

Pathology of the Domestic Ferret (*Mustela putorius furo*)

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GENERAL INFORMATION

Taxonomy and Species Characteristics

The ferret of the laboratory and the ferret as pet is a European derived species - *Mustela putorius furo*. The black-footed ferret *Mustela nigripes* is a native of Western North America and is an endangered species. The ferret is also known as the "polecat" of Northern Africa, Europe, and Asia. Two domestic varieties exist based on fur color: The common (wildtype) or fitch ferret with a brown coat and black mask-like facies, feet and tail and the English or albino ferret with yellow-white fur and pink eyes. The ferret has a long slim body, short powerful legs and a long tail. Males are much larger than females. Male ferrets ("hobs") weigh about 3-6 lbs (1.35 - 2.7 kg) and female ferrets (Gills) weigh 1-3 lbs (0.45 - 1.35kg). Both sexes undergo marked seasonal fluctuation of body weight because of changes in the amount of subcutaneous fat which accumulates in the fall and is lost in the spring. Fur also undergoes a seasonal change with molting in early summer.

Ferrets normally live for 5-6 years, but some life spans of 8-9 years are not uncommon. Young are born hairless and blind and eyelids open at 3-4 weeks. Adult weight is reached at about 4 months. Ferrets are described as having a friendly inquisitive nature, but may become irritable and bite if excited and hungry. Ferrets should be handled with gloves unless the history of gentle behavior is confirmed.

Ferrets tend to urinate and defecate in one area of the cage and are readily trained to use a litter box. These nocturnal animals are quiet and sleep much during the daylight hours. Ferrets hiss when disturbed and if frightened or hurt will scream out.

Anatomy and Physiology

The ferret in common with the mink has a relatively short intestine and no cecum and appendix. No external division exists between the ileum and colon and the gut grossly appears as one undifferentiated tube. At a point of about 8-10 cm from the anus, the muscular layers are interrupted by a band of fibrous connective tissue and this marks the division between ileum and colon. No extension of myoelectric complexes occurs from the ileum to the colon.

Ferrets as do the other mustelids have two anal sacs and associated musk-producing glands which produce an olfactant responsible for the odor of ferrets. These glands secrete when the ferret is excited and, at estrus, in females. Male ferrets lack the accessory sex glands: seminal vesicles and bulbourethral glands.

The ferret has a single central ascending artery (inominate artery I) instead of the common bilateral carotid arteries. This single artery appears to be a functional adaptation to insure adequate cerebral blood flow during the time the head is turned 180degrees. The ferret also has very compliant chest walls, large lung capacity and inspiratory reserve in relation to body size, and a long trachea and larger diameter airways. These anatomic features appear to be adaptations to the burrowing nature and

result in much lower pulmonary and airway resistance.

Regulation of heat loss is principally via panting as ferrets lack well-developed sweat glands. The ferret, as other mustelids, does not tolerate high temperatures; heat prostration results when environmental temperature approaches 90 degrees F.

Ferrets lack easily accessible veins and intravenous drug administration is difficult. Drugs may be given by intramuscular, intraperitoneal and subcutaneous injection using the same sites as described in the cat. Care must be exercised when injections are made subcutaneously because the ferret may have a thick layer of subcutaneous fat.

Reproductive Physiology and Behavior

The female ferret is seasonally polyestrous and an induced ovulator and has a breeding season normally extending from March to August. Ferrets reach sexual maturity at about 9-12 months of age. The male ferret has a longer potential breeding season probably related to a functional adaptation to allow time for adequate spermatozoal maturation. The testes of the male are located in the subcutis of the caudoventral abdomen and descend into the scrotum during the breeding season. The ventrally situated penis has a prominent os penis and glans penis with horn-like spines.

Estrus can be manipulated by alterations of the photo-period by artificial lighting. Onset of estrus in the female ferret is indicated by a swollen pink vulva which reaches its full size in about a month and regresses within 2-3 weeks following successful breeding. Mating should be initiated by bringing the estrous female to the male's cage on the 14th day following the onset of vulval swelling. Female not ovulated will have a turgid vulva and will remain in continuous estrus for up to 4 months.

Ferrets do not have delayed implantation as in the mink and other mustelids and the gestation period is about 41-44 days. From 5-13 ova are shed 30-40 hours post-breeding and the trophoblast attaches to the uterine epithelium on the 12-13 days post-breeding. Pseudopregnancy of 41-42 days follows the failed fertilization of liberated ova. In the ferret, placentation is zonal and of the endothelialchorial type. Litter size varies, but a useful average is about 8 kits. Jills have 4 pairs of mammae.

Females should be moved to individual cage about 2 weeks prior to parturition. Females in late pregnancy should not be disturbed as excited females tend to eat their young. Females appear pregnant at about 30 days of gestation. Blind and hairless kits weigh about 10grams at birth and have a large fat pad on the back of the neck. Kits grow rapidly, develop fur at 2 days, and have a fluffy coat by 2 weeks. Eyelids and external ears open at 4-5 weeks of age. Some kits begin eating solid feed at about 3 weeks and kits are weaned at 4-5weeks of age. Weaning body weights for males and females are about 300-450 grams at about 6 weeks of age. Males grow more rapidly after weaning (7-9 weeks of age).

Female ferrets have estrus either at about 2 weeks post weaning of a litter or in the next breeding season depending on the time of year. If female ferrets come into estrus 2-3 weeks after the first birth, they should be bred to reduce the inhibitory effects of estrogens on lactation. Reproductive cycle of the female ferret from the onset of proestrus to the end of lactation is about 14 weeks; breeding females will produce about 10-12young/year.

Breeding stock is generally replaced after 2 or 3 breeding seasons. Neonatal mortality is high due to killing of kits by females and to failure of lactation. Also, congenital abnormalities are of greater incidence in ferrets, up to 3% in some studies, and many of these are lethal. The 8-10% of neonatal mortality occurs mostly during the first 4 days after parturition and mortality decreases markedly after the kits reach 5 days of age.

Clinicopathologic Data

Hematologic values are presented in table 1, serum chemistry values in table 2 and urinalysis data in table 3 (Moody, et al, 1985). The hematologic and clinical chemistry values for ferrets are similar to those of the dog and cat except for a few differences. PCV in the ferret is relatively greater than in the cat. Because of the negligible erythrocytic sedimentation rate in ferrets, the microhematocrit sample must be centrifuged for a longer time. Ferrets have slightly greater numbers of platelets and greater erythrocyte counts than seen in the cat. Blood volume is estimated at 5-7% of body weight. Proteinuria is observed in most normal ferrets.

Blood samples may be collected from several sites. Only small amounts are obtained by toenail clipping (less 0.5 ml) and 1-3ml (in young) and 5-10 ml (in adults) may be obtained from the retro-orbital site. Cardiac puncture and caudal tail vein and jugular vein venipuncture are alternate techniques.

Nutrition

Nutritional requirements of ferrets are unknown but are considered similar to those of the mink. Ferrets should be provided with a diet with 30% fat and 35% protein. Feed consumption varies with sex and dietary factors, but ranges from 140-196 gms daily and daily diet is generally taken in numerous small feedings. Water should be available at all times and water consumption averages 75-100ml daily. Ferrets also are fed commercial dog and cat feed, but these may be deficient in protein content since feed consumption by ferrets is determined by their caloric requirement. Diets with much greater meat and fish and low in fiber are required for ferrets and diets with much content of polyunsaturated fatty acids, such as found in tuna, should be supplemented with vitamin E (provide 10mg/day) to prevent development of yellow fat disease (steatitis and myodegeneration). Canned meat, infant meat products and powdered milk may be added to ferret rations to provide adequate consumption of protein; adequate, up to 35%, protein is especially important for pregnant and lactating females.

Anesthesia and Euthanasia

Drugs and suggested doses for anesthesia are given in table 5 (Moody, et al, 1.985). The xylazine/ketamine combination along with supplemental halothane (with or without nitrous oxide) is considered a very satisfactory procedure for anesthesia in the ferret. Euthanasia can be performed by the use of carbon monoxide as used for the mink or by administration of an overdose of barbituates.

Housing

Various types of caging have been used for ferrets depending on the number of ferrets and the needs of owner or experimental laboratory. Indoor dog or cat cages may be used for ferrets and these may have either wire-mesh or solid-bottoms. The ferrets should have a small box in its cage for a place to sleep. Pregnant females should have small nest boxes with solid floors provided with bedding materials.

Vaccinations

Ferrets should be routinely given a modified live canine distemper vaccine propagated on chick embryo tissue culture systems. This vaccine is safe and effective for ferrets. The killed virus vaccine is not effective. The first dose should be given to kits 6-10 weeks of age with a booster injection 2 weeks later. Kits from unvaccinated jills should be given vaccine at 4 weeks of age with booster injections 3 weeks later. No other immunizations are proposed for ferrets as they are not susceptible to the production of disease by feline panleukopenia virus, mink enteritis virus, feline rhinotracheitis virus, and feline calicivirus. Vaccination for rabies is not recommended; no evidence vaccine products are effective in the immunization against the rabies virus.

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NERVOUS SYSTEM

Canine Distemper

Canine distemper virus, a Morbillivirus member of the Paramyxoviridae produces disease in a great variety of animals including various mustelids such as the mink, ferret, weasel, skunk, badger, otter, stoat and martin. The mustelids, especially the ferret and mink, are considered among the most susceptible species to infection with the distemper virus.

Canine distemper is the most serious disease in ferrets. Essentially 100% fatal, canine distemper virus results in an accelerated syndrome that closely mimics signs seen in dogs. The virus is shed in the nasal exudate of infected animals and is readily spread by aerosolization. Within a colony of ferrets, once infection is established, it is likely the entire stock will become infected until isolation of clinically healthy stock is undertaken. The virus after entrance into the upper respiratory tract replicates in respiratory epithelium and regional lymph nodes. Viremia develops within 4-5 days and virus spreads to essentially all tissues.

This pan trophic virus results in a variety of clinical signs, which in the ferret are fairly constant and predictable. Incubation period is 4-10 days and clinical signs develop generally within 7-9 days after exposure and begin with fever, anorexia and a mucopurulent conjunctivitis. Disease progression ranges from 12 days in ferret-adapted strains to approximately 42 in wild canine strains. Photophobia and an ocular discharge is often the first sign of infection and results in the development of crusts and adherence of the eyelids. Other ocular lesions include corneal ulceration, keratoconjunctivitis sicca, and blepharitis. Cutaneous lesions develop in the inguinal area, beneath the chin and on the foot pads. The cutaneous rashes begin as small vesicles and bacterial infection is followed by development of pyoderma. Pruritis follows the cutaneous infection. Hyperkeratosis of the foot pads is nearly diagnostic of distemper. Infection of respiratory tract is followed by catarrhal rhinitis which develops into a mucopurulent discharge. Some ferrets develop a fulminating pneumonia due to bacterial infection secondary to distemper infection of pulmonary tissues. The disease is profoundly immunosuppressive, with animals that survive the acute catarrhal phase of the disease succumbing to neurologic dysfunction within several weeks. Nervous system disease includes signs of myoclonus, paresis, muscular tremors, convulsions and coma prior to death.

Lesions at necropsy are similar to those seen in the dog and are often limited to cutaneous and ocular alterations. Gross lesions include oculonasal discharge, hyperkeratosis of the planum nasale and footpads, and a papular rash beginning on the chin and progressing to a generalized form. A catarrhal to mucopurulent rhinitis, tracheitis and bronchitis may be present along with severe purulent pneumonia.

Microscopically, brightly eosinophilic, 2-5 um intracytoplasmic and intranuclear inclusions may be seen in a wide variety of epithelial cells (urinary bladder, renal pelvis, stomach, conjunctiva, and biliary epithelium), neurons, and occasionally in white blood cells and megakaryocytes. Inclusions are found but are fewer in the epidermis and epithelium of hair follicles, small intestines and cornea. Inclusions are also found in astroglia and neurons of the central nervous system. Lymphoid necrosis may be widespread in the lymph nodes, spleen and lymph nodules of the intestines. Additionally, multinucleate cells may be found in any of these sites. Non-suppurative encephalitis with demyelination may be seen in animals with neurologic disease. The presence of suppurative bronchopneumonia in a young ferret is suggestive of this disease.

This disease in the U.S. is primarily seen in young kits from pet stores. Treatment is not recommended. Vaccination of ferrets for canine distemper should be with an attenuated virus vaccine propagated on chick embryo tissues. These vaccines are effective and safe. However, results from one study using modified live avian cell culture canine distemper virus suggest that there may be a high incidence of anaphylactic reactions after vaccination of domestic ferrets. Ferrets should be observed for at least 25 minutes after vaccination, and veterinarians who vaccinate ferrets should be prepared to treat anaphylactic reactions. The vaccines may be administered by either subcutaneous or intramuscular injections. Currently, there is one approved distemper vaccine for ferrets (Fervac-D, United Vaccines); however, many commercial modified live canine vaccines are used in ferrets. Recombinant vaccines using a canarypox vector are being developed for use in ferrets and exotic mammals. In one study, oral and subcutaneous delivery of an experimental canarypox recombinant canine distemper vaccine to Siberian polecats (*Mustela eversmanni*) demonstrated efficacy and the survival rate in animals receiving vaccine at the highest oral dose (10(8.0) PFU per dose) was 83.3%. Large numbers of animals may be routinely vaccinated by aerosolization of the vaccine.

The diagnosis of distemper in a ferret colony should be followed quickly by isolation of ferrets with clinical disease and the immediate vaccination of the ferrets without clinical signs. Canine cell products have been confirmed as a cause of transmission of distemper to ferrets and modified live chicken embryo vaccines has been responsible for distemper infections in black-footed ferrets. These ferrets within 3 weeks of vaccination developed clinical illness with signs of anorexia, decreased activity, ocular and nasal discharge, erythema of skin, diarrhea and dyspnea. Later in the clinical course, the ferrets were dehydrated, had hyperkeratosis of foot pads and neurologic signs of myoclonus, paresis and convulsions. Death occurred 1-2 days after onset of nervous signs. Diffuse interstitial pneumonia was present in the lungs; alveolar septums were thickened by infiltrates of lymphocytes, macrophages and neutrophils and

the alveoli contained cells and proteinaceous material with a few giant cells. A few intranuclear inclusions were found in the epithelium of bronchioles.

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Rabies

Ferrets, as well as any other mammal, are susceptible to rabies. Ferrets, however, have a low recorded incidence of rabies, with less than 25 confirmed cases since 1954. The disease can result in both furious (less common) and dumb forms, and often presents as a progressive hind limb paralysis. Researchers have shown that ferrets inoculated IM with virulent rabies virus do not secrete the virus in their saliva. In one study ferrets were inoculated im with European Bat Lyssaviruses (EBLV) type-1 and 2. All ferrets receiving a high dose of EBLV-1 succumbed to infection. In contrast, only three of seven ferrets inoculated experimentally with a lower EBLV-1 dose died. By comparison, all of the EBLV-2 infected ferrets survived infection. All 20 infected ferrets seroconverted. Using sensitive molecular tools, the virus was detected in different tissues, but it could not be found in any saliva samples taken during the 84-day observation period.

Currently, there is one approved killed rabies vaccine available for use in the ferret (Imrab, Rhone-Merieux). No gross lesions have been observed. Microscopic lesions are characterized by the typical non-suppurative encephalitis with intracytoplasmic eosinophilic viral inclusion (Negri) bodies especially within Purkinje cells that may be demonstrated on HE stains or on standard fluorescent antibody tests.

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Pseudorabies

Ferrets are susceptible to infection with pseudorabies, porcine herpesvirus, but spontaneously occurring disease has not been described in ferrets in North America. The inoculation of ferrets with pseudorabies virus was followed by clinical disease and death. Clinical signs included inappetence, decreased spontaneous activity, trembling, weakness, ataxia and posterior paralysis. Ferrets mutilated

themselves by biting the sites of infection and other reachable areas due to severe pruritis.

Necropsy findings were minimal and consisted of generalized enlargement of lymphoid organs and pulmonary edema was found in ferrets infected by the airborne route. In non-neural tissues, hyperplasia of reticular cells was present in spleen and lymph nodes and lymphoid necrosis was observed in the spleen, lymph nodes, tonsils and lymphoid nodules of intestines. Focal necrosis was found in the liver and vasculitis in several tissues. The neural lesions were nonsuppurative meningoencephalomyelitis and nonsuppurative poliomyelitis. Lesions were more severe in those ferrets with a longer clinical course. Mononuclear cells were present in the meninges and edema, gliosis and perivascular mononuclear cells infiltrates were found in brain stem nuclei. Degeneration of neurons was indicated by nuclear pyknosis and chromatolysis and cytoplasmic vacuolation. The neural changes were associated with gliosis, neuronophagia, perivascular cuffing and meningeal mononuclear cell infiltrates. Inclusion bodies were found in nuclei of neurons and glia cells. Spinal cord lesions of meningeal and perivascular mononuclear cell infiltrates and glia foci, neuronophagia and neuronal degeneration varied in location depending on the route of inoculation. When injection was made into the rear foot pad, the lesions were especially severe in the dorsal columns of the lumbar region of the spinal cord. Lesions were predominantly in 1-5 segments of cervical spinal cord when exposure was airborne. In the peripheral nervous system, lymphocytic and histiocytic infiltrates and neuronal degeneration with intranuclear inclusion bodies were lesions found in the mesenteric ganglia. Schwann cells and fibroblasts were more numerous in some ganglia. The distribution of lesions in the central nervous system appeared closely related to peripheral nerve pathways from the sites of inoculation. Also, the virus could have spread via lymph-blood vascular systems to nonneural visceral organs and tissues.

Ferrets have been used as experimental models to study the neuronal pathways by using the transneuronal transport of two recombinant isogenic strains of pseudorabies virus.

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Neural Tube Defects

NTD's are one of the most common birth defects in ferret kits. They may range from simple cranioschisis (external opening of the skull), to spina bifida, to craniorachischisis (opening of the skull and vertebral column with loss of cerebral tissue). Many variants are seen. Additionally, growth retardation and other birth defects (kidney defects appear commonly) may be seen in the fetus.

Gross lesions are characterized by agenesis of skin and musculature overlying various segments of the skull and/or spinal cord, with variable loss of neural tissue. Additionally, there may be fusion or other deformation of the vertebrae. With cranioschisis or craniorachischisis, there is often agenesis of the cerebrum and cerebellum, with a rudimentary medulla (cerebrovasculosa) remaining.

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Botulism

Ferrets are described as highly sensitive to toxic C produced by *Clostridium botulinum*, but only moderately sensitive to toxins A and B. This susceptibility of the ferret is similar to that described for

minks. Ferrets are less likely to be affected than mink because of management differences. However, improperly stored offal may have the anaerobic environment necessary for the growth of the bacterium and the production of toxin. Such "spoiled" offals should not be fed. Ferrets given contaminated feed develop clinical signs of muscle incoordination leading to flaccid paralysis within about 96 hrs of feeding. Death follows upon paralysis of the respiratory muscles. The disease is readily eliminated by the use of commercially prepared dry ferret feeds.

Under management situations in which offal is fed to ferrets, the animals should be given type C toxoid. The potency of vaccine against *Cl. botulinum* type C was tested in ferrets for its capacity to withstand challenge to toxin. Ferrets proved to be protected against high toxin doses. On the other hand the humoral antitoxin titer of the immunized animals was low after one injection. After a second injection or after challenge with toxin the titer increased considerably.

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Intervertebral Disc Syndrome

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GASTROINTESTINAL SYSTEM

Dental Disease

Broken teeth are common in older ferrets, most commonly affected are the upper canines. While few broken teeth result in clinical debility, exposure of the pulp requires extraction or root canal procedures. Accumulation of dental calculi is common in older ferrets on semi-moist or moist diets. Tooth root abscesses are occasionally seen in ferrets. Dental malformations, including supernumerary teeth or decrease numbers of adult teeth have also been documented. Grossly, discoloration of broken teeth suggests devitalization. Draining tracts may be seen, especially in the area of the zygomatic arch with tooth root abscesses.

Ferrets have been used as animal models for craniofacial research because of the similarity of many of the ferret's anatomical, metabolic and physiological features to those of man.

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Megaesophagus

The cause of megaesophagus is currently unknown in the ferret. It presents similarly to megaesophagus in the dog and cat. Occasionally, secondary *Candida* infections may be seen. The condition occurs in middle-aged to older ferrets, and treatment is usually ineffective.

Grossly marked dilation of the intrathoracic esophagus is observed. Ulcerations may be present anywhere along the length. Evidence of bronchopneumonia may be present due to aspiration.

Microscopic lesions are often absent. In chronic cases, there may be discernable atrophy of the muscular layers. In other cases, there may be hyperkeratosis of the lining epithelium, and the presence of numerous yeasts within the mucosa, inciting a lymphocytic and neutrophilic inflammatory response.

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Helicobacter mustelae

This bacterium causes gastric disease in significant numbers of ferrets over the age of four years via two mechanisms - a) the stimulation of a marked lymphoplasmacytic inflammatory response, resulting in loss of glandular epithelium, most prominently in the pylorus, and 2) the ability to increase the pH of the stomach. Animals over the age of 3 years rarely do not show evidence of *Helicobacter* infection. Gastric ulcers are also commonly seen in animals with severe *Helicobacter* infection. (see below) Recent evidence that *H. mustelae*-infected ferrets have elevated levels of gastrin suggests a possible relationship with peptic ulcer disease. Recently it has been shown that ferrets naturally infected with *H. mustelae* generated antibodies that reacted with parietal cells in the ferret gastric mucosa but not with duodenal or colonic mucosa. Sera from these ferrets did not react with the blood group A epitope on erythrocytes or *H. mustelae* lipopolysaccharide, and absorption with *H. mustelae* whole cells or red blood cells did not remove autoantibodies. These autoantibodies are not due to molecular mimicry. Also, *Helicobacter cholecystus* has been associated with chronic cholangiohepatitis coupled with cellular proliferation ranging from hyperplasia to frank neoplasia.

There are often no gross lesions in uncomplicated cases of gastric *Helicobacter*. Advanced cases may be coupled with gastric ulcers. In these cases, the gastric mucosa is often lined by moderate amounts of digested blood; gastric ulcers are often fine bleeding points concentrated in the pylorus.

Microscopically, the Warthin-Starry stain will demonstrate the presence of the bacteria in the superficial mucus and in extracellular locations within the gastric glands. The pyloric stomach is the preferred biopsy site, although low numbers of bacilli may also be seen in the fundus and duodenum in severely infected animals.

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Gastric ulcers

Ferret, like other mustelids, are extremely susceptible to stress-related gastric ulcers. This is a common finding in animals with other systemic diseases and often contributes to debility in older animals. They are often seen in association with gastric *Helicobacter mustelae* infection, however, a definitive cause-and-effect relationship has not been proven in this species.

Two distinct forms of gastric ulceration may be seen in the ferret. The most common form is the presence of digested blood within the stomach lumen. Ulcers are pinpoint, extremely difficult to see, and are present in the highest numbers in the pyloric region of the stomach. The second, less common form, is the presence of a single, focally extensive, ulcer in the pyloric stomach. These large ulcers may result in sudden death due to erosion into the submucosal blood vessels.

Microscopically, ulcers appear as full-thickness areas of glandular necrosis and loss which are well-demarcated from the surrounding tissue. Bleeding ulcers may be covered with a layer of brown hemoglobin pigment. Chronic ulcers have marked peri-lesion fibrosis accompanied by infiltrates of macrophages and lymphocytes in the lamina propria and submucosa.

Gastric ulceration has been observed in ferrets dying of end stage heart disease and as an incidental findings at necropsy and gastric surgery.

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Gastrointestinal foreign bodies

Gastrointestinal foreign bodies are commonly seen in young or bored, cage-bound ferrets. Ferrets commonly ingest latex, plastic, and foam rubber. Ferrets may also ingest towels or other forms of bedding. Anorexia and passage of abnormal stools are common presenting signs; abdominal pain is not commonly seen.

Grossly, a focal area of intestinal distention with or without hemorrhage may be seen. In many cases, the wall of the intestine at the site of the blockage is thinner than that of the adjacent intestine due to continuous peristaltic movements at the site of blockage. Intestinal perforation may rarely be seen. Microscopically, there is ulceration, necrosis and thinning of the muscular layers at the site of blockage. Marked attenuation of villi and granulation tissue may be seen in longstanding blockages.

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Eosinophilic enteritis

Although the etiology of eosinophilic enteritis is unknown, it is not an uncommon disease. Presumed cases have been treated successfully with ivermectin, suggesting some form of parasitic

origin. The wasting disease is most commonly seen in young male ferrets under 14 months of age. Peripheral eosinophilia may be seen in affected animals. A recent paper suggests that possibility of a connection between eosinophilic gastroenteritis and lymphoma; however, there is no concrete data aside from the single case report of one ferret with both diseases to back up this claim.

There are no gross lesions. Microscopically, eosinophilic infiltrates may be seen in the small intestine - a diffuse mucosal infiltrate and an eosinophilic vasculitis may be present. Additionally, prominent eosinophilic infiltrates may be seen in the mesenteric lymph nodes, and rarely in the liver. Aggregates of Splendore-Hoeppli material may be seen within the lymph nodes and rarely in the liver in areas of accumulated eosinophils.

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Proliferative colitis

Proliferative colitis is an uncommon disease which is usually seen in male ferrets less than one year of age. The disease is sporadic, with only one or two animals in a large colony being affected. Clinical signs include diarrhea, tenesmus, dehydration, weight loss and partial prolapse of the rectum and production of small, frequent bowel movements which often contain frank blood and mucus. The diarrhea is intermittent and persistent over several weeks. Weight loss is greater than 100 grams in most of the affected ferrets. The disease is caused by *Lawsonia intracellularis* which results in asymmetrical proliferation of immature epithelium, causing marked thickening of the wall. Some ferrets have a palpably thickened colon. This condition is subject to periodic periods of recrudescence, often during times of stress. If untreated, it may be fatal.

At necropsy, lesions are limited to colon and rectum and mesenteric lymph nodes. The diameter of affected portions is increased and the wall is turgid on palpation. The affected colonic wall is noticeable thickening and becomes opaque (normally you can see fecal material through the colonic wall). The mucosa is prominently "cobblestoned." The mucosal surface is moist, glistening and has thick longitudinal folds. Mesenteric lymph nodes are 2-3xnormal size.

Microscopically, the lesions vary in severity, but are similar with the principal lesions those of mucosal epithelial cell proliferation, hypertrophy of tunica muscularis and inflammatory cell infiltration of the lamina propria. In the mucosa, goblet cells are essentially absent and crypts are lined by either pleomorphic or tall columnar epithelial cells piled several layers deep. The intestinal glands are irregular, convoluted and branching. The proliferated epithelium extends through the muscularis mucosa into the submucosa and has a number of mitotic figures. Necrotic cellular debris is present deep in the crypts and the lamina propria contains mononuclear cellular infiltrates composed mostly of lymphocytes with a few macrophages and plasma cells. Lymphoid hyperplasia is responsible for lymph node enlargement. Clusters of comma-shaped bacteria are found in the apical mucosal cells by the Warthin-Starry stain. In electron micrographs, clusters of bacteria are present in colonic epithelial cells and are restricted to the apical cytoplasm.

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Campylobacteriosis

Infection of ferrets with *Campylobacter jejuni* has been associated with episodic diarrheic disease characterized by the passage of mucinous, blood-tinged feces. The clinical disease was reproduced by the inoculation of *C. jejuni*. Inoculated ferrets reduced their feed intake and passed bile-tinged, liquid feces containing mucus and blood. Infection is common, up to 61% in some surveys, but clinical disease is much less common. Ferrets are persistently infected with Campylobacteria and these animals are susceptible to stress related episodes of diarrhea. Such relapses of diarrhea have occurred in ferrets undergoing surgical operations, subjected to behavioral tests and after administration of hormone modulating drugs.

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Epizootic catarrhal enteritis

ECE is a coronaviral disease of ferrets (ferret enteric coronavirus) which causes epizootics of high morbidity (up to 100%), but low mortality. The diarrhea is rapidly dehydrating and most mortalities occur in older animals with concurrent illness. Symptoms include vomiting and passage of a dark green stool with abundant mucus ("green slime disease"). During the recovery phase, stools assume a "birdseed" like appearance. The only gross lesions are flaccid, fluid filled intestines. Microscopic lesions are mainly found in the jejunum. Early lesions include vacuolar degeneration and necrosis of apical enterocytes, with resultant marked villar atrophy, fusion and blunting. Later in the course of disease, there is a marked lymphocytic enteritis with large numbers of lymphocytes among mucosal epithelial cells.

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Rotavirus-Induced Diarrhea

Diarrheal disease affecting kits between 4-15 days of age; characterized by soft yellow to green

feces has been reported as a major problem in commercial breeding farms. Affected kits had fecal staining of fur, a rough hair coat and reddened anal and perineal areas. Up to 90% of all litters of primiparous females were affected litters with up to 25% of morbidity within litters. Mortality was low with prompt oral therapy with a broad spectrum antibiotic and fluid support. Microscopic alterations included mild blunting of the tips of the mucosal villi of the small intestine. Epithelial cells were cuboidal in size and shape. Rotavirus particles were detected in fecal samples by means of electron microscopic examination. Group A, B and C rotaviruses have been detected in fecal material.

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Salmonellosis

Infection with *Salmonella sp.* (gram negative, facultatively anaerobic rod) may be a cause of gastroenteritis and diarrhea in ferrets subjected to nutritional or other stress. Normal (unstressed) ferrets appear resistant to oral exposure to *Salmonella*. Ferrets are susceptible to infection with *Salmonella* when pregnant and infections can cause abortions. *Salmonella enteritidis ser typhimurium* was isolated from ferrets. Affected ferrets have clinical disease characterized by lassitude, anorexia, trembling, and diarrhea. The diarrheic stools may contain blood. The ferrets become moribund and die after a short illness.

Gross lesions include dilated, fluid-filled small intestines with lumens containing gas and red-black fluid material. Microscopically, the lesions were those of a necrohemorrhagic enteritis with bloody exudate in the lumen, ulceration of the mucosa and leukocytic infiltrates of the mucosa consisting of a few neutrophils, lymphocytes and histiocytes. Necrotic foci in the liver and spleen were lesions seen in the more chronic fatal infections.

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Aeromoniasis

Bacteria belonging to the genus *Aeromonas sp.* are gram negative, motile rods and identified as a cause of gastroenteritis, meningitis, endocarditis and septicemia in human patients. Few cases are described in fur-bearing animals and a single report has appeared of infection in ferrets. An isolate identified as *A. sobria* based on biochemical reactions produced nonspecific clinical signs of anorexia, lassitude and diarrhea. At necropsy, the liver had irregular-shaped white foci; hemorrhages and ulcers were present in the stomach and hemorrhages in the intestinal mucosa. Multifocal coagulative necrosis was found in the liver, spleen, lungs, heart, lymph nodes and adrenal glands. The necrotic foci contained colonies of gram-negative bacteria, but few inflammatory cells.

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Clostridium perfringens

Clostridium perfringens type A has been reported in black-footed ferret kits. Gross lesions: consist of gastric bloat and multifocal intestinal hemorrhages. Microscopic lesions are those of typical clostridial infections. There is marked coagulative necrosis of the intestinal mucosa with numerous adherent 2x6-8 µm bacilli.

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Intestinal Mycobacteriosis

This is a rare condition in ferrets which most commonly affects the gastrointestinal tract and mesenteric lymph nodes, although accumulation of macrophages containing acid fast organisms may be seen in any organ. Mesenteric lymphadenopathy is the most common gross lesion. The presence of large foamy macrophages with a grayish granular cytoplasm is suggestive of this disease - acid-fast stains reveal numerous bacilli within macrophages. One paper described a chronic granulomatous intestinal disease in ferrets caused by an acid-fast organism morphologically similar to *M. paratuberculosis*. The affected ferrets had a chronic, persistent diarrhea, progressive weight loss, and an unthrifty appearance which progressed to emaciation and death. Lesions were primarily in the gastrointestinal tract, mesenteric lymph nodes and the kidneys in some ferrets.

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Listeriosis

Ferrets have been a source of *Listeria monocytogenes* and may transmit the bacterium and have no clinical signs of disease. No clinical disease has been described in ferrets spontaneously infected with *L. monocytogenes*, gram-positive, beta-hemolytic, non- spore forming rods.

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Cryptosporidiosis

Cryptosporidiosis has been described in a variety of domestic and laboratory animals. The genus *Cryptosporidium* is a protozoan in the class Sporozoa and subclass Coccidia. It is apparently an uncommon cause of disease in ferrets, but subclinical infection may be common in young ferrets. Although both immunocompetent and immunosuppressed ferrets may have a subclinical infection with cryptosporidia, the competent host recovers within 2-3 weeks and the infection may persist for months in immunosuppressed ferrets (up to 5 months in ferrets given dexamethasone). Ferrets receiving dexamethasone die and have gross lesions of intestinal hemorrhages.

Microscopic alterations include the presence of numerous spherical to ovoid bodies in association with the brush border of the intestinal epithelium at the tips and lateral margins of villi. The organisms consistent with *Cryptosporidium* measured 2-5 µm, stain weakly with hematoxylin and eosin, and are observed only in small intestine. In electron micrographs, the organisms are enclosed by four unit membranes except at the zone of attachment with the outer membrane continuous with host plasma membrane. Several stages of the parasite are identified in electron micrographs. Trophozoites had such features as nucleus with a nucleolus, endoplasmic reticulum and Golgi anlagen. Schizonts are identified by the presence of membrane-bound merozoites free within parasitophorous vacuole. Macrogametes

contain large polysaccharide granules. Oocysts are free in the lumen of intestine. Mature oocysts contain four sporozoites and a residual body and are surrounded by two membranes. Cryptosporidial organisms may be found attached to the gut epithelium at several regions of the small intestine. The ileum is most commonly affected and generally is the site of the most severe infection. Other lesions are few and include a mild focal villous atrophy and inflammatory cell, often mostly eosinophils, infiltrates of the lamina propria of the small intestine. Such infiltrates are also observed in non-infected ferrets and the enteritis may have no association with the parasitic infection.

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Zygomatic Salivary Gland Mucocele

A zygomatic salivary gland mucocele was diagnosed in a 1-year-old female domestic ferret with exophthalmos. A T-shaped incision from near the lateral canthus to the base of the ear and continuing ventrally to the level of the commissure of the mouth was made to expose the mucocele. Surgical removal was complicated by the large open orbit of the ferret, adjacent cellulitis, extension ventromedial to the globe, and difficulty in identifying important motor nerves. Vision was maintained, but slight postoperative enophthalmos and mild upper eyelid paresis developed.

References

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Cystic Mucinous Hyperplasia in the Gallbladder

An 8-year-old male ferret had icterus, hepatomegaly and an enlarged gallbladder. Microscopically, the gallbladder had numerous mucinous cysts and papillary hyperplasia of the mucosa, consistent with a diagnosis of cystic mucinous hyperplasia.

References

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Intestinal parasites

With the exception of coccidia, intestinal parasites are uncommon in ferrets. *Toxocara cati*, *Toxascaris leonina*, *Ancylostoma* sp., *Dipylidium caninum*, and *Giardia* sp. have all been reported in ferrets. Three species of coccidia have been seen in ferrets: *Eimeria furo*, *Eimeria ictidea*, and *Isospora laidlawii*. While most coccidial infections are subclinical, lethal coccidial infections are occasionally seen in young kits. Ferrets have been experimentally infected with a number of intestinal parasites, including *Strongyloides stercoralis*

Generally there are no gross lesions, although digested blood may be present in the GI tract of kits severely affected with coccidial infections.

Microscopically, numbers of parasites range from very low to extremely high in severe infections where almost every enterocyte contains merozoites. All stages of the parasite, including micro- and macrogametocytes can be seen. Meronts contain up to 16 merozoites. Coccidial infections have also been seen in the hepatobiliary system.

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Neoplasia

The most common gastrointestinal neoplasm is, as in several other organ systems, lymphosarcoma. The lymphoblastic form of lymphosarcoma is the most common form in the intestine. (See hematopoietic system for a more detailed description of this condition.)

References

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RESPIRATORY SYSTEM

Endogenous lipid pneumonia

This condition, also known as "foam cell foci" or "subpleural histiocytosis" is a common incidental finding in mustelids at necropsy and is of no clinical significance. It is often mistaken at necropsy by practitioners as a dissemination neoplasm. The cause of this finding, and the origin of the lipid, is not known.

Gross lesions. Multiple to coalescing white to yellow foci are present within the subpleural pulmonary parenchyma. A transverse cut through one of these foci will reveal its superficial nature.

Microscopic lesions. The basic lesion is simply an aggregate of lipid-laden macrophages in the alveoli immediately subjacent to the pleura. As the lesion increases in size, it may include moderate numbers of lymphocytes and cholesterol clefts.

References

Aspiration pneumonia

Aspiration, either of orally administered medicants or of vomitus, is by far the most common cause of pneumonia in the ferret. Ferrets often resist liquid oral medication by fighting and squirming during administration, and often involuntarily inhale part of the medication.

In cases of aspiration pneumonia, there may be consolidation of the cranioventral lung lobes, either unilaterally or bilaterally. The severity of lesions seen with aspiration of vomitus is proportionate to the length of time since the event. In most cases, aspiration occurs as a terminal event, so minimal gross lesions are seen. In long-standing cases, gangrenous, cavitated lesions may be seen in the pulmonary parenchyma.

The primary microscopic lesion in aspiration pneumonia is in the small airways. Bronchioles contain a mixture of viable and degenerate neutrophils, sloughed epithelial cells, and variable amounts of eosinophilic proteinaceous material (which may be admixed with food particles when vomitus is aspirated). Often, there is an accumulation of foamy macrophages in the surrounding alveoli. In long-standing cases, there may be a pronounced granulomatous response, with numerous foreign body and multinucleate giant cells admixed with lymphocytes, plasma cells, and cholesterol clefts. Occasionally, you may find eosinophilic crystalline proteins within the cytoplasm of macrophages. In cases of aspiration of vomitus, the lesion is characterized by extensive necrosis of the airway and surrounding alveoli, with sloughing of the bronchiolar epithelium and coagulative necrosis of the adjacent alveolar septa. Colonies of gram-negative bacilli or mixed colonies may be seen in cases of aspiration of vomitus.

References

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Influenza

Ferrets are the only domestic animal species which is susceptible to the human influenza viruses (type A and B influenza viruses of Orthomyxoviridae). For this reason, they are a) often used as animal models in influenza research, and b) often infected by their human owners. The disease has been transmitted experimentally to ferrets by various routes of administration including intranasal inoculation. Also, the disease can be transmitted from affected ferrets back to humans. Influenza in otherwise healthy adult ferrets is a transient, non-fatal febrile illness similar to the disease occurring in large populations of human adults. Affected ferrets have signs indicative of infection of the upper respiratory tract. A mucoserous nasal discharge results in development of crusts about the external nares. Conjunctivitis results in ocular discharge causing the eyelids to adhere accompanied by photophobia. Ferrets have frequent fits of sneezing. Congestion of the upper respiratory tract and a sero-mucous rhinitis are the only usual gross lesions. Other less common clinical signs include coughing, pyrexia, anorexia, and malaise. In the neonatal ferret, influenza can be a fatal infection.

Gross lesions are generally minimal, with congestion and exudation of the nasal mucosa and mild reddening of the tracheal mucosa. Microscopic lesions are characterized by mild subacute inflammation and occasional necrosis of the nasal mucosa. A mild subacute interstitial pneumonia may be present. Experimentally, influenza virus infection by intranasal inoculation was invariably fatal in newborn ferrets. Severe lesions were present in the upper respiratory tract and pneumonic lesions in the lungs. The lesions included multifocal loss of cilia, epithelial erosions and epithelial cell necrosis. Focally, the epithelium was hyperplastic with nuclear pleomorphism, cytoplasmic basophilia and loss of polarity of superficial cells. Infection of nasal passages was later followed by extension into nasal sinuses and lungs. At about 3 days post inoculation, necrosis was extensive in the mucosae of sinuses, nasal passages and upper trachea. Squamous metaplasia associated with regeneration was present as early as day 5 postinfection.

Humans with influenza should avoid contact with ferrets, especially females with neonatal kits. If contact cannot be avoided, then sick humans should wear gloves and face masks to protect the ferret population.

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Infectious Bovine Rhinotracheitis

Infectious bovine rhinotracheitis virus (IBR) has been isolated from ferrets fed uncooked beef tripe and the virus replicates in the respiratory mucosa of ferrets producing disease and lesions similar to that produced in cattle. Ferrets were experimentally exposed to IBR virus by aerosol and ip injection. They developed clinical disease characterized by coughing and sneezing (for 3-4 days duration) and copious amounts of yellow, mucoid exudate in the posterior nares and pharyngeal region. Exudate of similar nature but of smaller amounts was present in the trachea. The lesions were those of acute purulent pharyngitis and tracheitis; the tracheal and pharyngeal mucosa and submucosa were infiltrated by neutrophils. Similar lesions were found in the esophagus, acute focal esophagitis was characterized by ballooning degeneration of epithelium and infiltrates of inflammatory cells in the mucosa and submucosa. Intranuclear inclusion bodies were observed in epithelial cells.

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Streptococcosis

Streptococci of Lancefield Group C were obtained from ferrets with clinical signs of fever, lethargy, dyspnea, and purulent nasal discharge. Gross lesions included rhinitis, pneumonia, abscesses and encephalitis. *Streptococcus zooepidemicus* has been isolated from pneumonic lungs, blood and infected uterus of ferrets. This bacterium and other members of Lancefield Group C have been associated with valvular endocarditis during septicemia in ferrets. Mixed bacterial infections of wounds is common in ferrets and the organisms including Streptococci, Staphylococci and *Corynebacterium* species result in development of dermatitis, cellulitis and abscesses.

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Actinomycosis

A single report describes 2 cases of actinomycosis in ferrets. One ferret had hard masses in the neck and the skin was adherent to the fibrotic masses. The lesions contained small abscesses filled with thick green pus. The second ferret had pneumonia with solid, firm, white, nodules beneath the visceral pleura. The mediastinal lymph nodes were enlarged and contained multiple small abscesses filled with creamy pus in which small green granules were visible.

The microscopic alterations were those of a pyogranulomatous inflammation. In both cases the masses were composed of granulation tissue with discrete or confluent abscesses. The purulent exudate with abundant macrophages was surrounded by young granulation tissue infiltrated with neutrophils. Colonies of organisms consistent with *Actinomyces* sp were present in the exudates. The largest colonies had characteristic club-like gram-negative structures among the intertwined and branching threads of gram-positive mycelium.

References

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Pneumocystosis

Pneumonia with proliferated *Pneumocystis carinii* in the lungs was produced in the ferret by immunosuppression produced by daily injections of cortisone acetate (10-20 mg/kg for 9-10 weeks). Focal areas of interstitial pneumonitis and alveolitis consisted of intraseptal and intra-alveolar infiltrates of mononuclear inflammatory cells. The cellular reaction was slight, but the number of organisms was abundant and consisted of both cysts and trophozoites. The organisms occurred in close association with type I cells.

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Blastomycosis

The single report was a ferret with an ulcerated lesion of the left metacarpal pad, fever and occasionally coughing and sneezing. Broad-based budding yeast forms consistent with *Blastomyces dermatitidis* was found in imprints of the cutaneous lesion. The ferret had radiographic evidence of an interstitial pneumonia. The ferret relapsed after a course of treatment with amphotericin B.

Necropsy lesions included a bilateral, diffuse granulomatous pneumonia with miliary white to tan nodules throughout the lungs. The spleen was firm and enlarged. Round, elevated plaques were on the costal pleura. Microscopically, the lesions were those of a lobar granulomatous pneumonia, bronchial lymphoid hyperplasia, granulomatous pleuritis and splenitis and multifocal granulomatous meningoencephalitis. Blastospores of *B. dermatitidis* were present in the lesions.

References

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Cryptococcosis

Infection of ferrets with *Cryptococcus neoformans* is rare. Tissues affected have included the meninges in one ferret with cardiomyopathy, the lungs, and abdominal viscera. The lesions produced in the meninges of one ferret consisted of a marked, diffuse nonsuppurative meningitis in which a diffuse lymphocytic meningeal infiltrate contained numerous round, pale-staining, bluish yeast forms with a wide capsule. A second ferret with cryptococcosis had been housed in an aviary which had attracted a number of pigeons. The ferret died suddenly, had pneumonia at necropsy, and the lungs contained budding yeast forms consistent with *C. neoformans*. A third ferret had died suddenly and the abdominal viscera were submitted for study. The viscera were covered with colorless, jelly-like material, and a few firm, white nodules were present on the serosal surface of the intestines and present in the spleen and liver. The jelly-like material was composed of cryptococcal organisms and their wide mucoid capsule. Organisms were present in macrophages and giant cells in small granulomas in the serosa of the intestines.

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Histoplasmosis

Infection of ferrets with *Histoplasma capsulatum* is apparently rare and there is a single report. The organisms were identified in the cells of an aspirate from one of several subcutaneous nodules. The cachectic ferret had chronic sneezing and weight loss in addition to the subcutaneous nodules. At microscopic examination, macrophages contained *H. capsulatum* and were found in granulomatous lesions in the subcutaneous nodules, the interstitium of the lungs and periportal areas of the liver.

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CARDIOVASCULAR SYSTEM

Cardiomyopathy

Cardiomyopathy is a common disease in the American lines of ferrets, which has a presumed genetic basis. Several forms of this condition may be seen - dilatative, hypertrophic, and a restrictive form in which there is marked replacement of myocardium by fibrous connective tissue, with minimal change in chamber area. Signs of cardiomyopathy may be seen as early as 1 year of age in severely affected animals, but are more common between 5 and 7 years of age. These ferrets have a clinical syndrome characterized by decreased activity, weight loss, dyspnea, polypnea, exercise intolerance, cyanotic mucous membranes and distention of the abdomen due to ascites. Muffled heart sounds and moist rales are also observed in some ferrets with increased thoracic and pericardial fluid. Electrocardiographic abnormalities and radiographic evidence of cardiomegaly, enlarged pulmonary veins and effusions have been observed in affected ferrets.

Gross lesions are similar to those seen in other domestic species. In subclinical cases, a congested, occasionally nodular liver may be the only gross lesion as a result of chronic passive congestion in this organ. The heart may appear enlarged, and the right ventricle may appear thin or flabby. With progressively severe cases, there is often an accumulation of a serosanguinous ascitic transudate in the abdominal cavity, the pleural cavity, or both. In severe cases, the lungs are atelectatic and compressed by the presence of a globose heart and abundant pleural effusion. In cases in which the heart is not enlarged, examination of the left ventricular free wall and the interventricular septum may reveal marked thickening and impingement upon the ventricular lumen. Rarely, the presence of fibrous connective tissue may be seen upon close inspection of the cardiac wall, and occasionally, due a previous ischemic event, a focally extensive area of the ventricular wall may be translucent and paper thin as a result of total loss of myocytes in this area and replacement by fibrous connective tissue.

Early microscopic lesions consist of an increase in fibrous connective tissue around myocardial vessels which extends into the interstitium. As the condition progresses, there is atrophy and loss of myocytes. Focal areas of myocyte degeneration may be present, with an infiltrate of moderate numbers of macrophages, lymphocytes, plasma cells, and rare neutrophils. In some cases of cardiomyopathy, there may be marked focal malalignment of myocytes, suggesting orientation in several different planes. Centrilobular fibrosis, edema, micronodular hemosiderosis, and loss of subcapsular hepatocytes with resulting fibrosis all attest to chronic hepatic congestion, which is a common finding in cardiac disease in the ferret. In contrast, the presence of chronic signs of left-sided heart failure is relatively uncommon. In terminal stages of the disease, there may be necrosis of centrilobular hepatocytes due to stasis and hypoxia. The presence of marked myocardial fibrosis with or without inflammation, and evidence of chronic systemic congestion are highly suggestive of cardiomyopathy in this species.

References

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Dirofilariasis

Ferrets are also susceptible to heartworm infection, but due to the fact that most ferrets are kept indoors, cases are still uncommon. Ferrets in heartworm endemic areas are usually maintained on monthly ivermectin at approximately 0.2 mg/kg. (The vast majority of cases of dirofilariasis in ferrets come from Florida.) Infection with *D. immitis* in ferrets produces signs of respiratory distress (cyanosis, dyspnea) and lesions of cardiac failure. Due to the small size of the ferret heart, as few as two heartworms may result in fatal cardiac insufficiency. Some ferrets have died with as few as one nematode present in the right side of the heart. As many as 21 adult worms have been found in the cardiac chambers, vena cava and pulmonary artery of another ferret.

Clinical diagnosis is sometimes difficult because affected ferrets are often negative for microfilaria and the antigen-detection tests available for diagnosing canine dirofilariasis have not successfully identified infected ferrets. The small numbers of heartworms in most animals necessitates the use of occult heartworm tests due to the low levels of circulating microfilaremia.

Ferrets present with weakness, lethargy, pale membranes, cyanosis, dyspnea and the clinical evidence of fluid accumulations. The parasites in the cardiac chambers obstruct cardiac outflow producing congestive heart failure. Lesions of heartworm disease in the ferret are essentially the same as cardiomyopathy (see above). Fluid accumulates in the chest and abdomen, the lungs are congested, and edematous, the membranes are pale, and heart sounds are muffled by fluid in the chest and pericardial sac. Aberrant cerebral heartworm migration has been noted in this species. The presence of heartworms within the right ventricles and pulmonary artery can be construed as the cause of death in any ferret in which it is observed.

Microscopic lesions are as expected with heart failure (see above). The lungs are congested and edematous and microfilaria are present in pulmonary vessels.

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Toxoplasmosis

Toxoplasma gondii has a wide range of both herbivorous and carnivorous intermediate hosts. These hosts include members of the family Mustelidae. Ferrets and other mustelids may be chronically infected with *T. gondii*, but clinical toxoplasmosis appears to be rare in mustelids. Toxoplasmosis in mink has been observed in association with distemper, an immunosuppressive disease. Outbreaks in ferrets are apparently rare.

Increased death rate among young farmed ferrets involved most litters on a ranch in New Zealand. No clinical signs were recorded. Some kits which survived the early phase of high mortality were

stunted. The adults of the ranch had a protracted period of anorexia prior to mating.

Toxoplasmosis in ferret is characterized by multifocal necrosis and toxoplasmic organism in several organs including the liver, heart, lungs, intestines, mesenteric lymph nodes and brain. Necropsy findings included multiple small white foci on the pleural surface of the lungs. Microscopically, the alterations included multifocal coagulative necrosis of myocardium with diffuse interstitial lymphocytic myocarditis. Toxoplasmic protozoa were found in myocardial fibers near to the foci of necrosis. Multifocal necrosis was found in the liver and protozoal organisms were located in hepatocytes. The pulmonary lesions consisted of diffuse pneumonia with alveoli filled with macrophages, multifocal coagulative necrosis and the presence of protozoal organisms within macrophages.

References

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HEMATOLYMPHATIC SYSTEM

Splenomegaly

The cause of this extremely common finding in ferrets is yet unknown; many theories abound. This condition is most commonly seen in middle-aged to older ferrets, but may be seen in ferrets as young as six months. As the incidence of neoplasia in enlarged spleens is somewhat less than 10%, this change may represent a response to chronic inflammatory disease. The previously reported syndrome of hypersplenism in a ferret is most likely not a distinct entity in this species. Marked enlargement of the spleen for any reason increases the spleen's phagocytic capability, resulting in increased RBC breakdown. Additionally, anemia of chronic disease may complicate many cases of splenomegaly. Lymphosarcoma is by far the most common splenic neoplasm, with hemangiosarcoma being rarely seen.

Enlarged spleens may range up to 10 cm. in length. While most spleens are diffusely enlarged, a small percentage of spleens will contain single or multiple discrete nodules, which are more likely to represent splenic neoplasms. Microscopically, 95% of cases consist of a combination of marked congestion and extramedullary hematopoiesis, representing erythrocytic, leukocytic, and megakaryocytic lines. Florid EMH may resemble lymphosarcoma in that a large percentage of the cells within the red pulp may have a markedly increased nuclear/cytoplasmic ratio and a high mitotic rate, but represent the immature forms of the various cell lines. The marked variation in cell size, and the presence of islands of erythrocytic precursors and megakaryocytes contrasts well with the monomorphic population of cells seen in most cases of lymphosarcoma.

Large areas of coagulative necrosis, often bordered by a combination of viable and degenerate neutrophils and various amounts of granulation tissue may be seen in grossly enlarged spleens. As enlarged spleens are prone to rupture, various signs of splenic trauma, including hematoma, siderotic plaques, and large areas of parenchymal fibrosis are commonly seen.

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Lymphosarcoma

Lymphosarcoma is the most common malignancy in the domestic ferret. These neoplasms most commonly arise spontaneously; however, a recent article documents horizontal transmission of malignant lymphoma in ferrets using cell or cell-free inoculum. This finding, coupled with the occasionally clustering

of lymphomas in a single facility, has prompted speculation that lymphosarcoma in the ferret may be the result of a retroviral infection. A viral agent has not, as of yet, been isolated from cases of lymphosarcoma in the ferret.

Several variants of lymphoma exist in the ferret. The most commonly seen form, in which the neoplastic cell is a mature, well-differentiated lymphocyte occurs in older ferrets, primarily resulting in peripheral lymphadenopathy, with visceral spread and subsequent organ failure late in the course of disease. A second form occurs primarily in young ferrets less than two years of age. This form, in which the neoplastic cell is a large blastic lymphocyte, is characterized by early visceral neoplasms, often with the production of a large thymic mass. An enlarging thymic neoplasm often results in compression of the lung lobes, dyspnea, and pleural effusion, and may often be misdiagnosed as pneumonia or heart disease by veterinarians with little experience in this species. A third, uncommon form, in which combinations of peripheral lymphadenopathy and visceral neoplasms and numerous bizarre blasts may be seen, is known as the immunoblastic polymorphous variant.

The main gross lesion in the adult (lymphocytic) form is diffuse lymphadenopathy. Splenic white pulp may be greatly expanded and grossly visible on cut section. In later stages, firm white nodules may be seen in a number of visceral organs, including the liver and kidney, and the spleen may be diffusely enlarged. The presence of a thymic mass is strongly suggestive of the juvenile (lymphoblastic) form of lymphoma. Diffuse hepatosplenomegaly is often seen due to massive infiltration of these organs also. Neoplastic cells may be seen in any organ, including the bone marrow.

Microscopically, in the adult form, peripheral lymph nodes reveal effacement of the normal architecture by an infiltrate of small non-cleaved lymphocytes which breach the capsule and extend into the surrounding tissue. However, extension into surrounding tissue may also be seen in cortical hyperplasia of the mesenteric nodes due to the attenuated and occasionally absent capsule seen in these nodes. The presence of tingible body macrophages scattered throughout the node ("starry-sky" effect) is commonly seen in this form. In the liver, neoplastic infiltrates are primarily seen extending from portal areas, which in the spleen, the earliest sign of lymphosarcoma is an expansion of the well-differentiated lymphocytes in the mantle of the periarteriolar lymphoid sheaths. Mitotic rates generally average 1-2/hpf.

In the juvenile form, examination of infiltrated organs often reveals effacement of normal architecture by a monomorphic population of large cleaved and non-cleaved lymphoblasts, which may be admixed with smaller, more well-differentiated cells. In the liver, neoplastic cells are more commonly seen as discrete nodules distending sinusoids and replacing hepatocytes, while in the spleen, the periarteriolar lymphoid sheath is totally replaced and expanded by a monomorphic lymphoblast population. Discrete nodules of blastic lymphocytes may be seen in any visceral organ; infiltration of lymph nodes is a late finding. The mitotic rate of the lymphoblastic cells is generally high, ranging up to 6/hpf. A recent immunophenotypic characterization of thymic lymphomas of young ferrets revealed that 9/10 were C3+ (T cell origin) and 1/10 was CD 79+ (B cell origin).

Finally, the distribution of the immunoblastic polymorphous variant resembles that of the lymphocytic form. However, scattered through infiltrated nodes is a subpopulation of atypical large cleaved, often multinucleate lymphocytes which may range up to 50 or 60 um in diameter. Occasionally, Reed-Sternberg-like cells may be present. Bizarre-looking lymphocytes in this condition may be misinterpreted as megakaryocytes, however, use of immunohistochemical techniques such as Factor VII antigen, CD3 and BLA-36 may be used to distinguish between the two cell lines in the spleen and bone marrow. The mitotic index in this form of lymphoma is also high.

A common request for pathologists working with ferrets is evaluation of splenic aspirates from animals with enlarged spleens. This task is fraught with pitfalls. As a general rule: extramedullary hematopoiesis will be seen in the VAST majority of cases. Evidence of erythrocytic precursors and abundant peripheral blood should lead the prudent pathologist to a diagnosis of EMH. Cases of splenic lymphosarcoma may be identified on splenic cytology by the presence of a monomorphic population of cells with large nuclei, prominent nucleoli, an absence of erythrocytic precursors, and minimal blood elements. Additionally, mitotic figures should be present.

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Aleutian Disease

Aleutian disease is caused by the same parvovirus that causes Aleutian disease in mink; however, the disease is quite different between these two species. In mink, Aleutian disease results in rapidly life-threatening immune-mediated glomerulonephritis, vasculitis, and hypergammaglobulinemia. In ferrets, there are notable similarities, including a hypergammaglobulinemia, and in late stages of the disease, an immune complex glomerulonephritis. However, the disease is much more insidious, with a progression of as long as 2 years. Ferrets in the late stages of disease will be hyperproteinemic (8-9 mg/dl, with >20% being comprised of gammaglobulins). Available serologic tests are of rather questionable value for diagnosing Aleutian disease in ferrets.

Gross lesions are seen only late in the course of disease. Splenomegaly and lymphadenopathy are the most common gross lesions with this disease; splenic infarction as a result of marked splenomegaly may complicate the clinical and pathologic picture. Enlarged, brown-tan kidneys may be present. In terminal cases, clotting abnormalities resulting from vasculitis and the marked hypergammaglobulinemia may result in petechial hemorrhage and hematuria.

Several characteristic microscopic findings are seen in ferret Aleutian disease as well as in the mink disease. Prominent plasmacytic infiltrates are seen in numerous organs, most prominently in the renal interstitium, hepatic portal areas, in the splenic red pulp, where an almost pure population of plasma cells expands the red pulp in the thymus, medullary cords of lymph nodes, in the lungs, and in bone marrow. Additionally, there may be marked plasmacytosis of numerous lymph nodes and the bone marrow. In most cases, there will be marked membranous glomerulonephritis and numerous ectatic protein-filled tubules as a result. Glomerulosclerosis is commonly seen in chronic interstitial nephritis in ferrets, but there is little evidence of tubular protein casts or plasmacytic infiltrate in such cases. Vasculitis may be seen in almost any organ.

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Tuberculosis

Tuberculosis is a rare disease in ferrets today, but was once common in ferret colonies in Europe and in the mid 1980's was found on ferret farms in New Zealand. Ferrets are susceptible to bovine, human and avian species of Mycobacteria. Reports of tuberculosis in ferrets dating to the late 1920's were of bovine origin and probably due to feeding of raw cows' milk. The bovine strain appears much more pathogenic for the ferret than the human and avian strains. The latter strains produce a chronic disease (Mycobacteriosis) with splenomegaly and none or few tubercles. The disease is chronic and older lesions are mainly found in the alimentary tract. Affected ferrets have nonspecific signs of disease characterized by a wasting syndrome (weight loss, inappetance, lethargy, muscle weakness). The enlarged mesenteric lymph nodes can be palpated and the liver and spleen are enlarged.

Grossly, tubercles are found in several organs with organ involvement varying among affected animals. Mesenteric lymph nodes may be greatly enlarged fused and have foci of caseous necrosis on cut section. Granulomas of varying size are distributed within the lobes of the lungs and can be widespread in the liver and spleen. Tubercles (firm, opaque, whitish tissue) have also been observed in the peritoneum and omentum which may be studded with firm grey nodules 0.05-0.3cm in diameter.

Microscopically, the granulomas contain enormous numbers of acid-fast organisms. The intracellular bacteria are more numerous toward the periphery of the granulomas and may be so abundant that the Ziehl-Neelson stained slides appear red to the unaided eye. Viable and degenerated macrophages are packed with bacilli. The granulomatous inflammatory tissue and necrosis replace most of the parenchyma of the spleen and lymph nodes in some animals. The cellular reaction appears sarcomatous in some areas without Langhans giant cells.

Diagnosis can be provided by mesenteric lymph node biopsy and positive tuberculin test (mammalian tuberculin 0.1 ml). Ferrets with tuberculosis should be euthanized as they pose a zoonotic threat.

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URINARY SYSTEM

Bacterial Urinary Tract Infections

Bacterial urinary tract infections are commonly seen in female ferrets, and uncommonly seen in male ferrets. The most common causative agent in the ferret is *E. coli*, with *Staphylococcus aureus* being isolated out of a significant number of cases. Bladder infections are often subclinical in female ferrets, and ascending infections resulting in pyelonephritis are not uncommon. Renal failure may result from severe pyelonephritis in this species.

Often there are no gross lesions. Hydronephrosis and hydroureter may be present in long-standing or resolved infections. Microscopic lesions are a ulcerative cystitis and/or a suppurative tubulointerstitial nephritis. Bacteria are rarely seen.

Prostatic Squamous Metaplasia

Squamous metaplasia of the prostate has only recently been recognized as a common cause of dysuria and urethral blockage in the ferret. The squamous change in the prostate is the result of excess estrogens liberated from proliferative adrenal lesions (see adrenal-associated endocrinopathy). Accumulation of secretory material and lamellated keratin results in the formation of multiple prostatic cysts. Impingement of the prostatic cysts upon the prostatic urethra results in dysuria, and finally complete urinary blockage in male ferrets. The bladder of blocked ferrets may be manually expressed, but ferrets cannot void on their own. In earlier literature, due to the close association with the bladder, the condition was referred to as the "triple bladder syndrome". Surgery is directed toward removal of prostatic cysts and the affected adrenal.

Grossly, single to multiple, variably-sized fluctuant cysts are present near the bladder trigone. The cysts are thick-walled, and firm on palpation. Identification of an enlarged adrenal gland or an adrenal neoplasm is often possible in these animals.

Microscopically, multiple cysts or fragments of cysts are often available for examination. Atrophic prostate glands (as a result of the effects of circulating estrogens) are often present at the periphery of the cysts, although in advanced cases, they may be lined by squamous, rather than glandular epithelium). The wall consists of multiple layers of squamous epithelium, surrounded by variable amounts of immature fibrous connective tissue. The luminal contents of the cyst may vary from lamellated keratin and keratin debris, to abundant purulent inflammation (in which case there is often a combination of chronic-active inflammation and granulation tissue in the cyst wall and prostate (overeager manual expression of the bladder?).

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Urolithiasis

Numerous references refer to the formation of struvite uroliths in ferrets; however, the actual incidence is probably overestimated, especially in light of recent findings of prostatic squamous metaplasia. Male ferret are more likely to develop uroliths than females; however, the syndrome has not been well characterized, and dietary influences have not been explored, although high ash cat foods are frequently blamed. In ferrets, urinary incontinence results in "wet belly". Clinical signs include frequent licking of the genital area, dysuria, anuria, and occasionally, hematuria. Reportedly, pregnancy may increase the incidence of urolithiasis in pregnant jills due to the effects of estrogen on the ferret's handling of calcium and phosphorus. Cystine crystals have also been reported.

Struvite uroliths often have a corrugated surface. Single or multiple uroliths may be present in the bladder, or rarely in the renal pelvis. Reports of struvite "sand" as may be seen in the feline urologic syndrome" are anecdotal. Microscopic lesions are similar to that seen in urolithiasis in other animals.

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Renal Cysts

Renal cysts are common incidental findings in the ferret. Although often submitted for histologic evaluation, they are of little clinical significance and have no effect on renal function. Rare cases of true polycystic disease may be seen in this species. Polycystic kidneys are enlarged, may be felt on external palpation, and may cause renal failure.

Gross lesions are characterized by single or multiple cysts in the cortex of one or both kidneys. When viewed from the capsular surface, they are thin, bulge slightly, and are fluid filled. Cysts may range up to 1 centimeter in diameter. Polycystic kidneys may be markedly enlarged and fill the posterior abdomen. They are composed of variable numbers of cysts with little intervening fibrous connective tissue.

Microscopically, in benign cysts, there may be little or no fibrosis surrounding the cyst, or the cyst may have a thick wall of fibrous connective tissue throughout which are scattered numerous atrophic glomeruli and tubules. In a reported case of polycystic disease in a ferret, the kidney contained multiple fluid-filled cysts in both the cortex and medulla which were lined by cuboidal epithelium. The cysts were separated by abundant fibrous connective tissue which contained moderate numbers of lymphocytes.

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Hydronephrosis

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Chronic Interstitial Nephritis

Chronic interstitial nephritis is a common finding in ferrets. Early lesions can be seen as early as 2 years, and advanced cases resulting in renal failure may occur as early as 4.5 years. The progression of the disease is most akin to that seen in older cats. Ferrets are generally maintained on a high protein diet with protein levels in excess of 34%. This is generally accomplished by feeding premium kitten chows or specially formulated ferret chows. Due to the prevalence of chronic interstitial nephritis in older ferrets, lowering of protein levels after three years of age is reached is generally advocated by most practitioners.

Grossly kidneys are generally pitted and large focal depressions may be seen in the outer cortex as a result of scarring. "Peeling" the renal capsule is recommended during the ferret necropsy. Severely affected kidneys may be asymmetric with respect to size.

Microscopically, the pattern of microscopic changes associated with chronic interstitial nephritis in the ferret is unique. At low magnification, there are linear bands of fibrosis which extend from the capsule inward. Glomerular and tubular changes are most commonly seen in these areas of fibrosis. There is periglomerular and glomerular fibrosis resulting in glomerulosclerosis. The interstitium is expanded by fibrous connective tissue throughout which is scattered moderate numbers of lymphocytes and plasma cells. Tubules within these radiating streaks of fibrosis exhibit variable degrees of atrophy. Pathologists with little experience with ferret tissues may be tempted to diagnose chronic infarction. As the disease progresses, there is a diffuse glomerulosclerosis throughout the cortex, as glomeruli outside of the areas of interstitial fibrosis are affected. Areas of fibrosis tend to coalesce into large areas devoid of functional glomeruli and tubules.

ENDOCRINE SYSTEM

Islet cell tumors

Islet cell neoplasms are the most common neoplasm of this species. These neoplasms generally result in hypoglycemia as a result of inappropriate secretion of insulin. Several cases of hypoglycemia have been described in ferrets. Affected ferrets have recurrent, intermittent and progressive episodes of abnormal behavior, weakness, ataxia, stupor, ptyalism, tremors, seizures, paraplegia and may progress to collapse, coma and death. The ferrets have hypothermia and are dehydrated. The plasma concentration of glucose in affected ferrets range from 30-60 mg/dl. Insulin values have been greater than 40 mU/ml. The hypoglycemia has been associated with the presence of beta cell neoplasms of the endocrine pancreas and/or metastases in regional lymph nodes and liver. Non-functional islet cell tumors are commonly seen in older animals at necropsy. While all islet cell tumors are potentially malignant, metastasis is rare, as opposed to islet cell neoplasms in the dog and cat.

Islet cell tumors are reddish-brown, well-defined nodules which range in size from 2mm-1 cm. They are firmer than the surrounding pancreatic tissue and may be multiple. These neoplasms must be differentiated grossly from foci of pancreatic exocrine hyperplasia, a common benign age-related finding. Foci of exocrine hyperplasia are generally the same color and consistency of the surrounding tissue, and may be numerous. Small reddish brown nodules may also be present in the mesentery adjacent to the pancreas.

Microscopic lesions are similar to islet cell neoplasms in other species. These tumors are most commonly unencapsulated, and resemble normal, albeit greatly enlarged islets of Langerhans. Identical foci may be present in the surrounding mesentery. Metastasis to visceral organs is rare. These neoplasms stain strongly for insulin with scattered glucagon staining.

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Adrenal-associated endocrinopathy

AAE is a common endocrine disorder of middle aged to older ferrets. The syndrome is the result of proliferative lesions in the adrenal cortex which secrete excess amounts of estrogenic hormones. As a result of this excess estrogens, affected ferrets exhibit a range of cutaneous, behavioral, and reproductive signs. While technically a form of hyperadrenocorticism, AAE should not be confused with Cushing's disease, or hypercortisolism. Only rarely are cortisol levels elevated in these patients. Interestingly, unlike dogs and cats, metastasis occurs extremely late in the course of disease with adrenocortical carcinoma, and early removal of affected adrenals carries a fair prognosis.

Gross lesions strongly suggestive of AAE consist of bilaterally symmetrical alopecia beginning over the tailhead and progressing forwards over the flanks and abdomen. Additionally, the presence of an enlarged vulva in a spayed female also strongly suggests AAE. These clinical signs may be the result of any of the three types of proliferative adrenocortical lesions - hyperplasia, adenoma, or carcinoma. The normal length of the ferret's adrenal gland ranges from 3-5 mm; glands exceeding 5 mm often contain proliferative lesions. Diameters exceeding 1 cm are highly suggestive of adrenocortical carcinoma in the ferret.

Proliferative lesions of the ferret adrenal cortex fall into three categories - hyperplasia, adenoma, and carcinoma. In a recent retrospective of 104 proliferative adrenocortical lesions, hyperplasia and carcinoma were present in 45% of cases each, while adenoma was present in 10%. The presence of necrosis, cellular atypia, and a mitotic rate greater than 1/10 hpf are strong indicators of malignancy. The presence of a single nodule in the adrenal cortex without factors associated with malignancy indicates adenoma, while the presence of multiple nodules is evidence of nodular cortical hyperplasia. Many neoplasms have a prominent spindle cell component which is primarily a proliferation of smooth muscle and has no prognostic significance. Extracapsular extension of proliferative cortical tissue may be seen in all three lesions, and does not occur indicate one lesion over another.

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Diabetes mellitus

Diabetes mellitus is a poorly-defined, uncommon disease which has been reported in both the domestic and the black-footed ferret. Blood glucose levels in affected ferrets generally range into the 500's, but levels as high as 725 g/dl have been reported. Diabetes mellitus occurs in aged ferrets. Polydipsia, polyuria, glucosuria, and loss of body condition have been reported in affected ferrets.

No gross lesions have been described. The most consistent microscopic lesion is glycogenic vacuolation of the islets of Langerhans. Glycogen accumulation may also be seen in renal tubular epithelium. In several cases lenticular cataracts have been noted.

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Thyroid Disease

Thyroid abnormalities are extremely rare in the ferret. One case of thyroid adenocarcinoma has been documented. In over 2500 cases on archive in the Registry of Veterinary Pathology at the AFIP, not one thyroid lesion has been catalogued.

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REPRODUCTIVE SYSTEM

Estrus-associated Aplastic Anemia (Hyperestrogenism)

Ferrets are induced ovulators - intact females remain in estrus until mated, spayed, or are cycled out by injections of human chorionic gonadotropin. 50% of unmated jills will develop marked bone marrow suppression as a result of high levels of circulating estrogens. All three bone marrow cell lines are affected - erythrocytes, leukocytes, and megakaryocytes. Initially, there is a mild thrombocytosis and leukocytosis, but the condition soon progresses to a non-regenerative anemia, leukopenia, and thrombocytopenia. The anemia may remain non-regenerative anemia up to 4 months past ovariohysterectomy in affected animals. In addition to thrombocytopenia, a liver-associated clotting abnormality may also be present. Hemorrhage is reported to be the most common cause of death. Similar signs may be caused by exogenous estrogen administration, but are not seen in cases of adrenal-associated endocrinopathy.

Gross lesions in affected female ferrets are prominently swollen vulvas in estrus. Signs of hyperestrogenism include pale mucus membranes, alopecia, melena, thin watery blood, hemorrhages throughout the body, hematuria, pyometra, bronchopneumonia, and vaginitis.

Diagnosis of aplastic anemia (normocytic and normochromic) is most commonly made on the combination of a low PCV (<20%) in a jill in estrus. The most characteristic lesion in affected jills is hypocellularity of the bone marrow. There is also no evidence of splenic hematopoiesis; small amounts of EMH may be seen in the liver. There may be evidence of hemorrhage (hemosiderin-laden macrophages, erythrophagocytosis) in lymph nodes and the spleen. Hemorrhagic anemia due to thrombocytopenia was the most common cause of death (mortality rate of 40% in some studies). Suppurative metritis or pneumonia may be seen as a result of the marked leukopenia.

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Mastitis

Mastitis is occasionally seen in pregnant jills in the first few weeks of lactation. Hemolytic *E. coli* is the most commonly isolated organism, and results in a syndrome of gangrenous mastitis. If untreated, jills rapidly become septic and/or endotoxemic. *Staph. aureus* is occasionally cultured from cases of mastitis and produces a more suppurative, less necrotic form of mastitis.

Mastitis produced by *E. coli* in the ferret was a rapidly progressive disease with high mortality. Infection was first detected in the inguinal mammary glands. The affected glands were enlarged, firm, discolored and non painful. Swelling increased in severity and with fine adjacent glands became involved. Alterations varied in severity among the affected mammary glands, but the basic tissue alterations were similar. Large areas of coagulative and liquifactive necrosis involved glandular tissue and adjacent adipose tissue and skeletal muscle. Areas of infarctions are well-demarcated by a line of degenerate neutrophils and cellular debris, and vascular thrombosis may be seen. Congestion and edema were extensive and hemorrhages were present in the intra-and perilobular tissues. A suppurative exudate was moderate, concentrated at periphery of the areas of necrosis, and infiltrated between and within lobules with little or no necrosis. The lesions contained abundant bacteria. Other signs of sepsis, or endotoxemia, including margination of neutrophils in the pulmonary capillaries and hypertrophy of Kupffer cells in the hepatic sinusoids may be seen, as well as colonies of gram-negative bacilli in numerous tissues. In *Staph aureus* mastitis, the mammary glands are hot, painful, and reddish in color; purulent exudate may be expressed from the lactiferous ducts. There is less evidence of infarction. A purulent galactophoritis and mastitis is present. Staphylococci are often prominent.

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MUSCULOSKELETAL SYSTEM

Trichinellosis

Naturally occurring *Trichinella* infection has been described for several genera of mustelids and for several species of the genus *Mustela* including mink, weasel, ermine, Siberian ferret. The domestic ferret has not been established as a natural host, but is highly susceptible to *T. spiralis*. About 30% of the

inoculated larvae are recovered as adult worms. Many larvae became encapsulated within muscles of infected ferrets. The course of *T. spiralis* infection in the ferret was basically similar to that in other laboratory species such as the mouse. The common characteristics included: (1) maturation of worms within a few days; (2) a preponderance of worms in the first three-quarters of small intestine; (3) a preponderance of female worms; (4) an abrupt decline in worm population associated with increase in number of worms in posterior part of the small intestine; (5) a reversal of sex ratio in the small residuum of worms; and 6) subsequent appearance of large numbers of encapsulated larvae in musculature.

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Chordoma

Chordomas are the most common neoplasm of the musculoskeletal system of the ferret. They arise in or adjacent to vertebra from remnants of primitive notochord, and are most commonly seen at the tip of the tail. Chordomas have also been documented in cervical spine. Early reports mischaracterized this neoplasm as a chondrosarcoma, and this mistake is still repeated by pathologists who are unfamiliar with ferret tissue. Chordomas are considered potentially malignant, however, metastasis has not been seen in neoplasms arising in the tail. Cutaneous metastasis was reported in one chordoma from the cervical spine.

Chordomas are most commonly seen as club-like swellings at the tip o the tail which involve the last caudal vertebra. Cervical chordomas present as lytic neoplasms in the neck of animals with posterior paresis. Physical exam shows a markedly decreased range of motion and pain upon movement of the neck.

Chordomas are locally aggressive neoplasms which often infiltrate vertebral bodies. The neoplasm is composed of foamy "physaliferous cells" which are separated by a moderate amount of myxomatous matrix. There are multifocal areas of well-differentiated cartilage and bone within these neoplasms.

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INTEGUMENTARY SYSTEM

Neoplasia

By far, the most common skin problem in ferrets is neoplasia. The incidence of cutaneous neoplasia increases with age in this species. While there are a wide range of cutaneous neoplasms that have been documented in the ferret, the two most common types of neoplasms seen in the skin of the ferret are 1) sebaceous epithelioma and 2) mast cell tumor.

Sebaceous epitheliomas appear as warty, verrucous lesions, which may arise anywhere on the animal's body, but have a predilection for the head and neck. Microscopic examination reveals an unencapsulated neoplasm composed of basal cells, of which a small percentage exhibit sebaceous and or squamous differentiation. Although early reports referred to these neoplasms as "basosquamossebaceous carcinomas", they possess no features of malignancy, and evidence of metastasis has not been seen.

Mast cell tumors are also common skin tumors in ferrets. Grossly, they most often appear as flat, alopecic, hyperkeratotic plaques, which are variably pruritic. Microscopic examination reveals a well-demarcated, unencapsulated neoplasm which is generally confined to the superficial dermis, and is composed of well-differentiated mast cells. The tumors resemble those seen commonly in cats. Low numbers of eosinophils are scattered through the neoplasm, but vasculitis and collagen degradation is hardly ever seen. Metachromatic stains such as toluidine blue or Giemsa reveal few cytoplasmic granules, so the diagnosis is primarily made (and rightly so) on the H&E section.

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Dermatomycosis

This is an uncommon disease in ferrets, but is occasionally seen in mink. Most cases occur either in very young animals kept in poor conditions, or in older, immunosuppressed animals. Both *Microsporium canis* and *Trichophyton mentagrophytes* have been seen in ferrets.

Grossly, dermatophytosis is similar to that seen in other domestic species - animals have areas of crusting alopecia with brittle hair and numerous broken hair shafts. In immunosuppressed animals, the rash can become generalized (at which time it must be differentiated from that seen with canine distemper infection). Biopsies from affected sites are generally covered with a thick layer of keratin debris, degenerate neutrophils, and entrapped fungal arthrospores and hyphae. There is ulceration of the skin, and follicles often contain numerous fungal arthrospores which occasionally invade the hair shaft. Many follicles may not contain a hair shaft, only lamellar keratin debris. There is generally a neutrophilic or lymphoplasmacytic dermal infiltrate in perivascular and periadnexal areas.

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Ectoparasites

Several of the ectoparasites commonly found on dogs and cats have been detected on ferrets. They are commonly infected with two types of ectoparasites: ear mites (*Otodectes cynotis*) and fleas (*Ctenocephalides sp.*). *Otodectes* mites belong to the family *Psoroptidae*. Most young ferrets and many

older ones have clinical cases of ear mite infection which require periodic treatment. The scab mites do not burrow and feed on the epidermal debris at the surface of the skin. Pruritus initiates the clinical signs of infestations such as scratching at the external ears and shaking of the head. Secondary bacterial otitis may spread to the middle and inner ear. Grossly, ferrets with ear mites have copious amounts of a thick brown-black wax; mites are small, light colored objects in the exudate. All stages of mites are present in exudate as mites spend entire life cycle on the host. However, swabs from the ears should be examined microscopically for the presence of adult mites or their eggs, as ferrets without mites may also have large accumulations of wax due to neglectful owners.

Sarcoptic mange has been reported in ferrets. This disease comes in two distinct forms in ferrets - a very pruritic whole-body form, and a variably pruritic form localized to the feet. Grossly this form is characterized by swollen feet, evident of self-mutilation, and nail loss. Histologically, the disease is similar to that in the dog, with marked ulceration and hyperkeratosis of the skin and a few cross sections of mites in the epidermis or deep under the overlying crust. Scabies can be transmitted to humans which develop cutaneous lesions of vesicles, papules, wheals and burrows. For the treatment of sarcoptic mange, topical sulfur ointments, lime/sulfur washes or carbaryl shampoos are applied and treatment repeated every 3 days (ointment) or weekly (washes/shampoo) to ensure killing of all stages of the mites. Ivermectin may be safely used as a miticide for treatment of mange in ferrets.

Demodectic mange is generally seen in older or immunosuppressed ferrets. Skin scrapings may demonstrate the presence of nymphs or adults. Skin biopsies reveal moderate hyperkeratosis and the presence of a few cigar-shaped mites within the hair follicles.

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Miscellaneous skin disorders

1. Bacterial skin disease: Due to the nature of ferret skin, bacterial skin disease is fairly uncommon. Traumatic wounds, or poor husbandry are generally required for bacterial skin disease to occur in this species. A case of superficial spreading pyoderma in the ferret following fire ant bites has been described.
2. Pemphigus foliaceus: A case of a skin lesion from a ferret with generalized eruptions revealed classic vesicular lesions consistent with pemphigus foliaceus in other species; i.e., intracorneal pustules containing rafts of acantholytic cells, a thickened epidermis, and prominent superficial lymphocytic and eosinophilic dermatitis.

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SPECIAL SENSES

Cataracts

There are several reports of cataracts in individual animals and breeding colonies. While many causes have been postulated, no definitive cause has been isolated. Cases in individual animals are considered to be spontaneous. Cataractous change may also be seen in the lenses of diabetic animals;

however, since the lifespan of diabetic ferrets is generally short, grossly visible cataracts generally have not formed.

Cataracts in ferrets generally involve both the cortex and nucleus of the lens. The microscopic appearance of cataracts in ferrets is similar to that in other domestic species, with formation of balloon cells in the outer cortex, initially, progressing toward the nucleus. Morgagnian change has not been described in ferrets.

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NUTRITIONAL, METABOLIC AND TOXICOLOGIC DISEASES

Nutritional Steatitis (Yellow-fatDisease)

Nutritional steatitis (yellow fat disease) is a generalized disease of adipose tissue characterized by necrosis and inflammation of adipose tissue and the accumulations of a lipopigment (ceroid/lipofuscin). It has been frequently observed in mink, which along with horses and pigs are considered especially sensitive. It is not common in ranch ferrets.

An outbreak (793 kits affected/183 died) was described in farmed ferrets fed a diet containing 40% squid offal, 20% other fish, 25% skunk meat and 15% poultry layer pellets. This diet provided elevated concentration of polyunsaturated fat and an inadequate amount of vitamin E. Affected kits were depressed, reluctant to move and cried out when handled by the lower abdomen. The kits had diffuse, firm, subcutaneous swellings and very prominent, bilateral, subcutaneous lumps in the inguinal areas. The affected kits had microcytic normochromic anemia. Necropsy lesions consisted of alterations in body fat without skeletal muscle or cardiac lesions. Adipose tissue was yellow-brown, coarsely granular and firm, especially in inguinal, flank and axillary regions. Adipose tissue in regions with gross lesions was diffusely infiltrated with macrophages, mononuclear cells and fibroblasts and, focally, neutrophils. The fat was necrotic and contained dense deposits of PAS-positive, fluorescent lipopigment both within macrophages and in extracellular locations.

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Zinc Toxicity

Zinc toxicity has been described in a group of ferrets. The animals were housed in galvanized wire cages cleaned by steaming for 20 minutes at 82 degrees C. This procedure resulted in the development of a coating on the wire-mesh of a fine white powder. The powder contained 2400 ppm of zinc. The ferrets obtained the zinc from raw meat pushed through the wire mesh and placed on the wire floor. Affected ferrets had signs of inappetence, muscular tremors, lethargy and coma followed by death. The necropsy findings included emaciated carcass, pale mucous membranes, no fat deposits, orange fatty liver, and enlarged pale soft kidneys. Histopathologic alterations in the kidneys were those of a diffuse subacute nephrosis. Bowman's space and cortical tubules were dilated. Some tubules contained eosinophilic proteinaceous casts and other dilated tubules contained cellular debris. Hepatic lesions were periacinar fatty degeneration. Concentrations of zinc in the liver and kidneys were 203 and 881 ppm in the liver and 785 and 943 ppm in the kidneys, respectively (controls 85-114 in liver and 102-138 in the kidneys). The zinc toxicity of ferrets was experimentally reproduced by feeding zinc at dietary concentrations of 1500 and 3000 ppm. Ferrets fed the 3000 ppm diet died in less than 2 weeks of feeding and both groups had lesions of diffuse nephrosis, hemorrhages in the intestines and macrocytic-hypochromic anemia. Ferrets treated with zinc had decreased serum ceruloplasmin oxidase activity

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NEOPLASIA (OTHER THAN PREVIOUSLY DESCRIBED)

Numerous neoplasms have been described in the ferret, most of which are similar both grossly and histologically to those seen in other animals. Neoplasms easily represent up to 60% of total surgical biopsies of ferrets, with the balance being islet cell tumors, adrenal neoplasms, chordomas, and the skin tumors already mentioned.

Reproductive: Tumors of smooth muscle are the most common neoplasm of this system, and are also seen in the endocrine system (generally arising in the adrenal gland) and rarely in the gastrointestinal system and subcutaneous tissue. Low grade leiomyosarcomas, demonstrating an infiltrative nature, moderate atypia, and a moderate mitotic rate are more common than leiomyomas in this species. Additionally, leiomyosarcomas have been reported as occurring "free-floating" in the abdomen. The majority of these tumors is attached to the adrenal gland, ovary, or testis, and is removed due to the organomegaly they cause. Therefore the prognosis is generally good. Metastasis of leiomyosarcomas has not been reported.

Testicular neoplasms: Interstitial cell tumors are the most common neoplasm of the ferret testicle, but combinations of two or more neoplasms are not uncommon. This illustrates the importance of removing cryptorchid testicles in this species - you can always find at least one neoplasm and often more in retained testicles.

Ovarian neoplasms: Tumors of germ cell or stromal cell origins are most commonly seen, epithelial neoplasms are rare. One teratoma has been reported.

Gastrointestinal system: The second most common neoplasms of the gastrointestinal system (after lymphosarcoma) are tumors of smooth muscle origin, arising from the muscular layers of the GI tract, especially low-grade leiomyosarcomas. Mesotheliomas are occasionally observed in the peritoneum and serosal surfaces of ferrets. They are locally aggressive, result in marked abdominal effusion, and warrant a poor prognosis. Pancreatic exocrine adenocarcinomas are occasionally seen in the pancreas. These neoplasms are locally aggressive with a moderate metastatic potential, most commonly to the liver. Intestinal adenocarcinomas are rare, locally aggressive neoplasms. Gastric carcinoma has been experimentally reproduced in the presence of *Helicobacter mustelae* with a carcinogenic compound.

Musculoskeletal system: Osteomas have been described arising from flat bones. They are expansile neoplasms composed of trabecular of well-differentiated bone lined by osteoblasts and a few osteoclasts. The trabeculae are wide and there is little intervening space. Marrow is not seen. Interestingly, osteosarcoma has not been reported in the ferret.

Integumentary system: Apocrine cysts are a common finding in ferrets. They most commonly occur around the head, neck, prepuce, and vulva, due to the large numbers of scent glands in these regions. Apocrine gland cystadenomas and carcinomas are not uncommon and have a similar distribution. Apocrine gland carcinomas are locally aggressive neoplasms with a moderate potential for metastasis. Hemangiomas and low-grade hemangiosarcomas are occasionally seen; metastasis has not been reported. Squamous cell carcinoma has been reported several times in the ferret and has a predilection for the face, where it is locally destructive with a low metastatic potential.

Urinary system: Transitional cell carcinoma has been reported in the ferret.

Hematolymphatic system: Cranial mediastinal thymomas were reported in 2 5-year-old ferrets and should be considered in the differential diagnosis for thoracic neoplasia.

Nervous system: Few granular cell tumors have been reported in the prosencephalon of ferrets. In one granular cells stained positively for glial fibrillary acidic protein, suggesting astrocytic origin. A single case of meningosarcoma has been reported.

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Summary of the Most Important Diseases in Ferrets

Disease	Etiology	Lesions	Notes
Proliferative colitis	<i>Lawsonia intracellularis</i>	Thickened colon/rectum Mucosal epithelial proliferation, no goblet cells, crypts lined by pleomorphic/tall columnar cells, piling, intestinal glands convoluted/branching, mitotic figures, necrotic debris in crypt	Clusters of comma-shaped bacteria in apical portion of cytoplasm of affected epithelial cells by WS
Campylobacteriosis	<i>Campylobacter jejuni</i>	Diarrhea, mucinous, blood-tinged feces	Infection common, disease less common
Gastric ulcers/gastritis	<i>Helicobacter mustelae</i>	Ulcers in pylorus, duodenum Chronic, peri-lesional fibrosis, macrophages and lymphocytes in lamina propria	Stain with WS
Colibacillosis	<i>E. Coli</i>	Mastitis, high mortality Coagulative/liquefactive necrosis of mammary gland and surrounding tissue, suppurative exudate, abundant bacteria	
Botulism	<i>Clostridium botulinum</i>	Muscle incoordination, flaccid paralysis No lesions	Toxin C
Salmonellosis	<i>Salmonella enteritidis</i> ser. typhimurium most common but many other ser. may occur	Necrohemorrhagic enteritis, leukocytic infiltration Spleen, liver, LNs are enlarged and often contain foci of necrosis.	
Tuberculosis	<i>M. bovis, tuberculosis, avium</i>	Tubercles in mesenteric LN, lung, liver, spleen, peritoneum Granulomas with acid-fast organisms towards the periphery within macrophages	Rare
Streptococcosis	<i>S. zooepidemicus</i>	Rhinitis, pneumonia, abscesses, encephalitis, valvular endocarditis	
Aeromoniasis	<i>Aeromonas sp.</i>	White foci in liver, spleen, lung, heart, LNs, adrenals with colonies of gram negative bacteria	
Listeriosis	<i>Listeria monocytogenes</i>	Carrier, no signs	
Canine distemper	<i>Paramyxoviridae Morbillivirus</i>	Mucopurulent conjunctivitis, pyoderma, hyperkeratosis of foot pads, fulminating pneumonia, encephalitis, eosinophilic intracytoplasmic (and intranuclear) inclusion bodies especially in epithelial cells	
Aleutian disease	<i>Parvovirus</i>	Hypergammaglobulinemia Perivasculitis and vacuolitis (fibrinoid degeneration, mononuclear cell infiltration), plasma cell proliferation in kidneys, thymus, medullary cords of LN, lungs, bone marrow, spleen	

Disease	Etiology	Lesions	Notes
Influenza	Orthomyxoviridae Influenzavirus A and B	Transmission to and from humans Mucoserous nasal discharge, crusts, conjunctivitis Loss of cilia, epithelial erosion, epithelial cell necrosis, focal epithelial hyperplasia with nuclear pleomorphism, squamous metaplasia	
Pseudorabies	Porcine Herpesvirus 1	Pruritus, self-mutilation Hyperplasia of reticular cells, lymphoid necrosis, focal necrosis of liver, vasculitis Nonsuppurative meningoencephalomyelitis, edema, gliosis, perivascular mononuclear cells cuffing Neuron degeneration, intranuclear inclusion bodies in neurons and glial cells Lymphohistiocytic neuritis, neuronal degeneration with intranuclear inclusion bodies in mesenteric ganglia and Schwann cells	
Rotavirus	Rotavirus (atypical – group C)	Neonatal diarrhea- blunting of villus tips, cuboidal epithelial cells	
Infectious bovine rhinotracheitis	Bovine Herpesvirus 1	From uncooked beef products in feed Acute, purulent pharyngitis, tracheitis, esophagus with ballooning degeneration, intranuclear inclusion bodies	
Rabies	Rhaboviridae, lissavirus		
Dirofilariasis	Dirofilaria immitis	Pulmonary congestion, edema, enlarged heart Microfilaria in pulmonary vessels	Highly susceptible
Cryptosporidiosis	Cryptosporidium	Intestinal hemorrhages Spherical/ovoid bodies associated with brush border of villus tips and lateral margins, 2-5 µm in Ø, mild villus atrophy, eosinophils in lamina propria	Uncommon
Toxoplasmosis	Toxoplasma gondii	White foci on lungs Interstitial pneumonia, alveolitis, intraseptal/alveolar mononuclear infiltrates, abundant cysts with trophozoites in close association with type I cells	
Trichinosis	Trichinella	Larvae encapsulated within muscles	
Otoacariasis	Otodectes cynotis	Dermatitis of external ear	
Scabies	Sarcoptes scabiei	Alopecia	
Blastomycosis	B. dermatitidis	Lobar granulomatous pneumonia, bronchial lymphoid hyperplasia, granulomatous pleuritis, splenitis, granulomatous meningoencephalitis	Rare
Cryptococcosis	C. neoformans	Viscera covered with jelly-like material, firm white nodules on serosa of intestine, spleen, liver Diffuse nonsuppurative meningitis with yeasts	

Disease	Etiology	Lesions	Notes
Histoplasmosis	<i>H. capsulatum</i>	Macrophages containing yeasts in granulomas	
Actinomycosis	<i>Actinomyces sp.</i>	SQ abscesses, pneumonia with white nodules, enlarged abscessed lymph nodes Pyogranulomatous inflammation, granulation tissues, abscesses, colonies of club-like gram negative structures intertwined with branching threads of gram positive mycelium	
Dermatophytosis	<i>Microsporum canis</i>	Alopecia, yeasts within hair shafts	
Nutritional steatitis	High fish diet low Vitamine E	Diffuse firm subcutaneous swellings, no muscle lesions, yellow-brown granular firm adipose tissue Macrophages, lymphs, fibroblasts, neutrophils, fat necrosis, deposition of PAS pos fluorescent lipopigment within macrophages and extracellular	
Aplastic anemia of estrus	Estrogen toxicity	Pale mucosa, enlarged vulva, anemia, leukopenia, thrombocytopenia Bone marrow hypoplasia of all cell lines	Prolonged estrus
Zinc toxicity	Zinc toxicity	Diffuse nephrosis, periacinar fatty degeneration	
Hypoglycemia	Beta cell neoplasms		
Diabetes mellitus	Aged		
Urolithiasis			
Cardiomyopathy	Aged	Thickening of mitral valve leaflet, myocardial and endocardial fibrosis Myofiber necrosis, hypertrophy, hypertrophy of media of coronary arteries, hepatic congestion and fibrosis	
Gastric ulcer	Stress	Hemorrhages	
Eclampsia/ pregnancy toxemia		Fatty liver	
Neoplastic Diseases	Mastocytoma Lymphosarcoma Malignant Megakaryocytic myelosis Plasma cell myeloma Squamous cell carcinoma Adenocarcinoma of preputial sweat glands Islet cell tumor Adrenocortical carcinoma Chordoma Black-footed ferret: Basal cell tumor Sebaceous adenocarcinoma Mammary adenocarcinoma		