

PATHOGENESIS OF SELECTED DISEASES OF ZOO MAMMALS

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The following is a brief synopsis of the pathogenesis of several major diseases in zoo mammals. Lectures will also include clinical, gross and histologic findings associated with the various diseases.

RUMINANTS:

Tuberculosis (*Mycobacterium bovis*): Bovine tuberculosis is a chronic disease characterized by caseating granulomas in the lung, lymph nodes and various other organ systems. Wildlife reservoirs, which maintain the infection and can transmit disease to domestic cattle include European badgers (*Meles meles*), brush-tailed opossum (*Trichosurus vulpecula*), bison (*Bison bison*), various species of deer (*Cervus elaphus nelsoni*; *C. elaphus elaphus* and *Dama dama*), elk, elephants and rhinoceros. Mycobacteria are nonmotile, nonspore forming gram positive bacteria that are transmitted via inhalation of droplet nuclei or dust particles. Important concepts in the pathogenesis include: mycobacterium survival in macrophages, and the role of cellular immune responses in granulomatous inflammation. Following infection, an initial innate immune response develops as macrophages secrete cytokines, particularly TNF α and C-C chemokines that recruit additional macrophages and lymphocytes to the site. Tuberculin, a protein-lipopolysaccharide component of the bacterial cell wall induces macrophage secretion of IL-12, which causes the transformation of naive CD4+ T cells to TH₁ cells. Activated TH₁ cells secrete IFN- γ , IL-2, TNF- α , and lymphotoxin. IFN- γ activates macrophages, improving their phagocytic ability, increases MHC II presentation, IL-12, PDGF, and TGF- β production. IL-2 stimulates proliferation of T-cells. TNF- α and lymphotoxin stimulate endothelial cells to secrete prostacyclin, increasing blood flow and vasodilation, increase expression of E-selectin (an adhesion molecule), and secrete IL-8 (a chemotactic factor). The cumulative effect is increased microvascular permeability, fluid and fibrin leakage, and the accumulation of monocytes and lymphocytes at the site of sensitization. Sensitized TH₁ cells enter the circulation and remain in the memory pool. Upon re-exposure (via the tuberculin test) memory TH₁ cells are activated by interactions with antigen presenting cells.

Capture myopathy: Exertional myopathies are a group of diseases (e.g. azoturia, tying-up, porcine stress syndrome, and capture myopathy) that are initiated by intensive or exhaustive activity of the major muscle groups (gluteal, femoral and lumbar muscles). Predisposing factors include diet/exercise and genetic predisposition. Following skeletal muscle damage there is a massive release of myoglobin, aspartate aminotransferase (AST) and creatine kinase into the circulation. There are two proposed routes for the skeletal muscle damage and necrosis.

1. Rapid, excessive production of lactic acid and development of hyaline degeneration of myofibers from anaerobic glycolysis. Preferential involvement of glycolytic type 2 fibers (fast-twitch) occurs.
2. Sarcolemmal sodium-potassium-adenosine triphosphatase activity impaired. Sodium release from the sarcoplasm is diminished and there is indirect interference with the efflux of calcium from the cell. Intracytoplasmic calcium increases and activation of neutral proteases disrupt myofibrils and trigger muscle damage.

Byproducts of skeletal damage are associated with renal damage. Myoglobinemia causes acute tubular necrosis via two pathways:

1. Iron released by the myoglobin heme group in the production of hydrogen peroxide causes epithelial damage by lipid peroxidation.
2. Renal ischemia secondary to shock activates the release of chemical mediators of inflammation.

Renal tubular damage leads to vasoconstriction of preglomerular arterioles via renin-angiotensin system or other mediators (e.g. adenosine, thromboxane, and endothelin), ultimately causing decreased GFR. Decreased GFR, backpressure, and oliguria/anuria results in tubular blockage, further tubular collapse and damage

Meningeal worm (*Parelaphostrongylus tenuis*): *Parelaphostrongylus tenuis* is a metastrongyle meningeal parasite of white-tailed deer (*Odocoileus virginianus*). The host range spans from the southeastern US to Canada. Affected deer usually have no clinical signs, but severe, often fatal neurologic disease is noted in aberrant hosts.

Lifecycle: Adults are located in the subdural space and venous sinus in the cranium → eggs are deposited in the venous circulation, eggs lodge in lung and develop to L1 → L1 larvae breach the alveolar wall, are coughed up, swallowed and passed in the feces → Larvae penetrate terrestrial mollusks (snails and slugs), which are the intermediate hosts, and develop to L3 → Definitive host (white-tail deer) ingests intermediate host and larvae migrate through the gut, peritoneum, spinal nerves, spinal cord and into subdural space where they become adults. Migrating larvae can cause granulomatous lesions in the alveoli; petechial hemorrhage in the abomasum and fibrous adhesions in the peritoneum. Infection in an aberrant host occurs following the ingestion of L3 stage gastropod → L3 larvae then migrate from gut to spinal cord. *P. tenuis* rarely matures in aberrant hosts and is not found in the feces.

EQUIDS:

Herpesvirus (EHV): Herpesviridae are widespread and are capable of producing several diseases including respiratory disease, pulmonary vasculotropic disease, enteric disease, abortion and myeloencephalopathy. Recognized equine herpesviruses and their associated disease syndromes include:

Alphaherpesviruses:

- EHV-1: Equine viral abortion, myeloencephalopathy, respiratory disease, chorioretinitis
- EHV-3: Equine coital exanthema
- EHV-4: Rhinopneumonitis virus
- EHV-8: (Asinine herpesvirus) interstitial pneumonia in donkeys
- EHV-9: (Gazelle herpesvirus) encephalitis

Gammaherpesviruses:

- EHV-2: Respiratory disease
- EHV-5: No disease specified

Infection with EHV-1 and 4 is common worldwide. Transmission occurs through inhalation of infective particles, ingestion of infective nasal discharge or aborted fetal material, or via fomites. The virus proliferates rapidly in nasal, pharyngeal, and tonsillar mucosa. Proliferation results in vascular penetration, viremia, association with lymphocytes, and spread to lungs, fetal tissues, endometrial arterioles and placenta at sites of microcotyledonary infarction. Subsequent vasculitis in placental or fetal tissues causes microthrombi, infarction of microcotyledons, ischemia and abortion. Latently infected animals are capable of shedding virus for life and viral reactivation results in shedding. Carriers can reactivate the virus, infect nonimmune in-contact mares, and initiate sporadic abortions or an abortion storm. Infection in older foals is typically a self limiting upper respiratory disease.

Laminitis: The pathogenesis of laminitis is not completely understood. Proposed causes include: carbohydrate overload, toxemia, sepsis, colic, excessive water intake after exercise, excessive consumption of lush pasture, black walnut toxicity, concussive repetitive hoof trauma, and corticosteroids. There are three current proposed mechanisms for the onset of laminitis:

1. Vascular hypothesis: Digital ischemia is the primary event resulting from vasoconstriction and shunting of blood through arteriovenous anastomoses causing laminar necrosis and breakdown.
2. Enzyme-mediated hypothesis due to metalloproteinase activation and release: Direct damage to the laminar epithelial cells or basement membrane is the primary event and vascular lesions are secondary. Following injury, there is a release of "laminitis trigger factors" resulting in overstimulation and activation of gelatinases (MMPs 2 and 9) that degrade basement membrane complexes. Increased apoptosis of basal layer cells may also contribute to lamellar separation.
3. Mechanical trauma induced by abnormally bearing weight on a limb contralateral to another severely lame limb

Regardless of mechanism, certain characteristics are shared: Pain from laminar degeneration results in catecholamine release, further decreasing blood flow. Reperfusion injury, cytokines and inflammatory mediators (Interleukin-1 β) affect the extent of local tissue damage. Hyperplasia and hyperkeratosis of laminar epithelial cells causes broadening and fusion of laminae, which decreases surface area and weakens structural support. Minimal epithelial and basement membrane damage results in regeneration and re-establishment of structural integrity, whereas more severe and diffuse injury results in chronic laminitis.

CANIDS:

Parvovirus: Parvoviridae infect a wide variety of species, causing enteritis in dogs (several species of wild canids), cats, and mink. Parvoviruses are non-enveloped, extremely stable and resistant to adverse environments. Parvoviruses are biologically distinct and vary in their hemagglutination characteristics, host cell ranges, infectivity, and virulence in experimentally inoculated hosts. Parvoviruses infect cells at any phase of the cell cycle. Replication is dependent on cellular mechanisms that are functional only during nucleoprotein synthesis prior to mitosis (greatest effects in tissues with a high mitotic rate). Following oronasal exposure there is uptake of the virus by epithelium over tonsils and Peyer's patches → Virus proceeds to the draining lymphoid tissue and replicates in lymphoblasts → Infected lymphoblasts disseminate and infection of other central and peripheral lymphoid tissues occurs → Lymphocytolysis releases virus, resulting in a cell-free viremia → Neutralizing antibody can be detected in circulation by 5-7 DPI, terminating the viremia → Infection of the gastrointestinal epithelium is secondary with maximal infection of Peyer's patches and crypt epithelium occurring about 5-9 DPI.

Systemic lesions associated with Parvovirus infection:

Gastrointestinal: Occurrence and severity of enteric signs are determined by the extent of damage to epithelium in intestinal crypts, a function of two main factors:

1. Availability of the virus influenced by the rate of proliferation of lymphocytes and their susceptibility to virus replication and lysis
2. Rate of proliferation in the progenitor compartment in crypts of Lieberkühn

Bone marrow: There is cytolysis of proliferating cells in the bone marrow. Circulating neutropenia in severely affected animals is secondary to failure of recruitment from the damaged marrow and peripheral consumption. Lymphopenia results from viral lymphocytolysis in all infected lymphoid tissues.

Heart: Nonsuppurative myocarditis: Acute or chronic heart failure is uncommon, as most dams transfer colostral antibodies. Passive immunity is usually strong enough during the period of actively replicating myocardial cells (first 15 days of life) to prevent heart manifestations.

Canine Distemper virus: Canine distemper is an important, ubiquitous infectious disease of dogs, other canidae, wild felidae, mustelidae, and pinnipeds worldwide. CDV belongs to the genus *Morbillivirus* in the *Paramyxoviridae* family. Other closely related Morbilliviruses of veterinary significance include: Rinderpest, peste des petits ruminants, and phocine distemper viruses. CDV is both pantropic and

epitheliotropic. Natural transmission is usually by inhalation, and the virus is shed in all excretions during the systemic phase of infection. Following inhalation of infective virions, the virus replicates in tonsils and bronchial lymph nodes. Cell associated viremia occurs within 2 DPI and virus spreads to all lymphoreticular tissues and blood lymphocytes. This massive infection of lymphoreticular tissue results in lymphocytolysis and leukopenia, ultimately leading to immunosuppression. There is systemic dissemination resulting in a multitude of disease syndromes that can be attributed to respiratory, GI, urinary, CNS, skin, and endocrine and exocrine glands. Secondary infections are common, especially *Bordetella bronchiseptica* and *Toxoplasma gondii*. Toxoplasmosis, neosporosis, coccidiosis, viral enteritis, cryptosporidiosis, giardiasis and canine adenovirus type 2 are common sequelae to the immunosuppressive effects of CDV.

FELIDS:

Parvovirus: see Diseases of Canids. Feline panleukopenia virus, mink enteritis virus and CPV-2 are considered host range variants of the feline parvovirus subgroup.

Feline infectious peritonitis: FIP is a variant of feline enteric coronavirus and affects domestic and wild felids worldwide. The virus has a propensity to replicate in the macrophage-monocyte system, effectively evading host immune responses. Disease syndromes include the effusive (wet) (most common) and non-effusive (dry) forms, which represent two extremes of a continuum. The virus is transmitted through the oral-fecal or respiratory routes. Initial viral replication occurs in tonsillar and gut epithelium and macrophages. Virus is then disseminated hematogenously in macrophages. Severity of disease depends on virus strain and host response (genetic susceptibility, immune status, concurrent infection). A strong cell mediated response terminates viral replication, although persistent infection may occur. Partial cell-mediated response results in the non-effusive form, whereas the effusive form develops if cell mediated responses are absent. A strong humeral response enhances phagocytosis of the virus by macrophages enhancing viral replication; therefore animals with antibodies to coronavirus may be more susceptible to disease.

Feline Rhinotracheitis: Feline herpesvirus 1 is a member of the Alphaherpesviridae family and is the cause of feline viral rhinotracheitis. All species of Felidae are believed to be susceptible. During periods of stress, carrier animals shed virus to susceptible animals via direct contact (infectious discharges or aerosolization). Viral replication is typically restricted to areas of lower body temperature (e.g. the upper respiratory tract). Viral replication and cytolytic infection of upper airway epithelial cells occurs from 2 to 7 days after infection, and the infection runs its course in 10-14 days. Viremia is uncommon. Disease is occasionally exacerbated by secondary bacterial infection. Cats that have presumably recovered may act as carriers (latency within the trigeminal ganglia).

MUSTELIDS AND PROCYONIDS

Rabies: Rabies, a lyssavirus in the family rhabdoviridae, causes a lethal nonsuppurative encephalomyelitis and ganglionitis of mammals. Reservoir hosts in the United States include foxes, skunks, raccoons and bats. There is viral tropism for the neural and salivary tissues, and transmission occurs through infected saliva in a bite wound or occasionally by aerosol transmission. The virus is inoculated into a wound. Replication initially occurs in myocytes, the virus then enters neural tissue, spreads to sensory paravertebral ganglion, peripheral nerves and the central nervous system. Virions multiply in neurons, migrate via peripheral nerves to the salivary gland. Further viral replication occurs in salivary acinar epithelial cells and is released directly into ducts. There is minimal immunologic response to the virus. The nerve cell receptor for the rabies virus is the acetylcholine receptor. Virus often concentrates in the limbic system, thereby causing the behavior abnormalities that favor its spread to other hosts.

Canine Distemper virus: see Diseases of Canids

INSECTIVORES:

Ringtail: Ringtail is a condition of young animals characterized by annular constrictions of the tail, sometimes with sloughing of the tissue distal to the constrictions. It is associated with high temperature and low humidity (below 40% relative humidity).

MARSUPALS:

Lumpy jaw (*Fusobacterium necrophorum*): *Fusobacterium* is an infectious, suppurative to pyogranulomatous disease occurring in numerous animal species, including cattle, dogs, cats, horses, swine and marsupials. The disease is caused by opportunistic, Gram-positive, non-acid fast, filamentous, beaded, branching, anaerobic or facultatively anaerobic bacteria that normally inhabit the oropharynx and bowel. Infection depends on disruption of mucosal or epidermal barriers by abrasion from coarse roughage, foreign body penetration, bite wounds, or secondary to chronic periodontal disease. The organism then spreads by direct extension along tissue planes and will invade adjacent structures, including bone. Hematogenous dissemination is rarely reported. Pneumonia may follow aspiration or esophageal perforation. *Fusobacterium* spp. induce neutrophil chemotaxis, activate macrophages and stimulate B-lymphocyte hyperplasia. Proteolytic enzymes from the macrophages and degranulated neutrophils disrupt connective tissue, facilitating spread of the bacterium through normal tissue planes. Systemic infection is associated with abscesses in the liver, lung, spleen, stomach, tail tip and hind toes.

RODENTS:

Yersiniosis: Plague is a reportable zoonotic disease caused by *Yersinia pestis*, a gram-negative, facultative anaerobic, non-spore forming, intracellular, coccobacillus. It is acutely infectious and often fatal in susceptible mammals. The majority of cases are reported in semi-arid places (Western US, SE Asia). *Y. pestis* is primarily transmitted by fleas, less commonly by eating of or exposure to infected mammals, and rarely by inhalation of aerosol droplets from animals with pneumonic plague.

- Enzootic rodent hosts - The few genera of rodents that are resistant to infection serve as a reservoir of plague infection for fleas.
- Epizootic rodent hosts include prairie dogs and squirrels, which have low to moderate resistance, serve as amplifiers of plague and increase risk of human infection.
- Resistant nonrodent hosts include ungulates and some carnivores; immune response usually prevents development of clinical signs.
- Susceptible nonrodent hosts include nonhuman primates, humans, domestic and wild cats, black-footed ferrets, and Siberian polecats; these species allow rapid proliferation of *Y. pestis* and have high mortality.

Keys to pathogenicity are invasiveness and evasion of host immune system. Virulence factors include:

- Protein pla (plasminogen-activator) has coagulase, fibrinolytic and C3 degradative activity to enhance tissue invasiveness.
- Yops (*yersinia* outer membrane proteins) inhibit phagocytosis and oxidative burst.
- F1 is a capsular structure that renders the organism resistant to phagocytosis.
- LcrV (low calcium response virulence) interferes with phagocytosis.
- pH6 antigen encodes fimbriae to assist in adhesion to enter phagocytic cells.
- pMT1 (mouse toxin) encodes a protein lethal to rodent species.

Malocclusion: Most commonly refers to overgrown incisors. This may be seen in both older and younger rats.

PINNIPEDS:

Vitamin E deficiency: Vitamin E is important as an intra- and intercellular antioxidant that prevents oxidation of unsaturated lipids within cells. Vitamin E deficiency allows for accumulation of excess lipid hydroperoxides. In mammalian species vitamin E / selenium deficiency is commonly associated with muscular degeneration and necrosis (white muscle disease), hepatic necrosis, steatitis, infertility, embryonic death, and retinopathy. A major function of vitamin E is as an antioxidant, scavenging free radicals (molecules with an odd number of electrons) that would otherwise react with and damage membrane lipids. With vitamin E deficiency there is a loss of antioxidant protection, leading to lipid hydroperoxide formation. Peroxidative damage of capillary membranes results in increased vascular permeability, thrombosis, ischemia, and ultimately tissue necrosis.

Hemochromatosis: Associated with exposure to high levels of iron in the water. Large amounts of iron accumulated in the hepatic parenchyma, biliary epithelium and lymph node cortex. The iron is primarily stored in lysosomes.

RHINOCEROS:

Tuberculosis (*Mycobacterium tuberculosis* and *M. bovis*): see Diseases of Ruminants

ELEPHANTS:

Herpesvirus: Endotheliotropic elephant herpesvirus (elephantid herpesvirus 1; EIHV-1) is apathogenic for African elephants (*Loxodonta africana*), but causes fatal haemorrhagic disease in Asian elephants (*Elephas maximus*). This is thought to occur through transmission from African elephants in places where both species are housed, such as zoological gardens. The virus has caused considerable losses in North American and European zoological gardens and thus severely impedes breeding of the endangered Asian elephant. Previously, the ultrastructural and genetic characterization of EIHV-1 from a male Asian elephant that died from the disease at the Berlin zoological gardens in 1998 have been reported.

Tuberculosis (*Mycobacterium tuberculosis* and *M. bovis*): see Diseases of Ruminants

URSIDS:

Biliary carcinoma: Tumors arising from intrahepatic bile ducts and gallbladder have been described in several species of domestic animals. Epithelial tumors of the extrahepatic biliary tree have been reported in animals on rare occasions, including bile duct carcinomas in bears, sea otters, cats, and dogs. In bears, genetic predisposition and diet changes have been incriminated in the development of extrahepatic bile duct carcinomas.