

Sheep are more susceptible to *B. anthracis* than are cattle, and local lesions do not occur except in the unusual instances of percutaneous infection, in which the lesion may take the form of spreading edema from the outset or initially appear as hard circumscribed nodules. The disease in sheep takes the same course as that in cattle except that it is even more rapid. Splenomegaly is not as prominent in sheep as in cattle, likely because of the greater level of collagen in the splenic capsule of sheep. The parenchyma is, however, dark and soft. Edematous effusions do not occur in sheep.

Clinical signs of anthrax in horses may last for several days and are characterized by colic or by large edematous swellings. The swellings, which can be very extensive, occur on the ventral part of the abdomen and thorax, the legs, in the perineal region and about the external genitalia. Dysentery may accompany the acute colic. When ingestion is the route of infection in horses, the primary lesion may be in the throat or the intestine, and death may occur from the local reaction and without septicemia. Intestinal lesions are similar to those described above for cattle, and pharyngeal lesions are similar to those described below for swine.

Pigs are relatively resistant to anthrax. They acquire the infection from eating infected flesh and the infection remains localized to the throat or intestine. Since septicemia is exceptional, splenomegaly is not a prominent part of the gross picture. The characteristic sign is swelling of the pharyngeal region and neck. Some pigs have diarrhea and dysentery, but it is unusual to have intestinal localization without pharyngeal localization. The local lesion of anthrax is swine is a typical carbuncle at the point of entry, with acute regional lymphadenitis and lymphangitis. In primary intestinal anthrax in pigs, the initial lesion is focal or multifocal hemorrhagic enteritis, with a central zone of diphtheresis that eventually ulcerates. The adjacent serosa and mesentery are thickened with edema fluid and yellow, with foci and streaks of hemorrhage; they are the site of focal hemorrhagic necrosis due to acute necrotizing vasculitis and lymphangitis. These mesenteric lesions extend only as far as the regional nodes, which show the type of lymphadenitis characteristic of anthrax in swine.

Dogs are reputedly quite resistant to *B. anthracis*, but a number of outbreaks have been observed in kennels in which the dogs have inadvertently been fed meat from an animal that has died of the disease. Anthrax in dogs may pursue a peracute course to sudden death, it may be of the pharyngeal type in which extensive edema develops in the face, head and neck, or it may be of the intestinal type with signs of acute gas-
troenteritis. Anthrax may occur in mink with high mortality after feeding fresh meat from infected animals.

5. Atrophic rhinitis

**Etiology and pathogenesis:** Nonprogressive atrophic rhinitis (NPAR), caused by *Bordetella bronchiseptica* and other factors, causes mild transient sneezing and nasal discharge, and is not usually of herd significance. In contrast, progressive atrophic rhinitis (PAR) is caused by toxin-producing strains of *Pasteurella multocida*, often in concert with other bacterial pathogens, and is a serious cause of production loss. PAR affects pigs of at least 6 to 12 weeks of age, causing sneezing, mucopurulent nasal discharge, unilateral epistaxis, nasal deformity, failure to thrive, and secondary bacterial bronchopneumonia. Freedom from PAR is a frequent requirement in minimal-disease herds, so differentiation of PAR and NPAR is of substantial significance. Toxigenic *P. multocida* infects rodents, cats, dogs, and ruminants, and may be of zoonotic concern. Both NPAR and PAR are multifactorial conditions for which air quality and the presence of other pathogens influence the severity of disease.

NPAR is primarily caused by strains of *B. bronchiseptica* that adhere to nasal cilia and tonsillar epithelium, and produce a toxin that causes mucosal edema, loss of cilia, and resorption of turbinate bone. Infection is acquired by inhalation of infected aerosol droplets.

Progressive atrophic rhinitis is caused by cytotoxin-producing strains of *P. multocida* type D or, less commonly, type A. Infection is acquired by inhalation following direct contact with infected pigs. Colonization of the nasal mucosa and tonsil is inefficient, but augmented by factors that harm the nasal mucosa, including *B. bronchiseptica* infection, ammonia, and dusts. The cytotoxin, also referred to as dermonecrotic toxin, is a secreted. Intranasal or intramuscular administration of *P. multocida* cytotoxin has similar effects on the nasal turbinates, including epithelial hyperplasia, glandular atrophy, resorption of turbinate bone by osteoclasts, reduced formation of bone by osteoblasts, and fibroblast proliferation. The cytotoxin does not directly affect osteoclast function; rather, hyperplasia and increased function of these cells are apparently stimulated by soluble mediators secreted from nearby stromal cells in response to the cytotoxin.

**Gross lesions and histopathology:** Distortion of the snout is a prominent external finding in pigs with chronic atrophic rhinitis. Brachygnathia superior occurs when the maxillary bones of the snout fail to grow. Lateral deviation toward the most severely affected side is common. Atrophy and malformation of the nasal turbinates are the principal lesions of atrophic rhinitis, and are more severe in the ventral than the dorsal conchae. In cross-sections of the snout at the level of the first or second upper premolar teeth, the normally scroll-like turbinates are misshapen and form irregular or jumbled finger-like protrusions. Turbinate atrophy may be partial or complete, leaving a hollow nasal cavity with an often-deformed nasal septum.
Histologic lesions in the nasal turbinates include osteoclast hyperplasia, osteoclast-mediated resorption of bone, and replacement by fibrous tissue containing many plump fibroblasts. Lymphocytes and fewer neutrophils infiltrate the nasal mucosa, and there may be squamous metaplasia of the ciliated epithelium.

The gross lesions of NPAR and PAR are qualitatively similar, although those of NPAR are generally less severe. Nevertheless, given the significance of a diagnosis of progressive atrophic rhinitis due to toxigenic P. multocida, definitive identification is usually warranted.

B. bronchiseptica and P. multocida can be readily isolated from swabs of nasal mucosa or tonsil, but definitive diagnosis of PAR depends on demonstrating P. multocida cytotoxin production using PCR or an ELISA. Various necropsy-grading systems have been described to assess the severity of nasal turbinate atrophy. These grading systems are not intended to differentiate NPAR from PAR, but are useful in monitoring the herd response to management or therapeutic interventions.

6. Bluetongue

**Etiology and pathogenesis:** Bluetongue is caused by a reovirus of the genus Orbivirus, family Reoviridae. Bluetongue virus (BTV) is spread by vector-competent Culicoides spp., also known as midges or gnats. The virus multiplies in the Culicoides within a week of the infected blood meal being ingested, and transmission can occur, following infection of the salivary glands, 10 to 15 days after the initial blood meal. Transovarial transmission of virus in Culicoides does not occur. BTV circulates in a broad belt across the tropics and warm temperate areas with incursions or recrudescence during the Culicoides season, annually, or at irregular longer intervals in cooler temperate areas.

Sheep, goats, and cattle are the susceptible domestic species, wherever bluetongue occurs. Sheep are the domestic species most highly susceptible to bluetongue, but there is considerable variation in expression of the disease, depending on the breed, age, and immune status of the sheep, the environmental circumstances under which they are held, and the strain of virus. Goats, though susceptible to infection, rarely show signs. Infection in cattle usually produces only inapparent infection or mild clinical disease. A wide variety of nondomestic ungulates and some small mammals may be inapparently infected. Bluetongue is responsible for significant mortality in all these species.

The pathogenesis of bluetongue is fundamentally similar in all species in which disease is seen. Primary viral replication following insect bite occurs in regional lymph nodes and spleen. Viremia about 4 to 6 days after inoculation results in secondary infection of endothelium in arterioles, capillaries, and venules throughout the body, but especially in lung microvascular endothelium. Microscopic lesions, fever, and lymphopenia begin a day or so later, about a week after inoculation. BTV in the blood ap-
pears to be closely associated with, or in, both leukocytes and erythrocytes, and it may co-circulate with antibody. Endothelial damage caused by viral infection initiates local microvascular thrombosis and permeability. This is reflected microscopically by the presence of swollen endothelium, and fibrin and platelet thrombi in small vessels, with edema and hemorrhage in surrounding tissue. These lesions in turn mediate the full spectrum of gross findings. These are fundamentally ischemic necrosis of many tissues; edema due to vascular permeability; and hemorrhage resulting from vascular damage compounded, in severe cases, by consumption coagulopathy due to thrombocytopenia and depletion of soluble clotting factors.

Bluetongue in sheep is highly variable; it may cause inapparent infection or an acute fulminant disease. Typically, leukopenia and pyrexia occur, even in mild infections, coincident with viremia. The degree and duration of fever do not correlate with the severity of the syndrome otherwise.

**Gross lesions and histopathology:** In the early phase there is hyperemia of the oral and nasal mucosa, drooling, and nasal discharge within a day or two of the onset of fever. Hyperemia and edema of the eyelids and conjunctiva may occur, and edema of lips, ears, and the intermandibular area becomes apparent. Hyperemia may extend over the muzzle and the skin of much of the body, including the axillary and inguinal areas. Focal hemorrhage may be present on the lips and gums, and the tongue may become edematous and congested or cyanotic, giving the disease its name. Infarcted epithelium thickens and becomes excoriated; erosions and ulcerations develop along the margins of the tongue opposite the molars, and the mucosa of much of the tongue may slough. Excoriation and ulceration also occur on the buccal mucosa, the hard palate, and dental pad. Affected areas of skin may also become encrusted and excoriated with time, and a break in the wool can result in parts or much of the fleece being tender or cast. The coronet, bulbs, and interdigital areas of the foot may become hyperemic. Coronary swelling and streaky hemorrhages in the periople may be evident as a result of lesions in the underlying sensitive laminae. These hemorrhages may persist in the hoof as brown lines that move down the hoof as it grows.

Internally, in acute cases, there is subcutaneous and intermuscular edema, which may be serous or suffused with blood. Superficial lymph nodes are enlarged and juicy. Bruise-like gelatinous hemorrhages and contusions, which may be small and easily overlooked if not numerous, are often present in the subcutis and intermuscular fascial planes. Focal or multifocal pallid areas of streaky myodegeneration may be present throughout the carcass, perhaps partly obscured by petechial or ecchymotic hemorrhage. Resolving muscle lesions may be mineralized or fibrous. Stiffness, reluctance to move, and recumbency seen clinically are due to these muscle lesions. Necrosis may be present deep in the papillary muscle of the left ventricle, and elsewhere in the myocardium. The lesion which is perhaps most consistent and closest to pathognomonic for bluetongue is focal hemorrhage, petechial or up to 1 cm wide × 2-3 cm long, in the tunica media at the base of the pulmonary artery. These hemorrhages are visible from both the internal and adventitial surfaces, and may be present
in clinically mild cases with few other lesions. Petechial hemorrhage may also be present at the base of the aorta and in subendocardial and subepicardial locations over the heart.

There may also be edema and petechial or ecchymotic hemorrhage in the pharyngeal and laryngeal area. In severe cases the lungs may assume a purple hue, with marked edematous separation of lobules, and froth in the tracheobronchial tree, probably due to pulmonary microvascular damage and heart failure. Animals with pharyngeal or esophageal myodegeneration suffer from dysphagia, or regurgitate, and may succumb to aspiration pneumonia.

Hyperemia, occasionally marked hemorrhage, or in advanced cases, ulceration of the mucosa may occur on rumen papillae, the pillars of the rumen, and the reticular plicae. In convalescent animals, stellate healing ulcers or scars on the wall of the forestomachs may be apparent.

Microscopically, acute lesions are characterized by microvascular thrombosis, and edema and hemorrhage in affected sites recognized at autopsy. In squamous mucosa and skin, capillaries of the proprial and dermal papillae are involved, resulting in vacuolation and necrosis of overlying epithelium. There is a mild, local neutrophilic infiltrate acutely, and a similarly mild mononuclear reaction in the dermis or propria in uncomplicated chronic lesions, which may granulate if widely or deeply ulcerated. Similar microvascular lesions are associated with necrosis and fragmentation of infarcted muscle. Muscle during the reparative phase follows the usual course of regeneration of fibers or fibrous replacement, depending on whether or not the sarcolemma retains its integrity.

7. Borna disease

**Etiology and pathogenesis:** Borna disease, named after the village of Borna in Germany, is caused by Borna disease virus (BDV), which is the only member of the genus *Bornavirus*, family Bornaviridae. The virus exists worldwide in many vertebrates but most commonly infects horses, sheep, cattle, cats, dogs, and ostriches. The traditional endemic area is central Europe, but antibodies to the virus are found in horses outside Europe, including the USA and Japan. The mortality rate may be high (>80% in horses, 5-40% in sheep); surviving horses may be asymptomatic carriers, or may suffer relapses of disease.

The virus replicates in the nucleolus of the host cell without cytopathic effect, persistently infects cells, and induces brain lesions by immune-mediated mechanisms. Acute BDV infection is followed by massive infiltrates in the brain of CD4 + Th1, CD8 + T, and NK cells with a predominance of Th1 cytokines that favors cell-mediated immunity. In the chronic stage (beyond 15 weeks of infection), the aforementioned cellular infiltrates significantly decrease and the predominant cytokines are of Th2 type, favoring the shift to a humoral immune response; the resultant antibodies are not
protective and have no significant effect on the disease. Due to this unique feature, infection of neonatal or immunocompromised animals does not lead to disease or to encephalitis.

The epidemiology of Borna disease, including reservoir, methods of transmission, and infection, remains obscure. Inflammation of the olfactory bulbs at the early stages of natural infection in humans suggests an intranasal route of infection followed by transaxonal migration to the olfactory bulb. Vertical transmission in horses and rats with life-long persistent infection is also suggested. Equids and sheep are the most susceptible animals, but natural disease is reported in many domestic species including but not limited to cattle, alpacas, cats, dogs, and ostriches. The incubation period is not less than 4 weeks and introduces a clinical syndrome that is purely neurologic but of varied course, death occurring in 1 to 3 weeks. The mortality rate in diseased horses is 90-100%. Recurrent episodes at time of stress occur in surviving animals. Clinical signs include pharyngeal paralysis, hyperesthesia, standing in awkward positions, circling, muscular tremors, and spasms; blindness is common. Drowsiness and flaccid paresis develop terminally.

**Gross lesions and histopathology:** There are no gross lesions. Virus and lesions are present mostly in the gray matter of olfactory bulbs (early stage), hippocampus, limbic system, basal ganglia, and brain stem. The dorsal cerebrum and the cerebellum are relatively spared. Lesions may be present in optic nerves and retina. Histologic lesions are those of nonsuppurative encephalomyelitis with predilection for the aforementioned areas. Perivascular cuffs can be dramatically thick (>7 cell layer) and usually there are neuropilar clusters of lymphocytes and plasma cells. Other lesions include neuronophagia and focal gliosis. The presence of inclusion bodies is fairly pathognomonic; these are mainly in nuclei, especially in the hippocampus, and are very occasionally cytoplasmic. They stain well and red with Giemsa, and have a clear halo.

8. **Borreliosis**

Etiology and pathogenesis: The cause of the disease is spirochetal bacteria Borrelia burgdorferi, which was first recognized in 1975 as a cause of a multisystemic disease (Lyme disease) in man. More recently, it has been associated with disease in domestic animals, including dogs, horses, cattle, and cats. In all species, infection is far more common than disease, but the host-bacterium interactions responsible are not well defined. Arthritis is a common feature of disease in animals and human patients with borreliosis. Other lesions include myocarditis and nephritis in dogs, ocular disease and probably encephalitis in horses, and abortion in cattle.

In North America, the three-host tick Ixodes dammini is the primary vector for B. burgdorferi. Tick eggs are deposited by engorged females in summer and hatch in about 1 month. Larvae engorge for a few days in the period May-September and about 2 months later molt to the nymphal stage. In the following spring-summer period they
feed, drop off and molt to the adult stage. This 2-year cycle may be extended to 4 years since unfed larvae and nymphs may overwinter. Larvae and nymphs feed mainly on birds and small mammals, when small rodents are the main mammalian hosts. The adults attach mainly to large mammals, and people are among the potential victims. Borrelia infection in the principal wildlife hosts is essentially asymptomatic. Similar epidemiological patterns involving ticks of the Ixodes ricinus group and various animal hosts exist in other parts of the world. B. burgdorferi has been isolated from flies, which are potentially effective mechanical vectors, and from mosquitoes, which are likely less important. Such vectors are significant only in areas where efficient tick vectors maintain infection among wildlife populations. Both transovarial and trans-stadial transmission of B. burgdorferi occur, but only the latter is epidemiologically important. Intrastadial and interstadial transmission, which occur when several larvae and nymphs feed on an infected host, is of greatest significance in the spread of infection.

Transmission of infection to large mammals is usually by the bite of an adult tick and requires attachment for about 24 h. The organism may be present in the urine of small rodents and cattle, but the prevalence of infection by direct contact is not known.

The most common clinical signs in dogs with borreliosis are anorexia, lethargy, and lameness in association with fever and lymphadenopathy. Severe depression occurs in some cases and may be due to meningitis. The arthritis is typically intermittent and involves one or more joints, often including the carpus.

**Gross lesions and histopathology:** Detailed pathologic descriptions are unavailable since antibiotic treatment appears to be successful. The arthritis may be recurrent, leading eventually to ulceration of cartilage. In experimentally infected rats, acute exudative arthritis, tendonitis and bursitis occur by 30 days postinfection, then regress, but exacerbations develop in some animals. Synovial, but not cartilaginous, ulceration occurs in rats, and there is villus hyperplasia with lymphoplasmacytic and macrophage infiltrates in the synovial membranes. Lymphoplasmacytic myocarditis also occurs in rats, and nonsuppurative myocarditis develops in a small proportion of affected dogs. Clinical evidence of renal disease is also seen in a few dogs and organisms can be demonstrated in the kidney, but the lesions are poorly defined.

In horses, signs of borreliosis include lethargy, low-grade fever, painful, swollen joints, and reluctance to move. Laminitis and panuveitis may also occur but are less common. The organism has been demonstrated in anterior chamber fluid and a probable case of encephalitis caused by *B. burgdorferi* is recorded in a horse. Few necropsies on affected horses are reported but it appears that arthritis is present and resembles that seen in dogs, with the addition of marked thickening and hyalinization of arterioles in synovial tissues.

Although there are few reports in cattle, it appears that the disease in this species is associated with abortion, and may develop into a chronic illness with relapses follow-
ing treatment, eventually leading to emaciation. In other respects, the disease resembles that seen in dogs and horses. Arthritis is common and there is limited evidence of myocarditis and nephritis.

In people, a characteristic skin lesion, *erythema chronicum migrans*, may develop at the site of the tick bite, and represents the first stage of Lyme disease. Similar areas of discoloration have been described on bovine mammary skin. *Borrelia burgdorferi* has been isolated from blood, urine, colostrum, and synovial fluid of cows, and the blood of a newborn calf. Antibodies in the blood of an aborted fetus suggest that the organism may cross the placenta.

Diagnosis of borreliosis is made to some extent by exclusion. *Borrelia burgdorferi* may be demonstrable by darkfield or phase-contrast microscopy in urine or synovial fluid and by silver, immunoperoxidase or immunofluorescent stains in synovial membranes or other tissues. Often the diagnosis is based on typical signs in an animal with a high titer and potential or known exposure to the organism.

9. Bovine respiratory syncytial virus infection

**Etiology and pathogenesis:** Infection with Bovine respiratory syncytial virus (BRSV) is common in North American and European beef and dairy herds. BRSV is an important cause of both acute outbreaks of respiratory disease and "enzootic pneumonia" in 2-week to 5-month-old dairy and beef calves, with a peak incidence at 1 to 3 months of age. BRSV certainly causes fatal bronchointerstitial pneumonia soon after arrival in beef feedlots. Finally, BRSV predisposes to bacterial pneumonia in feedlot beef cattle by impairing lung defenses, and occasionally causes respiratory disease in naive adult dairy cows. The disease is most prevalent in the autumn or early winter.

Clinical signs in calves and cows are similar and include high fever, coughing, tachypnea, and variable nasal discharge and conjunctivitis. Some animals develop dyspnea with open-mouth breathing and increased abdominal effort. Calves often maintain a reasonable appetite in the face of severe respiratory distress, in contrast to the consistent depression of cattle with bacterial pneumonia.

BRSV, a member of the genus *Pneumovirus* is in the family Paramyxoviridae. An understanding of the pathogenesis of BRSV pneumonia has been hindered by the difficulty of establishing experimental infections that are representative of naturally occurring disease. Airborne spread, probably by aerosol, is the common route of infection. In natural cases, viral infection is restricted to the respiratory tract, and viral antigen is most abundant in bronchiolar epithelium of the cranioventral areas of lung. Alveolar type II pneumocytes and macrophages express lesser amounts of viral antigen, and infrequent virus-infected cells are present in nasal, tracheal, and bronchial epithelium. The virus infects but does not replicate in lymphocytes in vitro. Following experimental infection of naive calves, viral shedding was first detected on the sec-
ond day after infection, was maximal at about 4 days, and was absent by 8 days after infection. Interactions with other agents may contribute to the severity of disease. Experimental BRSV infections result in more severe disease if calves are also infected with Bovine viral diarrhea virus. BRSV is an important predisposing factor in the development of bacterial bronchopneumonia in cattle, because the virus impairs alveolar macrophage function and destroys ciliated epithelium. As for many viral infections, CD8 + T-lymphocyte responses may be important in recovery of calves following BRSV infection.

**Gross lesions and histopathology:** Gross lesions in lungs of calves with naturally occurring BRSV pneumonia often differ in cranioventral and caudodorsal areas of lung. The cranioventral lung is atelectatic, collapsed, deep red or mottled, and rubbery in texture. In contrast, the caudodorsal areas fail to collapse and are edematous, heavy, and firmer than normal. Variations in these gross lesions occur commonly: first, occasional cases have a generalized rubbery texture and red discoloration, with no difference between cranial and caudal lung; second, calves that die in respiratory distress may develop marked subpleural and interlobular emphysema with formation of bullae; and third, the raised, consolidated, firm to hard lesions of bronchopneumonia may obscure the aforementioned viral lesions in cases with secondary bacterial infection. Apart from hypertrophy and edema of bronchial and mediastinal lymph nodes, lesions in other organs are usually not noted. Chronic cases of viral pneumonia with bronchiolitis obliterans, including those caused by BRSV, may die of heart failure due to pulmonary hypertension, as a result of hypoxic vasoconstriction. Lesions in these animals include hypertrophy of the right ventricle of the heart, subcutaneous edema, and ascites.

The histologic hallmarks of pneumonia caused by BRSV are bronchointerstitial pneumonia, characterized by necrotizing bronchiolitis, formation of bronchiolar epithelial syncytia, and exudative or proliferative alveolitis. The lesions and the presence of viral antigen are most obvious in the cranioventral areas of lung. In the acute lesions, from 1 to 8 days after infection, bronchioles are lined by flattened epithelium, bronchiolar lumens contain necrotic epithelial cells and modest numbers of neutrophils, and lymphocytes infiltrate around bronchioles. Alveoli contain moderate numbers of neutrophils and macrophages, and alveolar septa may be mildly thickened by mononuclear cells, but hyaline membranes are infrequent. Syncytia are prominent at this stage, and appear as multinucleate cells closely associated with the bronchiolar epithelium, sloughed into bronchiolar lumens or, less commonly, in the alveoli. Alveolar syncytia may closely resemble the multinucleate macrophages that clear fibrin from alveoli in cases of fibrinous pneumonia; but the presence of bronchiolar syncytia is a more reliable indicator of viral infection. Intracytoplasmic eosinophilic inclusion bodies are occasionally present in syncytial cells and uncommonly in bronchiolar and alveolar epithelium.

The histologic lesions of necrotizing bronchiolitis with syncytial cells should be highly suggestive of BRSV infection, but two caveats should be considered. First, Bovine
parainfluenza virus 3 infection may also induce the formation of syncytia with intracytoplasmic inclusion bodies. Second, alveolar multinucleate macrophages are a common finding in fibrinous bronchopneumonia, and probably represent an attempt to remove the fibrinous alveolar exudate. This can present a diagnostic dilemma, since many calves with BRSV develop secondary bacterial pneumonia.

10. Bovine viral diarrhea

**Etiology and pathogenesis:** Bovine viral diarrhea virus (BVDV) is an RNA virus of the *Pestivirus* genus in the family Flaviviridae. It is widespread in cattle populations and it or closely related viruses can infect most even-toed ungulates, including swine. As an RNA virus, BVDV is highly mutable, due to the error-prone nature of the RNA polymerases responsible for replication of viral RNA. As a result,"swarms" of viral mutants form "quasispecies" that circulate within an infected individual and among individuals in a population. While most quasispecies lack a selective advantage, preventing them from becoming dominant, the ability to generate mutants enables BVDV to adapt to host responses, and to establish chronic or persistent infections in some circumstances. While low virulence would seem to promote prolonged viral shedding, there may be advantages in high virulence that favor the emergence of quasispecies capable of causing severe disease and high virus shedding. Point mutation and recombination have produced a number of genotypes of *Pestivirus*, including Classical swine fever virus and Border disease virus. Two genotypes of BVDV occur, type 1 (BVDV-1) and type 2 (BVDV-2), each of which has a number of closely related subgenotypes, many of which circulate widely.

BVDV gains access to the oropharyngeal mucosa by ingestion or inhalation, and primary replication is in oropharyngeal lymphoid tissues, including tonsils. The outcome of the ensuing viremia is a product of the genotype and virulence of the virus, the immune status of the host, whether or not the animal is pregnant, and, if so, the stage of pregnancy. Infection of immunocompetent, seronegative, nonpregnant animals usually results in subclinical infection or mild clinical disease. Animals, mainly over 6 months of age, develop a more obvious clinical syndrome, with a high morbidity and low mortality - classical bovine viral diarrhea (BVD). After an incubation period of 5 to 7 days, the affected animals develop a fever, leukopenia, and viremia that may persist up to 15 days. The virus is present in leukocytes, especially lymphocytes and monocytes, and in plasma. There is a transient decrease in the number of B and T lymphocytes. Clinically, the disease is characterized by lethargy, anorexia, mild ocular-nasal discharge, and occasional mild oral erosions and shallow ulcers. Diarrhea may occur. In dairy herds there is a transient drop in milk production. Affected animals develop neutralizing antibodies that peak in 10 to 12 weeks, and probably are immune for life.

A syndrome of severe acute BVD, characterized by high morbidity and mortality in all age groups of susceptible animals, has been recognized since the early 1990s. Some-
times termed "BVD type 2," since it is caused mainly, though not exclusively, by primary infections with type 2 virus, this syndrome usually has a peracute to acute course, with fever, sudden death, diarrhea, or pneumonia. In some cases a thrombocytopenic syndrome, characterized clinically by epistaxis, hyphema, mucosal hemorrhages, bleeding at injection sites, and bloody diarrhea, is superimposed on the alimentary syndrome caused by type 2 BVDV, or occurs independently.

The pathogenesis of BVD type 2 is most frequently linked to increased strain virulence. However, production of inflammatory cytokines, in response to widespread infection of mononuclear phagocytes, has also been postulated as a cause for the severe disease seen clinically. Fetal infections may occur in pregnant immunocompetent seronegative acutely infected females, and in persistently infected counterparts. The outcome of fetal infection is primarily dependent on the stage of gestation. The most serious consequences occur if an noncytopathogenic (NCP) BVDV crosses the placental barrier during the first 4 months of gestation. It may result in fetal resorption, mummification, abortion, congenital anomalies, or a persistently infected calf. If the calf survives, it remains viremic for life, and it is also immunotolerant to homologous NCP BVD viruses, due to failure of the immature fetal immune system to recognize the infecting viral antigens as "not-self" or foreign.

Persistently infected (PI) calves may be clinically normal, weak, or undersized at birth. They may appear normal, but are often unthrifty, and may have a rough or curly hair coat. The prevalence of these calves in a herd is usually less than 2%, but may be as high as 25-30% in herds where a large number of naive cows, early in pregnancy, have been exposed to NCP BVDV. Most PI calves succumb to mucosal disease (see below), usually between the ages of 6 months and 2 years. PI animals are viremic, and lack antibody to the infecting virus, which they shed constantly, acting as the most important source of infection in the population.

Mucosal disease is a clinicopathologic syndrome occurring in PI animals that subsequently become infected with a closely related cytopathogenic strain, or probably more commonly, when the virus causing persistent congenital infection spontaneously develops a recombination. The result is an overwhelming infection that destroys cells, and to which the animal is incapable of responding. Characterized by low morbidity but very high mortality, mucosal disease most commonly occurs in cattle that are 6 months to 2 years of age. While deaths may occur within a few days of illness, and almost always within 2 weeks, some cases may survive for months.

Basically, there are two forms of clinically severe BVDV infection: mucosal disease in persistently infected animals, and the more recently recognized severe acute form of BVD caused by primary infections with very virulent strains of virus.

**Gross lesions and histopathology:** At necropsy, the gross lesions vary considerably, especially in acute cases, in which either upper alimentary or intestinal lesions rarely may be absent, and less so in the chronic disease, in which a broader patholog-
ic picture is often present, perhaps partially obscured by healing or evolution of lesions.

Crusts, erosions, and shallow ulcers are present on the muzzle and nares of many affected cattle. There is loss of epithelium from much of the oral cavity. The most conspicuous oral erosions are on the palate, on the tips of the buccal papillae, and on the gingiva. In more chronic cases, ulcers may have a margin of thickened proliferative epithelium. The tongue is not always affected; when present, lesions may be evident on all surfaces.

Esophageal lesions are usually present, most commonly in the upper third. In some acute cases, the lesions are shallow erosions, rather than ulcers. The erosions are more or less linear but otherwise irregular, have a dirty brown base, and little or no reactive hyperemia, and may be covered by shreds of necrotic epithelium in animals that have not been swallowing. In more advanced cases, discrete ulcerations occur. In many chronically affected animals, the ulcers are beginning to heal and have yellow-white slightly elevated plaques of proliferative epithelium at the periphery of the mucosal defect.

Lesions are found in the reticulorumen and omasum, but usually not in the esophageal groove. The ruminal content in chronically affected animals with prolonged anorexia is usually scant and dry. In most acute cases, the ruminal content is unusually liquid and putrid. The lesions on the wall of the rumen resemble those present elsewhere in the upper alimentary tract and. The omasal lesions are most numerous along the edges of the leaves, sometimes causing a scalloped margin or perforation. The morphogenesis of the lesions in the squamous mucosa of the upper alimentary tract begins with necrosis of the epithelium. In the early stages there is little or no inflammation of the lamina propria, but leukocytes infiltrate the necrotic epithelium. These necrotic foci enlarge progressively.

Changes are regularly present in the abomasum. The sides of the rugae bear ulcers that may be punctate to 1 cm or more in diameter. The histological changes in the glandular epithelium of the abomasum are characterized by epithelial necrosis, mainly in the depths of the glands, and accompanying interstitial inflammation.

The mucosa of the small intestine often appears normal over much of its length. However, in some cases the mucosa of the small intestine may have patchy or diffuse congestion. In acute cases, it is usual to find coagulated blood and fibrin overlying and outlining Peyer's patches, the covering of which is eroded. This, when present, is a very distinctive lesion that is only paralleled in rinderpest. Severely affected Peyer's patches are often obvious through the serosa as red-black oval areas up to 10 to 12 cm long on the antimesenteric border of the gut. Mesenteric lymph nodes may or may not be enlarged.

Lesions in the large bowel are highly variable. The mucosa may be congested, often in a "tiger-stripe" pattern following the colonic folds, a reflection of tenesmus. In acute cases there may be fibrinohemorrhagic typhlocolitis. In more chronic cases, fib-
ri nous or fibrinonecrotic lesions and focal or extensive ulceration may be present at any level of the large bowel, but particularly in the cecum and rectum.

The characteristic microscopic lesion in the intestinal mucosa is destruction of the epithelial lining of the crypts of Lieberkühn. In the duodenum, only a few crypts are affected, but more crypts are affected more severely in the lower reaches of the small intestine and in the cecum and colon. Affected crypts are dilated and filled with mucus, epithelial debris, and leukocytes. In the cecum and colon, extensive damage to crypts and attendant collapse of the lamina propria are the probable cause of ulceration seen grossly. Congestion of mucosal capillaries, and in acute or ulcerated cases, effusion of fibrin and neutrophils from the mucosal surface may be evident.

The microscopic lesions of Peyer's patches are distinctive in BVD, comparable lesions being caused only by rinderpest. In the acute phase of the disease, severe acute inflammation in the mucosa over Peyer's patches accompanies almost complete destruction of the underlying glands, collapse of the lamina propria, and lysis of the follicular lymphoid tissues. Later in the course of the disease, dilated crypts, lined by cuboidal epithelium and filled with necrotic epithelial cells, mucus, and inflammatory cells appear to herniate into the submucosal space previously occupied by involuted lymphoid follicles.

An important microscopic lesion is hyaline degeneration and fibrinoid necrosis of submucosal and mesenteric arterioles. A mild to moderate mononuclear inflammatory cell reaction is frequently present in the walls of the vessels and in perivascular areas. The vascular lesions may also be present in a variety of other organs, such as the heart, brain, and adrenal cortices. The vascular lesions in acute mucosal disease are less consistently present and are usually milder, and there is involution of lymphoid tissue in BVD.

Coronitis may extend completely around the coronary band, with some separation of the skin-horn junction causing disturbance and overgrowth of the horn.

Some animals with chronic disease develop mycotic infections secondary to lesions in the forestomachs, abomasum, and Peyer's patches. The lesions are areas of hemorrhagic necrosis involving the mucosa, submucosa, and sometimes deeper layers of the wall. Fungal hyphae are found invading the stroma and causing thrombosis in venules.

In addition to the early embryonic death and abortions that can be ascribed to BVDV, infections of seronegative immunocompetent dams, usually between 90 and 120 days of gestation, may result in a wide spectrum of teratogenic lesions, including microencephaly, hypomyellogenesis, cerebellar hypoplasia and dysgenesis, hydranencephaly, hydrocephalus, and defective myelination of the spinal cord. Ocular lesions, such as microphthalmia, cataracts, retinal degeneration, atrophy and dysplasia, and optic neuritis, have all been associated with fetal infections by BVDV.
11. Brucellosis

Etiology and pathogenesis: Bacteria of the genus *Brucella* are small, gram-negative bacilli or coccobacilli that are strictly parasitic, prefer the intracellular habitat, and produce in animals chronic infections with persistent or recurrent bacteremias typically manifested by abortion. Three classic species of *Brucella* were described and defined originally largely on the basis of host of origin - *B. melitensis*, goats, *B. abortus*, cattle, and *B. suis*, swine - but now by biochemical and serological reactions. The differences between the species are slight and quantitative rather than qualitative, and the number of biotypes within each species is large. This has led to the recommendation that all should be considered a single species, *B. melitensis*, and that present species and variants with fixed properties be regarded as biotypes of the one species. Cross-infections do occur and almost all domestic species are susceptible. Infections by any of these organisms of the genus *Brucella* are, initially at least, systemic, and relapsing bacteremic phases are well-established events in the persisting infections. Localization and persistence of infection may occur in many organs, perhaps to a greater extent with *B. suis* than with the other species. Some organs, however, notably the genitalia and placenta, are noted for the regularity with which they develop intense persistent foci of infection.

The usual source of infection for is an aborted fetus or placenta, or contaminated uterine discharges, and the usual route of infection is alimentary. Infection can also occur per vaginam, via the conjunctiva, and through the broken or unbroken skin. The relative importance of these latter routes is not known. Coital infection can occur but is uncommon, especially if genital infection in the male is longstanding, possibly because fewer organisms are excreted in semen from chronic lesions than from early lesions in the genitalia. Infection can be transmitted at artificial insemination if semen from infected animals is used. Irrespective of the route of infection, the development and establishment of infection are probably comparable and will depend on the age and reproductive status of the animal, its inherent resistance, and on the dose and virulence of the infecting strain of the organism. Once infection is established in sexually mature animals, females especially, it tends to persist indefinitely.

The organisms extend quickly to the lymph nodes regional to the point of entry, and there they provoke acute lymphadenitis. The inflamed nodes are enlarged, often much so, hyperplastic with no clear corticomedullary distinction, and frequently bear small or large medullary hemorrhages. The sinuses are infiltrated with neutrophils and eosinophils; germinal centers and proliferative activity become obvious; and there is slow but remarkable accumulation of plasma cells in the medullary sinuses. The changes in the regional nodes take some weeks to develop fully, and they persist for a prolonged period. There is no fibrosis or necrosis in the nodes. The infection may be overcome in the regional nodes, but once established, it is expected to spread during the phase of acute regional lymphadenitis. Spread is chiefly hematogenous and bacteremia may persist for several months, the duration of persistence apparently depending on the susceptibility or resistance of the host.
As the infection becomes chronic, bacteremia becomes intermittent, ceases in some animals, and recurs irregularly for at least 2 years in 5 to 10% of animals. Also, it tends to recur at parturition. It might be expected that the bacteremic episodes would result in localization and persistence of the organism in many tissues but, curiously, localization is largely restricted to the spleen, mammary glands, mammary lymph nodes, and pregnant uterus of the female, and to the lymphoid tissues, testis, and accessory glands in the male, and such localizations occur in the early bacteremic phases. The organism has little or no predilection for the kidney (although microscopic interstitial nephritis may be present), ovary, bone marrow, or mesenteric lymph nodes, and appears not to be excreted in the urine or feces. Localization does occasionally occur in synovial structures to produce purulent tendovaginitis, arthritis, or bursitis. Infected animals, almost without exception, excrete \textit{B. abortus} in the colostrum.

\textit{B. abortus} has special affinity for the pregnant endometrium and fetal placenta to which it spreads hematogenously during the initial or later bacteremia.

**Gross lesions and histopathology:** Gross lesions in the placenta are characteristic but not pathognomonic. Once the infection localizes in a pregnant uterus, it almost certainly remains there and remains active until the fetus and placenta are delivered and for some time thereafter. The nonpregnant uterus is not particularly susceptible to \textit{B. abortus}, and following abortion or parturition, the organism is cleared from the uterus in a few weeks, or longer in some cases. The external appearance of an infected pregnant uterus is normal. Typically, between the endometrium and chorion in the intercotyledonary area, there is more-or-less abundant exudate that is odorless, dirty yellow, slightly viscid and slimy, and which contains gray-yellow, pulpy floccules of detritus. The fetal membranes and the umbilical cord are saturated with clear edema fluid, and the membranes may be 1.0 cm or more thick. The placental lesions are not uniform; some cotyledons may appear more-or-less normal and others will be extensively necrotic. Affected cotyledons or portions of them are necrotic, soft, yellow-gray, and may be covered with the sticky, odorless, brown exudate that is usually referred to as resembling soft caramel candy.

Histologically, edematous placental stroma contains increased numbers of leukocytes, largely mononuclear but with some neutrophils. The chorionic epithelial cells are stuffed with bacteria. Testicular degeneration and epididymitis are the usual manifestations of disease. Necrotizing orchitis is characteristic of brucellosis. Severe periorchitis may reduce blood supply to the testis so that it dies and becomes a necrotic mass encased within the markedly thickened tunics. Necrotic areas are dry, yellow, often laminated, and slightly mineralized. The histological picture is ultimately one of coagulative necrosis bordered by fibrosis and inflammatory cells. Abscessation and fistulation through the scrotum may accompany necrotizing or other forms of orchitis. In most instances, the orchitis is acute and the lesion is irreversible. It may be unilateral but affected animals are sterile. The scrotum swells due to inflammatory changes in the tunics and to a lesser extent in the epididymis. Swelling of the
testis is limited by the inability of the tunica albuginea to stretch, and any swelling constricts venous and then arterial flow causing infarction. Scattered yellow foci of necrosis coalesce to produce total testicular necrosis. Sometimes the necrotic parenchyma liquefies and the organ then is a pus-filled cavity surrounded by a thick connective-tissue capsule. Microscopically, the inflammatory involvement of the tunics is similar to any serous membrane with organization resulting in adhesions between the parietal and visceral layers. Within the testes, the infection appears to progress along the lumen of the seminiferous tubules. The seminal epithelium becomes necrotic and desquamates. Large numbers of the organisms are visible in the lumen, especially when stained by the modified Ziehl-Neelsen method. There is often focal necrotizing epididymitis complicated by the development of sperm granulomas. The nongenital lesions consist initially of nonspecific enlargement of the retropharyngeal and mandibular lymph nodes. Later the lymph nodes throughout the body may be enlarged due to diffuse hyperplasia of lymphocytes and macrophages.

12. Canine distemper

**Etiology and pathogenesis:** Canine distemper is now uncommon in many vaccinat-ed dog populations but remains as a cause of periodic outbreaks, even in regions where vaccination is practiced, when naive groups of dogs are exposed to the virus. Canine distemper continues to be a frequent and serious disease in many parts of the world. Canine distemper virus (CDV) is in the genus *Morbillivirus*, family Paramyxoviridae. CDV infects a wide range of terrestrial carnivores, including Canidae (wild and dometic dogs), Mustelidae (ferrets, mink), and Procyonidae (raccoons). Ferrets are particularly susceptible. Some species of seals are vulnerable to CDV infection, but distinct phocid morbilliviruses are also important causes of distemper-like disease. Neurologic disease is reported in javelinas, or collared peccaries. Large felids develop a fatal neurologic disease caused by a variant of CDV.

Clinical disease is most common at 12 to 16 weeks of age, as puppies with waning passive immunity are exposed to subclinically infected dogs. The infection is systemic, and clinical signs are often referable to the respiratory, gastrointestinal, and nervous systems. Ocular disease, pustular and/or hyperkeratotic cutaneous lesions, dental defects, and abortion are other manifestations. In some cases, clinical signs are primarily due to secondary infections that are a consequence of virus-induced immunosuppression, probably an effect of viral infection of lymphocytes and macrophages. Secondary diseases include *Bordetella*, adenovirus, and *Pneumocystis* infections of the lung; toxoplasmosis, Tyzzer's disease, sarcocystosis and encephalitozoonosis; and enteric infections with *Cryptosporidium* or attaching-and-effacing *Escherichia coli*. The systemic form of the disease often begins as fever and conjunctivitis, with rapid progression to coughing, depression, anorexia, vomiting, and diarrhea. Affected dogs may die at this stage, fully recover, or develop neurologic disease 1 to 4 weeks later.
Virus is shed in secretions of the respiratory tract, and to a lesser extent in other secretions. Infection is usually acquired by inhaling aerosols or by close contact with infected dogs. The virus infects macrophages of the upper respiratory tract or lungs, which convey it to local lymph nodes and tonsils during the first 24 hours. The virus replicates further in local lymphoid tissues, and by 2 to 5 days after exposure is present in lymphoid tissues throughout the body, including bone marrow, thymus, spleen, and intestinal lymphoid tissue. Further development of the disease is highly dependent on the immune status of the host, the titer of antibodies to viral glycoproteins, the age of the host, and the strain of virus. Dogs with adequate humoral and cellular immunity are able to neutralize the virus and clear the infection by 14 days after infection, and may not shed virus from mucosal surfaces.

**Gross lesions and histopathology:** The histologic lesions of canine distemper are fairly specific when the disease is well developed, particularly if inclusion bodies are apparent. However, lesions in mild cases are nonspecific, particularly in dogs with clinical signs limited to the upper respiratory tract. Inclusion bodies are most numerous at 10 to 14 days after infection, but their numbers diminish rapidly by 5 to 6 weeks. Inclusions are most obvious in brain and epithelial tissues, and less easily identified in lymphoid tissues. Inclusion bodies can be found in the central nervous system before changes of encephalomyelitis are present, and they often persist in the neural tissue when they have disappeared from other sites. The inclusion bodies are eosinophilic and often intranuclear in nervous tissue but usually intracytoplasmic in other tissues.

Lymphopenia and lesions in lymphoid organs are regularly present. Lymphoid lesions may be inapparent on gross examination, or there may be either atrophy or edematous swelling. Thymic atrophy is particularly common. There is depletion of lymphocytes in the cortical zone of the lymph nodes within 6 days of infection. By day 9, the lymph nodes and spleen contain lymphocytic necrosis and depletion, and infiltration of neutrophils. Syncytial cells may form in the nodes and these often contain inclusion bodies. Approximately 2 weeks after exposure, hyperplasia of histiocytic cells develops, but repopulation of the node by lymphocytes may be delayed for weeks or months. Thymic atrophy is due both to loss of cortical thymocytes as well as to great reduction in the medulla.

Respiratory tract lesions are common. Serous, catarrhal, or mucopurulent exudate covers the congested nasopharynx. The lungs are edematous, and secondary bronchopneumonia is often present, particularly in subacute or chronic cases. The specific lesion of canine distemper is bronchointerstitial pneumonia, which usually appears as patchy, generalized, red-tan, rubbery lesions beneath the pleura and at the margins of the lung.

Histologically, bronchioles contain scant suppurative exudate, there is patchy necrosis and attenuation of bronchiolar epithelium, and lymphocytes are present around bronchioles. Inclusion bodies are often most obvious in the cytoplasm of bronchial and bronchiolar epithelial cells. Alveoli contain protein rich edema fluid, scant fibrin,
mononuclear cells, and necrotic epithelial cells. Alveolar septa are thickened by mononuclear cells. Proliferation of type II pneumocytes, which occasionally contain cytoplasmic inclusions, may result in a complete cuboidal lining to scattered groups of alveoli. Inclusion bodies are common in type II pneumocytes and alveolar macrophages, and alveolar epithelial syncytial cells are a characteristic feature when present. Chronic lesions in subpleural and peribronchiolar alveoli include macrophage accumulation, type II pneumocyte proliferation, and alveolar septal fibrosis. Inclusion bodies tend to persist in the bronchiolar and alveolar epithelium longer than in other nonneural tissues.

Intracytoplasmic and rarely intranuclear inclusion bodies are regularly found within swollen transitional epithelial cells of the urinary bladder and renal pelvis in the acute systemic disease. Inclusion bodies, mild degenerative changes, and mononuclear cell infiltrates may be present in a variety of other epithelia, including the gastric surface epithelium, chief and parietal cells of the stomach, cholangiolar epithelium in the liver, pancreatic ductular epithelium, epididymis, and testis.

In the central nervous system, the virus appears first in perivascular astrocytes and macrophages, but infection of the choroid plexus epithelium occurs early, and the cerebrospinal fluid contains large amounts of virus. Lesions in the white matter and gray matter differ histologically; these may occur concurrently or one may predominate. Demyelination in white matter tracts is most severe in the cerebellum, rostral medullary velum, optic tracts, spinal cord, and surrounding the fourth ventricle, and probably arises from distribution of virus through the cerebrospinal fluid. The lesions are multifocal or patchy in distribution, with vacuolation of the neuropil, loss of myelin (particularly notable with Luxol fast blue stain), and, in the early stages, preservation of axons. As the lesion progresses, gliosis and axonal degeneration may occur and mononuclear cells infiltrate the lesion in low numbers; however, the early lesion is noninflammatory. Animals that survive may be left with sclerotic astrocytic loci and myelin loss. Gray matter lesions, which are less frequent than lesions of white matter, often target the cortex of the cerebellum and cerebrum, brainstem, and spinal cord. In early stages, inclusion bodies are usually present in the nucleus or occasionally in the cytoplasm of neurons; these neurons undergo necrosis and mononuclear cells congregate around the dying neurons. With time, a nonsuppurative inflammatory response develops, and mononuclear cells aggregate around blood vessels and infiltrate the neuropil. Nonsuppurative meningitis is usually mild.

Old-dog encephalitis is a rare variant, possibly caused by infection with replication-defective virus. This syndrome is characterized by chronic progressive neurologic disease, widely distributed perivascular infiltrates of lymphocytes and plasma cells, and intranuclear inclusions in astrocytes and neurons. Viral antigen may be demonstrated by immunohistochemistry, but virus cannot be isolated from the brain. Canine distemper may occasionally result from administration of modified live CDV vaccines. Neurologic disease is the usual manifestation in these cases, and lesions in the gray
matter include neuronal necrosis, intranuclear inclusions, and lymphocytic encephalitis.

Dental lesions follow infection of young animals with CDV. Necrosis and cystic degeneration of ameloblastic epithelium of the developing tooth, associated with syncytiat and cytoplasmic inclusions, give rise to the defective enamel seen in animals that have recovered from infection. The defects vary from focal depressions to large, sharply demarcated areas of enamel hypoplasia.

Ocular lesions include conjunctivitis, keratitis, retinitis, and optic neuritis. Conjunctivitis is very common in the early stages of disease, and occasionally extends to the cornea to cause ulcerative keratitis. Retinal lesions, which are common following systemic infection, include intranuclear inclusions in ganglion cells and glia, degeneration of ganglion cells, photoreceptor loss, retinal edema, and perivascular cuffs of mononuclear cells. These lesions progress to neuronal loss, retinal scarring, and proliferation of retinal pigment epithelium in the chronic stages. Lesions in the optic nerve are inconstant, but papilledema may be observed in acute cases, and gliosis or demyelinating neuritis in chronic ones.

Cutaneous lesions of hyperkeratosis and parakeratosis affect the footpad and nose, and rarely the haired skin. The epidermis may contain syncytial cells, and nuclear and cytoplasmic inclusion bodies. Pustular dermatitis due to secondary pyoderma may be present. Experimentally infected dogs commonly develop bone lesions, with necrosis of osteoclasts and consequent persistence of the primary spongiosa. Pale streaks in the heart caused by multifocal myocardial necrosis and mineralization are described in association with canine distemper.

The histologic findings are characteristic if a spectrum of lesions is present and inclusion bodies are discovered.

13. Canine infectious tracheobronchitis

Etiology and pathogenesis: Infectious tracheobronchitis, or kennel cough, is a common clinical entity that is usually encountered following mixing of dogs at kennels, pet stores, and dog shows. Affected dogs develop persistent, harsh, nonproductive or productive coughing, but are often not febrile or anorexic. Most cases recover spontaneously, although signs can persist for 3 weeks or longer. Bacterial pneumonia is a well-recognized but uncommon complication of kennel cough in dogs.

Tracheobronchitis in dogs may be caused by a variety of infectious agents, and more than one agent can often be isolated from individual cases. There is emerging consensus that Bordetella bronchiseptica should be viewed as the primary agent of kennel cough, but that Canine parainfluenza virus 2 and Canine adenovirus 2, and to a lesser extent Canine distemper virus and Mycoplasma spp., have predisposing roles. However, Bordetella cannot be isolated in some outbreaks of kennel cough, suggesting that primary viral tracheitis may occasionally be of primary clinical significance.
*B. bronchiseptica* is a gram-negative coccobacillus that is commonly carried in the upper respiratory tract, but not the lungs, of healthy dogs and many other domestic animals. It is an opportunist that is associated with infectious tracheobronchitis in dogs, atrophic rhinitis in pigs, and suppurative bronchopneumonia in many species. Fimbriae allow *B. bronchiseptica* to attach to ciliated epithelial cells. Following attachment of bacteria to the mucosal surface, they secrete toxins that are important contributors to bordetellosis. Entry of toxins into leukocytes causes increased cyclic adenosine monophosphate production that impairs phagocytosis and oxidative burst. Some toxins stimulate host cells to produce nitric oxide that in turn induces ciliostasis and apoptosis of ciliated epithelial cells. *B. bronchiseptica* adheres to macrophages and neutrophils. Following adhesion, the bacteria are internalized and survive within macrophages without inciting an oxidative burst, and inducing apoptosis of these cells. In addition, *Bordetella* is able to enter and survive within nonphagocytic cells, presumably affording protection from host defenses and a ready supply of nutrients. Although the duration of clinical illness is usually only 2 to 3 weeks, *Bordetella* infections often persist for 2 to 3 months and infected dogs may remain a source of infection for others in the kennel.

Canine parainfluenza virus 2 (CPIV-2), also known as parainfluenza type 2, is commonly isolated from dogs with kennel cough. Clinical signs develop in infected dogs 3 to 10 days after infection. Virus is shed in nasal secretions for about 8 days after infection. Lesions are those of mild tracheobronchitis and bronchiolitis, with epithelial necrosis, mixed cellular inflammatory infiltrates, and submucosal edema. The virus does not replicate in macrophages and does not induce significant bronchointerstitial pneumonia in immunocompetent dogs. However, some strains may cause clinically detectable tracheobronchitis without concurrent *Bordetella* infection. In addition, CPIV-2 predisposes to bacterial pneumonia by impairing mucociliary clearance, and increases the bronchoconstrictive response to agonists such as histamine.

**Gross lesions and histopathology:** Gross lesions may be absent in dogs with kennel cough, or mucopurulent exudate may be noted in bronchi. Enlargement of tonsils and tracheobronchial lymph nodes is inconsistent.

Histologic lesions are by definition restricted to the trachea and bronchi; involvement of terminal bronchioles and alveoli would prompt a diagnosis of bronchopneumonia. Neutrophils infiltrate the tracheobronchial mucosa within 24 hours of infection with *B. bronchiseptica*, and increase in intensity as the disease worsens. Bacteria may be faintly visible as clumps of amphophilic material amid the cilia at the epithelial surface. Necrosis of ciliated epithelium is uncommon, but may result from underlying viral infection, neutrophil-mediated epithelial injury in areas with extensive purulent exudate, and effects of secreted bacterial toxins. As the disease progresses, there is lymphoid hyperplasia around bronchi and in draining lymph nodes. Infection is restricted to the respiratory tract and associated lymph nodes. Sequelae to tracheobronchitis include bronchiectasis and suppurative bronchopneumonia, which proba-
likely develop when the secreted toxins of *Bordetella* cause impairment of mucociliary clearance and leukocyte function.

**14. Canine parvovirus 2 infection**

**Etiology and pathogenesis:** The Parvoviridae are small nonenveloped DNA viruses. They replicate, and produce inclusion bodies, in the nucleus of infected cells. Members of the genus Parvovirus infect many species of laboratory and domestic animals. Among syndromes associated with parvovirus infection are: disease in cats, dogs, and mink dominated clinically by enteritis.

Though autonomous parvoviruses may infect cells at any phase of the cell cycle, replication is dependent on cellular mechanisms only functional during nucleoprotein synthesis prior to mitosis. Hence, the effects of parvoviral infection are greatest in tissues with a high mitotic rate. These may include a variety of tissues during organogenesis in the fetus and neonate. In older animals, the proliferative elements of the enteric epithelium, hematopoietic and lymphoid tissue are particularly susceptible. At the time of virus assembly, large basophilic or amphophilic nuclear inclusions may be found in infected cells. Parvovirus is demonstrated in these inclusions by electron microscopy.

Oronasal exposure results in uptake of virus by epithelium over tonsils and Peyer's patches. Infection of draining lymphoid tissue is indicated by isolation of virus from mesenteric lymph nodes 1 to 2 days after infection. Release of virus into lymph, and dissemination of infected lymphoblasts from these sites, may result in infection of other central and peripheral lymphoid tissues, including thymus, spleen, lymph nodes, and Peyer's patches, 3 to 4 days after infection. Lymphocytolysis in these tissues releases virus, reinforcing cell-free viremia. Viremia is terminated when neutralizing antibody appears in circulation about 5 to 7 days after infection. Moderate pyrexia occurs at about this time. Infection of the gastrointestinal epithelium is a secondary event, following dissemination of virus by circulating lymphocytes and cell-free viremia. Peyer's patches are consistently infected at all levels of the intestine, and epithelium in crypts of Lieberkühn over or adjacent to Peyer's patches usually becomes infected a day or so later. Infection of gastrointestinal epithelium at other sites in the gut is less consistent, but is usually more severe in the lower small intestine. Maximal infection of cryptal epithelium occurs during the period about 5 to 9 days after infection.

The occurrence and severity of enteric signs are determined by the degree and extent of damage to epithelium in intestinal crypts. This seems to be a function of two main factors. The first is the availability of virus, which is influenced by the rate of proliferation of lymphocytes, and therefore their susceptibility to virus replication and lysis. The second factor influencing the degree of epithelial damage is the rate of proliferation in the progenitor compartment in crypts of Lieberkühn. If many cells are entering mitosis, large numbers will support virus replication and subsequently lyse. De-
struction of cells in the crypts of Lieberkühn, if severe enough, ultimately results in focal or widespread villus atrophy and perhaps mucosal erosion or ulceration. Regeneration of cryptal epithelium and partial or complete restoration of mucosal architecture will occur, if undamaged stem cells persist in most affected crypts, and the animal survives the acute phase of clinical illness.

Diarrhea in parvoviral infections is mainly the result of reduced functional absorptive surface in the small intestine. Effusion of tissue fluids and blood from a mucosa at least focally denuded of epithelium probably also contributes to diarrhea. Dehydration and electrolyte depletion are the result of reduced fluid intake, enteric malabsorption, effusion of tissue fluid, and, in some animals, vomition. Hypoproteinemia is common, and anemia may occur due to enteric blood loss; both are exacerbated by rehydration. Anemia reflects hemorrhage into the gut.

Proliferating cells in the bone marrow are also infected during viremia. Lysis of many infected cells is reflected in hypocellularity of the marrow caused by depletion of myeloid and erythroid elements. The number of neutrophils in circulation drops quickly in severely affected animals. This is due to failure of recruitment from the damaged marrow, and peripheral consumption, especially in the intestine. In surviving animals, regeneration of depleted myeloid elements from remaining stem cells restores the circulating population of granulocytes within a few days. Neutrophilia with left shift may occur during recovery.

Lymphopenia, relative or absolute, results from viral lymphocytolysis in all infected lymphoid tissue. Relative lymphopenia is more consistently observed in dogs than neutropenia. In dogs surviving the lymphopenic phase, circulating lymphocytes return to normal numbers within 2 to 5 days, as regenerative hyperplasia occurs in lymphoid tissue throughout the body. Lymphocyte numbers increase rapidly, sometimes producing lymphocytosis in recovering dogs.

Canine parvovirus 2 (CPV-2) resulted from mutation of a closely related virus from wild carnivores, such as foxes. It appeared spontaneously and virtually simultaneously in populations of dogs on several continents in 1978, and rapidly spread worldwide. In addition to domestic dogs, several species of wild canids, including coyotes, gray wolves, and raccoon dogs, are susceptible to infection. As the prevalence of antibody due to natural infection and vaccination increased, the problem subsided to one of an enzootic disease. It now affects those animals with reduced levels of passively acquired maternal immunity, or scattered naive individuals. During the epizootic period, nonsuppurative viral myocarditis due to CPV-2 was prevalent in the offspring of naive bitches unable to protect pups with maternal antibody during the first 15 days of life, when replicating myocardial cells are susceptible to parvoviral damage. Myocardial disease in pups due to CPV-2 is now fairly uncommon, as most bitches have antibody.

Dogs with typical disease due to CPV-2 become anorectic and lethargic and may vomit and develop diarrhea, perhaps in association with transient moderate pyrexia. After
a period of 2 to 3 days, dogs either succumb to the effects of dehydration, hypoproteinemia, and anemia, or begin to recover.

**Gross lesions and histopathology:** Gross findings at autopsy of fatal cases are those of dehydration, accompanied by enteric lesions characteristic of the disease. There is often segmental or widespread subserosal intestinal hemorrhage, which may extend into the muscularis and submucosa. The serosa frequently appears granular due to superficial fibrinous effusion. Peyer's patches may be evident from the serosal and mucosal aspects as deep red oval areas several centimeters long. The intestinal contents may be mucoid or fluid; sometimes they look like tomato soup, due to hemorrhage. The mucosa is usually deeply congested and glistening, or covered by patchy fibrinous exudate. Severe mucosal lesions may be widespread or segmental, and their distribution is irregular; thus tissues from several levels of the small intestine should be selected for microscopic examination. Gross changes in the colon are similar, but less common. The stomach may have a congested mucosa and contain scant bloody or bile-stained fluid. Mesenteric lymph nodes may be enlarged, congested, and wet, or be reduced in size. Thymic atrophy is consistently present in young animals, and the organ may be so reduced in size as to be difficult to find. The lungs often appear congested, and have a rubbery texture.

The microscopic lesions in stomach, small intestine, colon, lymphoid tissue, and bone marrow due to CPV-2 infection do not differ significantly from those described in cats with panleukopenia (see *Feline panleukopenia*). Gastric lesions are perhaps more frequently encountered in dogs with parvoviral infection. Small intestinal lesions are invariably severe in fatal cases. The colon is involved in a minority of animals. Pulmonary lesions such as alveolar septal thickening by mononuclear cells, congestion, and effusion of edema fluid and fibrin into the lumina of alveoli may be related to terminal gram-negative sepsis and endotoxemia, which is common in fatal cases. Periacinar atrophy and congestion in the liver are attributable to anemia, hypovolemia, and shock, and prominent Kupffer cells probably reflect endotoxemia.

15. Classical swine fever (hog cholera)

**Etiology and pathogenesis:** Classical swine fever (CSF) is a highly contagious viral disease of swine; it may occur as acute, subacute, chronic, or inapparent syndromes. Acute CSF is a disease of high morbidity and mortality caused by a virulent strain of virus; low virulence virus may cause inapparent disease. Classical swine fever is caused by a *Pestivirus*, a member of the family Flaviviridae. The enveloped nature of the virus makes it sensitive to lipid solvents and to desiccation. However, the virus may persist for prolonged periods in uncooked pork products. Antigenic variation exists among strains of CSF virus, and field strains vary widely in virulence. Strains of virus are usually classified as being of high, moderate, or low virulence, or as being avirulent. Highly virulent strains produce the features of the classical acute disease in pigs of all ages; the morbidity may reach 100%, with a mortality rate of up to 90%.
Strains of moderate virulence induce subacute or chronic disease, and pigs may subsequently die or recover. In pigs infected postnatally, strains of low virulence produce few or no signs of disease and induce immunity, but may cause fetal abnormalities.

Transmission of the disease is usually by direct contact of infected pigs or wild boar with susceptible pigs; CSF is endemic in wild boar in parts of Europe. The virus is present in urine, feces, and lacrimal and oronasal secretions of infected pigs, as well as semen of infected boars. With the less virulent strains, the virus may be excreted in the urine for periods up to 3 months. The major mechanism of spread of virus of low virulence occurs from continuous virus shedding by chronic or persistently infected asymptomatic pigs. Minor modes of transmission include fomites and arthropods.

Classical swine fever is characteristically an acute disease of high morbidity and mortality, most animals surviving only to 14 days after showing the first signs of illness, namely anorexia, depression, fever, and leukopenia. Persistent infection (that is, survival of greater than 30 days) is caused by CSF virus strains of moderate or low virulence and may arbitrarily be divided into chronic and late-onset types. In chronic CSF, typical acute disease is followed by clinical improvement, the result of specific antibody formation, but later by immune exhaustion and chronic disease in which the pig is viremic and more susceptible to secondary bacterial infection. Late-onset CSF occurs in pigs that are persistently viremic and immunotolerant to virus as a result of fetal infection by CSF virus of low virulence. The latest date for the development of a persistent infection appears to be about day 70 of gestation; by day 85 viral antigen may be detected in a few fetuses, but virus cannot be isolated. Signs that develop in viremic, but previously asymptomatic, pigs include anorexia, depression, leukopenia, conjunctivitis, dermatitis, diarrhea, runting, and posterior paresis. The late-onset form of CSF is the porcine equivalent of mucosal disease in cattle, in which BVDV infection of fetal calves results in persistently viremic, immunotolerant animals.

The pathogenesis of CSF is not fully understood, but involves the effects of the virus on the immune system (lymphoreticular cells and macrophages), the vascular endothelium, and epithelial cells. CSF virus replicates in macrophages in lymph nodes and lymphoid tissues and can cause depletion of lymphocytes indirectly through expression of apoptotic cytokines, such as tumor necrosis factor. Similarly, intestinal epithelial necrosis appears be the product of release of chemical mediators from activated macrophages, rather than direct viral infection. Endothelial changes are primarily degenerative but some proliferative changes occur. Damage to endothelial and other cells leads to thrombocytopenia, consumption coagulopathy, and in turn disseminated intravascular coagulation and hemorrhage. The classical or acute form of the disease, which affects pigs of all ages, commences by entry of the virus through the mucous membranes with initial replication in the tonsillar epithelium. This is followed by spread to the cervical lymph nodes with viremia within 16 hours of infection. The virus has a propensity to replicate in cells of the immune system, particularly in lymph nodes, bone marrow, and other lymphoid aggregates such as the spleen.
and Peyer's patches. After 3 to 4 days, the virus invades endothelial cells and epithelial cells including those of the pharyngeal mucosa, gastrointestinal tract, gallbladder, pancreas, salivary gland, uterus, adrenal, and thyroid. The clinical signs are not specific and do not provide good correlation with pathologic changes, although in the acute disease they may be sufficient for presumptive diagnosis where the disease is endemic.

**Gross lesions and histopathology:** Superficially, the eyelids are frequently adherent and sticky, and the carcass is dehydrated and soiled by terminal diarrhea. The irregular erythema that can be seen in the animal when alive is less obvious, but hemorrhages, particularly in unpigmented areas of skin, may be seen. If present, they are most numerous on the abdomen and the inner aspects of the thighs. Diagnostic lesions may be sparse in CSF, especially if peracute, and it may be impossible to establish the diagnosis on the basis of the gross lesions in a single animal.

The lesions most commonly present are hemorrhages in the periphery of the lymph nodes and renal petechiae. The renal hemorrhages may be very few, and in all cases the kidney capsule should be removed and the surface examined in good light. Hemorrhages in the lymph nodes are more obvious; characteristically, only the periphery of the node is involved. In acute cases, this produces a distinctive bright red halo; if the case is more chronic, the halo may be the dirty brown of partially degraded hemoglobin. Less frequently, the hemorrhage in the node is diffuse. The nodal changes are generalized, but nodes most apt to show severe changes are the mandibular, colonic, hepatic, and iliac.

Splenic infarction is almost pathognomonic of acute CSF. Unfortunately, the tendency for infarcts to develop in the disease varies with the strain of the virus, with reports of incidence of 1-87%. When present, infarcts occur as single or multiple, dark red, pyramidal blebs 0.5-2 cm in diameter, usually along free edges but occasionally on the flat surface. The spleen in CSF is not enlarged, as it is in septicemias, and is red-brown so that the infarcts contrast quite sharply with the meaty parenchyma. In addition to the hemorrhages of the kidney, petechiae are common in the urinary bladder, the larynx, the gastric mucosa, the lung, and the epicardium, in about that decreasing order of frequency. There is usually a small amount of straw-colored fluid in the pericardial sac. There may be hemorrhagic lobular pneumonia. Irregular, but sharply outlined areas of necrosis develop in the tonsils and posterior fauces.

The stomach of an animal dead of CSF is empty except for a small amount of watery mucus and ingesta. The fundic mucosa is congested, and mild or severe erosions may be present. Specific lesions do not occur in the small intestine, but the mesentery is usually congested. It is in the colon and cecum that the virus combines with the intestinal flora to produce craterous mucosal defects, "button ulcers," which are characteristic of the subacute or chronic stage of the disease. These lesions begin as sharply outlined circular areas of hemorrhage and necrosis. The central area is yellow and dry. As the lesion ages, the rim, which is composed of necrotic epithelium, bacteria, and detritus, is raised above the surrounding mucous membrane and con-
centric rings form as if growth were cyclic. The center of lesions sinks giving a slight diskoid shape. If this necrotic tissue and debris is removed, a deep ulcer is revealed. Growth arrest lines may be seen in the ribs of chronically sick pigs.

Gross lesions are not usually present in the brain, but the brain should be removed because it is there that the histological changes can be best appreciated. Within the brain, all areas may be affected but the lesions are usually most conspicuous in the medulla, pons, mid-brain, and thalamus. The response is largely confined to the vessels and their supporting mesoderm. Many of the venules have eccentric cuffs, which are formed in part by transmural migration of monocytes. Mitotic figures and nuclear chromatin of necrotic cells are frequently present together in the cuff, as proliferation and necrosis are coexistent. Swelling and degeneration of the endothelial cells occur in the walls of the smaller vessels. The lumen is often compromised by these reactions. The vessels of the eyes, choroid plexuses, and the leptomeninges are similarly involved.

Vascular lesions usually are most severe in lymphoid tissue but may occur anywhere. The lesions vary from slight thickening of the capillary wall to fibrinoid necrosis of arterioles. As these changes develop, there is a tendency for extravasations to occur and for microthrombi to form. Microscopic areas of infarction are common in the lymph nodes and skin, but only in the spleen, tonsil, gallbladder, and large intestine are these areas usually large enough to be grossly visible. In general, in acute cases the degenerative changes are most prominent, whereas in chronic ones proliferative changes are more obvious. In the periphery of lymph nodes (the equivalent of the medulla in other species), lesions vary from slight edema and proliferation of the reticuloendothelial elements to extensive hemorrhage. Immune-complex-mediated mesangioproliferative glomerulonephritis occurs, with deposition of immunoglobulins in mesangial, subepithelial, and subendothelial sites, fusion of foot processes, infiltration of the mesangium by macrophages and later neutrophils, and the presence of viral particles in glomerular endothelial cells and podocytes.

16. Contagious pustular dermatitis

**Etiology and pathogenesis:** Contagious pustular dermatitis is a poxviral disease of sheep and goats, with incidental infections occurring in humans, camels, cows, and many wild ruminants, and very rarely dogs. The disease is caused by a Parapoxvirus. Synonym for contagious pustular dermatitis includes contagious ecthyma. The disease is geographically widespread and occurs wherever sheep or goats are raised. The virus can repeatedly infect sheep and goats. The economic significance of contagious pustular dermatitis results chiefly from loss of condition, since affected animals neither suckle nor graze.

Morbidity in a susceptible population may reach 90%, but mortality rarely exceeds 1% unless secondary infection intervenes, or unless the animals are immunosuppressed or stressed in which case mortality can be high. Mortality often results from the
invasion of primary lesions by the larvae of the screwworm fly (*Cochliomyia hominivorax*) or by bacteria such as *Fusobacterium necrophorum*. Cellulitis may complicate pedal lesions, mastitis may complicate mammary lesions, and necrotizing stomatitis and aspiration pneumonia may complicate oral lesions. Contagious pustular dermatitis affects sheep and goats of all breeds. It is predominantly a disease of lambs and kids. Infection is established through cutaneous abrasions, particularly those associated with dry and prickly pasture or forage. Clinically affected lambs may transmit the virus to the udder of the ewe. Chronically infected, reinfected or, possibly, latently infected carrier animals may allow the virus to persist in a flock for several years.

**Gross lesions and histopathology:** Gross lesions usually commence at the commissures of the lips and spread around the lip margins to the muzzle. Primary lesions sometimes occur on the face about the eyes. In severe cases, lesions may develop on the gingiva, dental pad, palate and tongue. The buccal lesions are raised, red or gray foci with a surrounding zone of hyperemia. Lesions on the limbs are less common than on the lips and tend to involve the coronet, interdigital cleft, and bulb of the heels. They may extend, in severe cases, to the knee or hock on the caudal aspect of the leg. Lesions of the mammary gland affect the teats and adjacent skin of the udder. Lesions may develop in other areas of sparsely woolled skin such as the inner thigh, axilla, and the edge of wounds in recently earmarked lambs, or tail-dock sites.

The vesicular stage is transient and pustules are flat rather than umbilicated. The most significant feature of the gross lesion is the layer of thick brown-gray crust that may be elevated 2-4 mm above the skin surface. Depending on the degree of secondary infection, regression is usually complete by 4 weeks.

The microscopic lesions of contagious pustular dermatitis are characterized by vacuolation and swelling of keratinocytes in the stratum spinosum, reticular degeneration, marked epidermal proliferation, intraepidermal microabscesses, and accumulation of scale-crust. The active site of viral replication was found to be the newly proliferative keratinocyte population, growing up under the superficial necrotic layer. Basophilic intracytoplasmic inclusion bodies are reported as early as 31 hr post-infection. By 72 hours postinfection, the keratinocytes show nuclear pyknosis and marked hydropic change, leading to reticular degeneration. The inclusion bodies persist for 3 to 4 days, as long as the hydropic cells are found. By 3 days postinfection, the epithelium is 3 to 4 times normal thickness and rete ridges are markedly elongated. Pseudocarcinomatous hyperplasia is common. Dermal lesions include superficial edema, marked capillary dilation, and an early influx of neutrophils, followed by a marked accumulation of MHC class II dendritic cells, with CD4+ T cells, CD8 + T cells, and B cells. A thick layer of scale-crust is built up, composed of ortho- and parakeratotic hyperkeratosis, proteinaceous fluid, degenerating neutrophils, cellular debris and bacterial colonies. The subsequent microscopic appearance of the lesions depends on the degree of secondary bacterial infection.
17. Cryptococcosis

**Etiology and pathogenesis:** Cryptococcosis is a mycotic disease of worldwide distribution. Cryptococcosis is the most common systemic mycotic disease of cats, and also affects dogs, horses, cattle, humans, and many other species. Disease is sporadic and, as is usually true for the systemic mycoses, the infection is apparently neither contagious nor zoonotic. Most cases have chronic nasal disease, with sneezing and serous or mucopurulent discharge. Other common manifestations include ulcerating cutaneous nodules, neurologic disease, chorioretinitis or panophthalmitis, and pneumonia.

*Cryptococcus neoformans* is a basidiomycete yeast-like fungus. *C. neoformans* is a saprophyte found in soil, pigeon or other avian faeces, and decaying organic matter. Most infected animals do not develop clinical disease. It is commonly assumed that, as in humans, clinical disease only develops if immune responses are impaired by malnutrition, corticosteroid therapy, or immunosuppressive lentiviral infection. However, predisposing causes of immunosuppression are not often discovered in naturally occurring cases in cats. Infection is mainly acquired by inhalation of basidiospores (yeast cells) from contaminated dust. Most cases develop nasal disease, and infection may progress by local spread to the brain, aspiration to the lung, or hematogenous spread to brain, eyes, lymph nodes, skin, and other organs. Occasional cases of cutaneous cryptococcosis are probably the result of local inoculation, and cryptococcal mastitis in cows is an ascending rather than hematogenous infection.

The major virulence factors of *Cryptococcus* are the capsule and the production of melanin. The thick capsule impairs phagocytosis, activates complement, and may suppress T-cell responses. The role of the capsule in concealing the yeast from the immune response is highlighted by uncommon strains of *Cryptococcus* that lack a capsule; these are readily phagocytosed, incite a strong granulomatous response, and are generally minimally pathogenic. The ability to synthesize melanin is associated with virulence, and attributed in part to the enzyme phenoloxidase. Melanin and/or phenoloxidase may scavenge oxygen radicals produced by activated macrophages, and modulate the host immunoinflammatory response.

**Gross lesions and histopathology:** The lesions take the form of gelatinous masses, granulomas, or ulcerating nodules. Facial swelling is a common feature of cryptococcal rhinitis of cats. Infection may spread locally from the nasal cavity to involve the skin, oral mucosa, eyes, or brain, and occasionally there is wider dissemination to local lymph nodes, lung, and other viscera. Skin lesions are often nodular and ulcerative. Visceral lesions consist of multifocal discrete white gelatinous lesions. Gross lesions in the brain are often subtle, but may include gelatinous material in meninges.

The prominent histologic lesion is a mass of yeast, and the abundant nonstaining capsular material lends a "soap bubble" appearance to the lesion. In contrast to other mycotic infections, the granulomatous reaction is often quite minimal, presumably
because the capsule masks the yeast from recognition by phagocytes. *C. neoformans* yeast bodies are 4 to 8 μm diameter, plus a capsule which varies from 1 to 30 μm thick. Occasional yeast have single buds that are attached by a thin stalk.

The diagnosis is usually based on identifying the yeast in histologic sections or cytologic smears. The thick capsule is characteristic - *C. neoformans* is the only pathogenic fungus with a capsule and it can be easily identified with mucicarmine. The yeast bodies stain with periodic acid-Schiff (PAS) or methenamine silver, and melanin production may be demonstrated with Masson-Fontana stain.

18. Dermatophytosis

**Etiology and pathogenesis:** Dermatophytosis ("ringworm") is a superficial fungal infection generally confined to the keratin layers of the skin, hair, and nails. In rare instances, deeper tissues are involved. The infection is caused by a group of fungi that are capable of using keratin as a source of nutrients and are among the few fungi that cause communicable disease. Infection can vary from mild to severe as a consequence of the host's reactions to metabolic products of the fungus, virulence of the particular species or strain, location of the infection, and local environmental factors. In general, the infection has no effect on growth rate or other measures of productivity, but economic losses may result from hide damage or inability to show infected animals.

The infection is caused by fungi of the genera *Microsporum*, *Trichophyton*, and *Epidemophyton*, which are cosmopolitan in distribution. Incidence and prevalence of dermatophytosis vary with individual host factors, health status, climate, season, natural reservoirs, and local environment. A variety of local and systemic factors may predispose an individual to infection. Areas of chronically warm, moist skin are more likely to become clinically infected. Long-term corticosteroid administration, cytotoxic drugs, diabetes mellitus, hematologic malignancies, and other causes of natural or iatrogenic immunosuppression are associated with susceptibility to dermatophytosis. Incidence of infection is increased with hot, humid weather and when populations of stable flies and mosquitoes are large. In confined animals, infection is common in fall and winter when animals are crowded together in wet, poorly ventilated, unsanitary conditions with decreased exposure to sunlight. Young animals appear to be more susceptible to infection than adults. Reasons for this apparent predisposition include immaturity of host immunity, lack of previous exposure, and age-related differences in biochemical properties of the skin.

Transmission of dermatophytosis occurs by direct contact with infected animals or indirectly by exposure to infective hair and scales in the environment (contaminated grooming equipment, bedding, saddles, cages, etc.). Hair fragments containing infectious arthrospores are the most effective means of transmission. They can remain infectious for more than 18 months if protected from the deleterious effects of ul-
traviolet light. This material is the major source of persistent environmental contamination.

Normal skin is relatively inhospitable to fungal growth because of low moisture conditions, antifungal substances in the surface film, and normal resident flora. Sebum contains fatty acids which are fungistatic and play an important role in resistance to infection. The process by which the stratum corneum is continually renewed may also present a form of defense against organisms because the process results in continuous shedding of the stratum corneum and thus removes infecting organisms with the sloughed keratin. Disruption of the stratum corneum, either by microabrasions or maceration, appears to be important in facilitating invasion by the fungus. Fungal cells adhere to keratinocytes and migrate to the follicular orifice. Dermatophytes produce keratinolytic enzymes, keratinases, which hydrolyze keratin and enable them to penetrate and invade the hair shaft. They grow downward within the hair shaft toward the hair bulb until they reach the keratogenous zone where they stop since they cannot grow in viable tissue. Hair shafts are weakened as a result of penetration by the fungi and they become brittle and easily broken. Dermatophytosis in healthy individuals is usually self-limiting, with lesions resolving in several weeks to two or three months.

**Gross lesions and histopathology:** The macroscopic signs of dermatophytosis are highly variable and depend on the host-fungus interaction. Expanding circular patches of scaling and alopecia or stubbled hairs are considered the classical lesion of dermatophytosis. Follicular papules and pustules, more extensive inflammation caused by furunculosis, and crusting are prominent in many cases. Lesions are typically nonpruritic, but occasionally pruritus is intense.

Infection of nails is called onychomycosis and is characterized by misshapen, crumbly or easily broken, and split nails that may be sloughed. In the skin, there are erythematous alopecic nodules that may ulcerate. They are usually solitary and most common on the face and forelimbs of animals that dig in the dirt. These lesions result from severe furunculosis producing locally extensive inflammation that may be confused for a tumor.

The microscopic lesions of dermatophytosis are as variable as the clinical lesions. Histopathology is not considered as sensitive as culture for diagnosis; but it can be used to confirm infection when the significance of a cultured organism is in question. Biopsies should be taken within the outer border of expanding alopecia as this is the most active site of infection and organisms are most likely to be present. In some cases, fungal organisms are evident in HE-stained sections, but in many instances, fungal stains (PAS, GMS) are necessary to demonstrate infection. Dermatophytes occur as septate hyphae that break up into chains of round to oval arthrospores in the surface and follicular keratin. Hyphae are also usually present in the hair shafts and arthrospores are formed on the outside of the hairs or within the hairs.
Ortho- and parakeratotic hyperkeratosis is a typical feature, and acanthosis is variable, ranging from mild to marked. Inflammation may be very mild and consist of low numbers of perivascular and perifollicular lymphocytes and macrophages. This is the case when infection is caused by a species of dermatophyte that is well adapted to its host.

Neutrophilic luminal folliculitis is a common lesion in dermatophytosis and may result in follicular rupture and development of discrete granulomas surrounding fragments of hair at the base of the follicles. Eosinophils may be numerous in these trichogranulomas. They consist of diffuse pyogranulomatous inflammation in the deep dermis produced by extensive furunculosis. This form of inflammation is most commonly caused by poorly adapted organisms.

19. Edema disease in pigs

**Etiology and pathogenesis:** Edema disease is a distinct syndrome in pigs, characterized by sudden death, or the development of nervous signs, associated with enteric colonization by verotoxin-producing *Escherichia coli* (VTEC), especially serotypes O138, O139, and O141. The disease occurs most commonly in pigs within a few weeks after weaning, or after other change in feeding or management. It often occurs in association with outbreaks of postweaning *E. coli* enteritis. Rare reports exist of edema disease in suckling and mature animals. The disease may be sporadic or occur as an outbreak, usually affecting the best animals in a group, and mortality often approaches 100% of affected animals.

Bacterial colonization of the gut is mediated by F18ab fimbriae. Susceptibility of pigs is genetic and related to the presence of receptors for the fimbriae. A Shiga toxin (Stx2e) producing vascular injury and edema has been incriminated in the pathogenesis of edema disease, and vaccination with Stx2e toxoid almost entirely prevents edema disease. Some strains of *E. coli* that cause edema disease also produce secretory enterotoxin. Diarrhea is not a usual concomitant of edema disease in individual animals. Significant gross or microscopic lesions in the intestinal mucosa do not occur in edema disease, which appears to be a classical enterotoxemia, the active principle being absorbed from the gut and acting at a distant site. However, the means by which the toxin enters the circulation is unknown.

The target of Stx2e toxin, is vascular endothelium, particularly of small arteries and arterioles. Preferentially affected organs include spinal cord, cerebellum, eyelid, and colon. Stx2e causes angiopathy, which, in its early stages is recognized by swelling of endothelial cells and mild intramural and perivascular hemorrhage. Pyknosis and karyorrhexis of smooth-muscle nuclei, often accompanied by fibrinoid degeneration or hyaline change in the tunica media, may be seen in subacute spontaneous cases. Proliferative mesenchymal elements are found in the tunica media and tunica adventitia in more advanced cases. However, inflammation is not at any stage a prominent component of the angiopathy, nor of the associated edema in most sites, and throm-
basis of vessels is rarely encountered. Edema is probably due to vessel damage during the early stages of the angiopathy.

The lesions are distinct from those expected with endotoxemia. Swine with edema disease may die without premonitory signs. Others may have anorexia, or, more characteristically, show nervous signs, usually of less than a day's duration. An unsteady staggering gait, knuckling, ataxia, prostration and tremors, convulsions, and paddling occur. A hoarse squeal, the hoarseness attributed to laryngeal edema and dyspnea, may also be noted clinically.

**Gross lesions and histopathology:** At necropsy gross lesions in acute deaths may be subtle or absent. Typically, edema is variably present in one or more sites. However, it may be mild and must be carefully sought, especially by "slipping" the suspected area over subjacent tissue. Subcutaneous edema may be present in the frontal area and over the snout, in the eyelids, and in the submandibular, ventral abdominal, and inguinal areas. Internally, there may be some hydropericardium, and serous pleural and peritoneal effusion, perhaps accompanied by mild or moderate pulmonary edema. More commonly, the serous surfaces merely appear glistening and wet. Edema of the mesocolon, of the submucosa of the cardiac glandular area of the stomach over the greater curvature, and of mesenteric lymph nodes is most consistently found. The gastric submucosal edema should be sought by carefully cutting through the muscularis to the submucosa. The edema fluid is clear, and slightly gelatinous. It is rarely blood-tinged, and overt hemorrhage is usually not present in uncomplicated edema disease. The stomach is often full of feed, but the small intestine is relatively empty and the mucosa is grossly normal. The colon may contain somewhat inspissated feces. In swine dying after a more prolonged clinical course, gross edema is often not present, though enlargement of mesenteric lymph nodes is present in a large proportion of cases. A few pigs may show foci of yellow malacia, usually bilaterally symmetrical, in the brainstem at various levels from basal ganglia to medulla.

Microscopically, edema in the sites of predilection mentioned above is the main lesion in swine dying acutely. It is generally devoid of much protein and contains few erythrocytes and inflammatory cells. A proportion of animals will also have meningeal edema and distended Virchow-Robin spaces in the brain. Vascular lesions may not be well developed in pigs dying suddenly. When present they usually consist of edema, hemorrhage, myocyte necrosis, and hyaline degeneration in the tunica media. Angiopathy is more consistently found in cases of longer standing. Affected vessels may be found in any tissue in the carcass. Brain edema and focal encephalomalacia in the brainstem are associated with the presence of lesions in cerebral vessels; necrosis may be a sequel to edema and ischemia.
20. Encephalitozoonosis

**Etiology and pathogenesis:** Encephalitozoon cuniculi is an obligate intracellular microsporidian parasite that affects a variety of mammalian hosts, most commonly the domestic rabbit. The organism is characterized by the presence of a coiled polar filament in the mature spore stage. Following the extrusion of the sporoplasm from the spore coat, the sporoplasm may then invade a susceptible host cell. Penetration may be due to the mechanical forces exerted by the extruded polar filament or due to an active migratory process by the sporoplasm. Following entry into the cell, multiplication occurs in association with a cytoplasmic vacuole. Sporoblasts develop into mature spores, and finally the cell ruptures, releasing organisms that can then repeat the cycle.

“Infectious motor paralysis” attributed to a protozoan parasite was first reported in laboratory rabbits in 1922. The incidence of seropositive animals in some conventional rabbitries may be relatively high, and in the past, seroconversion has been detected in specific-pathogen-free rabbits. The organism has a wide host range. Susceptible species include the mouse, guinea pig, squirrel monkey, cat, and dog. Encephalitozoonosis appears to be a more severe disease in species such as dogs and monkeys. In the large domestic rabbit, the disease is usually a subclinical infection, and renal lesions are frequently detected as an incidental finding. In surveys in the past, incidence of renal lesions attributed to *E. cuniculi* varied from approximately 5% to over 25%. Occasionally nervous signs, with mortality, occur in young New Zealand White rabbits with heavy infections. Dwarf rabbits appear to be especially susceptible to encephalitozoonosis. Torticollis, other neurological manifestations, ocular lesions, and renal lesions have been observed in infected pet dwarf rabbits.

The usual source of the infection is spores shed in the urine from rabbits actively infected with the disease. Transplacental infection has been reported to occur, although there is disagreement on this issue. Rabbits are readily infected experimentally by the oral or respiratory route, and invasion by inhalation is another possible portal of entry under field conditions. Following ingestion/oral inoculation, the spores appear to pass via infected mononuclear cells into the systemic circulation. Initially, target organs are those of high blood flow, such as lung, liver, and kidney. In rabbits inoculated orally with *E. cuniculi* and examined at 31 days postinoculation (pi), moderate to marked lesions were demonstrated primarily in the lung, liver, and kidney, and occasionally in the myocardium. No lesions were present in the central nervous system at 1 month pi. At 3 months pi, moderate to severe lesions were evident histologically in the kidney, and changes were minimal in the lung, liver, and heart. Lesions were evident in the brain at this stage postexposure. Serum titers may be detectable by 3 to 4 weeks pi and reach high titers by 6 to 9 weeks pi. Spores have been seen in the urine at 1 month pi and may be excreted in large numbers up to 2 months pi. Only small numbers are excreted thereafter. Shedding of spores is essentially terminated by 3 months pi. Spores survive for less than 1 week at 4°C but may remain viable for at least 6 weeks at 22°C.
**Gross lesions and histopathology:** At necropsy, affected animals are usually in good flesh, and frequently lesions seen macroscopically are regarded as an incidental finding. Lesions are usually confined to the kidney and appear as focal, irregular, depressed areas 1–100 mm in diameter. In severely affected kidneys, lesions frequently coalesce with adjacent foci. On the cut surface, indistinct, linear, pale gray-white areas may extend into the underlying cortex.

On histopathology, granulomatous lesions are evident in the interstitium of the lung, kidney, and liver by 1 month postexposure. In the lung, focal to diffuse interstitial pneumonitis, with mononuclear cell infiltration, may occur. Hepatic lesions are characterized by a focal granulomatous inflammatory response, with periportal lymphocytic infiltration. Focal lymphocytic infiltrates may also occur in the myocardium. In the kidney, early lesions consist of a focal to segmental granulomatous interstitial nephritis, with degeneration and sloughing of affected epithelial cells and mononuclear cell infiltration. Lesions may be present at all levels of the renal tubule, usually with minimal involvement of the glomeruli. Using tissue Gram stains, the spores are evident as ovoid, Gram-positive organisms approximately 1.5 x 2.5–5 μm in size. Staining procedures using carbol fuchsin will stain the organisms a distinct purple color. Spores may be present within epithelial cells, in macrophages, in inflammatory foci, or free within collecting tubules. At 1 to 2 months postexposure, organisms are usually readily demonstrated in the kidney. In renal lesions of longer duration, interstitial fibrosis, collapse of the parenchyma, and mononuclear cell infiltration are typical changes. The organism is usually eliminated from the kidney at this stage of the disease.

In the central nervous system, lesions normally do not occur until at least 30 days postexposure. Changes are those of a focal nonsuppurative granulomatous meningitis and encephalomyelitis, with astrogliosis and perivascular lymphocytic infiltration. Using appropriate stains, organisms may be evident as collections of spores within parasitized astroglial cells or as scattered organisms within granulomatous inflammatory foci. Characteristic lesions may also be present in the central nervous system in the absence of identifiable organisms.

In the dwarf rabbit, *E. cuniculi* infection has been associated with phacoclastic uveitis and cataract formation. Other changes seen in infected dwarf rabbits include meningitis, encephalomyelitis and focal radiculoneuritis. On histological examination of the cornea and anterior and posterior chambers of the eye, keratitis, rupture of the lens capsule, and inflammatory cell infiltrates comprised of heterophils, foamy macrophages, and multinucleate giant cells are typical changes. In the iris and ciliary body, lymphocytes and plasma cells are the usual cellular infiltrates. Using immunohistochemistry or tissue Gram stains, typical organisms can be identified, either interspersed around fragmented lens fibers or within macrophages. It is likely that the ocular lesions are due to intrauterine infections with *E. cuniculi*.
The identification of characteristic lesions and the demonstration of the organisms in tissue sections are the standard diagnostic procedures used to confirm the diagnosis. The organisms can be readily differentiated from other protozoal infections, such as toxoplasmosis, by the tissue tropisms and the staining properties of the organisms. *Toxoplasma* organisms are Gram-negative and do not stain with carbol fuchsin stains. Serology tests currently used include the carbon immunoassay, indirect immunofluorescence microscopy, and ELISA assays. An intradermal skin test has also been used to detect infected rabbits. There have been confirmed cases of *E. cuniculi* infection identified in AIDS patients and immunocompromised individuals. Manifestations described varied (keratoconjunctivitis, endophthalmitis and pneumonia).

21. Enteric clostridial infections

**Etiology and pathogenesis:** Most of the important enteric clostridial diseases occur in herbivores and are caused by one of the five toxigenic types of *Clostridium perfringens*. Enteritis in dogs is associated with *C. perfringens* and *C. difficile*, and the latter agent is implicated in fibrinous enteritis, especially in horses, neonatal pigs, and dogs. *C. piliforme* (formerly *Bacillus piliformis*) causes Tyzzer's disease, characterized by enteritis and colitis, usually with multifocal necrotic hepatitis and myocarditis, in many animal species. *C. chauvoei* may affect the tongue and the smooth muscle of the lower alimentary tract, causing blackleg-like myositis while *C. septicum* causes clostridial abomasitis (braxy) in sheep and calves. *C. botulinum* causes toxicoinfectious botulism in horses, and by ingestion of toxin, botulism in cattle.

There are five types of *C. perfringens*, designated A-E, which are differentiated on the basis of their production of the four major antigenic exotoxins, which, along with an enterotoxin, are the most significant virulence attributes of *C. perfringens* in the gut. The major exotoxins are *alpha*, *beta*, *epsilon*, and *iota*. There is not always a clear distinction among the different types of *C. perfringens*. Some strains lose their ability to produce one or more of their toxins when stored or cultured, and this complicates the identification of isolates and the assessment of their significance in disease outbreaks.

The alpha toxin is a lecithinase that acts on cell membranes, producing hemolysis or necrosis of cells. The beta toxin is a poreforming toxin that induces a variety of neurologic effects; it appears to have a paralyzing effect on the intestine. The epsilon toxin is produced during active growth, as an inactive prototoxin that is activated by enzymic digestion. The appropriate enzymes may be produced by the organism; in the intestine, trypsin is an effective activator. The iota toxin is also elaborated as a prototoxin and activated by proteolytic enzymes in the intestine; it increases capillary permeability.

Clostridial diseases of the intestine are often called enterotoxemias. Disease produced by *C. perfringens* type D, whose epsilon exotoxin is elaborated in the intestine but exerts its important effects on distant organs such as brain and kidney, is a true
enterotoxemia. The hemolytic disease attributed to type A is also an enterotoxemia, but in general the other types produce local intestinal lesions.

Most significant in food poisoning by type A strains in humans, it has also been associated with antibiotic treatment-related diarrhea and infantile diarrhea. It is activated by proteolysis and alters plasma membrane permeability of the mammalian cell.

The pathogenesis of enteric infection with *C. perfringens* and *C. difficile* requires a change in the enteric microenvironment favorable to massive expansion of luminal populations of clostridia. Such changes may include a change in feed, abnormally nutrient-rich digesta, antibiotic therapy, altered pancreatic exocrine function or trypsin inhibitors, reduced motility, and primary infections with agents such as Canine parvovirus, or coccidia in piglets and chickens.

These clostridia produce disease in three general ways: (1) local necrotizing effects of toxin on the mucosa, causing hemorrhagic, fibrinous, or necrotic enteritis; (2) secretory effects of locally acting enterotoxin, causing diarrhea and minor mucosal lesions; or (3) systemic absorption of (entero)toxin, with effects at sites distant from the gut.

Alpha toxin produced by *C. perfringens* type A and beta toxin produced by types B and C probably account for the severe mucosal necrosis and hemorrhage evident in these infections. Bacteria alone are not pathogenic; exotoxins are required to induce disease. Beta toxin is trypsin-labile, and circumstances such as low enzyme levels in young animals, very high levels of toxin, or trypsin inhibitors could be important. Sows' colostrum contains a trypsin inhibitor, but it is not known if colostrum in other species possesses this factor.

*C. difficile* produces two exotoxins, A, which is an enterotoxin, and B, which is a cytoxin. Tissue damage is probably due to the effects of both toxins, which glycosylate and inactivate Ras GTPases, disabling signaling pathways in the cell. As well, they glycosylate Rho, which regulates the actin cytoskeleton; it condenses, tight junctions open, cells round up, and undergo apoptosis. They also cause release of proinflammatory mediators, attracting neutrophils, and activate secretion stimulated by the enteric nervous system. Hence, disease is characterized by fluid intestinal content, with patchy areas of colonic epithelial necrosis, through which neutrophils exude into the lumen, producing a so-called "volcano" lesion.

Diagnosis of disease due to the toxin-producing clostridia is dependent on demonstration of toxin or enterotoxin in gut content or feces of affected animals, by the most specific test available. While the presence of large numbers of a particular type of *C. perfringens* is suggestive of involvement with disease, this organism is commonly present in the gut in a variety of circumstances, where it cannot be implicated as an etiologic agent.

**Gross lesions and histopathology:** The intestinal lesion is acute hemorrhagic enteritis with extensive mucosal necrosis and patchy diphtheritic membrane formations,
especially in the ileum. In cases with more severe and deeply penetrating mucosal ulcerations, there may be overlying peritonitis with red fibrin strands on the local mesentery and intestinal adhesions. On the mucosal surface, they are irregular but well defined by a sharp margin and rim of intense hyperemia, and they contain a yellow necrotic deposit; they may coalesce to form extensive areas of necrosis. Usually the intestinal contents are blood-stained and may appear to be composed of pure blood.

Histologically, the wall of the intestine is hemorrhagic, and the areas of necrosis extend deeply into the mucous membrane, in some cases penetrating to the external muscle layers and serosa. There are large numbers of typical bacilli in the necrotic tissue, and variable number of inflammatory cells.

The lesions present in other organs are those of severe toxemia. The liver is usually pale and friable, but may be congested. The spleen is normal or slightly enlarged and pulpy. The kidneys may be enlarged, edematous, pale, and soft from toxic degeneration. The pericardial sac contains abundant clear gelatinous fluid, the myocardium is pale and soft, and hemorrhages beneath the serous membranes of the heart are almost constant. The lungs are often slightly congested and very edematous.

22. Equine herpesviral infections

**Etiology and pathogenesis:** Equid herpesvirus 1 (EHV-1) and Equid herpesvirus 4 (EHV-4) are two antigenically related but distinct viruses in the genus *Varicellovirus*, subfamily Alphaherpesvirinae, family Herpesviridae. Both viruses are widespread in horses, have significant economic impact on the equine industry, and are responsible for several clinical conditions including respiratory disease, pulmonary vasculotropic disease, enteric disease, and abortion. Equine myeloencephalopathy is an important neurological disease characterized clinically by ataxia, paresis, and paralysis, and caused mainly by EHV-1 and incidentally by EHV-4. Almost all recent outbreaks have been associated with EHV-1 infection. Most horses show serologic evidence of exposure to EHV-1 and EHV-4 but are asymptomatic, and vaccination does not necessarily confer protection from neurologic manifestations.

Both viruses contain at least 13 glycoproteins, which are important virulence factors for attachment, entry to the host cell, and cell-to-cell dissemination. The natural spread of EHV-1 is through direct horse to horse contact, by inhalation of nasal aerosols from infected horses, or through direct contact with an infected aborted fetus or placenta. EHV-1 replicates first in upper respiratory tract epithelium and local lymph nodes, and then induces T-cell and monocyte-associated viremia that ends with invasion of endothelial cells of the CNS and pregnant uterus. This leukocyte-associated viremia protects the virus from humoral immunity. The virus is endotheliotropic, epitheliotropic, and neurotropic, but not neurovirulent. The replication of virus in endothelial cells of the CNS leads to initiation of the inflammatory cascade that ends in thrombo-occlusive necrotizing vasculitis. The resultant myeloencephalopathy is due to destruction of CNS tissue secondary to vasculitis. The vasculitis is either due
to direct viral cytotoxic effect or due to an immune-mediated mechanism. A similar mechanism is responsible for EHV-1 induced abortion and pulmonary vasculotropic disease. EHV-1 and EHV-4 have life-long latency in T cells and in neural tissue such as trigeminal ganglia. Latent virus can be reactivated after very high doses of corticosteroids and after stress (such as castration).

In contrast to the extensive studies on EHV-1, the pathogenesis of EHV-4 infection is poorly documented. The disease occurs sporadically, but in several recent outbreaks, most affected horses either died or were euthanized. The disease is common in late winter and spring, which is also the time of greatest prevalence of EHV-1 abortion outbreaks. The incubation period is 6 to 10 days and usually occurs in association with abortion and/or respiratory disease but can occur without preceding signs. All ages are susceptible, but pregnant mares and mares nursing foals are over-represented. Clinical signs start with fever and mild rhinitis. Neurologic signs are variable and depend on the part of the CNS affected by vasculitis, however common clinical signs include variable degrees of symmetrical ataxia and paresis that are more severe in pelvic limbs. Fecal and urinary incontinence are common, and clinical signs may end in hemi- or paraplegia.

It is reported that 95% of the abortions due to EHV-1 occur in the last 3 months of pregnancy, and naturally acquired infection has not been observed to produce abortion before 5 months of gestation. Exactly where the virus is, and in what state, during the protracted incubation period has not been determined.

**Gross lesions and histopathology:** Gross and histologic lesions are sequelae to vasculitis. Gross lesions are not always present, but small (0.2-0.5 cm) random multifocal areas of hemorrhage may be present throughout the meninges, brain, and spinal cord. In severe cases, multifocal necrohemorrhagic or malacic areas (up to 1.5 cm in diameter) can be present, especially in the white matter of spinal cord or the white or gray matter of the brain. The characteristic histologic lesions are nonsuppurative necrotizing vasculitis and thrombosis, with greater prevalence in the meningeal and parenchymal blood vessels of the brain stem and spinal cord. Perivascular edema, hemorrhage, focal areas of malacia, and infarction are present adjacent to the affected blood vessels. Occasionally, axonal swelling and mild nonsuppurative trigeminal ganglionitis are present. Extraneural lesions include uveal vasculitis and optic neuritis, especially in foals, and testicular and epididymal vasculitis in stallions.

The aborted fetuses may show characteristic and diagnostic lesions that are variable in their development and may be modest. Edema of the subcutis and fascia and accumulated amber fluid in the body cavities are common in aborted fetuses. There may be slight general icteric discoloration and meconium staining of the footpads and amnion. The most consistent gross lesion is severe pulmonary edema. The lungs are heavy and rubbery, show the impressions of the ribs, and exhibit a pitting response to pressure. There is also edema of the interlobular septa. Their color may be darker or lighter than normal, and tan-to-white foci of necrosis (2-4 mm in diameter) and petechial hemorrhages may be visible on the surface. Casts of fibrin are occasionally
present in the bronchi and, rarely, in the trachea. Beneath the capsule of the liver there are, in about 50% of aborted fetuses, gray-to-white foci of necrosis varying in size from minute up to 5.0 mm in diameter. Such foci may be few or numerous. The spleen is usually enlarged, with petechial hemorrhages on the capsule and unusual prominence of the follicles on cut surface. Petechial or ecchymotic hemorrhages may occur anywhere, but chiefly in the upper respiratory mucosae. Occasionally, there is hemorrhagic necrosis of the renal cortices.

Histologically, the pulmonary interlobular septa are edematous and infiltrated with mononuclear inflammatory cells. The edema and spotty necrosis and hemorrhage involve the whole organ uniformly; there is fibrinous alveolar exudation and necrosis of bronchial and alveolar epithelial cells. The acidophilic inclusion bodies found in the nuclei of the bronchial and alveolar epithelium are specific. The foci of hepatic necrosis are not so common as the changes in the lungs: they are often minute and may be missed in a section. Acidophilic inclusion bodies also form in the nuclei of hepatic parenchymal cells, but they are not constant and are never numerous. If present, they can usually be found around the areas of focal necrosis. There is edema of the liver, and leukocytic infiltration in the necrotic foci and portal triads is common. Rarely, there is a diffuse hepatitis without focal necrosis. Necrosis of germinal centers occurs in the enlarged splenic follicles and other lymphocytic tissues, including thymus. Intranuclear inclusion bodies may be found in the primitive reticular cells in such foci. There are hemorrhages in the splenic pulp and about the malpighian corpuscles. The placenta is normal. Foals infected with this virus in utero may be born alive at, or near, term. Many of them die in the first few days with severe interstitial pneumonia and secondary bacterial septicemia. Focal hepatic necroses are, as a rule, not present in these animals; however, focal necrosis of crypt epithelium with hemorrhage in the intestine is sometimes observed.

The diagnosis of abortion can be made on observing typical microscopic lesions, including the presence of inclusions. The demonstration of EHV-1 on cell cultures from samples of lung, liver, spleen, or thymus or by the immunoperoxidase technique on placenta is definitive.

23. Equine viral arteritis

**Etiology and pathogenesis:** This disease is caused by Equine arteritis virus (EAV), an RNA virus of the family Arteriviridae, genus *Arterivirus*, which is pathogenic only for horses and is cytopathic in equine kidney culture. Although serologic surveys indicate that infection with EAV is common in North America and Europe, clinical disease is uncommon. Most strains of EAV are avirulent, and mortality is rare in natural outbreaks. Long-lasting immunity follows recovery.

Transmission of virus occurs primarily by respiratory and venereal routes during the acute phase of infection; venereally infected mares can infect nonimmune mares by aerosol transmission. Long-term carrier stallions play an important role in
perpetuation and dissemination of the virus; a carrier state has not been demonstrated in mares or foals. The clinical disease is characterized by: fever; variable anorexia and depression; leukopenia; edema of the ventral body wall and limbs, especially the hindlimbs; skin rash, most commonly on the neck; serous, later mucopurulent, oculonasal discharge with rhinitis and conjunctivitis; and periorbital supraorbital edema. Dyspnea, coughing, ataxia, and diarrhea are less frequent. Pregnant mares often abort during or shortly after the febrile period, probably due to myometritis and decreased progesterone production by a hypoxic placenta. Specific lesions are present occasionally in aborted fetuses, and include necrotizing vasculitis, especially of the placenta, and inflammatory loci in various organs. Newborn foals may succumb to interstitial pneumonia.

The virus is pathogenic to endothelial cells and causes panvasculitis, that is, inflammation of veins, lymphatics, and arteries. Following initial replication of the virus in macrophages, endothelial cells are invaded beginning three days after experimental aerosol infection. As inflammation progresses and neutrophils damage the internal elastic lamina, medial cells are invaded. The most severe edema occurs at days 6 and 7 when phlebitis, lymphangitis, and capillary damage are most pronounced. Arterial necrosis peaks at day 10, when edema has largely disappeared. The vascular lesions will resolve if the horse survives. Antibody appears to play little role in the pathogenesis of the disease, in contrast to the immune-complex component of some other viral vasculitides.

**Gross lesions and histopathology:** The gross lesions of the disease, in addition to the changes observed clinically, consist principally of hemorrhages and edema. Petechial hemorrhages are found on all serous membranes, in the substance of the lungs and the gastric mucosa. Larger hemorrhages may be present in the adrenals. There is excessive fluid which contains much protein and some strands of fibrin in all serous cavities. As much as 10 L may be present in the pleural and peritoneal cavities. The connective tissues and mesenteries of the body cavities are saturated with edema fluid and the wall of the gut may be thickened by edema. Enteritis, hemorrhagic or diphtheritic in character and usually more severe in the large than in the small intestine, is regularly present. The lungs are more-or-less severely edematous.

Characteristic microscopic lesions occur focally or segmentally in the media of small muscular arteries. The muscle cells undergo necrosis and are replaced by hyaline or fibrinoid material. There is edema of the wall and adventitia and infiltration of leukocytes, chiefly lymphocytes, the nuclei of which undergo fragmentation with necrosis. The endothelium and intima may have been repaired so that thrombosis is unusual; thrombosis may however occur in the intestine and lungs. The arterial lesions occur in many organs but are perhaps most consistently present in the gut and adrenals. Infarction is most common in the intestines, particularly in the cecum and colon. Massive necrosis of lymph nodes also occurs. Extensive necrosis of the adrenals may result from direct viral injury and infarction.
24. Erysipelas

**Etiology and pathogenesis:** *Erysipelothrix rhusiopathiae*, the cause of porcine erysipelas, is a gram-positive bacteria with a wide geographic distribution and host range. It causes outbreaks of disease in pigs, lambs, and birds, and sporadic disease in the other domestic species. The organism is widespread in nature and is capable of survival, and perhaps growth, in decaying material of animal origin. It may be present in the soil and survives for 2 to 3 weeks on pasture spread with slurry. It is resistant to many disinfectants and is capable of infecting many species, some of them in epidemic proportions. *Erysipelothrix rhusiopathiae* can persist for many months in the lesions of diseased pigs, and it is often carried in the tonsils, intestine, bone marrow, and gallbladder of healthy swine. Porcine erysipelas occurs in pigs of all ages, but the most susceptible are those from 2 months to 1 year of age, and pregnant sows. The latter may abort or give birth to stillborn young, from which the organism can be cultured. The disease can be produced by ingestion of the organism, contamination of cutaneous wounds, or as a result of bites of infected flies. The manifestations of erysipelas in pigs vary from an acute septicemic form, which is usually fatal, to mild and chronic forms characterized by necrosis of the skin, endocarditis and polyarthritis. In epidemics, the septicemic form predominates, whereas in endemic areas the disease tends to be sporadic, with cases of septicemia, polyarthritis, or endocarditis occurring in varying proportions.

The acute disease is a febrile septicemia, which usually develops within 24 h of exposure to virulent organisms and produces disseminated intravascular coagulation (DIC). Endothelial cells of capillaries and venules throughout the body swell, monocytes adhere to them, and by 2 to 3 days microthrombi are widespread. By 4 days, accumulation of fibrin within and around vessels, bacterial invasion of endothelium and diapedesis of erythrocytes are prominent. Perivascular fibrin incites connective tissue proliferation in sites such as synovial membranes.

**Gross lesions and histopathology:** Grossly, there is purple discoloration of the skin due to congestion and, in some cases, thrombosis of dermal capillaries and venules. Lesions may not be specific in pigs that die at this stage. Petechiae or ecchymoses may be present on serous membranes, the spleen is almost always swollen and red, and there may be congestion and infarction in the gastric mucosa. The latter lesion occurs in many acute infections in pigs. Subsidence of the acute disease, or a milder initial course, often leads to swelling of joints, lameness, and characteristic erythematous lesions in the skin. The cutaneous lesions of porcine erysipelas are roughly rhomboidal and slightly raised. They are readily visible in light-skinned pigs and palpable when not visible in dark-skinned pigs. The skin within the rhomboid may be uniformly bright red or purple, but in some lesions only the margins and center are discolored. The latter lesions may progress to complete discoloration, or may return to normal within a few days. The uniform, bright red lesions may also resolve, leaving only an area of scurfiness as a residue. The dark red or purple lesions undergo dry necrosis and may eventually peel off or, if forcibly detached, expose a raw base. Oc-
casionally, the skin lesions coalesce over large areas and lead to extensive cutaneous necrosis. The tip of the tail and ears may also become dark, shrunken, and leathery due to ischemic necrosis. The articular lesions of acute erysipelas are typically those of fibrinous polyarthritis. The volume of synovial fluid is increased and the synovial membrane is hyperemic. In some cases, the synovial arterioles show necrotizing inflammation and extensive plugging by cellular thrombi. Lesions in other tissues are not specific.

Microscopically, there is neutrophilic infiltration of the walls of small dermal arterioles, many of which contain cellular thrombi. Suppurative inflammation of sweat glands is also a consistent microscopic finding, but otherwise the reaction is most severe at the junction of dermis and subcutis. Similar cutaneous infarcts occasionally occur in other septicemic bacterial diseases and the lesions should not therefore be considered pathognomonic for erysipelas. Confirmation requires culture of the organism from the undersurface of skin lesions or from other tissues. Lesions also may be found in visceral organs. In addition to splenic enlargement, numerous petechiae may be visible in the renal cortices and there is sometimes intense interstitial hemorrhage in the medulla. The renal cortical petechiae arise in part from small venules, but mainly from glomeruli. The characteristic glomerular lesion of erysipelas is focal fibrinoid necrosis of the tufts, with intracapsular hemorrhage. Less specific changes that might also be present include diffuse glomerulitis, characterized by swelling or proliferation of the glomerular endothelium, and segmental sludging of erythrocytes in some glomerular tufts. The latter lesion probably precedes fibrinoid necrosis and intratubular hemorrhage. Occasionally, gram-positive bacterial colonies are found in the necrotic tufts or in intertubular capillaries, where they are associated with tiny, intense foci of neutrophils.

Chronic erysipelas in pigs is characterized by vegetative valvular endocarditis and arthritis. Localization of the organism in heart valves and joints occurs as a sequel to either acute, nonfatal septicemia or mild, perhaps inapparent, systemic disease. The mitral valves are most often involved and pigs that die of endocarditis have congestive heart failure and embolism. Large infarcts in the spleen and kidneys are particularly common. The valvular lesions may be very large, consisting of layers of fibrin with variable numbers of trapped inflammatory cells. During the active stage, masses of grampositive bacteria can be found near the surfaces of the thrombi. In older lesions, the bacterial colonies are buried more deeply in the thrombi and usually cannot be cultured. Arthritis is a common expression of chronic erysipelas in pigs and may be unassociated with earlier acute or subacute signs of infection. The lesions in chronic erysipelas arthritis vary in severity. In mild cases, there is excess synovial fluid and villus hypertrophy, but the articular capsule may appear normal. In severe cases, there is extensive villus hyperplasia and hypertrophy over much of the synovial membrane, together with pannus formation and cartilage degeneration. The hypertrophic villi are hyperemic and infiltrated with mononuclear cells, including plasma cells. Diskospondylitis is also a feature of chronic erysipelas.
Exudative epidermitis of pigs

**Etiology and pathogenesis:** Exudative epidermitis is an acute, exudative, superficial pyoderma of young pigs caused by *Staphylococcus hyicus*. The disease has also been called greasy-pig disease, impetigo contagiosa suis, and seborrhea oleosa. The infection occurs worldwide wherever intensive pig production is carried out. It is most common in piglets 5-35 days of age, but mild cases occur in older pigs also. The morbidity ranges from 10 to 90% and mortality from 5 to 90%. Mortality is higher in young pigs with lower resistance. Usually, when a litter is affected, all piglets develop the disease. The infection may cause significant economic loss. Autogenous vaccines prepared from toxigenic strains of bacteria are used to prevent infection.

The pathogenesis of exudative epidermitis is incompletely understood. Both virulent and nonvirulent strains of *S. hyicus* are part of the normal skin flora of healthy pigs. The highest rates of carriage of the organism are found in the youngest piglets, suggesting that the organisms are acquired at birth. However, the presence of virulent organisms is not sufficient to produce disease. It is thought that infection develops as a result of trauma that breaches the skin barrier. Other factors that may predispose piglets to developing clinical disease include agalactia of the sow, concurrent infections, and nutritional deficiencies. *S. hyicus* strains are virulent by virtue of their ability to produce an exotoxin which is capable of producing exfoliative skin lesions in pigs which are typical of exudative epidermitis.

**Gross lesions and histopathology:** The disease can be divided into peracute, acute, and subacute forms.

- In the peracute form, most common in piglets only a few days old, there is abrupt onset of lesions around the eyes, snout, chin, and on the ears with extension to the medial aspect of the legs. Lesions then rapidly spread to the thorax, abdomen, entire legs, and hooves. Lesions begin as peeling of small areas of the stratum corneum leaving red, glistening, moist areas. These areas are quickly covered by greasy, dark brown exudate. Lesions become generalized in 24 to 48 hours and the entire body is erythematous and covered with brown, greasy, malodorous exudate. Erosions of the coronary bands and heels commonly develop. Conjunctivitis also occurs frequently and typically causes matted together of the eyelids and results in an inability to see. Death occurs within 3 to 5 days as a result of dehydration, electrolyte imbalance, negative energy balance, and septicemia.

- In the acute form, the course is more protracted. The skin becomes thick and wrinkled and the exudate covering the entire body becomes dry, hard, and cracked, producing a generalized furrowed appearance. The underlying skin visible in the furrows is red.

- The subacute form occurs in older piglets and skin lesions are milder and usually confined to the head and ears. The subacute disease may appear as a
dandruff-like scaling or as red-brown macules. Older piglets with less severe forms of disease frequently survive, however recovery is slow and the piglets are severely stunted. Additional lesions that may also occur in affected piglets are subcutaneous abscesses, necrosis of the ears and tail, and polyarthritis.

The earliest microscopic lesion is a subcorneal vesicular to pustular dermatitis. Extension of infection to hair follicles results in a superficial purulent folliculitis. In fully developed lesions, the skin is covered with a thick crust composed of ortho- and para-keratotic keratin, lakes of serum, accumulations of neutrophils, necrotic debris, and microcolonies of gram-positive cocci. The epidermis is variably acanthotic and rete ridges are elongated. Cells in the outer stratum spinosum exhibit variable intracellular edema. Neutrophilic exocytosis, intercellular edema, and spongiotic pustules may be seen in the epidermis and infundibular portion of hair follicles. The dermis is edematous, dermal vessels are congested, and there is a perivascular to interstitial neutrophilic infiltrate. Dermal inflammation is more intense and diffuse in areas of ulceration. In subacute cases, exudation is less severe and there is more marked epidermal hyperplasia, hyperkeratosis, and parakeratosis. Inflammation in the dermis becomes primarily mononuclear.

Microscopic lesions may also be seen in other tissues. Lymph nodes draining severely affected areas of skin contain loci of hemorrhage, purulent inflammation, and occasional microcolonies of bacterial cocci. Renal lesions are common and bacteremia is not required for them to be present. The lesions are distinctive, with early vacuolation of the epithelium of collecting ducts and renal pelvis progressing to epithelial degeneration and exfoliation. Intratubular casts of desquamated epithelium may be sufficiently severe to be evident macroscopically, leading to linear striations of the renal pelvis, and accumulation of cellular sediment in the pelvis and ureters. The process may be sufficiently severe to occlude the ureters. In cases in which bacteremia is present, purulent pyelonephritis is common. Animals with greasy pig disease may also have lesions in the oral cavity and conjunctiva, and the causative organism has been associated with abortion in sows.

26. Feline infectious peritonitis

**Etiology and pathogenesis:** The group 1 species in genus *Coronavirus*, family Coronavirusidae, includes Feline coronavirus (FCoV), and its two biological types Feline infectious peritonitis virus (FIPV) and Feline enteric coronavirus (FECV), as well as transmissible gastroenteritis virus of swine and Canine coronavirus. In domestic and wild felids, the various FCoV strains have a spectrum of virulence, from asymptomatic enteric infection and healthy lifelong carrier status, through symptomatic enteric infection, to virulent systemic infection, which is expressed as FIP. A small minority of cats resist infection, probably on a genetic basis. FIPV appears to have evolved as a deletion mutation of FECV. Antibodies produced against FIPV cannot be dis-
ttinguished readily from those stimulated by the other FCoVs. In comparison to FECV, FIPV strains have less tropism for the gut.

FIPV replicates in macrophages, which disseminate the virus to many parts of the body, and this is central to their virulence. Feline coronaviruses are ubiquitous in cats, but the disease FIP is sporadic, and has a low prevalence. Most cats do not develop disease when exposed to FIPV, and those cats that do develop the disease are usually under 2 years of age. Resistance to FIPV infection is cell-mediated, and systemic clinical disease only occurs if the cell-mediated response is ineffective. The cytokine response appears to be important in the response to FPV infection; immunity against FIPV may be associated with low tumor necrosis factor-α/high interferon-γ mRNA responses, whereas high tumor necrosis factor-α/low interferon-γ mRNA responses favor disease. Cats that recover from FIP have humoral immune responses and immune complexes that are demonstrable in blood, but, although clearance of virus occurs, persistence may extend for several months with fecal shedding.

Cats that do not clear FIPV develop either the dry or wet clinical forms of the disease depending on whether ineffective cell-mediated or humoral immunity dominates the clinical disease. Though often described as distinct entities, the wet and dry forms of FIP are the extremes of a continuum of syndromes, with vasculitis and pyogranulomatous inflammation as the hallmarks. Effusive disease is more common than the dry form. Enteric infection may produce mild, subclinical blunting and fusion of villi. Incidence of the disease is not higher in cats infected with Feline leukemia virus or Feline immunodeficiency virus; however FCoV replicates 10 to 100-fold more in cats infected with FIV, thus enhancing the probability of spontaneous mutations. Type III and type IV immune reactions occur in FIPV-infected cats with clinical disease. Reactions occur in the walls of small venules and arterioles, especially in the serosal surfaces and parenchymatous organs, such as liver and kidney. The cellular infiltrates around vessels are often characterized as pyogranulomatous, with mixed populations of neutrophils, macrophages, and lymphocytes. Endothelial damage also results in disseminated intravascular coagulation in the terminal stages of the disease, with thrombocytopenia and increased circulating fibrin split products.

**Gross lesions and histopathology:** Cats with the effusive form of FIP may develop abdominal distension. Pleural effusion is present in up to 25% of cases and may cause dyspnea. Cardiac tamponade due to pericardial effusion is rare. Ocular and central nervous signs are rare. The cats are hypergammaglobulinemic and may have leukocytosis and neutrophilia. Most go on to die; very few recover after passing through a phase of noneffusive disease.

Cats with noneffusive FIP have a chronic disease of insidious onset and frequently develop signs specific to organs severely affected by vascular lesions. These may include ocular disease; central nervous disorders such as ataxia, paraparesis, head tilt; specific nerve palsies, nystagmus, and behavioral changes; renal failure; and hepatic or pancreatic insufficiency. An uncommon intestinal manifestation may be seen as a protracted period of vomiting and diarrhea with a palpable mass usually at
or about the ileoceccolic junction. Peritonitis is present in most animals, although marked effusion is not found in those with the dry form.

Up to 1 liter of abdominal exudate may be present in cats with effusive FIP. The fluid is usually viscous, clear, and pale to deep yellow, although it may be flocculent and contain strands of fibrin. The serosal surfaces may be covered with fibrin, giving them a granular appearance. Fibrin is frequently prominent over the visceral peritoneum, and fragile adhesions may be present. There are white foci of necrosis or raised plaques or nodular cellular infiltrations on the serosa and extending into the organs or wall of the intestine. These vary in size from a few millimeters to a centimeter in diameter. The omentum may be contracted into a mass in the cranial abdomen, and adherent to itself and other abdominal surfaces. Mesenteries may be thickened and opaque. The kidneys may be enlarged and nodular, with few or many, small to large, white, firm nodules protruding from the cortex. Hepatitis and pancreatitis of variable degree may also be present, characterized by small, white foci of inflammation. The tunica vaginalis may be affected, resulting in periorchitis in intact males. Fibrin is usually less prominent in the thorax, but firm white foci may be present under the pleura, and the lungs may be dark and rubbery. Hydropericardium and epicarditis occur less frequently. Abdominal and thoracic lymph nodes may be enlarged and have a lobulated pattern on cut surface.

In cats with noneffusive FIP, there may be inflammatory foci in the abdominal or thoracic organs as described above, or lesions may be restricted to the eyes and nervous system. Diffuse uveitis or chorioretinitis may progress to panophthalmitis; fibrin is often present in the anterior chamber. Lesions in the central nervous system can involve the leptomeninges, spinal cord, or brain, but usually are visible grossly only in the leptomeninges as thickening or white streaks. Occasionally, hydrocephalus or syringomyelia may result from ependymitis. The isolated intestinal lesion is marked thickening of the affected segment by nodular, firm, white tissue extending through the wall of the intestine with adhesion to enlarged lymph nodes.

The characteristic microscopic lesion is generalized vasculitis and perivasculitis, especially of venules, with a focal mixed inflammatory reaction. This lesion occurs in the serous membranes, in the connective tissue of the parenchymatous organs, the eye, and the meninges. Neutrophils, lymphocytes, plasma cells, and macrophages accumulate in and around affected vessels. The endothelium swells, and medial necrosis may be evident, with narrowed vascular lumina; thrombosis may occur. The proportion of neutrophils in the reaction varies, and some lesions may be comprised mainly of a mixture of lymphoid and histiocytic cells. Fibroplasia is variable; occasionally, adventitial fibrosis occurs with little cellular infiltrate. The vascular lesion results in the serofibrinous and cellular exudate on the serosal surfaces, and the nodules visible on the surfaces and deeper in solid organs. The small random necrotic foci that are found in the parenchyma of the liver may be due in some cases to thrombophlebitis and infarction. The microscopic changes on the omentum, mesentery, and serosal tissues vary in severity. Mild changes are proliferation of mesothelial cells,
slight fibrin exudate with fibroblast proliferation, and scattered neutrophils and mononuclear cells. Severe changes result in a thick layer of fibrin adherent to the serosa, with necrosis and/or hypertrophy of mesothelium. Large numbers of neutrophils, mononuclear cells, and necrotic debris may be embedded in the fibrin. The vasculitis may extend from the serosa into the intestine, affecting the muscularis, myenteric ganglia, the submucosa, and the mucosa, which may be segmentally infarcted. Lesions in various organs are caused by the vascular damage that occurs in the capsule and stromal connective tissue. They may be found throughout the body. Subcapsular infiltrates occur particularly in the liver, lung, and pancreas, and perivasculitis can develop deep in the parenchyma, especially in the kidney. In addition to focal lung lesions, there may be diffuse interstitial pneumonia, sometimes most severe close to the visceral pleura. Similarly, severe focal or generalized lymphoplasmacytic interstitial nephritis may develop. In the spleen and lymph nodes, there is histiocytosis, and either depletion or hyperplasia of lymphoid follicles. Lymphoid depletion may be a result of apoptosis of noninfected lymphocytes. Cellular infiltrations in the spinal or cerebral meninges, the choroid plexuses, ependyma, and perivascular spaces tend to be more mononuclear and diffuse, with only occasional focal perivasculitis. Degenerative and necrotic lesions in the parenchyma of the central nervous system appear to be related to the vasculitis. The ependyma may be visibly roughened and develop reactive syncytia of lining cells. Ocular lesions are common, but usually subclinical.

Effusive FIP must be differentiated from bacterial peritonitis in particular, but noneffusive forms may be similar to manifestations of lymphosarcoma, steatitis, mycotic infections, and toxoplasmosis. With thorough necropsy, the constellation of lesions is usually sufficiently distinctive to allow a gross diagnosis with a high degree of accuracy. Testing by immunofluorescence or enzyme-linked immunosorbent assay may be useful in supporting a diagnosis of FIP but histopathology remains the only conclusive means of diagnosis of FIP.

27. Feline panleukopenia

**Etiology and pathogenesis:** The Paroviridae are small nonenveloped DNA viruses. They replicate, and produce inclusion bodies, in the nucleus of infected cells. Members of the genus Parovirus infect many species of laboratory and domestic animals. Among syndromes associated with parovirus infection are: disease in cats, dogs, and mink dominated clinically by enteritis.

Though autonomous paroviruses may infect cells at any phase of the cell cycle, replication is dependent on cellular mechanisms only functional during nucleoprotein synthesis prior to mitosis. Hence, the effects of paroviral infection are greatest in tissues with a high mitotic rate. These may include a variety of tissues during organogenesis in the fetus and neonate. In older animals, the proliferative elements of the enteric epithelium, hematopoietic and lymphoid tissue are particularly susceptible. At the time of virus assembly, large basophilic or amphophilic nuclear inclusions
may be found in infected cells. Parvovirus is demonstrated in these inclusions by electron microscopy.

Oronasal exposure results in uptake of virus by epithelium over tonsils and Peyer's patches. Infection of draining lymphoid tissue is indicated by isolation of virus from mesenteric lymph nodes 1 to 2 days after infection. Release of virus into lymph, and dissemination of infected lymphoblasts from these sites, may result in infection of other central and peripheral lymphoid tissues, including thymus, spleen, lymph nodes, and Peyer's patches, 3 to 4 days after infection. Lymphocytolysis in these tissues releases virus, reinforcing cell-free viremia. Viremia is terminated when neutralizing antibody appears in circulation about 5 to 7 days after infection. Moderate pyrexia occurs at about this time. Infection of the gastrointestinal epithelium is a secondary event, following dissemination of virus by circulating lymphocytes and cell-free viremia. Peyer's patches are consistently infected at all levels of the intestine, and epithelium in crypts of Lieberkühn over or adjacent to Peyer's patches usually becomes infected a day or so later. Infection of gastrointestinal epithelium at other sites in the gut is less consistent, but is usually more severe in the lower small intestine. Maximal infection of cryptal epithelium occurs during the period about 5 to 9 days after infection.

The occurrence and severity of enteric signs are determined by the degree and extent of damage to epithelium in intestinal crypts. This seems to be a function of two main factors. The first is the availability of virus, which is influenced by the rate of proliferation of lymphocytes, and therefore their susceptibility to virus replication and lysis. The second factor influencing the degree of epithelial damage is the rate of proliferation in the progenitor compartment in crypts of Lieberkühn. If many cells are entering mitosis, large numbers will support virus replication and subsequently lyse. Destruction of cells in the crypts of Lieberkühn, if severe enough, ultimately results in focal or widespread villus atrophy and perhaps mucosal erosion or ulceration. Regeneration of cryptal epithelium and partial or complete restoration of mucosal architecture will occur, if undamaged stern cells persist in most affected crypts, and the animal survives the acute phase of clinical illness.

Diarrhea in parvoviral infections is mainly the result of reduced functional absorptive surface in the small intestine. Effusion of tissue fluids and blood from a mucosa at least focally denuded of epithelium probably also contributes to diarrhea. Dehydration and electrolyte depletion are the result of reduced fluid intake, enteric malabsorption, effusion of tissue fluid, and, in some animals, vomition. Hypoproteinemia is common, and anemia may occur due to enteric blood loss; both are exacerbated by rehydration. Anemia reflects hemorrhage into the gut.

Proliferating cells in the bone marrow are also infected during viremia. Lysis of many infected cells is reflected in hypocellularity of the marrow caused by depletion of myeloid and erythroid elements. The number of neutrophils in circulation drops quickly in severely affected animals. This is due to failure of recruitment from the damaged marrow, and peripheral consumption, especially in the intestine. In surviving
animals, regeneration of depleted myeloid elements from remaining stem cells restores the circulating population of granulocytes within a few days. Neutrophilia with left shift may occur during recovery.

Lymphopenia, relative or absolute, results from viral lymphocytolysis in all infected lymphoid tissue. Relative lymphopenia is more consistently observed in dogs than neutropenia. In dogs surviving the lymphopenic phase, circulating lymphocytes return to normal numbers within 2 to 5 days, as regenerative hyperplasia occurs in lymphoid tissue throughout the body. Lymphocyte numbers increase rapidly, sometimes producing lymphocytosis in recovering dogs.

Feline panleukopenia virus (FPV) infects all members of the Felidae, as well as mink, raccoons, and some other members of the Procyonidae. FPV is ubiquitous in environments frequented by cats, and infection is common, though generally subclinical. The disease panleukopenia usually occurs in young animals exposed after decay of passively acquired maternal antibody, but it may occur in naive cats of any age. Infection of the fetus during late prenatal life by FPV causes anomalies of the central nervous system, mainly hypoplasia of the cerebellum. A tentative association has been made between infection of kittens with FPV and myocarditis, as well as subsequent cardiomyopathy.

**Gross lesions and histopathology:** At necropsy, external evidence of diarrhea may be present, the eyes may be sunken, and the skin is usually inelastic, with a tacky subcutis reflecting dehydration. Rehydrated animals may have edema, hydrothorax, and ascites due to hypoproteinemia. There is pallor of mucous membranes and internal tissues in anemic animals. Gross lesions of internal organs most consistently involve the thymus and the intestine. The thymus is markedly involuted and reduced in mass in young kittens. Enteric lesions may be subtle and easily overlooked. Hence it is mandatory that intestine be examined microscopically despite the apparent absence of gross change. The intestinal serosa may appear dry and nonreflective, with an opaque ground-glass appearance. Uncommonly in cats, there may be petechiae or more extensive hemorrhage in the subserosa, muscularis, or submucosa of the intestinal wall. The small bowel may be segmentally dilated. The content is usually foul-smelling, scant, and watery, and yellow-gray at all levels of the intestine. The mucosa may be glistening gray or pink, with petechiae, perhaps covered by fine strands of fibrin. Patchy diphtheritic lesions may be present, especially over Peyer's patches in the ileum. Flecks of fibrin and sometimes casts may be in the content in the lumen. Formed feces are not evident in the colon. Lymph nodes may be prominent at the root of the mesentery. Gross lesions elsewhere in the carcass are usually restricted to pulmonary congestion and edema in some animals, and pale gelatinous marrow in normally active hemopoietic sites.

Microscopic lesions are consistently found in the intestinal tract in fatal cases, and are usual in lymphoid organs and in bone marrow. The intestinal lesions vary with the severity and duration of the disease. Lesions may be patchy, and several levels of gut should be examined, preferably including ileum and, if possible, Peyer's patch. Du-
ring the late incubation period and early phase of clinical disease, cryptlining epithelium is infected. Intranuclear inclusions may be found, and damaged epithelium containing inclusions exfoliates into the lumen of crypts. Crypts are dilated and lined by cuboidal or more severely attenuated cells. The lamina propria between crypts contains numerous neutrophils and eosinophils at this time, and some emigrate into the lumen of crypts, where they join the epithelial debris. Subsequently, severely damaged crypts may be lined by extremely flattened cells, and by scattered large bizarre cells with swollen nuclei and prominent nucleoli. Enterocytes covering villi are not affected. But as they progress off the villus, they are replaced by a few cuboidal, squamous, or bizarre epithelial cells, so that villi in affected areas undergo progressive collapse. If cryptal damage is severe and widespread, the mucosa becomes thin and eroded or ulcerated, with effusion of tissue fluids, fibrin, and erythrocytes. Inflammatory cells are usually sparse in the gut of such animals, and superficial masses of bacteria may be present, occasionally accompanied by locally invasive fungal hyphae. In less severely affected animals with disease of longer duration, corresponding to about 8 to 10 days after infection, scattered focal drop-out of crypts, or focal mucosal collapse and erosion or ulceration, may be evident. In these animals, remaining crypts recovering from milder viral damage show regenerative epithelial hyperplasia. Mucosal lesions are often most marked in the vicinity of Peyer's patches.

Lesions in the colon generally resemble those found in the small bowel, though they are often less severe or more patchy in distribution. Colonic lesions are present in about half of fatal cases of panleukopenia. Gastric lesions resulting from damage to mitotic epithelium are relatively uncommon in cats.

Lesions of lymphoid organs during the early phase of the disease consist of lymphocytolysis in follicles and paracortical tissue in lymph nodes, in the thymic cortex and splenic white pulp, and in gutassociated lymphoid tissue. Lymphoid necrosis has been associated with induced apoptosis of virus-infected lymphocytes. Lymphocytes are markedly depleted in affected tissue and large histiocytes are prominent, often containing the fragmented remnants of nuclear debris. Follicular hyalinosis, the presence of amorphous eosinophilic material in the center of depleted follicles, may be seen. Erythrophagocytosis by sinus histiocytes may occur in lymph nodes, especially those draining the gut. Severely depleted Peyer's patches may be difficult to recognize microscopically. Later in the course of clinical disease, corresponding to the period beyond about 7 to 8 days after infection, prominent regenerative lymphoid hyperplasia may be found. In severely affected animals at the nadir of the leukopenia, virtually all proliferating elements in the bone marrow may be depleted. The extremely hypocellular, moderately congested marrow is only populated by scattered stem cells.

In the liver, dissociation and rounding up of hepatocytes, and perhaps some periacinar atrophy and congestion, may be evident. This is probably associated with dehydration and anemia. Pancreatic acinar atrophy is also common, reflecting inappetence.
The lung may be congested and edematous. In leukopenic animals, few white cells are seen in circulation in any organ.

28. Feline viral rhinotracheitis

**Etiology and pathogenesis:** Felid herpesvirus 1 (FeHV-1) infection is widespread in most cat populations, is an important contributor to upper respiratory tract disease in cats, and is a common cause of conjunctivitis and keratitis. Clinical signs are most common in kittens but occur regularly in adult cats, perhaps due to recrudescence of latent infections. Morbidity may be high in naive populations of kittens, but mortality is generally low and most cats recover in 10 to 14 days. Clinical signs include fever, oculonasal discharge, sneezing, coughing, and anorexia. Chronic rhinitis and sinusitis may develop due to intermittent reactivation of latent infections, loss of respiratory defenses due to epithelial or turbinate damage, or failure of drainage of sites of secondary bacterial infection in the sinuses.

FeHV-1, like other herpesviruses, causes cytolytic infections of mucosal epithelial cells and establishment of latency in the trigeminal ganglion, optic nerve, olfactory bulb, and cornea. Reactivation of latent infection is often of unknown cause, but may be triggered by corticosteroid therapy, stresses associated with environmental changes, or parturition. The virus replicates optimally at temperatures less than 37°C; thus, most infections are limited to the upper respiratory tract and conjunctiva.

FeHV-1 is transmitted by contact with infected nasal or ocular secretions, or by aerosol for a distance of about 1 meter. Transmission by fomites may occur, but the virus survives for less than 18 hours under most environmental conditions. The host range is limited to felids; occasional cases are reported in cheetahs. The incubation period is typically 2 to 4 days. In most cases, infection is restricted to the nasal mucosa, nasopharynx, sinuses, and tonsils, with lesser viral replication in the conjunctiva and upper trachea. Viremia may occur in neonates, but is not common in older kittens. It is likely that most cats that recover from the disease remain latently infected, and perhaps 20-40% of these cats intermittently shed infective virus during periods of stress, corticosteroid therapy, change in housing, or lactation.

**Gross lesions and histopathology:** The distribution of gross lesions corresponds to the predilection sites for viral replication - the epithelium of nasal passages, pharynx, soft palate, conjunctivae, tonsils, and, to a lesser extent, trachea. The initial serous inflammation becomes mucopurulent or fibrinous within a few days, and crusting is often present around the eyes and nares. Multifocal erosions of the nasal mucosa are covered by mucoid or mucopurulent exudate. The trachea may contain hemorrhage or fibrinous exudate. Tonsils are enlarged and contain petechiae or rare loci of necrosis. The regional lymph nodes are usually enlarged, reddened, and edematous. Ulceration of the tongue is rare and only in severely affected cats. This contrasts with the frequent finding of vesicular to ulcerative lesions on tongue, hard palate, or nos-
trils with Feline calicivirus infection. Ocular involvement is usually limited to purulent conjunctivitis, but it can progress to ulcerative keratitis.

Microscopically, large eosinophilic intranuclear inclusion bodies are present in many virus-infected cells during the period of active viral replication from 2 to 7 days after infection. They may be found in lesions from cats dying of the disease, but are rarely detected beyond 7 days after infection and cannot be relied upon for diagnosis. Infected cells undergo hydropic change with cytoplasmic swelling and pallor. There is loss of epithelial organization and the disrupted epithelium is soon eroded or ulcerated. An acute inflammatory reaction develops with exudation of fibrin and many neutrophils. Focal necrosis accompanied by acute inflammation may be found in tonsils and local lymph nodes. Pulmonary involvement is uncommon except in fatal cases. In fulminating cases of viral infection, there is widespread multifocal necrotizing bronchitis, bronchiolitis, and interstitial pneumonia, with extensive serofibrinous flooding of airspaces. Secondary bacterial bronchopneumonia is a more common complication of FeHV-1 infection than is primary viral pneumonia.

Systemic disease is uncommon in FeHV-1 infection. Multifocal hepatic, pancreatic, and adrenocortical necrosis are the expected features of systemic disease. A syndrome of nasofacial ulcerative dermatitis and stomatitis with histologic lesions of eosinophilic inflammation and infrequent epithelial intranuclear inclusion bodies may be associated with corticosteroid therapy or crowding.

29. Foot and mouth disease

**Etiology and pathogenesis:** Foot and mouth disease (FMD) is a highly contagious viral infection of all cloven-hoofed animals. It is a problem of worldwide concern, being enzootic in large areas of Africa, Asia, and parts of Europe and South America. FMD is an acute febrile condition characterized by the formation of vesicles in and around the mouth, on the feet, teats, and mammary glands. The disease is not notable for high mortality, except in sucklings, but morbidity is very high, with a concomitant loss of productive efficiency. The virus belongs to the genus * Aphthovirus* (aphtha = ulcer) in the Picornaviridae family. The virus is highly resistant under many circumstances, but is inactivated by direct sunlight, due to drying and increase in temperature, and by moderate acidity (pH < 5.0). The acid production that accompanies rigor mortis in carcasses and meat inactivates the virus. However, the alteration in pH is not dependable and the virus survives in offal, viscera, lymph nodes, and bone marrow for an indefinite period under refrigeration. Next to the movement of infected animals, contaminated animal products are likely the most common mechanism of spread. It may survive on hay and other fomites for several weeks. The carrier state has been observed in cattle, sheep, goats, and African buffalo (*Syncerus caffer*), but not in pigs. The carrier state may persist for up to 2 years postinfection in cattle, even in animals with a significant level of serum-neutralizing antibody. Sheep
and goats are considered to be a frequent inapparent source of dissemination of the virus.

Of equal importance to the persistence of the virus is its antigenic heterogeneity and instability. There are seven principal antigenic serotypes, namely, the classical A, O, and C types, and SAT-1, SAT-2, SAT-3, and Asia-1. These can be distinguished by serologic tests. Six of the seven serotypes (O, A, C, SAT-1, SAT-2, SAT-3) are known to occur in Africa, four (O, A, C, Asia 1) in Asia, and three (O, A, C) in Europe and South America. These serotypes are sufficiently different immunologically that infection with one type does not confer resistance to the other six.

The main portal of entry and primary site of viral multiplication are the pharynx and lung. Subsequent to the first round of replication, there is widespread viremic dissemination to surface epithelium, with subsequent development of lesions in sites of mechanical or physiologic stress, such as oral and pedal epithelium, or teats in lactating animals. FMD virus probably gains entry to these areas via Langerhans cells, with replication in a contiguous group of cells in the stratum spinosum. The resulting cellular degeneration and lysis result in an epidermal vesicle, which is the hallmark of the disease. Virus is present at high titer in the vesicular fluid, and is present in large amounts in expired air from acutely infected animals, which is the main source of spread. Virus persists in lesions for 3-8 days after the appearance of significant neutralizing titers in serum, but seldom beyond day 11 of clinical illness. It is believed that FMD virus is localized in epithelial cells of the oropharynx during persistent infection, so that virus may be found in esophagopharyngeal fluid for a considerable period of time. Animals are resistant to reinfection with homologous strains by natural exposure for about 2 to 4 years; susceptibility increases as the antibody titer declines.

Gross lesions and histopathology: Gross lesions are only seen in those animals which are examined at the height of disease. Lesions heal or are obscured by secondary bacterial infection. Lesions develop mainly in areas subject to trauma: the oral mucosa, especially the tongue; the interdigital cleft; and the teats in lactating animals. In cattle, there is appreciable loss of weight and the buccal cavity may contain much saliva. In the living animal, there is diffuse buccal hyperemia and mild catarrhal stomatitis, but the hyperemia disappears at death. Vesicles form on the inner aspects of the lips and cheeks, the gums, hard palate, dental pad, and especially on the sides and rostral portion of the dorsum of the tongue. Sometimes they form on the muzzle and exterior nares. The primary vesicles are small, but coalesce to produce bullae which may be 5 to 6cm across; these bullae rupture in 12 to 14 hours, leaving an intensely red, raw, and moist base to which shreds of epithelium may still adhere. The eroded to ulcerated area may be replaced by regenerated epithelium in less than 2 weeks. Secondary infection may complicate this course. Foot lesions occur in the majority of cases. There is inflammatory swelling with blanching of skin of the interdigital space in ruminants, coronet in swine, and heels in all species a day or so before vesicles form. The swellings persist until the vesicles rupture and the re-
sultant erosions heal; healing may be considerably delayed on the feet. Vesicles may also occur in the other sites, but much less frequently. A malignant form of the disease, without vesiculation, does occur in young animals and occasionally in adults. In these, death is common, due to myocarditis. Poorly defined pale loci of variable size are seen anywhere within the ventricular muscle. Although historically referred to as "tiger-heart" these gross lesions are no different from those generated in any other syndrome of severe, acute myocardial damage, but necrosis of fibers may be striking. Chronic lesions include myocardial necrosis and scarring, pancreatitis with acinar necrosis and regeneration.

Sheep are, in general, less susceptible than cattle, and the infection runs a milder course, though there may be exceptions. Lesions may not develop. When they do, the dental pad is the preferred site in the oral cavity. Lingual lesions tend to occur on the caudal dorsal portion as underrunning necrotic erosions rather than vesicles. These are small and easily missed, and they heal within a few days. Lameness may be prominent in acute outbreaks. Typical vesicles develop in the interdigital cleft, on the coronet and bulb of the heel. They may occasionally involve the entire coronet and lead to eventual shedding of the hoof. Vesicles also occasionally occur on the teats, vulva, prepuce, and on the pillars of the rumen. The peracute form with myocardial necrosis may occur in lambs. The disease in goats is, in general, similar to that described for sheep. Both species may be inapparent carriers, and many outbreaks worldwide have been due to transport of apparently infected small ruminants.

In pigs, lesions occur in the usual sites, although more commonly on the feet than in the mouth. They may be present on the snout and behind its rim, and on the teats of lactating sows. Abortion and stillbirth of infected piglets are recorded. The peracute form, with high mortality due to myocarditis, occurs in sucklings, often before vesicle formation is noticed in sows.

FMD must be differentiated from other viral vesicular diseases such as vesicular stomatitis, vesicular exanthema, and swine vesicular disease in susceptible species, and in the latter stages, from diseases producing erosive/ulcerative lesions of the oral cavity. Definitive diagnosis requires virus isolation and characterization, demonstration of viral antigen by enzyme-linked immunosorbent assay, or detection of viral genome by polymerase chain reaction or reverse transcriptase-polymerase chain reaction in lesional material.

30. Glanders

**Etiology and pathogenesis:** Glanders is a disease of historic importance, and flourished especially among cavalry horses. It has disappeared from many countries, but still exists in Eastern Europe, Asia, and South America. It is caused by *Burkholderia (Pseudomonas) mallei* and typically affects horses. Disease may occur in carnivores, sheep, and goats, but not in cattle or pigs. Humans are also susceptible. *B. mallei* is sensitive to the external environment, and infection is acquired directly or indirectly
from excretions and discharges of affected animals. In the absence of definitive information, it is assumed that the organisms traverse the pharyngeal mucosa, and perhaps the intestinal mucosa, and are conveyed to the lungs, where lesions almost always occur. From there, hematogenous spread is believed to result in nasal, cutaneous, and lymph node lesions.

**Gross lesions and histopathology:** Glanders is characterized by nodular lesions in the lungs, and ulcerative and nodular lesions of the skin and respiratory mucosa. Lung lesions are present in all cases. There is a generalized distribution of pinpoint to 2 cm diameter pyogranulomatous nodules throughout the lung, often with central areas of liquefactive necrosis.

Histologically, the nodules are composed of a central core of neutrophils, often with necrosis of neutrophils and liquefaction of the tissue, and a peripheral rim of epithelioid macrophages and fibrosis. The relative proportions of neutrophils, macrophages, fibrosis, and mineralization are variable. Nasal lesions are often unilateral, with copious, purulent, green to yellow exudate. Multiple small nodules in the submucosa each consist of an inner core of neutrophils and a periphery of macrophages. The core liquefies and the overlying mucosa may slough, leaving a crateriform ulcer that heals to form a white stellate scar. Similar pyogranulomatous ulcerative lesions line the pharynx, larynx, and trachea. Hematogenous metastases are common in the spleen and less common in other tissues. Enteric lesions are rare. The cutaneous lesions of glanders are termed "farcy". These consist of chains of nodules or ulcers that follow lymphatic vessels, and represent purulent lymphangitis with extensive leukocyte necrosis.

**31. Hepatic coccidiosis in rabbits**

**Etiology and pathogenesis:** *Eimeria stiedae* infections occur in both domestic and wild rabbits and represent an important cause of poor weight gains, disease, and mortality in commercial rabbitries. Following the ingestion of sporulated oocysts (sporocysts), sporozoites invade the duodenal mucosa and migrate to the lamina propria prior to systemic migration. Sporozoites have been demonstrated in the regional mesenteric lymph nodes within 12 hr postexposure and in the liver by 48 hr. Organisms have been reported to migrate to the liver in mononuclear cells via lymphatics. However, viable sporozoites have also been demonstrated in the peripheral blood and bone marrow in *E. stiedae*– inoculated rabbits, and the hematogenous route has been proposed as a means of migration to the liver.

In the liver, sporozoites invade the epithelial cells of the bile ducts and schizogony begins. Following the gametogenesis, oocysts are formed, released into the bile ducts, and passed to the intestine. The prepatent period is approximately 15 to 18 days. Oocysts may be shed in the feces for up to 7 or more weeks postexposure. Oocysts are normally resistant to environmental change; thus contaminated premises and fomites may be a source of infective sporulated oocysts for several months. *E. stiedae* infecti-
ons may be manifest either as clinical or subclinical disease. Weanling rabbits are most often affected.

In the past, a significant number of livers collected from fryer rabbits in abattoirs have been condemned because of hepatic coccidiosis. A dose-related effect has been observed in experimentally infected animals. In young rabbits inoculated orally with varying numbers of sporocysts (100–100,000 per animal), mortality rates in animals that received either 10,000 or 100,000 sporocysts were 40% or 80%, respectively. No fatalities occurred at lower dosages. Significant variations in liver enzymes and blood chemistry have been observed during the course of the disease. Four stages have been proposed: (1) the initial stage of metabolic dysfunction that coincides with hepatocyte damage during schizogony; (2) the cholestatic stage, with elevated transaminases and serum bilirubin; (3) the stage of metabolic dysfunction, characterized by hypoglycemia and hypoproteinemia; and (4) the period of immunodepression in heavily infected animals resulting in an inability to curtail the production of oocysts in the biliary system.

**Gross lesions and histopathology:** At necropsy, affected animals are frequently thin and potbellied and lack body fat reserves. There may be dark brown to green soiling in the perineal region. Ascites is a variable finding. Depending on the degree of liver involvement, there may be hepatomegaly, and in severe cases, icterus. In the liver, there are variable numbers of raised, linear bosselated, yellow to pearl gray circumscribed lesions 0.5–2 cm in diameter scattered throughout the hepatic parenchyma. The gall bladder is thickened and contains viscid green bile and debris. On cut surface, lesions contain fluid green to inspissated, dark green to tan material.

Microscopically, there is marked dilation of bile ducts, extensive periportal fibrosis, and mixed inflammatory cell infiltration in the periportal regions. In affected bile ducts, there is hyperplasia of epithelium, with papillary projections lined by reactive epithelial cells overlying collagenous tissue stroma. Infiltrating periductal inflammatory cells include lymphocytes, macrophages, and a sprinkling of polymorphs. Large numbers of gametocytes and oocysts are usually present in parasitized ducts. In lesions of some duration, organisms may be sparse to absent in bile ducts, with prominent periportal fibrosis.

The diagnosis may be confirmed at necropsy by wet mount preparations. Oocysts are usually readily observed in aspirates from the gall bladder or in impression smears of sectioned lesions. The characteristic proliferative biliary changes and organisms seen histologically are pathognomonic of the disease.

**32. Infectious bovine rhinotracheitis**

**Etiology and pathogenesis:** Bovine herpesvirus 1 (infectious bovine rhinotracheitis virus, BoHV-1), which is in genus *Varicellovirus*, subfamily Alphaherpesvirinae, has been associated with a wide range of clinicopathologic syndromes in cattle. These
include necrotizing rhinotracheitis, conjunctivitis, infectious pustular vulvovaginitis and balanoposthitis, vesicular lesions of the udder, abortions, and latent infection. A systemic form of the disease, which usually involves the alimentary tract, may occur spontaneously in neonatal calves (in which it may be congenital, or acquired shortly after birth) and in feedlot cattle.

The pathogenesis of systemic infection with BoHV-1 is poorly understood. Colostrum-deprived calves are especially susceptible, and the disease can be prevented by feeding colostrum from actively immunized dams. The virus probably spreads from the mucosa of the upper respiratory tract to other tissues by circulating leukocytes. Peripheral blood mononuclear leukocytes may exhibit apoptosis in response to BoHV-1, but the significance of this is unknown. Experimental infection of calves with non-cytopathic Bovine viral diarrhea virus (NCP-BVDV) followed by BoHV-1 inoculation results in dissemination of the latter to a variety of tissues. BVDV impairs cellmediated immunity, and this may allow BoHV-1 to escape from the respiratory tract and lead to a systemic infection. Dual infections of BVDV and BoHV-1 occur under field conditions, but coinfection of these two viruses is not a prerequisite for the disease to develop.

Source of Infection of the respiratory tract induces clinical disease after an incubation period of 2 to 6 days, and virus is shed in nasal secretions for at least 10 to 16 days. Clinical IBR is primarily an effect of lytic infection of nasal and airway epithelial cells. Functional abnormalities such as serotonin- or dopamine-induced bronchoconstriction may also contribute to clinical signs. Secondary bacterial pneumonia in calves with IBR is a consequence of the destruction of ciliated epithelium by lytic viral infection, and impairment of the ability of alveolar macrophages to phagocytose bacteria and secrete neutrophil chemotactic factors. These impairments of lung defenses are maximal at 4 to 5 days after viral infection.

Specific form of IBR is infectious pustular vulvovaginitis, wchich is highly contagious. It is frequently transmitted by coitus, but it can also be transmitted by other mechanical means and is contagious by close contact. It may involve individual or a few animals in a herd, but frequently spreads rapidly to involve all exposed females in a few days. The disease subsides in about 10 days, leaving immunity that is fragile and transient. Reinfection can occur, but early reinfection produces only mild disease. The incubation period is 1 to 3 days but may be as brief as 12 hours. The lesions are restricted to the genital tract, but a viremic phase probably occurs because there is early fever and leukopenia.

**Gross lesions and histopathology:** Clinically affected animals have hyperemic oral and nasal mucosae, and focal areas of necrosis, erosion, and ulceration on the nares, dental pad, gums, buccal mucosa, palate, and the caudal, ventral, and dorsal surfaces of the tongue. Characteristically, the lesions tend to be punctate with a slightly raised margin; the necrotic areas are covered by a gray-white layer of fibrinonecrotic exudate, which leaves a raw red base when removed. The lesions may extend into the esophagus, usually only the upper third, and the forestomachs. In the esophagus, the
erosions and ulcers may be irregular, circular, or linear, and often they have a punched-out appearance and a hyperemic border. The ruminal lesions, which are most commonly located in the dorsal and cranioventral sacs, vary considerably. The earliest lesions consist of foci of necrosis and hemorrhage, a few millimeters in diameter. In some cases, the necrosis may involve almost the entire surface of the ruminal mucosa, which becomes covered by a thick, dirty gray layer of exudate, resembling curdled milk, which adheres tightly to the wall. Similar lesions may be evident in the reticulum. Focal areas of necrosis result in the formation of holes, as large as 1.5 cm in diameter, in the leaves of the omasum. In addition, these calves may have focal areas of necrosis in the abomasal mucosal folds, which may coalesce to form areas of necrosis 2 to 3 cm in diameter. The intestines are red and dilated, and the serosal surface may be covered by a thin layer of fibrinous exudate.

The enteric lesions may be accompanied by changes in the upper respiratory tract. When present, the respiratory lesions are similar to those described for older cattle, although they are milder and generally limited to the nasal mucosa, larynx, and upper third of the trachea. Gray to yellow necrotic loci 2 to 5 mm diameter may be evident macroscopically on the capsular and cut surfaces of the liver, the adrenal cortices, the spleen, and in Peyer's patches.

Microscopically, the lesions in the squamous mucosa are characterized by focal areas of necrosis, erosion, and ulceration. Severe necrosis may involve the entire papilla or mucosa more diffusely. Nuclear inclusions may be present in epithelial cells in the periphery of the lesion, although these are an inconsistent finding. They are more likely to be found if tissues are collected in the early stages of the disease and fixed in Bouin's fluid. The abomasal lesions consist of necrosis of glandular epithelial cells. Affected glands are dilated, and filled with necrotic debris. Focal necrotic lesions involving crypts and lamina propria may be present in both the small intestine and large bowel. Abomasal and intestinal lesions may predispose to the development of secondary mycosis, which is a common complication. Foci of coagulative necrosis may occur in the liver, lymph nodes, thymus, Peyer's patches, spleen, and adrenal cortices. Typically, there is little inflammation associated with the necrosis. Herpesviral inclusions are inconsistently seen in cells at the periphery of the necrotic foci.

Respiratory gross lesions of IBR are usually restricted to the nasal cavity, larynx, and trachea. Pustules erupt early after infection, but are fragile and rarely observed. Petechiae, a granular appearance of the mucosa, and serous exudate may be present in acute lesions. More commonly, there is intense hyperemia of the mucosal tissue, multifocal coalescing erosions with loosely adherent plaques of white debris, or diffuse ulceration covered by a mat of fibrinonecrotic and suppurative exudate forming a pseudodiphtheritic membrane. When the exudate is peeled from the surface of the trachea or nasal cavity, dull granular eroded tissue remains. In contrast, in cases of bacterial pneumonia in which expectorated material accumulates on the tracheal or nasal mucosa, gentle removal of the exudate reveals a shiny intact mucosal surface.
In severe cases, obstruction of the laryngeal or tracheal lumen by abundant exudate may prove fatal. Emphysema is a sequel to dyspnea in severely affected calves.

The earliest histologic lesions, in the first 2 days after infection, include cytoplasmic vacuolation and pallor and nuclear pyknosis or karyolysis. Eosinophilic intranuclear inclusion bodies are present in the epithelium of the nasal turbinates, tracheal submucosal glands, and bronchi, but are rare in the tracheal surface epithelium. Inclusions are absent in most diagnostic cases, and the lesions at these later times include erosion or ulceration of nasal and tracheal mucosa, with necrosis and exfoliation of infected epithelial cells and exudation of neutrophils and fibrin. Neutrophils and mononuclear cells infiltrate the lamina propria. Mild perivascular infiltrates of lymphocytes may be detected in the trigeminal ganglion and brainstem. Pulmonary lesions of primary viral pneumonia are uncommon, but young calves may develop bronchointerstitial pneumonia without significant upper respiratory lesions. There is erosion of bronchiolar epithelium and proliferation of type II pneumocytes. Epithelial syncytia may be numerous in alveoli, and eosinophilic intranuclear inclusion bodies are more common than is seen in IBR.

In the genital form of the IBR, the vaginal and vulval mucosa is hyperemic with focal hemorrhages in the lymphocytic follicles of the submucosa. The severity of the vulvovaginitis increases rapidly, and edema of the vulva and mucopurulent vaginal discharge develop. The focal lesions replace the hemorrhages over the lymphoid follicles and consist of small (2-3 mm) pock-like foci, slightly elevated, pale, soft, and friable. The focal lesions, being related to the lymphoid follicles, may be in short linear arrangements. The epithelium in the focal lesions erodes or ulcerates so that in a few days the foci are flat, gray, semitransparent plaques the size of the original lesions. There is ballooning degeneration of the epithelial cells, and, at about 24 hours, intranuclear inclusions can be found in the epithelium. The infected cells undergo necrosis, and epithelial disruption and ulceration occur, accompanied by an intense infiltration by neutrophils. Vesicles and true pustules do not form. Acute inflammation occurs in the lamina propria, with hyperemia and edema and the exudation of numerous plasma cells and lymphocytes. Many of the small vessels are occluded by adventitial and endothelial swelling. The lymphocytic follicles are remarkably hyperplastic and edematous. Although most cows that are served naturally by infected bulls do not appear to experience infertility, susceptible heifers, which are inseminated with semen containing virus, fail to conceive. The virus can produce similar lesions on the mucous membrane of the penis of infected bulls.

33. Infectious canine hepatitis

**Etiology and pathogenesis:** *Canine adenovirus 1* (CAdV-1) infection can cause infectious canine hepatitis, a severe liver disease in dogs and other canids. Vaccination has made the disease rare in many countries in which it was endemic. Deaths from infectious canine hepatitis are usually sporadic, although small outbreaks can
occur among young dogs in kennels. Fatalities seldom occur among dogs more than 2 years of age. In areas where the disease is not controlled by vaccination, it is probable that most dogs in the general population contact CAdV-1 in the first 2 years of life and suffer either inapparent infection or mild febrile illness with pharyngitis and tonsillitis. In more severe cases, there is vomiting, melena, high fever, and abdominal pain. There may be petechiae on the gums; the mucous membranes are blanched, and only occasionally are they slightly jaundiced. Nervous signs of nonspecific character occur in a few cases. There is also a peracute form of the disease in which the animal is found dead without signs of illness, or after an illness of only a few hours. In convalescence, there may be a unilateral or bilateral opacity of the cornea caused by edema, which disappears spontaneously.

Canine adenovirus 1 has special tropism for endothelium, mesothelium, and hepatic parenchyma, and it is injury to these that is responsible for the pathologic features of edema, hemorrhage (which is predominantly serosal), and hepatic necrosis. The histologic specificity of the lesions depends on the demonstration of large, solid intranuclear inclusion bodies in endothelium or hepatic parenchyma. Inclusions are occasionally observed in other differentiated cells but always have the same morphologic features, being deeply acidophilic with a blue tint.

The detailed pathogenesis of infectious canine hepatitis has yet to be worked out. Many infections appear to be clinically silent, and other dogs recover after mild febrile disease with tonsillitis. Some sudden deaths in this disease are associated with midbrain hemorrhage, and others occur with, at most, slight structural evidence of liver injury. The tonsillitis is sometimes quite severe and may be fatal with extensive clear edema of the throat and larynx. Fever accompanies the tonsillitis and apparently precedes the viremic phase, which is of short duration and accompanied by severe leukopenia. Hepatic necrosis develops at about day 7 of infection. Originally it was assumed that the widespread tendency to hemorrhage in this disease was due to leakage from damaged vascular endothelium, coupled with an inability on the part of the damaged liver to replace clotting factors. While these effects play a role, it is now known that the exhaustion of clotting factors is in large part due to their accelerated consumption, as the widespread endothelial damage is a potent initiator of the clotting cascade.

**Gross lesions and histopathology:** The morbid picture of spontaneously fatal cases is usually distinct enough to allow a diagnosis to be made grossly at necropsy. Superficial lymph nodes are edematous, slightly congested, and often hemorrhagic. Blotchy hemorrhages may be present on the serous membranes, and there is usually a small quantity of fluid, clear or blood-stained, in the abdomen. Hemorrhages on the serosa of the cranial surface of the stomach are usually linear, the so-called paintbrush type. Jaundice, if present, is slight. The mesenteries are slightly moist, and the serosa of the small intestine has a groundglass appearance. The liver is slightly enlarged, with sharp edges, and is turgid and friable, sometimes congested, with a fine, uniform, yellow mottling. Red strands of fibrin can be found on its capsule, especially between
the lobes. In the majority of cases, the wall of the gallbladder is edematous; when edema is mild, it may be detected only in the attachments of the gallbladder. In cases in which the gallbladder is edematous, it may be also darkened by intramural hemorrhages. Gross lesions in other organs are inconstant. Small hemorrhagic infarcts may be found in the renal cortices of young puppies. Hemorrhages may occur in the lungs, and occasionally there are irregular areas of hemorrhagic consolidation in the caudal lobes. Hemorrhages in the brain occur in a small percentage of cases. These are capillary and venular hemorrhages best appreciated when darkened by formalin, and then, depending on their concentration, the affected portions of brain appear gray or dark brown. Microscopic hemorrhages occur in any part of the brain, but when numerous enough to be grossly visible, they are confined to the midbrain and brainstem, avoiding the cerebral cortex and cerebellum. Hemorrhagic necrosis of medullary and endosteal elements occurs in the metaphyses of long bones in young dogs, and the hemorrhages are readily visible through the thin cortex of the distal ends of the ribs.

The histologic changes in the liver are quite reminiscent of the zonal necrosis of acute hepatotoxicities. There is an as yet unexplained susceptibility of the periacinar parenchyma to necrosis in this disease. Close to the portal triads, the hepatocytes may be near normal in appearance, except for loss of basophilia and the presence of a scattering of inclusion bodies. In spontaneously fatal cases, most of the parenchyma of the peripheral and central portions of the acini is dead, the hepatocytes having undergone granular acidophilic coagulative necrosis, and in some of these, ghosts of inclusion bodies may be detectable. The margin between necrotic parenchyma and viable tissue is usually quite sharp, although in the viable tissue there are many individual hepatocytes undergoing apoptosis, most of them without inclusion bodies. Fatty changes are common but not constant. The dead cells do not remain long, so the sinusoids become dilated and filled with blood. The reticulin framework remains intact, an observation in keeping with the fact that, in recovered cases, restitution of the liver is complete. Massive necrosis with collapse does not occur. As is typical of severe periacinar necrosis, the necrotic zones, initially eccentric areas about hepatic venules, extend and link up to isolate portal units. Intranuclear inclusions can be found in Kupffer cells in variable numbers. Many of the Kupffer cells are dead, others are proliferating, and others are actively phagocytic in the removal of debris. Leukocytic reactions in the liver are mild and are directed against the necrotic tissue; mononuclear cells are present, but neutrophils, many degenerating, predominate. There is some collection of bile pigment, but it is moderate, in keeping with the short course of the disease.

Microscopic lesions in other organs are largely due to injury to endothelium. Inclusion bodies in endothelial cells can be difficult to find and are looked for with most profit in renal glomeruli, where endothelium is concentrated. Occasionally, they are found in the epithelium of collecting tubules. When areas of hemorrhagic consolidation of the lungs are present, there is hemorrhage, edema, and fibrin formation in the alveoli, and in these consolidated areas, inclusions are often common in alveolar
capillaries and even in dying cells of the bronchial epithelium. Changes in the brain are essentially secondary to vascular injury and may be absent. Hemorrhages, if present, are from capillaries and small venules, and inclusions in endothelial nuclei can usually be found in vessels that have bled. Other endothelial and adventitial cells are hyperplastic and mixed with a few lymphocytes. Small loci of softening or demyelination may be present in relation to the hemorrhages. Lymphoreticular tissues are congested, and inclusions may be found in the primitive reticulum cells of follicles, in the red pulp of the spleen, and in macrophages anywhere.

Corneal edema is a late development. It may occur by day 7 of infection, but is usually delayed to between 14 and 21 days. Viral antigen can be detected in these eyes by fluorescent techniques, but not in the corneal structures. Inflammatory edema is present in iris, ciliary apparatus, and corneal propria, and inflammatory cells are abundant in the filtration angle and iris. The infiltrates are principally plasma cells, and there is evidence that the ocular lesion is a hypersensitivity reaction to viral antigen.

34. Jaagsiekte

**Etiology and pathogenesis:** Ovine pulmonary adenocarcinoma (OPA), also known as jaagsiekte or ovine pulmonary adenomatosis, is a contagious retroviral bronchioloalveolar carcinoma of sheep, and may rarely affect goats. The disease is common in South America, South Africa, and Scotland, where 5-20% of necropsy cases contain pulmonary tumors. OPA occurs regularly in the rest of Europe, Africa and Asia. Mortality rates tend to increase gradually for several years following introduction of infection, and subsequently decline gradually. Clinical disease is most common in 2 to 4-year-old sheep, but 3-month-old lambs have also been affected. Clinical signs include progressive dyspnea, tachypnea, exercise intolerance, nasal discharge, coughing, and weight loss; fever and anorexia are unusual unless secondary infections occur. Drainage of lung fluids from the nose following elevation of the hindlimbs is a characteristic clinical sign seen in some sheep.

Ovine pulmonary adenocarcinoma virus (OPAV; Jaagsiekte sheep retrovirus), the agent of OPA, is a 100 nm diameter, enveloped, betaretrovirus. OPAV is consistently present in neoplastic cells but not in nonneoplastic epithelium or stroma, the disease can be reproduced with cell-free OPAV-containing filtrates of tumor tissue, and the incubation period is dependent on the amount of retroviral reverse transcriptase. Many aspects of the pathogenesis of OPA remain nebulous. The disease is presumably acquired by direct contact with infected nasal secretions. The typical incubation period has been estimated to be 2 years, but is age- and dose-dependent; tumors may develop in 10 to 20 days if high doses of virus are administered experimentally to neonatal lambs. Disease is more common in certain breeds of sheep, but the reasons for this familial predisposition are unknown. Oncogenes have not been identified in OPAV, but the envelope protein is sufficient to induce similar tumors in
immunodeficient mice, and is the likely mechanism of tumor formation in sheep. Acquired resistance to disease has been identified in endemically infected flocks, and this disease resistance has been attributed to immunotolerance as a result of expression of related endogenous retroviruses.

**Gross lesions and histopathology:** Lungs of sheep with OPA contain multiple, firm, raised, gray or white, moist masses in the cranial and middle lung lobes, with less extensive involvement of caudal lobes. Affected lungs are heavy, up to three times their normal weight, and airways are filled with foamy secretion from the neoplastic cells. The tumors are expansile, do not commonly form intrapulmonary metastases, and metastases to regional lymph nodes are present in fewer than 10% of cases. Maedi and/or bacterial pneumonia are often present in sheep with OPA, and the diffuse lymphocytic interstitial pneumonia or cranioventral suppurative bronchopneumonia induced by these diseases may complicate the gross and histologic appearance of the tumors.

The histologic appearance is of a well-differentiated bronchioloalveolar carcinoma. Within the neoplastic masses, the alveolar architecture remains, but alveoli are lined by cuboidal or columnar neoplastic epithelial cells. Proliferation of neoplastic cells results in papillary or acinar structures filling alveoli and obscuring their outline. Alveoli adjacent to the tumors are atelectatic and contain many macrophages, and interstitial fibrosis may be present in advanced cases. Neoplastic cells exhibit ultrastructural features of type II pneumocytes, including cytoplasmic lamellar bodies and surface microvilli; less commonly, the presence of dense core granules suggests a Clara cell phenotype.

The pulmonary lesions of OPA are characteristic, as spontaneous or noninfectious bronchioloalveolar carcinoma is rare in sheep. The disease may be confused with proliferative interstitial pneumonia, which may occasionally be multifocal rather than diffuse.

### 35. Lawsonia intracellularis infection

**Etiology and pathogenesis:** *Lawsonia intracellularis* infects a variety of species, including swine, horses, donkeys, deer, hamsters, guinea pigs, mice, rabbits, foxes, dogs, ferrets, several species of nonhuman primates, ostrich, and emus. In most, it causes a characteristic proliferative lesion of cryptal epithelium in distal small intestine and/or large bowel, associated with a diarrheal syndrome, ill-thrift, and, in emus, rectal prolapse.

*L. intracellularis* is a gram-negative, curved or S-shaped rod bacteria. It is an obligate intracellular organism; hence, cultivation requires the use of tissue culture. *Lawsonia* is prevalent in swine worldwide, and it is in this species that infection is most important. Once infected, pigs shed the organism for weeks. The disease in swine is known as porcine proliferative enteropathy (PPE). Although proliferative enteropathy due to
L. intracellularis is primarily a disease of swine, it has been reported uncommonly in a number of other species, the most important among domestic animals being the horse, in which it mainly affects animals 3 months to 2 years of age. Disease occurs most commonly in feeder pigs. However, piglets as young as 3 weeks of age, and adults, may have lesions of PPE. Clinical effects may vary from subtle subclinical disease with a mild decrease in growth rate to diarrhea and unthriftiness. Animals with extensive lesions may have anorexia, intermittent or persistent diarrhea, and severe weight loss. Death may follow a period of diarrhea and progressive cachexia, or it may occasionally occur as a result of perforation of an ulcerated intestine, or through peracute hemorrhage. Mortality may be very high.

The pathogenesis is dependent on undefined interactions with other bacteria in the gut, because gnotobiotic pigs inoculated with L. intracellularis fail to develop disease, whereas conventional pigs are quite susceptible. The pathogenicity of L. intracellularis is related to its active uptake by epithelial cells, in which they replicate, and cause to become hyperplastic. In PPE, infection of cells lining mucosal glands may occur initially in the vicinity of Peyer's patches and mucosal lymphoid aggregates in the ileoceccolic region. L. intracellularis organisms internalized within membrane-bound vesicles are released into the apical cytoplasm of glandular epithelium where they lie free and replicate. Cell division is required for bacterial replication, which may explain its tissue tropism. Bacteria are passed on to daughter epithelial cells and exit via extrusion from the cytoplasm of enterocytes on villi or between crypt openings. Infected epithelium is transformed to a population of highly mitotic cells, and goblet cells disappear. Glands are lined by crowded, dysplastic pseudostratified columnar epithelium, with basophilic cytoplasm. Infected glands become elongate, dilated, and branching, causing thickening of the mucosa. Isolated plaques of affected mucosa may project above adjacent tissue. The use of the term "adenomatosis" to describe such a change is obvious.

**Gross lesions and histopathology:** Villi in infected small intestine undergo progressive atrophy, so that they may be entirely absent in well-established lesions. Adenomatous areas merge sharply with adjacent normal mucosa. Masses of L. intracellularis are readily recognized in silver-stained tissue sections, as curved rods, infecting especially the apical cytoplasm of cells in adenomatous glands.

Lesions are always found in the terminal portion of the ileum, extending proximally from the ileoceleal-colic orifice for usually less than a meter, though sometimes they can be found more cranially. In a proportion of cases, they occur in the cecum and proximal third of the spiral colon, but not without ileal involvement. Typical widespread lesions cause the thickened mucosa to form irregular longitudinal or transverse folds or ridges. The surface may be intact, but commonly, small foci of fibrin exudation or necrosis may be evident. Thickening of the adenomatous mucosa, and perhaps some edema of the submucosa, is reflected in accentuation of the normal reticular pattern on the serosa of the ileum. This results in a cerebriform or gyrate pattern of projections and depressions on the serosal aspect of the intestine which
is readily recognized, and virtually pathognomonic for this condition. Mucosal lesions in the large intestine often form thickened plaque-like or almost polypoid masses, which may be confluent in some areas, and are often eroded, with fibrin exudation. Serosal folds may be evident on extensively affected large intestine. The ileocolic lymph nodes are enlarged and hyperplastic. Coagulative necrosis of adenomatous mucosa commonly occurs and is referred to as necrotic enteritis. Caseous yellow-brown or blood-tinged necrotic mucosa may be found focally or widely in the distal ileum and proximal large intestine. While necrotic enteritis may be a sequel to other enterocolitides in swine, adenomatosis is the most common primary lesion.

Microscopically, coagulative necrosis of the mucosa may be focal and superficial, with local effusion of neutrophils and fibrin into the lumen, and an acute inflammatory infiltrate at the margin of the necrotic tissue. Frequently, necrosis extends to involve most the thickness of the mucosa, sometimes penetrating to the submucosa. A few islands of viable adenomatous crypts or glands may be left deep among the necrotic debris. Masses of bacteria, presumably fecal anaerobes, are found superficially in the necrotic tissue. With time, granulation tissue develops in ulcerated areas. As the distal ileum experiences bouts of proliferation, necrosis, and ulceration, such granulation of ulcerated gut may result in progressive stricture of the lumen. This is the syndrome of PPE known as regional ileitis. There is often hypertrophy of the external muscle layer.

Acute or subacute intestinal hemorrhage and anemia occur in PPE, and were considered a distinct syndrome, proliferative hemorrhagic enteropathy, within the porcine intestinal adenomatosis complex. Animals may exsanguinate so quickly as to die without passing blood. This syndrome is more common in young adults, rather than growing pigs. Animals dead of this massive intestinal hemorrhage are pale, and the perianal area may be smeared with blood. Fluid blood or a loose or firm fibrin and clotted blood may be present in the ileum, and the contents of the cecum and colon may contain dark bloody digesta and feces. The mucosa of the affected ileum usually resembles that in uncomplicated PPE.

In other species, the lesions and pathogenesis of proliferative enteritis seem similar to those in PPE. In all species, including swine, diarrhea is probably related to loss of functional mucosal surface area in distal small intestine and large bowel, while ill-thrift or wasting syndromes are attributable to protein-losing enteropathy. Clinical signs and lesions associated with hypoproteinemia predominate in young horses, and diarrhea is an inconsistent finding, perhaps related to the large absorptive capacity of the equine colon. In horses, adenomatosis may involve a considerable amount of the small intestine.

A presumptive diagnosis of PPE in swine, and of proliferative enteritis in other species, can be based on typical gross and histologic lesions, accompanied by Warthin-Starry staining to visualize the intracellular bacteria. Confirmation can be obtained by immunohistochemistry using a specific antibody for *L. intracellularis* or by specific polymerase chain reaction.
36. Leptospirosis

Etiology and pathogenesis: Leptospirosis is an important, largely hidden, complex spirochetal infection of animals and humans caused by serovars of *Leptospira interrogans*. It is particularly important as a cause of abortion and stillbirth in farm animals but also causes loss through acute disease (septicemia, hepatitis, nephritis, meningitis) in these and other animals. Leptospirosis can be caused by any of the 180 serovars belonging to the 19 serogroups of what used to be recognized as one species, *Leptospira interrogans* (sensu lato), but which now contains 10 species of pathogenic *Leptospira*.

The natural reservoir of pathogenic leptospires is the proximal convoluted tubules of the kidney, and in certain maintenance hosts the genital tract. In maintenance hosts particularly, transmission may be direct, through urine splashing, in postabortion discharges, venereally, through milk, or transplacentally in congenitally affected animals. Infection of incidental hosts is more commonly indirect, through environmental contamination by the urine of carrier animals. Leptospirosis occurs especially in the autumn in temperate climates (“fall fever”), and in the winter in tropical climates, seasons that also often coincide with the greatest population sizes of wildlife shedders. Leptospires penetrate exposed mucosal surfaces or water-softened skin and disseminate throughout the body, in a leptospiremic phase lasting up to 7 days, but multiply especially in the liver, kidneys, lungs, placenta, udder, and cerebrospinal fluid. Infection may cause acute or subacute systemic disease (nephritis, hepatitis, endotoxemia, sometimes hemoglobinuria) during the leptospiremic phase or, after leptospiremia has ceased, chronic disease in the form of abortion or stillbirth, infertility, or recurrent uveitis. Acute and often severe disease may occur in the leptospiremic phase, particularly in young animals. Jaundice is a common manifestation of acute disease and occurs because of hemolysis due to hemolysin production, and because of hepatocellular injury of both toxic and ischemic origin.

Renal failure is a clinically recognized consequence of infection. Interstitial nephritis can be caused by all serovars. The interstitial phase is accompanied by marked vascular alterations that produce hyperemia, edema, and endothelial swelling. Tubular epithelial degeneration is likely the combined result of hypoxia due to hypovolemia and red cell loss and of the interstitial inflammatory reaction to leptospires. Tubular degeneration is well established by 2 weeks and is accompanied by interstitial infiltration of plasma cells and lymphocytes, which may be focal or diffuse. Leptospiral antigen is present in peritubular macrophages. The renal lesions may be insignificant, or may cause chronic debility or death in uremia.

Abortion, stillbirth, or the birth of congenitally infected young may follow weeks or months after maternal leptospiremia and is the most important form of the disease in ruminants and pigs. Horses are particularly likely to develop recurrent uveitis (“periodic ophthalmia”), but uveitis can develop in other species following leptospirosis.
Gross lesions and histopathology: The postmortem appearance of an animal that dies of acute leptospirosis is characterized by icterus and severe anemia. Hemorrhages may be absent, or ecchymoses may be numerous on serous membranes and in the subcutis. The lungs are pale, edematous, and expanded, and fluid, stained by bilirubin, widens the septa. The liver is enlarged, friable, anemic, and bile-stained. It may contain hemorrhages and small zones of necrosis about the central veins, but necrotic foci are not usually seen grossly. Hemoglobinuria is to be expected but may not be present. The most consistent gross lesions occur in the kidneys, and in acute cases consist of subcapsular hemorrhages with multifocal ecchymotic and petechial hemorrhages throughout cortical areas but most prominent in subcapsular regions. With chronicity, these foci become pale and the capsule is increasingly adherent. The kidneys are swollen; during a hemolytic crisis they are dark, but later the pigmented foci become restricted to small groups of tubules and have an appearance suggestive of numerous small hemorrhages. Still later, the kidneys show more or less numerous small gray foci of interstitial reaction that are rather indistinct and more numerous in the cortex than in the medulla.

The histologic changes in leptospirosis are neither prominent nor specific. Edema of the lungs is apparent, and in scattered groups of alveoli and septal lymphatics, there are thin laces of fibrin. Zonal necrosis occurs in the liver; it is usually periacinar and typically a change of severe anemic anoxia. Kupffer cells are hyperplastic and contain excessive amounts of hemosiderin, and there is diffuse but mild cellular infiltration in the portal triads. There can be necrosis in the liver and dissociation of the cords of hepatic cells occur. If the survival period in the acute hemolytic disease is sufficiently long, the biliary canaliculi become distended with bile. In the acutely fatal disease, there are often marked degenerative changes in the epithelium of the cortical renal tubules, the changes varying in severity from hydropic swelling to necrosis and desquamation. The desquamated epithelium produces, in the tubules, granular and cellular casts in addition to the hyaline ones of albuminuria and hemoglobinuria and those due to direct bleeding into the tubules. Pigmentation by intracellular hemoglobin and biliary pigments does not become fully evident until 2 days, and the tubules, which are then strikingly involved, occur in clusters. There is also edema of the kidneys, with distension of the interstitial tissues with fluid, and in this there is mild but diffuse infiltration of plasma cells and lymphocytes. In the acute disease, the organisms can often be demonstrated by appropriate stains in the liver, in which they are partly intracellular, and in the kidneys, in which they occur in the tubular epithelium and frequently as clusters in the tubular lumen. Leptospires may be stained by Giemsa or by silver-impregnation techniques of Warthin-Starry.

37. Listeriosis

Etiology and pathogenesis: Listeriosis is caused by *Listeria monocytogenes*, a Gram-positive, facultative anaerobic bacillus that is ubiquitous in the environment and can multiply in diverse environmental conditions - it can grow in a temperature
range from 4 to 45°C and at a pH range of 5 to 9. It is remarkably viable in the external environment, being able to survive in dried media for several months and in suitably moist soil for more than 1 year. The organism is commonly isolated from tissues of normal animals, including tonsils and other gut-associated lymphoid tissue, and in large numbers from the feces of ruminants.

Listeriosis is of worldwide distribution. The organism has been isolated from diseased mammals and birds of many species and produces septicemia, meningitis, and abortion in humans. In domestic animals, the disease is most important in ruminants. *L. monocytogenes* is an intracellular pathogen of macrophages, neutrophils, and epithelial cells. Listeriosis behaves as three separate diseases or syndromes. They seldom overlap so that each syndrome probably has a separate pathogenesis. The three recognized syndromes are: infection of the pregnant uterus with abortion, septicemia with miliary visceral abscesses, and encephalitis. Additional syndromes of clinical significance in ruminants include conjunctivitis, possibly from contaminated silage dust, endocarditis, and mastitis. The uterine infection in ruminants causes abortion in late gestation. The uterine infection is probably hematogenous and the bacteremic phase is asymptomatic, and localization occurs only in the uterus.

Septicemic (systemic) listeriosis occurs in aborted fetuses and neonatal lambs, calves, and foals up to 1 week of age and in others that are several months of age, and is characterized by multisystemic bacterial colonization and multifocal multisystemic areas of coagulative necrosis or microabscess formation. The necrotic areas or microabscesses are miliary in distribution, very numerous in the liver, but much less numerous in the heart and other viscera, and characterized by tissue lytic necrosis with infiltration of neutrophils and fewer macrophages. Neonates generally become infected in utero.

Listerial encephalitis occurs almost solely in adult ruminants; its pathogenesis is partially understood. Listerial encephalitis may be sporadic or occur in outbreaks in which the morbidity may be 10% or higher. Outbreaks are usually associated with heavy feeding of silage, with disease most likely occurring in winter and early spring when the animals are indoors. The organism will multiply in spoiled silage that is incompletely fermented and with a pH of 5.5 or above. Ingested *Listeria* is likely to breach the oral mucosal barrier through pathological or physiological wounds, e.g., erupted teeth wounds. After invading the oral mucosa, the bacteria invade the trigeminal nerves and travel centripetally via axons to the brain. In animals, *Listeria* has a remarkable affinity for the brain stem, the lesions being most severe in the medulla and pons and less severe rostrally in the thalamus and caudally in the cervical parts of the spinal cord. Bacteremias with localization in the CNS regularly cause meningitis, choroiditis, and cerebral abscesses. The endophthalmitis of the natural disease is produced by local invasion. Rhinitis is clinically apparent in many cases of encephalitic listeriosis.

The neurological signs are characteristic, there is deviation of the head to one or other side without rotation of the head; when such an animal moves it does so in ci-
ircles, hence the name "circling disease". There is frequently unilateral paralysis of the seventh nerve causing drooping of an ear, eyelid, and lips. There may also be paralysis of the masticatory muscles and of the pharynx.

The course of the disease in sheep and goats is a few hours to 2 days; survival occurs but usually with neurologic handicaps. Listeriosis in swine is comparable to the disease in ruminants, but is relatively rare. Outbreaks of encephalitis may be observed with lesions of usual distribution in the brainstem. Alternatively, there may be abortion and neonatal death. The usual expression of the disease is visceral with miliary abscesses in the liver and heart. The patterns of listeriosis in other domestic species appear to follow the general scheme but are rarely observed. The encephalitic form in adult horses, the septicemic form in foals, and abortions in mares are reported. Several cases of encephalitis caused by *L. monocytogenes* are reported in dogs.

**Gross lesions and histopathology:** Gross lesions are usually not observed in the brain in listerial encephalitis. Occasionally, the medullary meninges are thickened by green gelatinous edema, and gray foci of softening may be found in the cross-section of the medulla. The initial lesions are parenchymal; involvement of the meninges, which is almost constant, is secondary to the parenchymal lesions. Mild meningitis commonly affects the cerebellum and cranial cervical cord, and less commonly is found in patches over the cerebrum and down the spinal cord. The characteristic parenchymal lesion is a microabscess. It may begin in a tiny collection of neutrophils, but more usually begins in a minute focus of microglial reaction. The glial nodules may persist as such, the cells taking on the characters of histiocytes, but the tendency is always for the nodules to be infiltrated by neutrophils and for their centers to liquefy. The focal lesions do not expand much, but suppurative foci may streak through the white matter. Apparently, the organism is not highly toxigenic because the parenchyma surrounding the glial nodules and focal abscesses may be little changed. Commonly however, the white matter is edematous and rarefied. Such areas may be large and lightly, but diffusely, infiltrated by neutrophils and hypertrophied microglia. Focal softening occurs and may coalesce. They are related to vessels that are occluded by inflammatory and thrombotic changes.

Acute vasculitis with exudation of fibrin occurs in the white matter in relation to suppurative foci. The vasculitis is secondary to drainage in the Virchow-Robin spaces from the primary parenchymal foci. Perivascular cuffing is heavy. The cuffs are composed mainly of lymphocytes and histiocytes with a few admixed neutrophils and eosinophils; granulocytes predominate in some cases.

Demonstrating gram-positive intracytoplasmic or intracellular bacilli in tissues in association with the aforementioned lesions is pathognomonic for listerial encephalitis.
38. Maedi-visna and CAE

**Etiology and pathogenesis:** Visna/maedi virus (VISNA) of sheep and caprine arthritis encephalitis virus (CAEV) of goats, in the genus *Lentivirus* of the family Retroviridae, are small-ruminant lentiviruses (SRLV). CAEV is the causative agent of caprine arthritis-encephalitis of goats and VISNA is the causative agent of the visna/maedi disease complex of sheep. In both natural hosts, four clinical and pathological syndromes are recognized, namely mastitis, arthritis, interstitial pneumonia (maedi and ovine progressive pneumonia) and encephalomyelitis (visna of sheep). Within endemic situations, any one or combination of the four syndromes may be present and when in combination one syndrome usually predominates.

Once infected, the virus is never eliminated and, while present, it is active even though there may be no clinical sign of neurologic deficit. Typically for this type of virus infection, the virus is highly cell-associated and replicates only slowly, infection persists for the life of the animal, the incubation period before seroconversion may be several months and before clinical disease may be months or years, the clinical disease is progressive, and the lesions are dominated by active mononuclear inflammatory cells. Transmission of small ruminant lentiviruses through colostrum or milk is the major method of disease spread. Inhalation of nasal secretions following prolonged close contact is a recognized mode of horizontal transmission. The virus is shed in semen, but infection by coitus or artificial insemination has not been documented. In utero transmission occurs rarely or never. Ovine lentivirus infects a variety of cell types, including choroid plexus epithelium, fibroblasts, endothelial cells, and monocytes. However, viral replication is restricted in these cells, and complete viral replication and assembly only occur in mature macrophages. Viral antigen is widespread, having been detected in lung, bone marrow, mammary gland, lymph node, spleen, synovium, brain, and spinal cord of sheep with maedi, and is most abundant in areas of lymphocytic inflammation. Similarly, viral nucleic acid is demonstrable in lung, liver, spleen, lymph nodes, brain, synovium, intestine, kidney, and thyroid gland of goats with CAE.

**Gross lesions and histopathology:** The disease in the brain is chronic and demyelinating. There are no gross neural changes in this disease, and the histologic change is one of patchy demyelinatining encephalomyelitis. The distribution of lesions, involving principally the white matter, is unlike the distribution produced by other neurotropic viruses. There is a mild to severe mononuclear type of cerebrospinal meningitis. The parenchymal lesion may be well-established by 1 to 2 months, and these early lesions are intensely inflammatory with perivascular cuffing and gliosis. They reveal clearly that the process begins in, and immediately beneath, the ependyma diffusely throughout the cerebrospinal axis. In this early stage, the myelinated fibers in the inflammatory foci remain remarkably intact; the gray matter of the cord is irregularly but often intensely affected by a nonsuppurative reaction even 2 to 3 months after inoculation. In the paralytic and terminal stages of the disease, the periventricular destruction of white matter in the cerebrum and cerebellum is extensive,
and in some sections of the brain, especially in the cerebellum, almost every bit of white matter is destroyed leaving the gray matter free. Destruction of myelinated fibers in the spinal cord is patchy and not due to progressive spread of the pericentral inflammation. The demyelinated plaques are characteristically peripheral and triangular in shape with a base on the pia mater. Although dorsal and lateral tracts are most frequently involved, there is no selectivity for particular fiber tracts and no symmetry. The degenerating loci are almost malacic in their severity, and the plaques contain numerous reactive microglia and astroglia. Spinal nerve roots share in the degenerative process. Germinal centers may form in the choroid plexus. In areas of intense inflammation, liquefactive loci of necrosis occur in the white matter and the loss of myelin is expected to be of Wallerian type. In the spinal cord, evidence of remyelination can be found indicating that oligodendrocytes are not target cells and that demyelination may be primary.

The lungs of sheep with maedi are remarkably heavy, pale gray or tan, and fail to collapse when the chest is opened. The lesions are generalized but most obvious in the caudal lobes, and vary from a diffusely firm or rubbery texture, to multiple coalescing gray and firm foci. Mediastinal and bronchial lymph nodes are enlarged, white, and edematous. Lesions of cranioventral bronchopneumonia caused by Pasteurella multocida or Arcanobacterium pyogenes are commonly superimposed on the lesions of maedi. Lungworms Dictyocaulus or Protostrongylus are common in sheep with maedi, and an association between maedi and retroviral pulmonary adenomatosis has been described.

The histologic pulmonary lesions are of interstitial pneumonia. Infiltrates of lymphocytes, plasma cells, and macrophages thicken alveolar septa and form cuffs around blood vessels and airways. The tendency for these cellular infiltrates to form lymphoid nodules with germinal centers is a characteristic feature of maedi. In addition to the cellular infiltrate, alveolar septa are thickened by hypertrophy of smooth muscle and by mild interstitial fibrosis. Mild hyperplasia of bronchiolar epithelium is occasionally present.

Mastitis is an uncommon clinical presentation of VISNA infection, but is a frequent subclinical lesion. There is diffuse firmness and pallor of the mammary gland, and histologic lesions include follicular aggregates of lymphocytes, plasma cells, and macrophages in the mammary interstitium. Similarly, histologic lesions of lymphocytic leukoencephalomyelitis, gliosis, demyelination, and meningitis are occasionally encountered in sheep with maedi, and tend to be most severe adjacent to the ependyma.

Caprine arthritis-encephalitis (CAE) appears to be widely distributed, but the expression of the infection is highly variable, and many infected goats show little or no clinical disease. Clinical disease of the nervous system affects kids 2 to 4 months of age and is frequently fatal. Animals that develop the early nervous disease or have early inapparent infections tend to develop synovitis and periartthritis in adulthood. The clinical signs of CAE are referable to motor spinal dysfunction without signs of cerebral
disease. Onset is indicated by hindlimb lameness and ataxia with paresis that progresses over several weeks to paralysis. The inflammatory lesions in the CNS may remain active for several years in goats that survive. In the early clinical phase of the disease, changes are widely distributed in the white matter of the brain and cord, particularly in the subependyma and beneath the pia in the cord. The distribution and character of the lesions in the nervous tissue in the goat are, in general, similar to those in visna of sheep. The extent of perivascular infiltration by mononuclear cells is also greater in kids than in sheep. In addition to the encephalomyelitis, mastitis, and arthritis seen in CAE, interstitial pneumonia occurs in some natural and experimental cases. Goats with arthritis commonly have unilateral or bilateral carpal lesions, but tarsal, fetlock, stifile, and atlanto-occipital joints may be affected. Histologic lesions include striking villus hyperplasia of the synovium, and synovial infiltrates of lymphocytes, plasma cells, and macrophages. Fibrosis, mineralization, and necrosis of synovium and joint capsule develop in chronically affected animals.

39. Malignant edema

**Etiology and pathogenesis:** The muscles, especially if devitalized in some manner, are highly susceptible to bacteria of the genus *Clostridium*, and these organisms, when they proliferate, are highly toxigenic and cause extensive necrosis of muscle, with blood-stained edema and the formation of gas. Death occurs as a result of systemic intoxication.

These bacteria are gram-positive bacilli, to a greater or lesser degree anaerobic, and they exist in the environment as resistant spores. Conditions for the growth of these bacteria are best produced in deep penetrating wounds. Since the pathogenic clostridia are frequently found in soil and feces, any contamination of an open wound is likely to introduce those potential pathogens. Although their presence in a wound always carries a threat of gas gangrene, the very great majority of wounds thus infected heal without ill effect; in these, the local conditions in the wound must be regarded as unsuitable for germination, vegetation, or the production of toxins.

The species of the genus *Clostridium* that are of most importance as the agents of gas gangrene are *C. septicum*, *C. perfringens* and *C. novyi*. These organisms not only cause gas gangrene, which is usually a mixed infection, but in animals they are, as pure infections, responsible for a number of specific diseases. Ruminants, horses, and swine are highly susceptible to these infections, whereas carnivores are rarely affected with gas gangrene. Since deep wounds are the ones most suitable to the development of gas gangrene, the common causes of such susceptible wounds in animals are castration, shearing, penetrating stake wounds, injuries to the female genitalia during parturition and, especially in swine, inoculation sites. The distinctive characteristics of these local infections are severe edema, the formation of gas bubbles that give crepitation, discoloration of the overlying skin, coldness of the affected part, and, in
particular, the constitutional signs of profound toxemia with prostration, circulatory collapse, and sudden death.

If the muscle is devitalized by the initial trauma, or subsequently as a result of toxic injury to the blood vessels, the development of true gangrene is in order; in this manner, malignant edema or anaerobic cellulitis may develop into gangrene. The pathogenesis of clostridial myositis and cellulitis is obviously not simple and is not initiated merely by the presence of spores or vegetative forms in the wound; it may begin only when the organisms have produced enough toxin to immobilize and destroy any adjacent leukocytes and enough toxin to cause death of tissue. The spread of bacteria is facilitated by increased capillary permeability, the edema fluid separating the muscle fibers and fascia, assisted in this by gas bubbles. Once the process is started, it may progress with extraordinary rapidity. If clostridial myositis is to develop in a wound, there is usually evidence of it within 24 hours.

**Gross lesions and histopathology:** In gas gangrene, there is extensive disintegration of muscle and saturation of the tissues with exudate that is in part serous and in part profusely sanguineous. When lysis of exuded red cells occurs, the tissues become stained darkly with hemoglobin. The tissues have a rancid odor in the beginning and an exceedingly foul odor in the end.

Histologically, edema fluid, poor in protein, separates the muscle fibers from each other and the endomysium. The degenerating muscle fibers stain intensely with eosin, the sarcolemma and its nuclei degenerate, but the striations are unduly persistent. Such a histologic picture is always seen at the advancing margin of the lesion. Neutrophils are never numerous; a few are loosely scattered at the advancing margin of the lesion and slightly greater numbers in the dermis, but they are rapidly and effectively immobilized and destroyed by the toxins. Deeper within the lesions, muscle fibers are fragmented. Fragmentation is by no means a constant feature of gas gangrene and the absence of it at the periphery of lesions indicates only that, in the later stages of the disease, muscle activity is drastically reduced in a recumbent animal. Bacteria are seldom numerous in the lesions, but collections of them may be seen either in muscle fibers or in connective tissue. Involvement of adjacent adipose tissue by the necrotizing process liberates fat droplets that may become embolic.

As well as the local lesion, there is at postmortem severe pulmonary congestion and evidence of profound toxic degeneration of the parenchymatous organs. By very few hours postmortem, there is extensive gas formation in all organs and they crepitate. The liver, especially, may be honey-combed with bubbles, and cut blood vessels continuously release gas bubbles.

**40. Myxomatosis**

**Epizootiology and pathogenesis:** Domestic rabbits are susceptible to several different pox viruses and poxvirus strains. Myxomatosis virus is a poxvirus (leporipoxvi-
rus). This large DNA virus is closely related antigenically to strains of rabbit fibroma virus.

Myxomatosis was first recognized in European rabbits of the genus *Oryctolagus* acquired for experiments in a South American laboratory in the late 19th century. The name “infectious myxomatosis” was used to denote the myxoid appearance of the subcutaneous masses associated with the disease. In the original cases described, the virus was believed to have been transmitted by insect vectors from the relatively resistant tropical forest rabbit (*Sylvilagus brasiliensis*). Myxomatosis was recognized in North America in 1930, where outbreaks of the disease occurred in rabbitries in southern California. Myxomatosis remains enzootic in the western United States, and sporadic cases occasionally occur in domestic rabbits. The brush rabbit (*Sylvilagus bachmani*) has been implicated as a reservoir host in that area. Myxomatosis virus is an example of an infectious agent used as a means of biological control of a specific population. Around 1950, the virus was introduced into the wildlife population in Australia in an effort to reduce (or eliminate) the massive numbers of European rabbits (*Oryctolagus cuniculus*), which had become a major economic problem in that country. Mortality rates of up to 99% subsequently dropped to around 25% within a few years. The dramatic reduction in mortality appears to be related to the natural selection for genetically resistant rabbits in the wild and the emergence of less-virulent strains of the virus. In 1953, myxomatosis virus was released into the rabbit population in France by a citizen who was disenchanted with the wild rabbit problem. The virus subsequently spread to other countries in western Europe, including England. Transmission of the virus is usually mechanical and by arthropod vectors, primarily mosquitoes in North and South America and Australia and fleas in Europe.

**Gross lesions and histopathology:** Following inoculation by an arthropod vector, viral replication results in the development of a primary subcutaneous myxoid mass, usually within 3 to 4 days. Within 6 to 8 days, mucopurulent conjunctivitis, subcutaneous edema, and multiple subcutaneous skin tumors are usually observed. In rabbits that die with a peracute form of the disease, the animal may be found dead, and other than redness of the conjunctiva, there may be no other evidence of disease. Microscopically, in the subcutaneous masses there is proliferation of large, stellate mesenchymal cells (“myxoma cells”) interspersed within a homogeneous matrix of mucinous material, with a sprinkling of inflammatory cells. Hypertrophy and proliferation of endothelial cells occur, and changes in the epithelium overlying the lesions may vary from hyperplasia to degeneration. Intracytoplasmic inclusions may be present in the affected epidermis and in epithelial cells of the conjunctiva. Proliferation of alveolar epithelium, hypertrophy and hyperplasia of reticulum cells in lymph nodes and spleen, focal necrosis, hemorrhage, and proliferative vasculitis have also been described. Lymphoid depletion of the spleen is a common finding.

The presence of characteristic gross and microscopic lesions in rabbits of the genus *Oryctolagus*, particularly in areas where the disease is known to occur, are useful diagnostic criteria. Demonstration of the virus by the intracutaneous inoculation of
young susceptible rabbits with suspect material, recovery and identification of the virus from lesions following inoculation onto chorioallantoic membrane, or cell culture, have been used to confirm the diagnosis. In confirmed cases of myxomatosis, identification of the source of the virus, including possible wildlife reservoirs, and the elimination and exclusion of insect vectors are primary considerations.

41. Paratuberculosis

Etiology and pathogenesis: Paratuberculosis also known as Johne's disease is caused by Mycobacterium avium subsp. paratuberculosis infection. The etiologic agent of Johne's disease has been reduced to subspecies status within M. avium on the basis of the high (>90%) DNA homology among typical paratuberculosis strains and type strains of M. a. avium. The virulence attributes of M. a. paratuberculosis are poorly understood, but presumably reside in resistance to killing in macrophages, through inhibition of the conversion of phagosomes to phagolysosomes. The organisms proliferate in cytoplasmic vacuoles, and transmit to adjacent macrophages, expanding the population of infected cells and recruiting elements of the humoral and cell-mediated arms of the immune system to the site. Diffuse foci of granulomatous inflammation accumulate, reflected in a distinct profile of local cytokine expression. Infected macrophages traffic via lymphatics to the draining lymph nodes and via the portal venous drainage to the liver, ultimately gaining the central circulation.

The disease is most common in domestic ruminants, but infections by M. a. paratuberculosis can also be produced in pigs, and spontaneous disease occurs in a number of free-ranging and captive wild ruminants, camelids, and, rarely, in equids and captive primates. Numerous species of wild mammals, including lagomorphs, rodents, and carnivores, and several species of wild birds, are naturally infected, though not necessarily diseased. The infection can be transmitted experimentally to mice, hamsters, guinea pigs, rabbits, and macaques. A debate exists as to the role of M. a. paratuberculosis in the genesis of Crohn's disease in humans, a chronic granulomatous enteritis.

The epidemiology and pathogenesis of Johne's disease are best understood in cattle, and are assumed to be similar in sheep and goats. Infection is systemic, and organisms may be present in milk, semen, and urine, and may cross the placenta. However, exposure is mainly by ingestion of organisms shed in the feces. Susceptibility to infection is greatest in the first 30 days of life, although clinical disease does not usually develop in cattle until 2 to 5 years of age. Adults may become infected, but are less likely to develop the disease, and often recover from the infection. In addition, evidence is accumulating that the epidemiology is influenced by the soil and pasture type, presumably because these factors can affect the survival and proliferation of organisms in the environment.

Bacteria are taken up by M cells of the dome epithelium over lymphoid follicles and transported to macrophages in Peyer's patches. The major lesions of Johne's disease
are usually confined to the ileum, large intestine, and draining lymph nodes. However, the infection is generalized, because in both clinical and subclinical cases, the organism can be cultured from a variety of parenchymatous organs and widely distributed lymph nodes. In fulminating infections, there is bacteremia, in blood or in infected phagocytes.

The incubation period of Johne’s disease is protracted and irregular. Some carriers, in which bacteria persist in the mucosa and draining lymph nodes, may be infected for life without showing signs. Exacerbations of clinical disease are often associated with parturition, a low nutritional plane, heavy milk yield, and intercurrent disease.

The pathogenesis of Johne’s disease is related to the granulomatous immunoinflammatory response in the lamina propria in the small intestine, and the associated villus atrophy that develops. Malabsorption in the ileum, and filtration secretion from inflamed mucosa, overloads the capacity of the colon to resorb electrolyte and fluid; the function of the colon itself may be compromised by mycobacterial infection. There is malabsorption of amino acids, and enteric loss of plasma proteins, causing reduced productive efficiency, and when negative nitrogen balance occurs, a decline in body condition, and ultimate emaciation. Hypoproteinemia, when it develops, will further promote filtration secretion. Clinically affected cattle are usually 2 years of age or older. The typical manifestation of Johne's disease is profuse diarrhea passed effortlessly. Clinical signs may be intermittent, with long intervening periods of remission. Emaciation is progressive and ultimately fatal, but the appetite is often retained and animals remain bright until the terminal stages.

**Gross lesions and histopathology:** Grossly, advanced cases of Johne's disease have marked loss of muscle mass and serous atrophy of fat depots, intermandibular edema, and fluid effusion in the body cavities. Plaques of intimal fibrosis and mineralization may be evident in the thoracic aorta. Specific gross lesions occur in the intestine and regional lymph nodes. The mesenteric nodes, particularly the ileocecal, are always enlarged, sometimes remarkably so, pale, and edematous, especially in the medulla. Lymphangitis is common, and the lymphatic vessels can often be traced as thickened cords from the intestinal serosa through the mesentery to the mesenteric nodes. Often lymphangitis is the only recognizable gross change, and is specific enough to justify a presumptive diagnosis of Johne's disease at necropsy. The intestinal serosa often has a slight granular and diffusely opaque appearance because of subserosal edema and cellularity. Mucosal lesions may occur from the duodenum to the rectum; they may be segmental or continuous. They are usually best developed in the lower ileum, and in the upper large intestine. The ileocecal valve is frequently described as enlarged, and this area is considered by some to be the earliest and most consistently affected, but abnormalities in this vicinity may not be notable.

The classical intestinal change is diffuse thickening of the mucosa, which is folded into transverse rugae, the crests of which may be congested. When well developed, the mucosal folds cannot be smoothed out by stretching. This lesion is due to accumulation of chronic inflammatory cells and edema in the mucosa and submucosa.
When gross lesions are well developed, the characteristic microscopic change, transmural granulomatous enteritis, is obvious. But in cattle in which gross changes are minimal or absent, the microscopic abnormalities are more subtle. In these the lamina propria is diffusely infiltrated with lymphocytes and plasma cells, and a large number of eosinophils. There may be very few macrophages, and the most characteristic change is an infiltrate of lymphocytes and plasma cells in the submucosa, and associated with the submucosal and mesenteric lymphatics. In more clear-cut cases, villi are moderately to markedly atrophic, and macrophages are focally or diffusely distributed, in the villi, or deeper in the lamina propria, as part of an increased chronic inflammatory cell infiltrate. Giant cells may be present. The inflammatory infiltrate may abnormally separate and displace crypts, which are elongate, with hyperplastic epithelium. Crypts may be distended with mucus and exfoliated cells, probably due to compression and obstruction of their mouths by edema and inflammatory cells. Masses of epithelioid macrophages may accumulate in the submucosa. Foci of necrosis may occur within these aggregates of macrophages, but in cattle, caseation and mineralization are extremely rare.

Lymphangitis is one of the most consistent changes. Initially the lymphatics are surrounded by lymphocytes and plasma cells and many contain plugs of epithelioid cells in the lumen. Granulomas may form in the wall and project into the lumen. These nodules may undergo some central necrosis. Granulomatous lymphadenitis occurs in mesenteric lymph nodes in advanced cases. In the early stages, there is histiocytosis of the subcapsular sinus. Ultimately, nodular or diffuse infiltrates of epithelioid macrophages and giant cells may replace much of the cortex, and infiltrate the medullary sinusoids.

The organism is usually readily demonstrable in macrophages and giant cells in the lesions when appropriately stained by acid-fast techniques. Johne's disease in sheep, and especially in goats and deer, may resemble tuberculosis, on account of caseation and mineralization in granulomatous foci, and for such cases, and in any other situation where there is uncertainty about the acid-fast organism involved, positive identification of the etiologic agent is necessary. Polymerase chain reaction techniques are useful for confirming the diagnosis in individual cases. For isolation, the ileocecal lymph node, and affected segments of gut, are candidate sites for culture to confirm a diagnosis.

42. Porcine circoviral infection

**Etiology and pathogenesis:** Porcine circovirus (genus *Circovirus*, family Circoviridae) has recently emerged as a common pathogen of swine. Porcine circovirus type 1 (PCV1) has been recognized for many years as a nonpathogenic cell culture contaminant. In contrast, Porcine circovirus type 2 (PCV2) was first isolated in 1997 from pigs with a novel disease, postweaning multisystemic wasting syndrome (PMWS). Se-
rum antibody to PCV2 is widespread in swine herds, and PCV2 infection is common in herds with no clinical evidence of PMWS.

PMWS is usually a slowly progressive disease within the herd, with most cases developing in 5 to 12-week-old pigs. Morbidity is typically 5-10% but may be up to 20%, and most affected animals die or are euthanized. Pigs with PMWS lose weight or gain poorly, and have a variable combination of tachypnea, respiratory distress, diarrhea, pallor, and jaundice. Porcine circoviruses are nonenveloped DNA viruses. Porcine circoviral antigen and nucleic acid are most consistently present in the cytoplasm of monocytes, macrophages, and dendritic cells throughout the body, and less often in the nuclei and cytoplasm of epithelial cells in bronchioles, pulmonary alveoli, liver, renal tubules, stomach and intestine, and pancreas. Vascular smooth-muscle and endothelial cells occasionally express circoviral antigen.

Transmission is poorly characterized. Current evidence indicates that PCV2 is sufficient to cause PMWS. However, co-infection with PCV2 and other pathogens, including parvovirus or PRRSV, results in more severe disease. Immunostimulation itself, either as a consequence of viral infection or vaccination, precipitates more severe disease. Thus, activation of the immune response may encourage replication of PCV2, resulting in more severe manifestations of PMWS.

**Gross lesions and histopathology:** The spectrum of gross lesions present and their severity are highly variable. Swine with PMWS are often thin, pale, and may be jaundiced. Lymph nodes throughout the body - particularly the inguinal, mesenteric, and bronchial nodes - are enlarged, soft, and white or gray-tan, and this lymphadenopathy is the most consistent feature of PMWS. Lung lesions, which are common, consist of interstitial pneumonia with generalized firm or rubbery texture, failure to collapse, and mottled color. Cranioventral bronchopneumonia is a frequent concurrent lesion. The liver may be atrophic and discolored yellow-orange. Kidneys may contain patchy pallor or obvious white foci. Lesions resembling dermatitis-nephropathy syndrome may also occur, including swelling and edema of the kidneys, and cutaneous hemorrhages and necrosis.

The characteristic histologic lesions of PMWS in many tissues are granulomatous infiltrates and lymphoid depletion, with formation of distinctive inclusion bodies within the cytoplasm of macrophages. Inclusions are usually multiple within a single macrophage, 1-3 μm diameter, round, and basophilic. Inclusion bodies are most numerous and obvious in lymphoid tissues, including lymph nodes, Peyer's patch, tonsil, splenic periarteriolar lymphoid sheaths, and thymus. In these tissues, there is depletion of lymphocytes from B-cell follicles, with striking infiltration of macrophages into follicles and, to a lesser extent, T-cell-rich paracortical areas. Multinucleate histiocytes may be present amid the granulomatous infiltrates.

Histologic examination of the lungs of pigs with PMWS reveals diffuse or patchy granulomatous interstitial pneumonia. Epithelioid macrophages, multinucleated macrophages, lymphocytes, and fewer eosinophils or neutrophils infiltrate alveolar
septa and may fill the alveoli. Lymphocytes and macrophages often encircle bronchioles and blood vessels. Bronchiolar necrosis is a variable finding, and may progress to bronchiolitis obliterans in chronically affected pigs. Liver lesions are highly variable, progressing from mild aggregates of lymphocytes in portal tracts, to single-cell necrosis of hepatocytes, periacinar necrosis, or widespread hepatocellular loss with condensation of hepatic stroma. Perivascular infiltrates of lymphocytes and macrophages may be present in other organs, including kidney, myocardium, leptomeninges, pancreas, adrenal, stomach, and intestine. Vasculitis, with necrosis of tunicamembranaris accompanied by lymphohistiocytic infiltrates, and exudative glomerulonephritis are less common lesions.

Infection with PCV2 is usually identified using immunohistochemistry or polymerase chain reaction. It is critical to recognize that demonstrating PCV2 infection does not in itself indicate a diagnosis of PMWS. A diagnosis of PMWS is mainly based on the demonstration of consistent clinical findings and gross and histologic lesions, and is supported by the demonstration of active PCV2 infection by immunohistochemistry or polymerase chain reaction. PRRS is the major differential diagnosis for lesions of interstitial pneumonia and lymphadenopathy in pigs. The following are helpful differentiating features, but the lesions of PMWS and PRRS may be difficult to distinguish, and many pigs are co-infected with PCV2 and PRRSV:

- Multiple basophilic inclusion bodies in macrophages are a diagnostic feature of PCV2 infection, and support the diagnosis of PMWS.
- Bronchiolar necrosis is present in some cases of PMWS (and swine influenza), but is not a lesion of PRRS.
- Lung lesions of PMWS tend to be dominated by macrophages, whereas lesions in PRRS are more lymphocytic, although there is much overlap in the morphology of these diseases.
- Granulomatous infiltrates and multinucleate macrophages in lymphoid organs are more typical of PMWS than of PRRS, although both lesions may be present in PRRS.

43. Porcine inclusion body rhinitis

**Etiology and pathogenesis:** Porcine cytomegalovirus (PCMV) infections are ubiquitous and occur throughout the world, but clinical disease is much less frequent. Inclusion body rhinitis is typically an acute to subacute disease of 3 to 5-week-old suckling piglets. Piglets exhibit fever, sneezing, catarrhal nasal exudate, shivering, and occasional dyspnea. Morbidity is high and mortality is low unless secondary bacterial infections develop. Systemic cytomegalovirus infections usually affect piglets less than 3 weeks of age. These may be found dead without premonitory signs, or exhibit sneezing, lethargy, and anorexia, subcutaneous edema of the jaw and tarsal
joints, and dyspnea. Infection of naive pregnant sows induces mild lethargy, anorexia, and delivery of stillborn or weak piglets.

Inclusion body rhinitis is caused by PCMV, a β-herpesvirus. Piglets commonly shed the virus soon after weaning at 3 weeks of age, suggesting that infection is usually acquired by contact with nasal secretions of infected cohorts. Other pigs, particularly those that develop generalized disease, are probably infected from the sow in the neonatal period. The virus replicates in nasal submucosal and lacrimal glands. Viremia develops at 5 to 14 days after infection, depending on the age of the pig, and leads to infection of epithelial cells in renal tubules, liver, duodenum, and elsewhere. Pulmonary alveolar and splenic macrophages may be additional sites of viral replication. Virus is shed in nasal and ocular secretions, in the urine, and in vaginal secretions of sows.

**Gross lesions and histopathology:** Gross lesions in pigs infected with cytomegalovirus are usually only seen in piglets less than 3 weeks of age with generalized disease, and may include catarrhal rhinitis, hydrothorax, hydropericardium, pulmonary and subcutaneous edema, and renal petechiae.

Histologically, large 8-12 μm basophilic intranuclear inclusion bodies are numerous in the epithelial cells of the nasal submucosal glands and their ducts. Affected glands are not diffusely distributed but tend to occur in irregular clusters. As the inclusion forms, cytomegaly and karyomegaly develop. The nuclear membrane becomes indistinct and the inclusions appear as blue-gray smears, and the necrotic epithelium sloughs into the lumen. The developing immune response incites a lymphocytic infiltrate in the lamina propria, macrophages and lymphocytes cluster within degenerating glands, and there is squamous metaplasia of the surface epithelium. Systemic lesions develop following viremia, with intranuclear inclusion bodies in epithelial cells of renal tubules and glomeruli; lacrimal, Harderian, and salivary glands; and less commonly in hepatocytes and sinusoidal lining cells, adrenal gland, esophageal submucosal glands, lymph nodes, spleen, renal medulla, lung, and elsewhere. Inclusions are most numerous in epithelium but also occur in macrophages and endothelial cells; this vascular disease accounts for the petechiation and edema. Inclusion bodies are often accompanied by cytomegaly, lymphocytic infiltrates, and occasionally focal necrosis. Focal gliosis with intranuclear inclusions in scattered glial cells occurs throughout the central nervous system. The viremic phase may last for 2 to 3 weeks and is followed by persistent infection in pulmonary macrophages.

Inclusion bodies, cytomegaly, and karyomegaly are pathognomonic when present. Adenovirus is the only viral agent likely to cause similarly large basophilic intranuclear inclusion bodies, but adenovirus does not induce cytomegaly and is usually restricted to intestinal epithelium in swine. The intranuclear inclusions of pseudorabies are eosinophilic, less obvious than those of cytomegalovirus, focal necrosis is more prominent, and lesions are most prominent in brain, respiratory tract, and lymphoid tissue.
44. Porcine reproductive and respiratory syndrome

**Etiology and pathogenesis:** Porcine reproductive and respiratory syndrome (PRRS) was first identified in the late 1980s, and is now worldwide in distribution. It is an important cause of reproductive failure and interstitial pneumonia, and a predisposing factor for bacterial pneumonia and septicemia. The disease varies greatly in severity and clinicopathologic presentation depending on the strain of the virus (PRRSV), the age of pigs affected, the level and distribution of immunity within the herd, and the presence of other pathogens. On initial exposure, infection spreads slowly through the naive herd and causes a variety of clinical presentations: anorexia and lethargy of all age groups; reproductive failure characterized by late term abortion, stillbirth, mummified fetuses, and weak-born piglets; and interstitial pneumonia causing fatal hyperpnea, dyspnea, and lethargy in suckling pigs infected in utero or in the neonatal period, in weaned pigs, and to a lesser extent in grower-finisher pigs. "Sow abortion and mortality syndrome" describes a devastating disease resulting from PRRSV infection of naive herds, in which up to half of the sows may abort and sow mortality may reach 10%. Viral infection often persists and circulates within the herd indefinitely, the result of prolonged viral shedding from individual animals and continuous entry of naive animals.

The PRRS virus is an enveloped, RNA virus in the family Arteriviridae. The common mode of transmission of PRRSV is direct nasal, oral, or coital contact with saliva, oropharyngeal mucus, urine, semen, serum, mammary secretions, or perhaps feces of infected pigs. Transmission of PRRSV by artificial insemination has been documented, and transmission by contamination of pharmaceutical preparations or needles with infected serum is a potential risk. Aerosol transmission is apparently of limited importance, but can occur at low frequency over short distances.

The pathogenesis of PRRS centers on infection of macrophages at the site of nasal, tonsillar, or pulmonary infection, extension to associated lymphoid tissue, rapid viremia, and infection of macrophages throughout the body. Viral antigen is expressed within 12 hours of infection by nasal and tonsillar macrophages and epithelium, pulmonary alveolar, intravascular, and interstitial macrophages, bronchiolar epithelium, and endothelial cells of pulmonary arterioles. Viremia occurs rapidly, in some cases within 12 hours of infection, and leads to widespread infection of monocytes and tissue macrophages. Viral antigen may be detected in myocardial macrophages and endothelium, follicular macrophages and dendritic cells in lymph node, interdigitating cells in the thymus, macrophages and dendritic cells in the spleen and Peyer's patches, and macrophages in hepatic sinusoids, adrenal gland, interstitium of the kidney, and choroid plexus. Persistent infection is a key feature of PRRSV. Animals remain infectious for in-contact naive pigs for at least 22 weeks after infection. Infection with PRRSV impairs host defenses, and increases susceptibility to infection with *Streptococcus suis, Haemophilus parasuis, Salmonella choleraesuis*, and other opportunistic pathogens. The ability of PRRSV to infect and reduce the function of pulmonary intravascular macrophages is one mechanism whereby PRRSV predispo-
ses to septicemia; a similar impairment of alveolar macrophage functions - including phagocytosis, oxidative burst, and cytokine secretion - may reduce lung defenses against bacterial bronchopneumonia.

**Gross lesions and histopathology:** The major lesions of the postnatal form of PRRS include interstitial pneumonia, generalized lymphadenopathy, and lymphocytic infiltrates in multiple organs. Gross lung lesions vary from undetectable to affecting the entire lung, and tend to be most striking in younger age groups. The lungs fail to collapse when the diaphragm is incised, occasionally retain impressions of the ribs, and have generalized, patchy, lobular, or diffuse distributions of lesions. Affected areas of lung are discolored tan or red, and have a firm texture reminiscent of thymus, which contrasts with the crisp hard texture of bacterial pneumonia. A cut section reveals separation of lobules and oozing of edema fluid. In pigs that develop bacterial bronchopneumonia secondary to PRRS, lesions of cranioventral consolidation may be superimposed on the diffuse interstitial pneumonia. In these cases, the lesions of PRRS may be subtle, yet play a critical role in the development of pneumonia in the herd. Lymph nodes throughout the body - most notably the bronchial, mediastinal, cervical, and inguinal nodes - are enlarged, white or tan, solid, and rarely contain multiple clear cavitations on cut section. Periocular and subcutaneous edema, and mild serous effusions into body cavities, are variable findings.

Histologic lung lesions are of interstitial pneumonia. Alveolar septa are thickened due to infiltration of lymphocytes and macrophages. This feature is easily obscured by atelectasis in routinely prepared samples, but can usually be confirmed by searching for areas of lung in which alveoli are not collapsed- where a single row of erythrocytes is visible in alveolar septal capillaries. Alveoli contain a cellular infiltrate of macrophages, lymphocytes, and fewer neutrophils, and scattered clusters of alveoli are filled with necrotic cells with pyknotic nuclei or karyorrhexis. The latter is highly suggestive of PRRS, and probably represents clusters of apoptotic macrophages. Type II pneumocytes are increased in number, but may or may not form a continuous layer of cuboidal epithelium lining the alveolus. Bronchiolar epithelium is not affected by PRRSV, and a finding of bronchiolar necrosis should incite a search for an alternative or additional diagnosis.

Histologic examination of lymph nodes, tonsils, and spleens of pigs with PRRS may reveal follicular and paracortical hyperplasia, and apoptosis of follicular lymphocytes. Multinucleate cells, probably of histiocytic origin, may be present. Although this lesion is also common in Porcine circovirus type 2 (PCV2) infection, it has been described in PRRSV-infected pigs that have no evidence of PCV2 infection. Perivascular infiltrates of lymphocytes, macrophages, and plasma cells occur in many organs in PRRS. Commonly affected sites include the nasal mucosa, heart, kidney, and brain. Severe neurologic disease occasionally occurs in association with other manifestations of PRRS, possibly related to the infecting viral strain, and lesions of the central nervous system include lymphocytic meningoencephalitis, lymphocytic perivascular cuffs, and focal gliosis. PRRSV may cause vasculitis in the lung and
other organs, manifesting as necrosis of the walls of large and small blood vessels in addition to perivascular and mural infiltrates of lymphocytes and plasma cells.

Aborted fetuses usually lack gross or histologic lesions, and, when present, the lesions are often not specific for PRRSV. Infection may progress from one fetus to another, resulting in live, stillborn, and mummified fetuses in the same litter. Fetal lesions that suggest PRRS include segmental or diffuse hemorrhage of the umbilical cord due to fibrinoid necrosis and suppurative inflammation of the umbilical artery, mild interstitial pneumonia, pulmonary arteritis, lymphocytic myocarditis and encephalitis, and retroperitoneal and mesocolonic edema.

45. Pseudorabies

Etiology and pathogenesis: Pseudorabies is also known as Aujeszky's disease, mad itch, infectious bulbar paralysis, and porcine herpesvirus infection. The causative agent, Suid herpesvirus 1 (SuHV-1; Pseudorabies virus, PRV), belongs to the genus Varicellovirus, subfamily Alphaherpesvirinae, family Herpesviridae, but is unusual for a member of that group in its relative lack of host specificity and by being spread laterally as well as vertically in swine. Trigeminal ganglion, olfactory bulb, and tonsil are the most consistent sites of latency of PRV. In these organs, viral DNA can be detected in the absence of infectious virus. The pig is the only natural host, but the common domestic species are naturally susceptible; there are very few reports in horses and goats. Progressive infections do not occur in humans. The disease is reported worldwide, except for Canada and Australia. Natural infections occur in rats and mice and various species of wildlife and on fur farms. Of the laboratory animals, the rabbit is the most susceptible and is preferred for identification of the virus because of the fairly consistent development of intense local pruritus following subcutaneous inoculation. Guinea pigs are less susceptible and may resist subcutaneous inoculation but succumb to intracerebral and, occasionally, to intraperitoneal inoculation.

The virus is maintained in enzootic areas in wild and domestic swine, for which it is highly contagious but usually asymptomatic, and probably in brown rats. Transmission can occur by ingestion, but the usual method of spread between pigs is thought to be by contact of infective secretions with nasal mucosa or abraded skin. Animals are susceptible to intranasal inoculation and, regardless of the route of infection, the virus can be found in nasal secretions. The virus may also be present in saliva and urine. It is also present in blood, but this is of no significance for epidemiology or transmission. The infection will occur in pigs by contact very readily and probably by direct nose-to-nose transmission, but it does not appear to be contagious between individuals of other species and they probably acquire their infection by contact with swine or, possibly, rats. Pigs may harbor virus for many months in tonsils and nasopharyngeal secretions after exposure, but in other domestic species the virus is fairly strictly neurotropic, and therefore is not excreted unless given experimentally
in large doses. Ingestion of infected pig meat is the usual source of infection for dogs and cats. Cattle and sheep may become infected by direct contact with carrier swine or by aerosol exposure, but there is strong circumstantial evidence implicating contaminated feed.

The pathogenesis of the infection following local inoculation is well established for the rabbit and is probably comparable in other species. The virus causes a local reaction at the site of inoculation if percutaneous and then spreads centripetally along the related nerve to the spinal cord; it then spreads outwards again along other peripheral nerves as other segments of cord are progressively invaded by spread within the CNS. Because of the progressive advance of infection along the cord, death may occur before demonstrable amounts of virus reach the brain and before lesions have time to develop there. Intracerebral inoculation produces encephalitis, and virus spreads to the cord and centrifugally along peripheral nerves to an extent that depends on survival time. Because the virus also circulates in the blood, there is some possibility but no evidence that it invades the brain directly, the evidence instead suggesting that it localizes in viscera and invades the nervous system along autonomic nerves. Following nasal or intraocular exposure, the virus spreads along the related nerves. The route of invasion following ingestion is by retrograde transneuronal infection. Transplacental infections occur in pigs causing abortion in about 50% of sows pregnant in the first month, and the delivery of macerated, mummified, and normal fetuses when infection occurs at later stages of gestation. The virus is reported to be present in the semen of carrier boars.

The signs and course of pseudorabies in pigs are very variable. Most cases are of mild febrile illness without pruritus or nervous signs. Age is a very important factor governing the severity of the disease in swine; the mortality rate in nursing pigs and young weaners may be very high. Very young sucklings do not show specific nervous signs but rapidly become prostrate and die in 12 to 24 hours. In slightly older piglets, incoordination progresses rapidly to paralysis with muscular twitchings, tremors, and convulsions. Some pigs showing severe signs of encephalitis recover. The disease in older pigs is often characterized by fever, rhinitis, and coughing. There may be generalized pruritus in natural cases but it is not severe, being expressed usually by rubbing of the nose or head. Fetal resorption, mummification, stillbirths, and abortions are frequently reported. The characteristic clinical sign of pseudorabies in animals other than pigs is intense cutaneous irritation developing at the point of inoculation or at the terminal distribution of a nerve trunk which passes the point of inoculation. This does not occur until the virus reaches the related segment of cord. Dogs may become frenzied, and besides the intense pruritus (mad itch) there may be jaw paralysis and drooling reminiscent of rabies. The clinical course in these species, which always ends in death, is frequently acute (a few hours) and never longer than 1 week. Pseudorabies may occur in sporadic, although significant, outbreaks in sheep and cattle. The mortality rate is very high. Death may occur without signs of illness or within 1 to 2 days of the onset of clinical signs. There is fever, and the itching may be on any
part of the body but is most frequently about the head or hindlimbs. Other neurological signs are variable but constantly present.

**Gross lesions and histopathology:** There are no specific gross lesions of pseudorabies. At the site of cutaneous infection, there is acute serofibrinous inflammation, ballooning degeneration, and epithelial necrosis with rare intranuclear inclusions. Self-trauma due to intense itching may exacerbate these lesions. The intense pruritus at the site of inoculation is likely due to stimulation of regional sensory nerves by viral spread and multiplication. Gross changes are seen mostly in young pigs. There may be necrosis of tonsils and sometimes of the trachea and esophagus. Rhinitis with patchy epithelial necrosis is common. The lungs may be edematous. Tiny foci (1 to 2 mm) of hemorrhagic necrosis typical of alpha-herpesviral infection may be seen in liver, spleen, lung, intestines, adrenals, and placenta.

The histologic lesions reflect the neurotropic and epitheliotropic nature of the virus. Lesions are similar in all susceptible species, however, epitheliotropic lesions are more commonly seen in young, aborted, or stillbirth piglets and rarely seen in ruminants or carnivores, where the brain lesions are more common. In brain, the gray matter especially is affected, but death may occur before there are clear indications of neuronal degeneration or inflammatory reaction in the brain. With naturally acquired infections, the inflammatory changes are nonsuppurative. In addition, focal gliosis and lesions typical of neuronal degeneration (neuronophagia and satellitosis) are usually present. There is severe ganglioneuritis in paravertebral ganglia. The specificity of the reaction in the brain depends on the development of acidophilic intranuclear inclusion bodies in neurons and astroglia. These inclusion bodies occur in all species, including pigs; fixation in a mercurial fixative is helpful for their demonstration. Inclusions in swine are solid and amphophilic, but in other species the inclusions are granular and often small and multiple in an affected nucleus. By any route of infection, piglets tend to develop panencephalitis with most severe lesions in the cerebral cortex, brain stem, spinal ganglia, and basal ganglia of the brain; in other domestic species, the distribution of lesions in the CNS is local to, and determined by, the route of exposure. Lymphoplasmacytic inflammation with neuronal degeneration of the gastric myenteric plexi is also described.

Epitheliotropic lesions include the presence of tiny areas of coagulative necrosis in the liver, tonsils, lung, spleen, placenta, and adrenals with the presence of the characteristic intranuclear inclusions. Pulmonary lesions may be mild or severe. Edema and mild cellular infiltration may be diffuse and there may be focal or confluent necrotizing, hemorrhagic pneumonia. Hemorrhage and necrosis is present in lymph nodes, and foci of necrosis may be found in tonsils, liver, spleen, and adrenal. Necrotizing vasculitis is described in natural infections in sheep and experimentally in piglets. In aborted or stillborn piglets, which are suitable for examination, there is usually no evidence of encephalitis, but foci of necrosis may be found in liver and other parenchymatous tissues together with focal bronchiolar necrosis and interstitial pneumonia.
46. Pseudotuberculosis

**Etiology and pathogenesis:** *Yersinia pseudotuberculosis* is a gram-negative coccobacillus in the family Enterobacteriaceae. The DNA of *Y. pestis*, the cause of human plague, and *Y. pseudotuberculosis* are at least 90% interrelated. Six serogroups of *Y. pseudotuberculosis* are recognized based on immunoreactivity of the O antigens. *Y. pseudotuberculosis* causes ileitis, lymphadenitis, and abscessation in humans, and infects a wide variety of domestic, laboratory, and native animals and birds throughout the world. The organism is frequently isolated from the feces of normal cattle, and from abortions in sheep, goats, and cattle. In sheep the organism also causes abdominal abscessation and inflammation in the testis and epididymis.

The organism regularly produces disease, often in epidemic proportions, only in rodents and birds. Sporadic infections with this organism and occasional outbreaks of disease occur in domestic species, laboratory colonies, mink and chinchilla colonies, and zoos. Cats, because of their contact with rodents and birds, are the domestic species most apt to be secondarily involved by outbreaks of the disease in its natural hosts. Losses of serious proportion, however, occur in sheep which are exposed to large numbers of organisms during outbreaks of the disease in rodents during cold weather. The ovine disease is known as "pyemic hepatitis". The general pattern of this disease is the same in all species.

*Yersinia pseudotuberculosis* is a facultative intracellular parasite, which explains the latent carrier state and the need for strong cell-mediated immunity for protection from infection. The route of transmission is by ingestion and, in susceptible animals, organisms enter the body through the intestine.

Yersiniosis has emerged as a significant cause of disease in farmed ruminants, including deer. Affected deer may be found moribund or dead, but animals under observation are systemically ill with profuse diarrhea.

In view of the extraordinarily wide host range of *Y. pseudotuberculosis* in natural infections, it is surprising that the infection is not recorded more often. This may be due in part to a preference of the organism for growth at room temperature rather than at 37°C.

The related organism *Yersinia enterocolitica* causes gastroenteritis and mesenteric adenitis in a wide variety of species, including wild and domestic animals and is increasingly isolated from cattle. The organism has been isolated from deer, rabbits, dogs, pigs, horses, mink, various avian species, as well as sheep and goats.

**Gross lesions and histopathology:** Small necrotic foci develop in the Peyer's patches of the ileum and colon, and extend as lymphangitis to the regional nodes. The organism becomes septicemic and may kill susceptible rodents at this stage; more typically, and in all domestic species, caseonecrotic foci form in the mesenteric nodes, spleen and liver, often in association with fibrinohemorrhagic inflammation in the small intestine. The hepatic foci, which are the most obvious, are 1-10 mm in dia-
meter, white and have no or scant tendency to encapsulation or softening. They are interspersed with irregular areas of parenchymal collapse that probably result from vasculitis and thrombosis.

Microscopically, there is necrosis, with bacterial colonies and fragmented leukocytes surrounded by macrophages. Giant cells are absent, even from later contracting granulomas. The mesenteric nodes and spleen contain similar foci, and are enlarged by lymphoid and histiocytic hyperplasia. The mesenteric nodes in the cat may be 2 to 4 cm in diameter and can be grossly confused with intestinal toxoplasmosis or lymphomatosis.

In addition to the mesenteric lymphadenitis and hepatitis, enteritis is consistently present and characteristic in its histologic expression. Numerous bacterial colonies are present in the lamina propria, associated with multiple suppurative foci or a diffuse suppurative enteritis.

47. Rabbit haemorrhagic disease (Calicivirus infection)

**Etiology and pathogenesis:** Rabbit haemorrhagic disease (RHD) was first recognized in the People’s Republic of China in 1984 and subsequently has been diagnosed in many other countries, including Germany, Italy, Switzerland, Russia, Spain, Republic of North Korea, Poland, Hungary, several countries in Africa, Mexico, the United Kingdom, and the United States. The problem of systematic characterization has been hampered by the inability to grow the virus in cell culture. RHD virus is closely related to the calicivirus causing the European Brown Hare Syndrome (EBHS). However, attempts to infect rabbits and hares with the heterologous virus have failed to result in clinical disease. Scientists in Australia recognized the potential of RHD virus as a means of biological control for the wild rabbit population in that country. The virus “escaped” in 1995, and subsequently, millions of wild rabbits have succumbed to the disease. In 1997, RHD virus was surreptitiously introduced into New Zealand as a means of biological control of the rabbit population in that country.

The virus appears to be species-specific, and the small mammals and domestic animals tested to date have been resistant to the infection. The virus can be spread in a variety of ways including direct contact, aerosols, insect and animal vectors, fomites, and contaminated carcasses. In countries where the disease is endemic, inactivated virus vaccines have been used to immunize replacement stock in order to afford protection against the infection. RHD is frequently manifest as an explosive outbreak of the disease. The morbidity may vary from 30% to 80% or higher. After an incubation period of 1 to 2 days, clinical signs are characterized by incoordination, shaking, and a variety of other nervous signs, and death in 2 to 3 days. The mortality in affected rabbits may be up to 80% or more. The highest mortality rates occur in adult rabbits. Rabbits less than 8 weeks old appear to be relatively resistant and frequently survive. It has been suggested that these animals may serve as long-term carriers of the virus.
**Gross lesions and histopathology:** Virus replicates in tissues such as lung, liver, small intestine, and spleen, with subsequent viremia and hemorrhage. Leukopenia, thrombocytopenia, and elevated liver enzymes are typical findings in blood collected from affected animals. Disseminated intravascular coagulation is considered to play an important role in the pathogenesis of this disease. At necropsy, frequently there is blood-stained nasal discharge, pulmonary hemorrhage and edema, hepatomegaly, splenomegaly, perirenal hemorrhage, and serosal ecchymoses on areas such as pericardium and intestine.

Histological findings usually include necrosis of hepatocytes with striking dissociation of hepatic cords. Crypt necrosis occurs in areas of the small intestine. Pulmonary edema, hemorrhage, and necrosis of lymphocytes in splenic follicles and lymph nodes are typical findings. Fibrin thrombi are present in small vessels of multiple organs, including kidney, brain, adrenals, heart, testes, and lung. Erythrophagocytosis may be evident in the spleen. Viral antigen can be demonstrated in infected tissues by immunohistochemistry.

RHD is a disease of major economic importance to the rabbit industry in many parts of the world. Additional characterization of the virus, the epizootiology of the disease, and the potential of RHD virus as a means of long-term biological control remain under study.

48. Rabies

**Etiology and pathogenesis:** Rabies is caused by Rabies virus (RABV), which belongs to the genus *Lyssavirus* of the family Rhabdoviridae. There are seven genotypes of the virus defined by phylogenetic analysis. Type 1 is the classical Rabies virus of animals and vampire bats, and of all other bat lyssaviruses in North America. Type 2 (Lagos bat virus), type 3 (Mokola virus), type 4 (Duvenhage virus) are African genotypes. Types 5 (EBLV-1) and 6 (EBLV-2) are European bat lyssavirus 1 and 2, and type 7 (Ballina virus) is the Australian bat lyssavirus.

The establishment of infection ordinarily depends on inoculation of the virus into a wound, such usually being inflicted by the bite of a rabid animal. Contamination of a flesh wound by infected saliva or tissues is much less dangerous. The virus replicates in myocytes around a bite wound for a short period of time, and then buds from the plasma membrane. Viral particles invade the local neuromuscular junction through conjugation of the viral glycoprotein with the nicotinic acetylcholine receptor, and then invade neurotendinous spindles and ascend to the CNS and paravertebral ganglia via axoplasmic flow. Viral replication in the CNS is followed by centrifugal spread to major exit portals, such as the adrenal gland, nasal mucosa, and salivary glands; the virus is secreted with the saliva for a few days prior to the appearance of clinical signs. The incubation period is variable from weeks to months. Although there are species differences in susceptibility, rabies is one disease to which all mammals are susceptible. The disease can be regarded as one of carnivores because it is almost
always transmitted naturally only by bites, and man, herbivores, etc. are dead-end hosts. There are exceptions to the rule that RABV is bite-transmitted: aerosol infection can occur, as in dense congregations of colonial bats in bat caves, probably as droplet infection from salivary secretions; and a variety of aberrant circumstances may provide transfer opportunities for infectious virus, as has been reported for corneal transplants.

Reservoir hosts vary from time to time and from region to region. The principal reservoir vectors are foxes, dogs and wolves. Sylvatic vectors are responsible for most transmissions to man and domestic animals in countries where dog populations are controlled. Oral vaccination of wild carnivores, by using vaccine-laden baits, and routine vaccination of dogs have led to almost complete elimination of canine-transmitted rabies in developed countries. Rarely, vaccination of severely stressed animals with vaccines containing modified-live virus may induce postvaccinal rabies. In tropical areas where domestic and feral dogs are not controlled, these animals are the principal hazards for man and livestock. Bats present a special epidemiologic problem in South and Central America.

Aberrant behavioral patterns can be recognized in affected animals during epizootics. The period of salivary excretion of virus before the onset of neurological signs is expected to be not more than a few days, vampire bats possibly excepted, and the duration of clinical disease to be a few days only. Once expressed clinically as neurologic disease, rabies is almost invariably fatal; recovery with or without neurologic deficit is quite rare but has been observed in several species following experimental exposure. Progressive infection and clinical disease do not inevitably follow exposure; up to 25% of feral populations may have specific antibodies as evidence that the infection provoked an immune response without progression to neurologic disease.

**Gross lesions and histopathology:** Specific gross lesions are not present at necropsy, but self-inflicted wounds and foreign bodies in the stomach of a carnivore should raise suspicion.

The histologic lesions of rabies, when present, are typical of nonsuppurative encephalomyelitis, with ganglioneuritis and parotid adenitis. Inflammatory changes are usually present, but they may be very mild or absent. The severity of lesions reflects the duration of the clinical disease. In the CNS, inflammatory and degenerative changes are most severe from the pons to the hypothalamus and in the cervical spinal cord, with relative sparing of the medulla. This relative sparing of the medulla appears to apply to all domestic species. The most severe lesions of the disease are generally found in dogs whereas other species, especially ruminants, which are highly susceptible, may show little more than an occasional vessel with a few cuffing lymphocytes and a few very small glial nodules (Babes' nodules), and this in spite of having numerous Negri bodies. These reactive phenomena probably reflect largely the degree of neuronal degeneration, and this may be remarkably slight in herbivores and remarkably severe in dogs. The reaction is typically one of perivascular cuffing and focal gliosis. The cuffs are 1 to several cells thick and composed solely of lympho-
cytes; ring hemorrhages confined largely to the perivascular space are common about cuffed vessels. Hemorrhages are occasionally severe enough to be visible grossly in the spinal cord of horses and cattle. The Babes' nodules are composed of microglia, and they occur in both white and gray matter. The nodules vary greatly in size, some containing only six or seven cells and some containing 100 or more. Diffuse as well as focal gliosis occurs in areas of gray matter such as the pons and in the spinal cord, both horns of the latter being involved.

Neuronal degeneration in carnivores may be very extensive and quite out of proportion to the observed reactive changes, but may be very slight in pigs and herbivores. Neuronal and/or gray matter neuropilar vacuolation (rabies-induced spongiform encephalopathy) is reported to occur in experimental and natural rabies. The specificity of the neuronal changes and of the whole pathologic picture depends on the inclusion bodies of Negri. These are always intracytoplasmic and are present most commonly in the hippocampus of carnivores and in the Purkinje cells of herbivores. They have also been found, but rarely, in ganglion cells of the adrenal medulla, salivary glands, and retina. Negri bodies are round or oval structures usually up to 2-8 μm in diameter. Those in the dendrites, seldom observed except in Purkinje cells, are oval and those in the cell body are usually rounded. There may be one or more per cell, and affected cells are otherwise only little changed. The inclusions are surrounded by a clear thin halo.

Fluorescent antibody techniques are required for positive identification and are essential in the rare chronic cases which may not yield virus on mouse inoculation. If there is no ganglioneuritis in the paravertebral ganglia, then the possibility of the animal having rabies is very remote. If there is ganglioneuritis, it may be part of rabies or something else. Inflammatory changes in the trigeminal ganglion in rabies may be present without inflammatory or neuronal changes being clearly evident in the brain. The ganglionic changes are of the same character as those in the brain, namely acute degeneration of ganglion cells, proliferation of capsule cells, and microglial nodules.

The natural transmission of RABV depends on virus being present in the saliva and, therefore, in the salivary glands. Degenerative changes are reported in the epithelium of the mandibular salivary gland, but not in the parotid, in dogs. The diagnosis of rabies is made by utilizing fluorescent antibody labeling on fresh or fixed tissue, or by virus isolation in cell culture.

49. Rinderpest

**Etiology and pathogenesis:** Otherwise known as "cattle plague," rinderpest is an acute or subacute highly contagious disease of cattle, characterized by erosive or hemorrhagic lesions of all mucous membranes. The distribution of the disease is progressively shrinking, but it is still enzootic in parts of Africa and Asia.
Rinderpest virus (RPV) belongs to the family Paramyxoviridae, genus Morbillivirus. It is a highly pleomorphic RNA virus. The virus is highly fragile under ordinary environmental conditions; it is incapable of surviving more than a few hours outside the animal body under normal circumstances. Probably all cloven-hoofed animals are naturally susceptible to infection, but the expression of infection varies considerably. Infection in Asiatic pigs may be severe but it tends to be mild in European breeds, which are considered "dead-end" hosts for rinderpest. The infection impacts heavily on wildlife populations in close contact with cattle, and they are important in virus spread.

The nasopharyngeal mucosa appears to be the main portal of entry in rinderpest. The virus uses glycoproteins expressed on activate lymphocytes and monocytes and on dendritic cells as receptors, and destruction of such cells may be a means by which it causes immunocompromise. It localizes and replicates initially in the palatine tonsils and regional lymph nodes. This is followed after an 8 to 11-day incubation by a 2 to 3-day period of viremia that coincides with the fever seen clinically. In circulation, the virus is associated with mononuclear cells. After the viremic stage, the virus replicates in all lymphoid tissues, the bone marrow, and the mucosa of the upper respiratory tract and the gastrointestinal tract. Nasal, oral, and ocular secretions, as well as feces, contain high titers of the virus. In general, excretion of virus ceases by about day 9 of the clinical disease, with the onset of neutralizing antibodies. Death occurs in 5-8 days. Explosive outbreaks with high morbidity and mortality are more likely to occur in naive populations. Vaccinated or recovered animals usually have lifelong immunity. Secondary bacterial, viral, protozoal, and rickettsial infections are common.

**Gross lesions and histopathology:** The gross morbid anatomical changes in rinderpest are characteristic but not pathognomonic, and are similar to mucosal disease. The lesions in the upper alimentary tract are necrotizing and erosive-ulcerative. RPV has an affinity for the alimentary epithelium. Most severely affected areas in the oral cavity are those contiguous with lymphoid aggregates. Consequently, the caudal part of the oral cavity is affected preferentially. In nonfatal cases, there is rapid regeneration of the oral mucosal lesions. Esophageal erosions are usually mild and affect the proximal portion. The forestomachs rarely exhibit any lesions.

The histologic lesions of stratified squamous epithelium originate in the stratum spinosum. Entrance into the epithelium may be via infected Langerhans cells that then pass virus along to adjacent cells. Immunohistochemically, irregularly shaped rafts of acanthocytes are infected with virus. These same cells then undergo degeneration and necrosis. Multinucleate syncytia form in the epithelium and these may have cytoplasmic and nuclear inclusions. Abrasion causes the necrotic tissue to lift off and produce shallow erosions or ulcers. This occurs so readily that they are usually the first lesions observed. Their margins are sharp, and the bases are reddened by the underlying congested capillaries. The initial minute erosions enlarge and coalesce to form extensive defects.
The abomasum is often severely reddened. Lesions in the intestine are severe and severity correlates with amount of lymphoid tissue in subjacent areas. Consequently, greatest mucosal damage is seen in ileum and the proximal colonic patch. Peyer's patches are almost universally involved. These areas become hemorrhagic and necrotic, and are associated with necrosis of the overlying mucosa, leaving deep ulcers. There is replication of virus at all levels of intestine, with both crypt and villus epithelium involved. Replication is associated with formation of inclusion bodies, both nuclear and cytoplasmic, degeneration, necrosis, denuding of epithelium, formation of crypt abscesses and, if prolonged enough, villus atrophy.

RPV is tropic for lymphoid tissues. Infection and replication have been documented in both lymphocytes and macrophages. Necrosis of follicular lymphocytes is extreme, and gross inspection, which reveals little abnormality of nodes, is misleading. Multinucleate cells, similar to those in the oral mucosa, occasionally form in the lymph and hemolymph nodes. All or only some follicles may be involved and there is often an increase of other leukocytes in the sinuses. Similar lesions occur in the spleen, tonsils, and, as already noted, in the Peyer's patches.

Acute congestion and edema of the conjunctiva may be followed by purulent conjunctivitis and corneal ulceration. Petechiae are common in the mucosa of the upper respiratory tract, which is usually covered with mucopurulent exudate.

The gross lesions resemble those of severe acute bovine viral diarrhea and mucosal disease, but rinderpest is distinguished microscopically most readily by the presence of syncytia and inclusion bodies.

50. Salmonellosis

**Etiology and pathogenesis:** The bacterium *Salmonella* is in the family Enterobacteriaceae. It is a facultative anaerobe, a gram-negative rod, and usually motile. The taxonomy of *Salmonella* is confusing and has recently been modified, based on molecular genetic analysis. The genus *Salmonella* is now considered to be comprised of two species, *S. bongori* and *S. enterica*. There are six subspecies and many (>2200) antigenically distinct serotypes or serovars. About 60% of *Salmonella* serotypes belong to *S. enterica enterica*, and occur in birds and mammals. Members of *S. e. enterica* are the predominant cause of salmonellosis in humans and domestic animals. Identification of isolates at the subserotype level, by phage typing, plasmid profile analysis, or other molecular techniques, is desirable when there is evidence of zoonotic transmission, or when epidemiologic tracing is necessary.

The clinical and pathologic syndromes of salmonellosis typically vary from localized enterocolitis to septicemia; abortion may also occur, with or without obvious systemic disease. While some serotypes are strongly host-adapted, others have a very wide host range. Highly host-adapted serotypes, such as *S. Typhi* (humans), *S. Dublin* (cattle), and *S. Choleraesuis* (swine), tend to produce severe systemic disease in
adult, as well as juvenile animals, whereas serotypes with a broad host range, e.g., S. Typhimurium, tend to affect predominantly young animals in most species, and mainly cause enterocolitis, though septicemia may occur. Asymptomatic *Salmonella* carriage may be common, depending on the species, and transmission can occur directly, or indirectly, by contamination of feed, water, or the environment from which the organism is ingested or inhaled. Stressors that compromise immune competence or disrupt the enteric bacterial ecosystem are often implicated in salmonellosis, and disease is usually more common and severe in young animals. The more common "stressors" associated with salmonellosis in domestic animals include transportation, starvation, changes in the ration, overcrowding, pregnancy, parturition, exertion, anesthesia, surgery, intercurrent disease, immunosuppressive drugs, and oral treatment with antibiotics and anthelmintics.

The pathogenesis of salmonellosis may be divided into several stages: entry of the bacteria into the host and attainment of the primary site of infection, usually the enterocyte; attachment to the surface (colonization); and invasion of enterocytes. The organisms usually invade the cells through the brush border; however, they may also enter the mucosa through the intercellular junctional complex. In the cytoplasm, the bacteria are located within membrane-bound vacuoles, which may also contain remnants of microvilli and cytoplasmic debris. Most organisms remain intact and multiply during their transcellular migration in endosomes. Often, many bacteria are present in a single enterocyte during the early stages of infection, but cellular damage is mild and transient. Diarrhea in salmonellosis is an outcome of active secretion of electrolyte, malabsorption due to reduced mucosal surface area and enterocyte competence, and inflammatory exudation, which may contain sufficient fibrinogen to form a pseudomembrane over the affected surface. The volume of fluid originating in lesions in the small intestine may overwhelm the capacity of the colon to compensate; as often as not in salmonellosis, the large intestinal mucosa is also involved, further compounding the compromise to electrolyte and water homeostasis in the gut. Enteritis in salmonellosis is thus characterized by fibrinous or fibrinohemorrhagic exudates over denuded small and large intestinal mucosae, directly mediated by the apoptosis and necrosis induced by invading bacteria, and by the necrotizing effects of local neutrophil activity and microvascular thrombosis.

**Gross lesions and histopathology:** At autopsy, there is blue or purple discoloration of the skin, which may be very intense about the head and ears. There may be superficial ischemic necrosis of the ears. Typically there are petechial hemorrhages in many organs and tissues. The lymph nodes are almost invariably hemorrhagic. The visceral nodes are more frequently and obviously involved than the peripheral ones, with the exception of those of the throat, which are usually hemorrhagic. The mesenteric lymph nodes are greatly enlarged, and they may be speckled with hemorrhages. There may be hemorrhages, petechial or as small discrete blebs, on the laryngeal mucosa. The lungs do not collapse because there is fluid in the respiratory passages. They may be pale blue or purple. Beneath the visceral pleura there are small dark foci of hemorrhage. The lungs are wet and there is fluid in the interlobular
tissue. The changes are best appreciated in the caudal lobes, because the cranial lobes are often the seat of acute lobular pneumonia. These pulmonary changes, attributable in part to endotoxin, account for the respiratory signs observed clinically. The pneumonia is interstitial due to endotoxemia and embolic organisms. The lobar cranioventral pneumonia may be due to ascending *Salmonella* alveolitis and bronchiolitis. Occasionally, the injury to the alveolar septa by *Salmonella* results in extensive fibrinous pneumonia of the caudal lobes. The cardiac serosae often bear petechiae, and in some more virulent infections there is fibrinohemorrhagic pericarditis with scant fluid exudation. The spleen is enlarged, deep blue, firm with sharp edges. There may be petechiae on the capsule. The liver is usually congested, and focal hemorrhages may be visible in the capsule. In some cases the hemorrhages are very large, involving up to half of the central area in a lobule. They may be scattered at random throughout the liver or grouped, often at the edge of a lobe. In some, there are tiny yellow loci of necrosis, referred to as "paratyphoid nodules". Pinpoint hemorrhages are consistently present in the renal cortex. The stomach shows the intense red-black color of the severe congestion and venous infarction. If the animal survives a week or more, the superficial necrotic layer of the affected gastric mucosa sloughs. There may be catarrhal enteritis or, more frequently, the enteritis is hemorrhagic, increasing in severity lower in the tract and terminating in a hemorrhagic ileitis. The mucosae of the colon and cecum may be normal but, if the course is prolonged, there is hyperemia, fibrinohemorrhagic inflammation, or button ulcers. Petechial hemorrhages may occur in the meninges and brain, but there is no gross inflammation. Localization sometimes occurs in synovial membranes, producing polyarthritis.

The histologic changes that occur in internal organs in acute disease are mainly associated with endothelial damage due to endotoxin, and focal localization of bacteria. The discoloration of the skin is initially due to intense dilation, congestion, and thrombosis of capillaries and venules in the dermal papillae. There is activation and necrosis of the endothelial cells in affected vessels. The renal lesions vary but principally affect the glomeruli. In some there is diffuse glomerulitis, and this is associated with mild nephrosis and hyaline casts. In others, the glomerulitis is exudative and hemorrhagic and in these a great many capillary loops contain hyaline thrombi. Embolic bacterial colonies are occasionally seen in the glomerular and intertubular capillaries. Fibrin thrombi may also be found in the afferent arterioles and interlobular arteries. The pulmonary lesions are also characterized by thrombosis and vasculitis and a largely mononuclear cellular response in alveolar septa. There is flooding of the alveoli by edema fluid and moderate numbers of alveolar macrophages. This is the usual histologic picture; the extremes are acute fibrinous inflammation or a few scattered parenchymal hemorrhages. In the liver, the paratyphoid nodules may be found in all transitional stages from foci of nonspecific necrosis to reactive granulomas. Typically there are few neutrophils, and whether the nodules are necrotic or reactive depends on their duration. The initial change is focal coagulative necrosis. About the margin, the macrophages accumulate and form small histiocyti
granulomas which expand and displace the surrounding parenchymal cords. In the spleen there are some scattered hemorrhages, but the overall histologic impression is of increased histiocytes with a scattering of neutrophils. The follicles are small and rather inactive. Very small foci of necrosis, containing many bacteria, may be sparse or relatively numerous, and these develop a reactive macrophage response and form the typical paratyphoid nodules. Meningoencephalomyelitis occurs in a proportion of cases of septicemic salmonellosis. The lesion is fundamentally a vasculitis. There may be petechiae in the meninges but, microscopically, there is infiltration of large mononuclear cells in the pia-arachnoid and concentrated about the veins. The organism is relatively fastidious and cultures from postmortem samples may not be uniformly positive.

It is suspected that the organism may penetrate the bloodstream from a mucosal surface, resulting in transient bacteremia, which, in a pregnant animal, results in placental localization and abortion. Abortion is usually a single event in a herd or flock but is occasionally multiple. Abortion may occur at any stage of gestation. The fetus may be severely autolyzed or well preserved, and gross lesions are visible in the placenta, trachea, and lung. The placenta is often retained and when submitted may be heavily contaminated. Gross examination of portions submitted reveal marked autolysis and suppurative placentitis with yellow-to-brown exudate over swollen edematous cotyledons. In some fetuses, a hemorrhagic cast is present in the trachea. On gross examination of the lung, it is dark red and swollen with minute yellow foci visible on the surface. On microscopic examination of the placenta and fetus, lesions may be modest (with large numbers of bacteria but no inflammatory cells in placenta and lung) or excessive (with a severe necrotizing, suppurative process in the placenta and acute fibrinous bronchopneumonia in the lung).

51. Streptococcal infections

Streptococci cause a variety of infections in domestic animals, including septicemia, meningitis, polyarthritis, bronchopneumonia, and endocarditis. Here are mentioned only some of the important infections in animals.

*Streptococcus suis* type 2 is carried in the palatine tonsils of pigs, and infection is probably by the respiratory route. In infected herds, it is isolated from up to 80% of clinically normal pigs and is commonly found in nasal turbinates and pneumatic lungs, where it is probably a secondary invader. Limited outbreaks do occur but sporadic, isolated disease is more common. The incubation period varies from 1 to 14 days and the clinical course from 4 to 48 h. Affected pigs are usually about 10 to 14 weeks of age and the most significant lesion is purulent meningitis, which, along with polyserositis, is visible grossly in about 50% of pigs. The bacteria probably enter the cerebrospinal fluid within monocytes via the choroid plexuses. Purulent arthritis occurs in a few animals, usually those at the lower end of the age range. Fibrinous-purulent pericarditis, endocarditis, or hemorrhagic, necrotizing myocarditis occur in
some pigs. Endocarditis most often affects the mitral valve. The myocarditis grossly may resemble mulberry heart disease but the histologic lesions of necrotizing vasculitis and diffuse inflammation associated with bacteria are distinctive. Occasionally, *Streptococcus suis* type 2 causes septicemia in newborn piglets.

Otitis media as a clinically obvious entity is most frequent in feeder pigs. The infection is usually unilateral and associated with hemolytic streptococci. The epithelium lining the tympanic cavity is hyperemic, edematous, and may be ulcerated. Neutrophils exuding from the reactive vessels under the epithelium enter the tympanic cavity, joining the initially serous or serofibrinous exudate to make it progressively more purulent. Exudate may temporarily drain into the pharynx via the Eustachian tube, which is soon sealed by inflammatory swelling of its epithelium. In severe infections, the exudate escapes via inflammatory lysis of the tympanum or, rarely, the bone on the ventral floor of the tympanic bulla. Chronic inflammation is characterized by inspissation of exudate, lysis of the ossicles and, occasionally, the tympanum, and spread to inner ear and brainstem.

*Streptococcus equi* ssp. *equi* infection (strangles) is a common acute contagious disease of horses characterized by inflammation of the upper respiratory tract and abscession in the regional lymph nodes. The disease commonly occurs in young horses following exposure to carriers or diseased horses. Clinical signs may include purulent nasal discharge, inappetence, fever, depression, unilateral or bilateral swelling of the throat region, stertor, and dysphagia. *S. equi* in exudates can survive for many months in the external environment, and may be transmitted by fomites. The initial source of infection, however, is usually a carrier animal or one with active but not necessarily obvious clinical disease. The incubation period of strangles is 3 to 4 days, although it may be as short as 2 or as long as 15 days.

The pathogenesis of the infection involves rapid transport of bacteria from the tonsil to local lymph nodes, and adhesion to nasopharyngeal epithelial cells. There is intense chemotaxis of neutrophils to the mucosa and regional lymph nodes, yet the organisms resist phagocytosis and neutrophil-mediated killing. The submandibular and retropharyngeal nodes are the first and usually the most severely affected. The swollen lymph nodes are initially firm, but this swelling becomes fluctuant as the suppurative exudate liquefies. The typical and favorable outcome of the lymphadenitis is for the abscesses to rupture on to the skin 1 to 3 weeks after onset of infection, releasing creamy yellow-white pus containing numerous infective bacteria. The nasal lesions are those of a purulent rhinitis but are otherwise nonspecific. Twenty percent of clinically affected animals develop complications. These may involve extension of infection to adjacent structures, resulting in purulent sinusitis, guttural pouch empyema, periorbital abscessation, facial cellulitis, or local damage to cranial nerves, resulting in laryngeal paralysis (roaring), facial nerve paralysis, or Horner's syndrome. More serious complications of pneumonia or pleuropneumonia, myocarditis, mesenteric lymph node abscesses, and purpura hemorrhagica are often fatal. Retropharyngeal abscesses may discharge into the pharynx, allowing pus to be aspirated into the
lungs where localized areas of necrotizing pneumonia develop. Metastatic abscesses occasionally form in the liver, kidneys, synovium, and brain, but are most common in mediastinal and mesenteric lymph nodes. Abscesses in these lymph nodes tend to be very large and, although rupture is unusual, the suppurative process can permeate to adjacent serous membranes and cause purulent pleuritis or peritonitis. There is edema of the head and limbs, petechial hemorrhages on mucosal and serosal surfaces and in muscles, and occasionally glomerulonephritis. Because similar, but usually more mild, lesions may be caused by *S. zooepidemicus* or other bacteria, definitive diagnosis relies on isolation of *S. equi* from purulent exudate.

52. Swine dysentery

**Etiology and pathogenesis:** Swine dysentery, caused by *Brachyspira* (formerly *Serpulina, Treponema*) *hyodysenteriae*, is a well-recognized production-limiting disease of swine worldwide, characterized by large-bowel diarrhea with mucus, blood, or fibrin in the feces. Swine dysentery occurs as a highly infectious disease, mainly of weaned pigs.

*B. hyodysenteriae* is a gram-negative, anaerobic spirochete, 6-9 μm long and 0.4 μm in diameter. The organism is motile, moving in serpentine fashion; it is loosely coiled and has 7 to 13 periplasmic flagella. Originally thought to have a very narrow host range, *B. hyodysenteriae* has also been associated with necrotizing typhlocolitis in rheas. There is apparently a synergistic action between the spirochete and other anaerobes, mainly *Bacteroides* and *Fusobacterium*. Several studies have documented the importance of a diet low in fiber and high in rapidly fermentable carbohydrates for the successful establishment and pathogenicity of *B. hyodysenteriae*.

The pathogenesis of swine dysentery is still incompletely understood. The only virulence factor consistently associated with *B. hyodysenteriae* is the production of hemolysin, and how or whether it contributes to disease is unclear. *B. hyodysenteriae* colonizes the mucus on the mucosal surface, in the lumen of colonic glands, and in goblet cells. Lesions, including exfoliation of surface epithelium, are associated with the presence of large numbers of spirochetes and other anaerobic bacteria on the mucosa. When spirochetes invade surface epithelial cells, they appear to do so through lateral membranes, and do not attach to and penetrate the luminal membrane. *Brachyspira* do not usually invade beyond the epithelial cells. The factors responsible for local necrosis or exfoliation of superficial epithelium in *B. hyodysenteriae* infection are unknown. However, the suite of associated lesions - hyperplasia of the proliferative compartment in crypts; goblet-cell hyperplasia; premature exfoliation of surface epithelium between crypt openings; and an associated mixed mucosal inflammatory cell infiltrate is reminiscent of the changes in cell-mediated villus atrophy in the small intestine, raising the possibility that the lesion is at least in part immune-mediated. The result is mucosal colitis, characterized by superficial erosion, with hyperplasia of cells in colonic glands, hypersecretion of mucus, and a mixed inflam-
matory infiltrate in the lamina propria. Thrombosis of capillaries and venules in the superficial areas of the colonic mucosa and in the gastric fundic mucosa (gastric venous infarction) is probably due to absorption, through the damaged mucosa, of endotoxin released by gram-negative bacteria.

The diarrhea in swine dysentery is due to malabsorption of fluids and electrolytes in the colon. This presumably results from damage to the superficial colonic epithelium. The normal colon of the pig has tremendous absorptive capacity. Interference with colonic absorption results in severe diarrhea and dehydration. Active fluid secretion by the colon, associated with bacterial enterotoxins, does not occur in swine dysentery. Fluid and electrolyte transport are normal in the small intestine.

There is usually an introduction of pigs, presumably carriers, into a herd prior to an outbreak. Once established in a herd, the infection tends to remain enzootic, and although treatment can effect a rapid clinical amelioration, it may not be curative, and relapses at greater or lesser intervals can occur. Apparently infection is not followed by a substantial immunity, although individual carrier pigs are resistant to further challenge with *B. hyodysenteriae* after recovery from disease. The morbidity may reach 90% and mortality 30%. The disease occurs in pigs of all ages over 2 to 3 weeks old, but particularly in pigs 8 to 14 weeks of age. Once initiated, it spreads rapidly by pen contact. The disease is initially febrile, but, with the onset of diarrhea, fever tends to subside. The initial diarrheic feces are thin, semisolid, and without blood or mucus; it is usually only after 1 to 2 days of diarrhea that blood and mucus appear in the feces. Some pigs die peracutely without showing diarrhea, and many that show diarrhea do not have dysentery, but pass feces which contain much mucus.

**Gross lesions and histopathology:** Grossly, pigs that die of swine dysentery are usually gaunt with a contracted abdomen; the eyes are sunken; and there may be blue discoloration of the abdominal skin. Associated lesions may include pericardial serous effusion, and intense congestion of the gastric mucosa due to venous infarction. The intestinal lesions, especially in young pigs dying acutely, and those that have been treated, can be easily overlooked because the mucosal colitis may be mild, patchy, and often more catarrhal than fibrinous. In typical cases, dehydration gives a semiopaque ground-glass appearance to the serosa, and the wall of the cecum and colon is thickened. The colonic content in these cases is usually scant, and dirty gray to red-brown and greasy in appearance. The mucosa, with patchy foci of light fibrin exudation, has the velvety thickening of catarrhal secretion. The most severe lesions approach those of salmonellosis in the extent and severity of fibrin effusion. The production of mucus in swine dysentery becomes copious in many chronic cases due to remarkable goblet-cell hyperplasia.

The earliest microscopic lesions are characterized by discrete areas of epithelial erosion on the superficial mucosa. Thin layers of fibrinocellular exudate cover the eroded areas. In more advanced cases, these areas become more diffuse but remain merely erosive, and exudation is more copious. There may be minor bleeding from small vessels in eroded mucosa. Fibrin thrombi are evident in the capillaries and
venules of the superficial lamina propria. There is usually some edema of the lamina propria, submucosa, and serosa. Initially mucus is expelled from the basilar portions of the crypts. In concert with the increased turnover of epithelial cells associated with the superficial erosion, there is hyperplasia of cells deeper in the glands. The crypts are elongated, lined by proliferative basophilic epithelial cells that have large nuclei, and few differentiated goblet cells. Often, crypts subsequently become dilated and contain necrotic debris.

53. Toxoplasmosis

Etiology and pathogenesis: Toxoplasmosis is one of the most common protozoal diseases affecting humans and animals and is caused by *Toxoplasma gondii*. Felids are the only definitive host and they also can act as an intermediate host. Other intermediate hosts include humans and other mammals. *T. gondii* has three infectious stages: tachyzoites, tissue cysts, and oocysts. Tachyzoites and tissue cysts are found in both intermediate and definitive hosts, however, oocysts are only present in the definitive host. Tachyzoites and tissue cysts are present more commonly in neural tissue and muscles, but can be present in virtually any tissue. Felids become infected by ingestion of tissues contaminated with tissue cysts, and shed oocysts in their feces. Human and other intermediate hosts including felids can become infected by ingesting sporulated oocyst-contaminated food, water, or soil. Transplacental transmission is important in cats, goats, and sheep. *T. gondii* has a thin wall (<0.5 μm), is 5-70 μm in size, and contains several bradyzoites 0.7-1.5 μm. Tachyzoites are 2-6 μm in size. The encephalitic form of toxoplasmosis is most likely to occur in immunosuppressed dog and cats or kittens. Toxoplasmosis in pigs is generalized and can cause devastating disease with lesions including nonsuppurative encephalomyelitis with intralesional *T. gondii* stages.

Five stages of asexual development are recognized in the intestinal epithelium of cats infected with tissue cysts from intermediate hosts. The gametocytes also develop in epithelium on villi, especially in the ileum. In heavy infections, exfoliation of infected epithelium from villi is associated with the development of villus atrophy, and occasional spontaneous cases of diarrhea in kittens seem to be caused by *Toxoplasma*-induced atrophy of villi and malabsorption. In intermediate hosts, and in cats, extraintestinal asexual development occurs in a variety of organs and tissues. Rapidly dividing forms (tachyzoites) may proliferate in cells in many sites for an indefinite number of generations, and are the stage associated with acute toxoplasmosis in cats and other species. Eventually, tachyzoites induce the formation of a cyst wall in a host cell, and divide slowly, forming bradyzoites, which reside in quiescent tissue cysts.

Transmission may occur by a number of different routes. The shedding of oocysts in the feces of cats and wild Felidae has been mentioned earlier. Transplacental infection occurs commonly in sheep and goats and sporadically in swine and humans. Carnivorous animals and humans may become infected by ingesting oocysts from
cats, or more commonly from cysts containing bradyzoites in tissues of infected animals.

Systemic toxoplasmosis occurs most often in young animals, especially immunologically immature neonates and in immunocompromised hosts. Low levels of γ-interferon and the associated inability to activate macrophages are predisposing factors for systemic toxoplasmosis. After ingestion, *Toxoplasma* organisms penetrate the intestinal mucosa. In cats, the enterointestinal cycle and systemic infection occur almost simultaneously. In other animals the tachyzoites are the first stage of infection, after invasion of the lamina propria by sporozoites released from the oocyst, or by bradyzoites released from the tissue cyst digested from food in the intestine. Dissemination of *Toxoplasma* occurs in lymphocytes, macrophages, granulocytes, and as free forms in plasma. From the intestine the organism may follow two routes. It may spread via the lymphocytes to the regional nodes and from there in the lymph to the bloodstream, or it may pass in the portal circulation to the liver and from there to the systemic circulation. Focal necrosis in tissues is common, and appears to be directly related to the rapid replication of tachyzoites in the cells. Lesions in visceral organs are usually evident within 1 to 2 weeks after oral infection. Immune animals develop a chronic or dormant form of *Toxoplasma* infection that is characterized by the formation of cysts, containing bradyzoites. These are mainly located in the brain, skeletal muscle, and myocardium. Cysts may form as early as 1 to 2 weeks after infection and they may persist for months, possibly years.

Systemic toxoplasmosis has been reported in most species of domestic animals. The hallmarks are interstitial pneumonia, focal hepatic necrosis, lymphadenitis, myocarditis, and nonsuppurative meningoencephalitis.

**Gross lesions and histopathology:** Macroscopic lesions in the lung vary from irregular gray foci of necrosis on the pleural surface to hemorrhagic pneumonia with confluent involvement of the ventral portions. Careful examination of the liver usually reveals either areas of focal necrosis or irregular mottling, and edema of the gallbladder. The spleen is enlarged, as are lymph nodes, which are wet and often red. Pleural, pericardial, and peritoneal effusions occur irregularly. Pale areas may be evident in the myocardium and skeletal muscle. Occasionally, the pancreas is the most severely affected organ, in which case an acute hemorrhagic reaction may involve the entire organ. Yellow, small, superficial intestinal ulcers with a hyperemic border have been reported in piglets. Large pale areas of necrosis may be present in the renal cortices, mainly in goats and kittens.

Microscopically, the early pulmonary lesions are characterized by diffuse interstitial pneumonia; the alveolar septa are thickened by a predominantly mononuclear inflammatory cell reaction with a few neutrophils and eosinophils. Macrophages and fibroblasts exude fill the alveoli. Foci of necrosis involving the alveolar septa, bronchiolar epithelial cells, and blood vessels are scattered throughout the lobules. These lesions are soon followed by regenerative changes that are characterized by hyperplasia and hypertrophy of alveolar lining cells, mainly type II pneumocytes: so-called epithelia-
lization of alveoli. Tachyzoites are usually evident in alveolar macrophages and may also be found in bronchiolar epithelial cells and the walls of blood vessels.

In the liver, irregular foci of coagulative necrosis are scattered at random throughout the lobules. There is usually little evidence of inflammation associated with the necrotic areas. Variable numbers of tachyzoites may be present in hepatocytes and Kupffer cells, usually at the periphery of the lesions, but often at some distance. If the pancreas is involved, there is extensive peripancreatic fat necrosis, with areas of coagulative necrosis in parenchyma. Numerous tachyzoites are usually evident in both ductal and acinar cells.

Lesions in lymph nodes are often associated with infection in the corresponding organ. They are characterized by irregular areas of coagulative necrosis, mainly in the cortex. A moderate inflammatory reaction may be evident at the periphery of the necrotic areas. There may be necrosis and depletion of lymphocytes in the follicles. Similar lesions may occur in the spleen. Necrotic areas are mainly located in the red pulp in this organ.

In the heart and skeletal muscle, foci of necrosis and mononuclear cell inflammation may be part of toxoplasmosis. There is often some difficulty in distinguishing between tachyzoites and mineralization of mitochondria in myocytes but, at some distance from areas of acute reaction, inert cysts can usually be identified in healthy fibers.

Brain lesions may vary in appearance. In the most fulminating cases cerebral lesions may be relatively inconspicuous. They consist of nonsuppurative meningoencephalitis with multifocal areas of necrosis and often malacia. There is swelling of endothelial cells, necrosis of vessel walls, and vasculitis. There may be marked perivascular edema and hyperplasia of perithelial cells. Tachyzoites and occasionally cysts may be found in vessel walls and in necrotic areas in both gray and white matter at all levels of the brain. If survival is prolonged, residual cerebral lesions consist of microglial nodules along with perivascular fibrosis that tends to make the vessels very obvious. At this stage tachyzoites are rare, and cysts 30 μm in diameter with a wall of amorphous acidophilic material 0.5 μm thick, located in areas away from the lesions, may be the only form seen.

The finding of tachyzoites and/or cysts in association with areas of coagulative necrosis in one or more organs is highly suggestive of toxoplasmosis. Often the Toxoplasma organisms are difficult to distinguish within the necrotic foci, and immunohistochemical techniques have proved very useful in highlighting their presence.

54. Transmissible gastroenteritis in swine

**Etiology and pathogenesis:** Transmissible gastroenteritis virus (TGEV) belongs to group 1 species of genus Coronavirus. Transmissible gastroenteritis (TGE) may affect swine of any age, causing vomiting, severe diarrhea, and, in piglets, high mortality. The disease is recognized throughout most of the world. The epizootiology of TGE
depends on the overall immune status of the herd and of the various age groups within the herd.

Introduction of TGEV into a naive herd results in rapid spread of disease with high morbidity affecting all age groups. Sows and older pigs will show transient inappetence, possibly diarrhea and perhaps vomiting. Signs may be more severe in sows exposed to high virus challenge from infected baby pigs. Agalactia may occur in recently farrowed sows, perhaps related to TGEV infection of the mammary gland. Suckling piglets develop severe diarrhea, and mortality may approach 100% in piglets under 10 to 14 days old. Older pigs usually develop less severe signs and have lower mortality. In herds with enzootic infection, high piglet mortality may occur in the offspring of recently introduced naive sows, and diarrhea with lower mortality may occur in piglets over about 2 to 3 weeks of age as milk intake and concomitant lactogenic immunity wane. TGE is more prevalent in the winter, perhaps because the virus is not resistant to summer environmental conditions of warmth and sunlight.

Baby pigs that are chilled also seem less able to survive the effects of infection. The severity of disease in baby pigs is partly related to their inability to withstand dehydration, due to their small size, and to their susceptibility to hypoglycemia. Probably as significant is the differentiation, and low rate of turnover, of small intestinal epithelium in the neonate. The surface epithelium is mature and has an extensive vesicular network in the apical cytoplasm associated with uptake of macromolecules and colostrum during the first day or two after birth. Crypts are short and relatively inactive. The population of epithelium susceptible to infection on each villus is therefore large, and the capacity to regenerate new enterocytes is small. By about 3 weeks of age, epithelium is actively proliferative. Virus production by infected enterocytes in older pigs seems less efficient, and replacement of cells lost to infection is more rapid, contributing to the relative resistance seen in swine over about 3 weeks of age.

**Gross lesions and histopathology:** Piglets with TGE have the nonspecific gross appearance at necropsy of undifferentiated neonatal diarrhea. The stomach may contain a milk curd or bile-stained fluid. The small bowel is flaccid and contains yellow frothy fluid with flecks of mucus; chyle is not usually evident in mesenteric lymphatics since there is fat malabsorption.

The microscopic lesions are those of villus atrophy due to exfoliation of surface enterocytes, the severity of which is a function of the age of the pig and the stage of the disease. In young piglets, the lesions are most severe about the time of the onset of diarrhea. In later phases or in older pigs there may be subtotal to moderate atrophy, and the mucosa may be lined by cuboidal to low columnar epithelium, with irregular nuclear polarity and an indistinct brush border. Severe atrophy is readily recognized at necropsy of neonatal piglets, by examination of the mucosa under a dissecting microscope. Lesions are most common in the middle and lower small intestine, and villi in the duodenum are usually tall and cylindrical. Lesions may be patchy, and several areas of lower small intestine must be examined before atrophy is considered not to be present. In animals beyond the neonatal age group, atrophy may not be so
severe and readily recognized under the dissecting microscope, and the contrast with the normally shorter villi in the duodenum of older pigs is not as marked. Histologic assessment of the gut is essential.

55. Trichinellosis

**Etiology and pathogenesis:** Muscle is the habitat for encysted larvae of the nematode *Trichinella* spp., which may survive there for many years. The muscle belongs to the animal that earlier harbored the adult worm in its duodenum, and since animal-to-animal transmission of infection is accomplished by the consumption of infected muscle, most of the species regularly involved are carnivores or scavenger species. Man, dogs, and a variety of wild Canidae, cats and wild Felidae, pigs, rats, mustelids, bears, polar bears, raccoons, and mice become hosts to the adult and their persistent larvae. Other species including horse and birds may become infected when muscle tissue is included in their feed; horsemeat has been a natural source of trichinellosis in man. Trichinellosis is a zoonotic disease sometimes occurring in spectacular outbreaks in man and animals. Humans become infected when they consume uncooked or incompletely cooked meat of pigs, bears, or aquatic mammals.

The parasitic cycle for *T. spiralis* begins with ingestion of infected meat fibers. Gastric juices liberate the encysted larvae, which then molt twice, grow to a length of 1-4 mm as threadlike fourth-stage worms, and molt again. Maturity is reached in about 4 days following ingestion, the adults copulate and the male dies. The ovoviviparous females penetrate via the crypts of Lieberkühn to the submucosal lymphatics where they deposit 0.1 mm long larvae into lymph vessels. The persistence of females in the duodenum is dependent on the state of surface immunity (probably IgA antibody produced locally in the gut wall) and varies from days to 5 to 6 weeks. Some larvae may be passed in feces as the female moves out of the duodenal crypts. The remaining larvae migrate with the lymph, then the blood, to reach the pulmonary and systemic circulations. Those that find their way to muscle may achieve a safe haven away from developing immunity by entering a muscle fiber; those that arrive elsewhere may survive for a brief period but are soon destroyed. In a previously sensitized host, few of the approximately 500 larvae produced by each female are able to enter a muscle fiber in time to ensure survival.

**Gross lesions and histopathology:** Within the muscle fiber, the larva grows, coils and enlarges a segment of the host muscle fiber, which is induced to develop some unusual changes as the "nurse cell." Nuclei enlarge, myofibrils are greatly reduced, the basal lamina is very greatly increased in its thickness and number of folds around the affected segment of muscle fiber, and the sarcoplasmic reticulum, which is in intimate contact with the worm, proliferates. Mitochondria in the immediate vicinity increase in number as they are reduced in size. After a month, the larvae are up to 100 μm long and coiled in a figure of eight. There is usually one per fiber. Larvae are
not normally visible by naked eye inspection of muscles unless they are old and mineralized.

On routine microscopic examination of muscle, larvae lie in bulging glassy segments of muscle fiber that may be loosely encircled by eosinophils, and in due course, by a scattering of lymphocytes, plasma cells, and macrophages. If the parasitized muscle segment degenerates, the larva is exposed and soon dies to become the center of a more acute inflammatory, but still predominantly eosinophilic, reaction. Segments of muscle fiber adjacent to the encysted larva may show evidence of degeneration or subsequent regenerative repair with basophilia and centrally located nuclei. In a heavy infestation, a large proportion of the muscle fibers in predilective muscle sites may be taken up with either the parasite or adjacent reactive zones. Purely physical replacement of functional muscle accounts for most of the clinical signs of infestation when they are present, though usually they are absent. In 2 to 3 months, the cellular reaction subsides and the muscle fibers enclosing larvae become further modified to give the impression, on light microscopy, of a fibrous capsule. Since parasite survival can only be assured by intracellular seclusion, the "capsule" is, in reality, modified muscle cell components or, perhaps more correctly, modified satellite cells and basal lamina. Once the larvae are encysted in this way, further change, apart from muscle fiber degeneration, is usually confined to deposition of mineral in the encapsulating muscle structure, but this does not seem to affect parasite viability. The larvae may survive more than 20 years although the average life span is probably a good deal less depending on host longevity and the occurrence of fiber degeneration.

Several features of this parasitism are unexplained, including the distribution of larvae within the host. Certain muscles such as the respiratory and masticatory muscles are preferentially and heavily infected while other muscles contain a reduced burden. Activity alone is not responsible because a paralyzed diaphragm is still preferentially susceptible. Concentration of larvae in preferred sites may be influenced by blood distribution, increased larval survival, the presence of some needed nutrient, or preferential shielding from normal body defense mechanisms. Heart muscle is sometimes involved, but not heavily; the muscles most involved are tongue, masseter and laryngeal muscles, diaphragm, intercostal muscles, and muscles of the eye, but no striated muscle is exempt. Since some of the selectively involved muscles are small, heavy infestation may have a significant clinical effect in the form of muscle weakness, paralysis, or reduced responsiveness. Usually parasitic infestations of muscle are asymptomatic, and this feature enhances the transfer of infection from animals to man.

Five species of *Trichinella*, with eight genotypes identified by DNA analysis, are parasites of muscle:

- *Trichinella spiralis* is the parasite of pigs, rodents, and man in temperate and tropical climates, and is the most prevalent strain. It is moderately resistant to short-term freezing, and its infectivity is not reduced by freezing and thawing.
• *Trichinella nativa* is found in colder climates and is the species most often encountered in polar bears, bears and aquatic mammals. Its cycle is similar in most respects to that of *T. spiralis* but the larval form is much more resistant to freezing for long periods.

• *Trichinella nelsoni* is found in carnivores in eastern and southern Africa and also in central and eastern Europe.

• *Trichinella britovi* has been reported in southern Europe.

• *Trichinella pseudospiralis* is found in northeastern Europe and differs from the other species in its failure to encyst in muscle.

56. Tuberculosis

**Etiology and pathogenesis:** Tuberculosis, caused by bacteria of the genus *Mycobacterium*, is a chronic disease characterized by caseating granulomas in lung, lymph nodes, and other organs. The classical tubercle bacilli are *M. tuberculosis* (human), *M. bovis* (bovine), and *M. avium* (avian). Two other closely related species are *M. microti* from voles and *M. africanum*. Differing strains of *M. avium* are now commonly included with strains of the very closely related *M. intracellulare* as the *M. avium-intracellulare* complex. To avoid confusion surrounding the term tuberculosis, convention limits it to diseases caused by *M. tuberculosis* or *M. bovis*. Other conditions are referred to as mycobacteriosis or atypical mycobacteriosis. Saprophytic mycobacteria are widespread in soil and water, on vegetation, and in mucous membranes of the oropharynx. These organisms typically cause disease in immunologically compromised hosts, and the manifestations are cervical lymphadenitis, pulmonary lesions similar to tuberculosis, or cutaneous lesions associated with local penetration of organisms through wounds.

The three main species of tubercle bacilli, *M. tuberculosis*, *M. bovis*, and *M. avium*, occur most frequently in their respective hosts, but cross-infections do occur and various other species of animals are affected.

• Bovine tuberculosis refers mainly to disease in cattle caused by *Mycobacterium bovis*, but the term is also used to describe the pathogenic effects of this agent in other hosts. The host range of *M. bovis* is broad, including cattle, deer, elk, bison, buffalo, goats, camels, llamas, swine, elephants, rhinoceros, dogs, foxes, cats, mink, badgers, and nonhuman and human primates. Natural disease is most common in cattle, cervids, humans, and swine.

• *M. avium* causes mycobacteriosis chiefly in birds and is occasionally found in cattle, swine, horses, sheep, and monkeys.

• *M. tuberculosis* is chiefly responsible for tuberculosis in humans, and occasionally infects pigs, captive monkeys, dogs, cats, cattle, and psittacine birds.
Human infections with *M. bovis* are well documented, but are much less common than *M. tuberculosis*. Immunosuppressed individuals, such as those with the acquired immunodeficiency syndrome (AIDS), are at particular risk. Ingestion of milk from cows with mammary tuberculosis is a major route of infection in humans, typically inducing cervical lymphadenitis or other nonpulmonary forms of disease.

Mycobacteria are nonmotile, nonspore-forming pleomorphic coccobacilli. They are gram-positive but almost unstainable by the simpler bacterial stains because of their high content of lipids. They are routinely stained with carbol-fuchsin, and then resist decoloration by inorganic acids. The mycobacterial cell wall contains a large hydrophobic layer of mycolic acids, which bestows hydrophobicity on the cell wall, conferring environmental and antimicrobial resistance.

The method of transmission influences the spectrum of lesions of bovine tuberculosis. Inhalation of droplet nuclei or dust particles containing *M. bovis* is the most common route of infection and leads to infection of the upper and lower airways. Oral infection requires a greater dose of bacilli than airborne infection to cause disease, and elicits lesions in the gut and associated lymph nodes. Transplacental transmission is a sequel of endometrial tuberculosis, and leads to fetal lesions in hepatic and portal lymph nodes. Less common routes of infection include percutaneous inoculation, genital transmission, and intramammary infusion of contaminated pharmaceutical preparations. Important concepts in the pathogenesis of tuberculosis include the ability of mycobacteria to survive within macrophages, and the role of cellular immune responses in inciting granulomatous inflammation and enhancing the ability of macrophages to kill bacilli. The outcome of infection depends on bacterial factors, including the dose and virulence of infecting bacteria, but also on host factors, including the state of immune competence and heritable resistance to tuberculosis.

In the early phases of infection, bacilli are phagocytosed by macrophages and may be eliminated. Alternatively, infected macrophages may remain at the site of primary infection for prolonged periods before the disease progresses. Macrophages stimulated by exposure to mycobacteria secrete interleukin-12, which skews the immune response to favor secretion of interferon-γ and interleukin-2 by CD4+ T-helper-1 lymphocytes. These interferon-γ-producing T-helper lymphocytes signal the development of cell-mediated immunity, first detected at 14 to 28 days after infection. The arrival of these antigen-specific lymphocytes is crucial for host defense, activating macrophages and thus allowing them to overcome the block in phagosome maturation, and upregulate production of bactericidal products, including reactive nitrogen and oxygen intermediates and lysosomal enzymes, killing intracellular bacilli. Activated macrophages appear epithelioid, with abundant cytoplasm and indistinct cell borders, or form multinucleate giant cells. Cell-mediated immune response, called delayed-type hypersensitivity, kills heavily infected macrophages, forming the caseous center of tuberculous granuloma. Bacilli within the caseous center do not multiply but may remain dormant as latent infections that may persist for years, until immunosuppression caused by diseases, drugs, hormones, or malnutrition, or other
unidentified factors disturb the balance between host and agent, allowing proliferation of the pathogen and reactivation of the disease. In summary, the final determinants of the nature and intensity of lesions are the magnitude of the bacterial infection, the intensity and appropriateness of the immune response, and the modifying influences of the structure of the tissue involved.

**Gross lesions and histopathology:** Thorough examination of lymph nodes throughout the body is necessary before declaring a carcass free of visible lesions; only a single lesion is present in most cattle with gross lesions of tuberculosis. The distribution of lesions of bovine tuberculosis depends on the mode of transmission. In most cases, gross lesions are restricted to the respiratory tract and associated lymphoid tissues. Tubercles or craterous ulcers in gut or mesenteric lymph nodes suggest an oral route of infection, or ingestion of infected sputum that has been coughed up from the lung. Generalized disease is less common but well described. In respiratory infections, lesions are most common in retropharyngeal, bronchial, and mediastinal lymph nodes, and less frequent in mandibular and parotid lymph nodes and palatine tonsils. Lung lesions are detected in only 10-20% of cattle with gross lesions, and often affect the caudal lobes. The classic gross lesion is the tubercle: a circumscribed, often encapsulated, 1-40 mm diameter, pale-yellow or white focus of granulomatous inflammation, often with caseous necrosis and mineralization. Larger lesions may contain liquefied or suppurative exudate and be mistaken for abscesses caused by pyogenic bacteria. Bacilli are released from expanding tubercles into the airways, and coughing up of infected sputum may spread the infection by ingestion to cause lesions in intestine or mesenteric lymph nodes, by adherence to laryngeal or tracheal mucosa to incite ulcers or ulcerating tubercles, or by aspiration to seed secondary sites in the lung. Erosion of pulmonary tubercles through the pleura may result in implantation of bacilli throughout the pleural cavity, with development of multiple granulomas on pleural surfaces. Lymphatic spread has been suggested as an alternative route of pleural infection.

Generalized lesions are reported in about 1% of animals with gross lesions of tuberculosis, and probably result from hematogenous dissemination of bacilli following erosion of the wall of a blood vessel by an expanding tubercle. Embolic lesions are most common in lung, and may involve lymph nodes, bone, liver, kidney, mammary gland, uterus, pleura, peritoneum, pericardium, and meninges. Lesions are rare in salivary gland, pancreas, spleen, brain, myocardium, or muscle. In some instances, presumably following substantial release of bacilli into the blood, the presence of innumerable tiny white foci justifies the term "miliary tuberculosis". Erosion through serosal or mucosal surfaces by expanding tubercles spreads the infection by implantation on pleural, peritoneal, pericardial, or meningeal surfaces or along the airways, intestine, or urinary tract.

Histologic features of the tubercle include: (1) a central coagulum of caseous necrosis, consisting of eosinophilic homogeneous material with scant nuclear debris and a variable degree of mineralization; (2) a mantle of macrophages and Langhans-type
multinucleate giant cells; (3) a capsule containing lymphocytes, clusters of neutrophils in some cases, and a rim of collagenous connective tissue in chronic lesions; and (4) rare to numerous acid-fast bacteria within macrophages and giant cells of the mantle zone or extracellularly in the caseous core.

Tuberculosis in horses is often alimentary, with lesions in retropharyngeal and mesenteric lymph nodes and intestine. Intestinal infection may cause localized ulcers or thickened mucosal lesions reminiscent of paratuberculosis (Johne's disease) in cattle. Tubercles in horses are usually uniform, gray, smooth (lardaceous), with little caseation or mineralization but abundant fibrosis.

Tuberculosis in small ruminants is rare, but similar in most respects to the disease in cattle.

Tuberculosis in swine is often systemic, and the morphology depends on the infecting pathogen. *M. bovis* produces caseous and mineralized tubercles similar to those that occur in cattle, and the lesions are often surrounded by a fibrous capsule. In the liver, there is a tendency for the caseous centers to liquefy. *M. avium* produces lesions that are proliferative in nature and consist of tuberculous granulation tissue resembling the lardaceous lesions described in equine tuberculosis. The histologic appearance is of diffuse infiltration of macrophages, epithelioid cells, and Langhans' giant cells accompanied by extensive fibroplasia and numerous bacilli.

Tuberculosis in dogs and cats usually appears as granulation tissue in which macrophages are scattered at random and giant cells are rare. Discrete tuberculous granulomas are uncommon, and composed principally of epithelioid cells surrounded by narrow zones of fibrous tissue in which there are scattered small collections of lymphocytes and plasma cells. Necrosis is often present in the centers of larger granulomas. Giant cells are rare. The presence of central necrosis and fairly small numbers of acid-fast bacilli in lesions of cats helps to distinguish lesions of tuberculosis from those of feline leprosy. The primary foci in the lungs of dogs develop in most cases in the dorsal part of the caudal lobes. Dissemination within the lungs occurs quite rapidly and is predominantly intrabronchial with the production of tuberculous bronchitis and bronchiolitis rather than bronchopneumonia. Pleuritis or peritonitis often accompanies primary infections in the lungs or intestine, respectively, with diffuse or finely nodular pleural thickening by granulation tissue containing few macrophages and bacilli.

57. Tularemia

**Etiology and pathogenesis:** Tularemia is caused by *Francisella tularensis*. The disease was first described in Tulare county of California, USA. The organism is a tiny, gram-negative, very pleomorphic coccobacillus that is a strict aerobe and shares many cultural and epidemiological features with *Yersinia pestis*, the cause of bubonic plague. *Francisella tularensis* is found worldwide except for Australia. *Francisella*
Francisella tularensis infects a wide range of species, including most domestic animals, humans, and wild rodents, and it is in these last two that the disease is most often fatal.

The organism is abundant in nature as an infection of many species of rodents, and it is from these, either directly or by the mediation of insect vectors, that humans and domestic animals acquire the infection. The organism is able to penetrate intact skin and mucous membranes, but it is also infective by ingestion, inhalation, and inoculation by biting insects and ticks. Tularemia in humans is a severe systemic disease, with various manifestations depending on dissemination or localization.

Francisella tularensis is probably common as an infection in animals, but the disease tularemia is not common. It is probable, too, that the infection may remain latent in domestic animals for long periods without causing ill health and with or without focal lesions, as has been observed in dogs. As a facultative intracellular parasite, it may persist for years as a latent infection, for which effective immunity is cell-mediated. Naturally acquired, latent (subclinical) infections with F. tularensis have been observed in dogs and cats but, as a general rule, these species are resistant to the disease.

Fatalities due to tularemia have been observed in foals and sheep in association with heavy infestations by ticks, and it is probable that the disease is endemic in sheep in areas where the reservoir rodents and ticks, especially Dermacentor sp. and Amblyomma sp. abound. The disease in foals is characterized by a systemic and febrile illness with, at autopsy, enlargement of liver, spleen and kidneys, and the presence of the typical small necrotic loci of this disease. Tularemia in sheep is also associated with a heavy infestation of ticks; recovery can occur if the ticks are removed before the illness is far advanced. Affected sheep have high fever, stiffness of gait, depression, diarrhea and an increased respiratory rate. Lesions may be confined to the superficial lymph nodes or show the more classical localization.

**Gross lesions and histopathology:** The disease in rabbits and rodents is recognized by the presence of miliary white foci 2 mm or more in diameter in the liver, spleen and lymph nodes. They are indistinguishable grossly from the lesions caused by Yersinia pseudotuberculosis.

Histologically, the lesions are characterized by very focal but complete necrosis. Neutrophils and pus may be present early and macrophages accumulate, but in slightly older and larger lesions there is total coagulative necrosis with a granularity that resembles caseation. A very few fibroblasts and macrophages produce a sharp, narrow margin for the lesion. The bacteria can be demonstrated quite readily in lesions, in clumps in macrophages and especially as dead but still distinguishable ones in the center of the focus. The lesions in lymph nodes are often larger than those in the liver and may be readily visible grossly as wedge-shaped areas of cortical necrosis demarcated by a narrow zone of intense reactive hyperemia. The affected nodes are palpably enlarged in the living animal and may discharge a thin red pus on to the
skin. The lymphadenitis may be generalized or restricted to the nodes draining the site of infection which, if visible, is an ulcerated papule.

58. Vesicular stomatitis

**Etiology and pathogenesis:** Vesicular stomatitis (VS) affects horses, cattle, and pigs, and may also affect wildlife species such as white-tailed deer, raccoons, feral swine, and some rodents. In humans, the virus may cause an inapparent infection or a mild influenza-like condition. Persistence of viral RNA has been shown in both experimentally and naturally infected cattle, but the reservoir of the virus is unknown. The disease is important because it causes a loss in production, especially in dairy herds, and it must be differentiated from foot and mouth disease in cattle and pigs. VS is the only vesicular disease naturally occurring in horses.

VS virus (VSV) belongs to the Rhabdoviridae family, genus *Vesiculovirus*. It is an enveloped single-stranded RNA virus. Apart from being inactivated by pasteurization temperatures, it shares qualities of resistance with the aphthoviruses. There are several serologically and immunologically distinct types of virus based on epitopes of the surface glycoproteins.

The disease has a seasonal occurrence; outbreaks occur in the warmer seasons and usually cease with the onset of cold weather. The seasonal nature of the disease suggests that it is transmitted by insects; however, insect transmission is not essential and contact transmission has been proven experimentally. VSV has been isolated from both biting and nonbiting insects and black flies have transmitted the virus to pigs. Biting insects most likely become infected from feeding on lesions rather than blood, since viremia is transient, if present. Nonbiting insects act as mechanical carriers of the virus. The intact mucosa is resistant to infection, but abrasions in a susceptible site readily result in infection when contaminated with saliva or exudate from a lesion. Environmental factors that increase the chance of causing abrasions to the skin, teats, or oral mucosa may predispose to infection. Morbidity in lactating dairy cows may be as high as 100%, although only about 60% of the affected animals drool or froth around the mouth. The lesions of VS occur mainly on the oral mucosa; occasionally they do occur elsewhere, including on the feet, and in swine, foot lesions are common. This is by no means a dependable feature, and outbreaks of the disease in cattle have been described in which the lesions were predominantly on the teats. The incubation period following exposure by abrasion is 24 to 72 hours and the viremic phase seems to be short-lived, because the virus cannot be cultured from blood. Secondary lesions are rare. Infectious viral particles can be recovered from a wide variety of tissues within 6 hours postinfection, including salivary gland, tonsils, snout, skin, and lymph nodes.

**Gross lesions and histopathology:** The lesions of VS are indistinguishable from those of foot and mouth disease. Initially, in cattle, there is a raised flattened palepink to blanched papule a few millimeters in diameter in or near the mouth.
These papules rapidly become inflamed and hyperemic. In the course of a day or so, they develop into vesicles 2 to 3 cm in diameter and by coalescence may involve large areas. The shallow erosions which follow rupture of vesicles heal within 1 to 2 weeks unless secondary infections occur. Oral and mouth lesions heal rapidly in swine, but coronary band lesions often become secondarily infected to the point where the claw may separate and slough.

The first microscopic changes are seen in the deeper layers of the stratum spinosum, where the virus replicates. Increasing prominence of the intercellular spaces and stretching of the desmosomes are accompanied by a reduction in volume of the cell cytoplasm. This dissociation of cells proceeds to distinct intercellular edema (spongiosis) followed by further cytoplasmic retraction until the affected epithelial cells float freely in enlarging vacuoles which in turn are loculated by strands of cytoplasmic debris. There is no hydropic degeneration of the epithelial cells and the nuclei until now remain normal. There are no inclusion bodies. With the onset of epithelial cell necrosis there is a pleocellular inflammatory reaction in the mucosa and underlying lamina propria.

In light of the similarity of VS to foot and mouth disease, laboratory confirmation of VS is essential. Vesicular fluid and mucosa from the tongue are good sources of the virus. Diagnosis is accomplished through virus isolation in tissue culture or embryonated eggs, fluorescent antibody techniques, complement fixation to identify viral antigen, polymerase chain reaction, and inoculation of suckling mice.
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